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Neural substrates of appetitive and aversive prediction error

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Abstract

Prediction error, defined by the discrepancy between real and expected outcomes, lies at the core of associative learning. Behavioural investigations have provided evidence that prediction error up- and down-regulates associative relationships, and allocates attention to stimuli to enable learning. These behavioural advances have recently been followed by investigations into the neurobiological substrates of prediction error. In the present paper, we review neuroscience data obtained using causal and recording neural methods from a variety of key behavioural designs. We explore the neurobiology of both appetitive (reward) and aversive (fear) prediction error with a focus on the mesolimbic dopamine system, the amygdala, ventrolateral periaqueductal gray, hippocampus, cortex and locus coeruleus noradrenaline. New questions and avenues for research are considered.

Keywords

reward; fear; learning; attention; noradrenaline; amygdala; dopamine; periaqueductal gray; opioids

Associative learning is incredibly adaptive. It offers a way to predict and engage with the environment we live in. We have known for some time that associative learning depends on prediction error, which is a broad term for a class of theoretical signals that detect the discrepancy between predicted and received outcomes. Prediction error signals are theorized

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Competing interests

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to alter the associative strength between predictive cues and outcomes, such that the greater the error in prediction the greater the change in learning.

Types of prediction error.

Prediction error can occur in two directions, when an outcome exceeds the prediction or when the prediction exceeds the outcome. A *positive* prediction error occurs when there is a 'positive' discrepancy (outcome exceeds prediction) and serves to increase the associative strength between predictive cues and their outcomes. A *negative* prediction error occurs when there is a 'negative' discrepancy (prediction exceeds outcome) and serves to decrease associative strength. A *signed* error occurs when positive and negative error are observed in a directional manner. For example, a neuron carrying a signed error may increase spiking activity over baseline to surprising outcome presentation (positive error), but decrease spiking activity below baseline to surprising outcome omission (negative error). *Unsigned* error also occurs when there is a discrepancy between the prediction and the delivered outcome, only now the absolute value of the discrepancy is reported. In this case, the error is in the same direction irrespective of whether the outcome exceeds the prediction or the prediction exceeds the outcome. A neuron carrying an unsigned error may show equivalent increases in spiking activity over baseline to surprising outcome presentation *and* to surprising outcome omission. Lastly, prediction error can be specified in terms of outcome valence. An *aversive* prediction error refers to error about aversive outcomes such as footshock, whereas an *appetitive* prediction error refers to error about appetitive outcomes such as sucrose, the most famous one being reward prediction error.

The focus of this review is to outline some of the key neural substrates that have been implicated in prediction error in learning about appetitive (reward) and aversive (fear) outcomes. We will present some of the evidence implicating the classic dopamine (DA) signal in the ventral tegmental area (VTA) in reward prediction error. This signal serves as a textbook example of a signed prediction error and, in the present review, it aids in situating the role of other brain areas and neurotransmitters in prediction error. In addition, we review literature on the role of the amygdala and associated neural structures in aversive prediction error, as well as noradrenaline particularly in the context of negative prediction error. Investigations into the neurobiology of prediction error necessarily integrate two different but related fields, namely learning theory and neuroscience. The present review brings together these diverse fields and hopes to introduce the neuroscientist to the multifaceted and informative behavioural designs that learning theory can offer in the quest for understanding how the brain regulates behaviour. Further, we hope that by reviewing the neuroscience literature on prediction error, we highlight the natural fit of these two domains. Finally, due to the diverse nature of the content reviewed herein, individual sections in the present review can be considered as stand-alone, allowing the reader to focus on those of interest.

Associative learning depends on prediction error.

Traditionally, associative learning is established by pairing an initially neutral stimulus such as a light or a tone with a biologically significant outcome such as sucrose or footshock. However, this approach confounds two constructs that support associative learning: the

temporal contiguity between events and the error in prediction. The classic behavioural design that isolates the role of prediction error in learning is Kamin's blocking (Kamin, 1968; 1969). It does this by holding the temporal relationship between events constant and manipulating the error in prediction between groups to examine its role in associative learning. The design consists of two phases (Table 1: Blocking). In Phase 1, a cue (e.g., a light) is repeatedly paired with a biologically significant event (e.g., sucrose reward or footshock), establishing it as a good predictor for that event. This learning is indexed behaviourally by a conditioned response such as increased magazine approach of the port where reward is delivered or conditioned freezing/suppression in the case of fear. In Phase 2, the previously conditioned cue (i.e., the light) is presented in compound with a novel *target* cue (e.g., a tone) and the compound is paired with the same outcome as that used in Phase 1. When learning about the association between the target cue and the outcome is assessed during a non-reinforced test, behavioural responding is low, indicating that little learning had taken place during Phase 2. To show that pretraining is critical to blocking, a control group is trained with the same compound in Phase 2, but in the absence of Phase 1 training. In this condition, learning about the target cue is robust, resulting in considerable levels of conditioned responding. That is, in the blocking group, the establishment of an associative relationship between the target stimulus and an outcome is attenuated in the presence of an established predictor for that same outcome. In the control group, associative learning between the target and the outcome is intact because it occurs in the absence of a previously-established predictor for that outcome.

The similarities and differences provided by the blocking and control conditions require emphasis. In both cases, the pairing between the target cue and the outcome occurs in the presence of another cue, and the temporal contiguity between the events is equivalent. The critical difference between the two conditions is the error in prediction during compound conditioning. In the blocking condition, this error is negligible because the pretrained cue signals upcoming outcome delivery. In the control, the error is maximal because the upcoming outcome is not predicted. The smaller error in the blocking condition compared to the control limits learning to the target cue during the compound phase. In a series of behavioural studies, Holland (2010) confirmed that the blocking effect was indeed due to failure of acquisition and not retrieval.

Prediction error is directly coupled to prediction. If the predicted outcome is altered in any way, then the prediction is no longer accurate, which augments the prediction error and in turn reinstates learning about the target cue. For example, the delivery of an additional unexpected outcome, the omission of an expected outcome, or changes in the identity of the delivered outcome in Phase 2 lead to unblocking, that is, learning about the target cue (Dickinson & Mackintosh, 1979; Dickinson, Hall & Mackintosh, 1976; Holland, 1984; Mackintosh, Dickinson, & Cotton, 1980; Rescorla, 1999; Wagner, Mazur, Donegan, & Pfautz, 1980; but see Williams, 1994). These instances of unblocking are interesting because they show that prediction error is induced by increases and decreases in the number, intensity or value of a reinforcer as well as changes in its identity or sensory properties (provided value or valence are kept constant). That is, predictions are multifaceted and errors in prediction are due to many aspects of reinforcer delivery.

Reward prediction error: The role of the mesolimbic dopamine signal

Positive reward prediction error.

Uncovering the neural mechanisms of prediction error is central to understanding how the brain learns about associative relationships. Investigations into the neurobiological mechanisms of *reward* prediction error have consistently implicated phasic firing of VTA DA neurons. The classical response of VTA DA neurons is elevation in firing rate to an unexpected reward, a reduction in firing rate to the same but expected reward, and a depression of firing rate when expected rewards are omitted (Mirenowicz & Schultz, 1994; Schultz, Dayan, & Montague, 1997; Tobler, Fiorillo, & Schultz, 2005). Variations in the conditions of reinforcement such as reward probability and reward magnitude modulate the DA signal (Fiorillo, Tobler, & Schultz, 2003; Tobler et al., 2005). Many aspects of this signal have been replicated across species and labs (Cohen, Haesler, Vong, Lowell, & Uchida, 2012; Day, Roitman, Wightman, & Carelli, 2007; D'Ardenne, McClure, Nystrom, Cohen, 2008; Diederen, Spencer, Vestergaard, Fletcher, & Schultz, 2016); Pan, Schmidt, Wickens, & Hyland, 2005; Roesch, Calu, & Schoenbaum, 2007; Waelti, Dickinson, & Schultz, 2001) providing consistent evidence that the VTA DA signal tracks changes in prediction error.

To illustrate the role of VTA DA in prediction error, Waelti et al. (2001) examined the neural profile of these neurons during blocking. Elevation in neural firing of VTA DA neurons was seen at time of reward delivery in the control condition (the reward was unexpected) but not in the blocking condition (the reward was expected) in Phase 2. That is, VTA DA neurons signaled prediction error in the control but not the blocking condition. To further examine the profile of VTA DA neuron firing when prediction errors were generated, the authors presented the control and blocked cues under reinforcement and non-reinforcement. When the cues were presented non-reinforced on test, behavioural responding confirmed that the monkeys expected reward upon exposure to the control but not the blocked cue. As a result, a depression in the dopamine signal was seen at the time of reward following the control but not the blocked cue. When the cues were reinforced, neural responding was elevated at the time of reward only following the blocked but not following the control cue. These data are in agreement with the reward prediction error hypothesis. It has since been shown that changes in the value or identity of an expected reward (in a classical conditioning task) increase phasic firing of VTA DA neurons (Takahashi et al., 2017a).

To determine if there is a causal relationship between VTA DA neural firing and reward prediction error, researchers have manipulated the VTA DA signal on a millisecond timescale and examined its effect on associative learning. Steinberg et al. (2013) used TH-Cre transgenic rats in conjunction with optogenetics to manipulate neuronal firing of tyrosine hydroxylase (TH) positive neurons. TH-Cre rats were infused with a Cre-dependent virus carrying channelrhodopsin (ChR2) in the VTA, which restricted the expression of ChR2 to TH+, that is, DA neurons. Using a blocking design (Table 1: Blocking), the authors showed that boosting VTA DA transients at the time of the expected reward during Phase 2 enhanced learning about the target cue. In a separate study, Keiflin and Janak (2017) provided additional evidence that this artificial unblocking led to an association between the

target cue and reward and any changes in the value of that reward translated in corresponding changes in conditioned responding to its predictor.

Armed with the knowledge that the prediction error can be artificially increased by stimulating DA neurons optogenetically, Schoenbaum and colleagues examined whether artificial attenuation of the DA signal can counteract a behavioural boost of the prediction error and prevent unblocking (Table 1: Blocking). Delivery of an additional reward during Phase 2 in blocking resulted in unblocking, that is, learning about the target cue. VTA DA attenuation when the additional reward was delivered disrupted unblocking (Chang, Gardner, Di Tillio, & Schoenbaum, 2017). Interestingly, suppression of VTA DA firing also attenuated unblocking when the *identity* (chocolate to banana or vice versa) of the expected reward is altered. These data provide evidence that suppression of VTA DA firing can prevent learning by disrupting increases in value or identity prediction errors.

The role of VTA DA transients as a teaching signal extends beyond simple binary associations. To show this, Sharpe et al. (2020) used two occasion setting designs: In the feature positive design, a target cue was reinforced when it was preceded by another cue but not when it was presented alone (Table 2: Feature positive) and in the feature negative design, a target cue was reinforced when presented on its own but not when it was preceded by another cue (Table 2: Feature negative). The acquisition of this normally difficult discrimination was facilitated when VTA DA neurons were stimulated at the start of the target cues (A and B) during the patterning trials, thus providing evidence for the role of mesolimbic dopamine in learning complex associative relationships.

Negative reward prediction error.

The delivery of an unexpected event generates a positive prediction error and serves to support the acquisition of associations between events. When an expected event is not delivered, or more generally, when the expected reward is greater than the actual delivered reward, a negative prediction error is generated and it serves to reduce the expectation of previously delivered events. Extinction is the most commonly used example of such learning. In extinction, a previously established predictor for reward delivery is non-reinforced which generates a negative prediction error and results in a reduction in the conditioned response (Table 1: Extinction). Negative reward prediction error has been reported to depress the VTA DA signal (Mirenowicz and Schultz, 1994, Waeli et al., 2001). When the pause in the DA signal was counteracted with optogenetic stimulation, extinction learning slowed down (Steinberg et al., 2013).

Another method used to generate a negative prediction error and reduce conditioned responding to a previously trained cue is overexpectation (Table 1: Overexpectation; Rescorla, 1970). It is done by enhancing reward expectation while maintaining reward delivery. Specifically, in over-expectation two individual cues, a target and a control, are trained to signal a reward in Phase 1 (Table 1: Overexpectation). During Phase 2, the cues are presented in compound which yields the expectation of double reward, but only a single reward follows this compound. The discrepancy between the expected double reward and the delivered single reward generates a negative prediction error, which downregulates the association of the target cue with reward and reduces conditioned responding on test.

Using a variation of the overexpectation design, Chang et al. (2016) provided evidence for the role of VTA DA inhibition in negative prediction error. Following Phase 1 training, instead of reinforcing the overexpectation compound with a single reward, the authors delivered the expected double reward, thereby keeping the prediction error at minimum. Behaviourally, this modification to the over-expectation design would leave the associative relationship between the target cue and the reward established in Phase 1 unchanged. To examine whether suppression of VTA DA firing could induce a negative prediction error, the authors optogenetically suppressed the VTA DA signal during the second expected reward in Phase 2 of overexpectation. As predicted, this manipulation downregulated the association between the target cue and reward and reduced conditioned responding to the target on test.

The role for negative prediction error described so far has been one of updating or downregulating previously established associations. Negative prediction error, however, can also support learning about novel cues by establishing those cues as signals for the *absence* of rewards (Rescorla, 1969). Such cues are termed conditioned inhibitors. To create a conditioned inhibitor, a target cue is presented in compound with a pretrained cue that signals reward delivery. However, this compound is *not reinforced* (Table 1: Conditioned Inhibition). To confirm that the target is indeed a conditioned inhibitor two types of tests are used: summation and retardation (Table 1: Conditioned Inhibition - Test). A summation test examines whether the conditioned inhibitor, but not another equally familiar cue, lowers responding to other predictors of reward (conditioned excitors). A retardation test examines whether conditioned inhibitors, again relative to other equally familiar cues, take longer to become associated with reward.

VTA DA neurons track changes in learning during conditioned inhibition. Tobler, Dickinson, and Schultz (2003) reported a suppression in the phasic firing of VTA DA neurons at the time of an omitted reward when a novel stimulus in compound with a reward-predicting stimulus was not reinforced. Importantly, the novel stimulus became a conditioned inhibitor and its presentation also elicited a depression in DA neuron firing (Tobler et al., 2003).

Chang, Gardner, Conroy, Whitaker, and Schoenbaum (2018) examined the causal relationship between the phasic firing of VTA DA neurons and conditioned inhibition. The authors used the conditioned inhibition design (Table 1: Conditioned Inhibition) in conjunction with bidirectional optogenetic modulation of VTA DA neuronal firing. When a negative prediction error was generated naturally during non-reinforced compound conditioning trials in the conditioned inhibition design, optogenetic activation of VTA DA neurons at time of reward omission prevented the development of conditioned inhibition. That is, the cue trained as a conditioned inhibitor passed the summation and retardation tests only in the non-stimulation control condition but not in the stimulation condition. In a modified version of the conditioned inhibition design, Chang et al. (2018) delivered the normally omitted reward, thereby preventing the generation of a negative prediction error. To examine the bidirectional role of DA in learning, the authors artificially induced a negative prediction error through inhibition of the VTA DA signal when the normally-omitted reward was delivered. This optogenetic manipulation resulted in the establishment of conditioned inhibition to the target cue, again evidenced through the summation and retardation tests.

Temporal difference reward prediction error.

A lynchpin of the prediction error signal, according to temporal-difference reinforcement learning (TDRL) models, is that it should propagate backwards to the earliest reliable predictors of reward (Sutton, 1988). Phasic firing of VTA DA neurons complies with this prediction: Cues that reliably predict upcoming rewards increase firing of VTA DA neurons (Schultz et a., 1997). This *cue-evoked* neural signal is also proportional to the value of the rewards they predict (Tobler et al,, 2005). However, whether this DA signal propagates to cues that precede reward-predicting cues, that is, whether the cue-evoked VTA DA signal serves to reinforce learning about reward-predicting cues remained unknown till recently. To address this, Maes et al. (2020) used second-order conditioning to determine if that was the case. In second-order conditioning, a cue established as a signal for reward delivery is then used to reinforce learning about a novel target cue (in the absence of additional reinforcement; Table 1: Second-order Conditioning). This training leads to the target cue acquiring reward predicting power, resulting in reward-based (magazine approach) and cue-based (rearing, orienting) conditioned responding (Holland, 1980; Holland & Rescorla, 1975). Critically, Maes et al. (2020) attenuated the cue-evoked VTA DA signal to the good predictor during second-order conditioning, disrupting learning to the target cue. These data provided the missing evidence that the backpropagation of the VTA DA signal to predictors of reward could reinforce learning.

There are two hypotheses that could account for the disruption in second-order conditioning following attenuation of the cue-evoked DA signal. One holds that attenuation of the cue-evoked DA signal disrupted the *prediction error* evoked by the cue, and the other that it disrupted the *prediction* about upcoming reward. To distinguish between these two possibilities, Maes et al., (2020) used a blocking design (Table 1: Blocking). The two hypotheses make different predictions about the fate of the blocking effect following attenuation of the cue-evoked dopamine transients. If cue-evoked dopamine transients represent prediction about upcoming reward, then blocking would be disrupted, resulting in unblocking. If this signal represents a temporal-difference prediction error, then attenuating the cue-evoked DA signal would prevent the pre-trained cue from reinforcing learning about itself (as revealed by second-order conditioning, described above) but would leave the prediction about upcoming reward and blocking intact. Maes et al. (2020) reported that optogenetic attenuation of the cue-evoked dopamine signal spared blocking. These data were the first to provide causal evidence for the role of the VTA DA signal in *temporal-difference* prediction error.

Learning about neutral cues.

The majority of research into the role of the VTA DA signal in prediction error has focused on learning about rewards. However, learning is not limited to events of motivational significance and incidental learning about relationships between neutral cues has been reported (Brogden, 1939). This learning is also driven by prediction error mechanisms (Wagner, 1978). The quintessential design used to reveal learning between neutral cues is sensory preconditioning (Table 1: Sensory preconditioning). This design consists of pairings between two neutral cues in Phase 1 followed by conditioning of one of those cues with reward in Phase 2. A non-reinforced test of the sensory preconditioned cue that was not

directly paired with reward reveals that this cue has acquired reward-predicting power (Brogden, 1939).

Sadacca, Jones and Schoenbaum (2016) recorded activity from VTA DA neurons during a sensory preconditioning design. Despite no direct pairings with reward, a sensory preconditioned cue evoked a phasic firing response in DA neurons which was greater than that seen to a control cue of equal salience and familiarity. In a clever version of the sensory preconditioning design that combined blocking, which will be greatly simplified here, Sharpe et al. (2017) used a causal method to determine whether VTA DA transients regulate learning about neutral cues in the absence of reward delivery. The authors used a sensory blocking design (Table 1: Blocking) in which the outcome was a sensory cue as opposed to a reward. In much the same way as Steinberg et al. (2013) had done previously (see above), Sharpe et al., (2017) stimulated VTA DA activity during the predicted sensory cue in Phase 2 of sensory blocking and unblocked learned between sensory events. These data are important because they provide evidence that the VTA DA prediction error signal supports the development of associative relationships beyond those that require pairings with reward.

VTA circuit complexity.

VTA DA neurons do not signal reward prediction errors in isolation. They are part of a complex circuit that involves local GABAergic input from neighbouring cells (e.g., Cohen et al., 2012; Omelchenko & Sesack, 2009; Tan et al., 2012; van Zessen et l., 2012) that receive input from the lateral hypothalamus (Nieh et al., 2016) as well as the tail of the VTA/rostromedial tegmental nucleus (RMTg; e.g., Balcita-Pedicino et al., 2011; Barrot, Sesack, Georges, Pistis, Hong, & Jhou, 2012; Bourdy & Barrot, 2012; Jhou et al., 2009a, 2009b; Kaufling, Veinante, Pawlowski, Freund-Mercier, & Barrot, 2010). RMTg neuronal activity opposes that of the DA reward-prediction error signal, showing inhibition to rewards and predictors of reward, and excitation to reward omissions (Barrot et al., 2012; Jalabert et al., 2011; Jhou et al., 2009, Hong et al., 2011; Lecca et al., 2011, 2012; Matsui and Williams, 2011). The lateral habenula (LHb) is also implicated in reward prediction error showing a profile opposite to the of VTA DA neurons (Matsumoto & Hikosaka, 2007) likely through direct (Lammel et al., 2012) or indirect (via the RMTg; Jhou et al., 2009) projections to the VTA. Another contributor with direct links to the VTA is the ventral pallidum which was has been reported to show a prediction error signal (Ottenheimer et al., 2020). Further, DA encoding of reward prediction errors are disrupted by lesions of the orbitofrontal cortex (Takahashi, Roesch, Wilson, Toreson, O'Donnell, Niv, & Scheoenbaum, 2011; Takahashi, Stalnaker, Roesch, & Schoenbaum, 2017b) and the ventral striatum (Takahashi & Schoenbaum, 2016; Takahashi, Langdon, Niv, & Schoenbaum, 2016). The reward prediction error signal carried by VTA DA neurons reaches target sites such as the nucleus accumbens, the basolateral amygdala and the prefrontal cortex, which likely use this signal to regulate learning and behaviour (e.g, Hart, Rutledge, Glimcher & Phillips, 2014; Nieh et al., 2013; Lammel et al., 2011; 2012; Parker et al., 2016; Tang et al., 2020).

Despite these strides in uncovering the role of VTA DA signal in associative learning, some important questions remain unanswered. For example, whether this signal regulates *aversive* prediction error. Some exciting research suggests that omissions of expected aversive events

evoke an elevation in the VTA DA signal similar to that of rewards (Oleson, Gentry, Chioma, & Cheer, 2012; Salinas-Hernández, Vogel, Betz, Kalisch, Sigurdsson, & Duvarci, 2019; Luo, Uematsu, Weitemier, Aquili, Koivumaa, McHugh, & Johansen, 2018; see below) and research by Stephan Lammel has linked the response of VTA DA neurons to aversion (Lammel REFs). The research reviewed above shows that VTA DA stimulation enables associative learning across many paradigms, many of which are supported by distinct associative architecture (Holland, 1992; Holland & Rescorla, 1975; Daw, Niv & Dayan, 2005). Whether increases in the VTA DA signal can alter this associative architecture, in essence transitioning from model-free (stimulus-response associations) to model-based (stimulus-stimulus associations) learning, remains unknown.

It is noteworthy that VTA DA is not the only signal implicated in reward prediction error and it cannot function in isolation to instruct learning across the brain (e.g., McDannald, Lucantonio, Burke, Niv, & Schoenbaum, 2011). Input from and output to other brain areas and other neurotransmitters are fundamental for providing information about expectations (e.g., Cohen et al., 2012; McDannald et al., 2014; Takahashi, Stalnaker, Roesch, & Schoenbaum, 2017b), and to directing attention to cues on the basis of unsigned prediction errors (Holland & Maddux, 2010; Lee, Youn, O, Gallagher, & Holland, 2006; Roesch, Calu, Esber, & Schoenbaum, 2010). Below we describe research on the role of prediction error that extends beyond the VTA and reward.

Aversive prediction error: the role of the amygdala and associated neural circuits

Success in identifying ventral tegmental area dopamine neurons as a neural source of a signed reward prediction error (Glimcher et al., 2005; Roesch et al., 2007; Schultz et al., 1997) has buoyed to efforts to identify neural sources of aversive prediction error. Their existence would be expected based on associative learning theory, which makes little distinction between rewarding and aversive outcomes (Rescorla and Wagner, 1972). Even more, foundational experiments in support of a prediction error account of associative learning used foot shock outcomes (Dweck and Wagner, 1970; Kamin, 1969; Rescorla, 1968). The amygdala is a logical starting point for investigations into the neural source of aversive prediction error, but it is now clear that a larger network is involved. In the sections below, we review amygdala and non-amygdalar brain regions implicated in aversive prediction error.

Amygdala

The amygdala, and in particular the basolateral subregion (BLA), is critical for Pavlovian fear conditioning. An enormous body of work has refined our understanding of amygdala function during fear learning, expression, retrieval and extinction (see Dejean et al., 2015; Duvarci & Paré, 2014; Janak & Tye, 2015 for recent reviews), with most of this knowledge derived from simple Pavlovian conditioning and extinction studies. Nevertheless, how this learning is influenced by prediction error is poorly understood. Indeed, the neural sources of prediction error(s), the nature of these errors and the circuits receiving and implementing error to influence learning are only beginning to be described. Here, we review the evidence

suggesting that learning-dependent BLA activity is regulated by an expectancy-modulated teaching signal and highlight recent efforts that have contributed to our understanding of error signalling within the BLA.

Positive aversive prediction error.

Error-correction models state that the amount of learning varies across simple fear conditioning. Prediction error is highest during initial trials and gradually decreases as the cue increasingly predicts the aversive outcome e.g. electric shock. Thus, the effectiveness of the outcome as a reinforcer decreases across training to reduce increments of associative strength across trials (Rescorla & Wagner, 1972). This pattern of decline across fear learning is also observed in outcome-evoked BLA activity as measured by various neural recording methods including single unit recordings (Johansen, Tarpley, LeDoux, & Blair, 2010), hemodynamic tissue oxygen responses (T_{O2}) (McHugh et al., 2014) and calcium imaging restricted to principal neurons (PNs, Krabbe et al., 2019), in line with the corresponding decrements in prediction error. Indeed, outcome-evoked activity is negatively correlated with the cue response as measured by freezing (Grewe et al., 2017; Johansen, Tarpley, et al., 2010; Krabbe et al., 2019). This declining outcome response is attributed to learning, rather than just habituation, because presentation of unsignalled (i.e. surprising) shocks (Johansen, Tarpley, et al., 2010; Krabbe et al., 2019) restored outcome-evoked activity. Consistent with this idea, BLA activity is greater to a less predictable aversive outcome (e.g. following a partially reinforced cue) compared to a predictable aversive outcome (e.g. following a continuously reinforced cue; Belova, Paton, Morrison, & Salzman, 2007; Dunsmoor, Bandettini, & Knight, 2008). Most importantly, this outcome-evoked BLA activity is necessary for learning because silencing BLA PNs at the time of shock during fear conditioning impaireds learning (Namburi et al., 2015; Sengupta et al., 2018; Wolff et al., 2014) whereas excitation of BLA PNs during shock outcome facilitates learning (Johansen et al., 2014; Kim, Pignatelli, Xu, Itohara, & Tonegawa, 2016). There is recent evidence suggesting that this outcome-evoked activity is at least in part regulated by DA, because silencing VTA DA projections to the BLA at the time of shock also impairs fear learning (Tang, Kochubey, Kintscher & Schneggenburger, 2020).

Although simple fear conditioning and partial reinforcement designs have been informative, they do not explicitly manipulate prediction error. As mentioned in the previous section, the blocking design (Table 1: Blocking) best isolates the role of prediction error in learning. Eippert, Gamer and Büchel (2012) used functional imaging to study human BLA during blocking of Pavlovian fear conditioning. In a within-subjects aversive version of the blocking design similar to that described above (Table 1: Blocking), subjects were presented with two compound cues paired with shock in Phase 2. One compound was made up of a cue previously paired with the shock (the blocking cue) and a novel cue (the blocked cue) whereas the second compound was made up of two novel cues (control cues). Subjects reported greater shock expectancy to the control cue compared to the blocked cue, demonstrating blocking. Furthermore, BLA activity was modulated in a manner anticipated by error correcting learning rules, with stronger BLA BOLD signal observed to the control cue associated with fear compared to the blocked cue.

Studies using rodents have causally demonstrated the role of the amygdala in blocking. Iordanova (2010) first used a contextual blocking design to reveal a role for DA receptors in the amygdala in regulating aversive prediction error. Microinfusion of the DA antagonist cis-(z)-flupenthixol in the amygdala prior to Phase 2 training prevented blocking. More critically, Iordanova (2010) used a two-trial Phase 2 design to determine whether DA modulation of prediction error in the amygdala regulates learning on the current to future trials. The DA antagonist was microinfused either prior to the first, prior to the second, or prior to both trials. If DA modulation of amygdala function affects direct error processing, then infusion prior to either trial should prevent blocking because presentation of the feared cue in compound with the novel cue on the first trial immediately renders the aversive outcome to be ineffective for driving learning on that same trial. On the other hand, if the DA mechanism regulates indirect error processing, then blocking should only be successful from the second trial onwards, because the low prediction error produced at shock onset at the end of the first trial can only affect the attentional processing of the blocked cue on the next trial. So, an infusion prior to the first trial is required to prevent blocking. DA antagonism prevented blocking regardless of when it was infused, providing strong evidence that DA signalling in the amygdala is important for regulating the direct actions of prediction error as described by the Rescorla-Wagner model (Rescorla & Wagner, 1972). More recently, Sengupta, Winters, Bagley & McNally (2016) expressed the excitatory DREADD hM3Dq receptor in rat BLA PNs and studied how chemogenetic excitation of these neurons affected blocking. CNO-induced activation of BLA PNs during Phase 2 increased fear learning about the blocked cue, thus prevented blocking. That is, increasing the activity of BLA PNs increased positive error to enable learning. How DA signalling interacts with activity of BLA PNs to influence prediction error driven fear learning is currently unclear and awaits further investigation (but see Tang et al., 2020).

Negative aversive prediction error.

As mentioned earlier, extinction provides a behavioural method to observe negative prediction error (Table 1: Extinction). Theoretically, some learning rules employ fully signed/bidirectional error signals (e.g., Rescorla-Wagner, 1972) whereas others do not (e.g., Pearce-Hall, 1980). The presence of a bidirectional error signal, where activity increases in response to positive error and decreases in response to negative error, is therefore diagnostic of the nature of the learning rules employed by a circuit. To date, only one study has reported BLA activity to decrease below baseline at outcome omission (McHugh et al., 2014) in mice as measured by T_{O2}, a tissue oxygen signal derived by similar mechanisms to the BOLD signal in fMRI imaging. This finding lends support to the idea that BLA may be responsive to a bidirectional prediction error. However, other studies using single unit recordings (Johansen, Tarpley, et al., 2010) or calcium imaging of PNs (Grewe et al., 2017) in rats or mice have not detected such inhibitions at outcome omission. Instead, these studies reported no observable changes to BLA single unit activity or calcium transients at omission of an expected outcome. A key difference between these studies is the timescale of the recordings. The evidence for a decrease in the T_{O2} signal at outcome omission in the McHugh et al. (2014) study was observed sometime (15 – 30s) after outcome omission. This is well beyond the timescale employed in single unit or calcium imaging experiments. Although it is possible that this delay is due to a lag in hemodynamic response, it has been

known for some time that fear responses, even to a single cue presentation, can be long lasting (Solomon & Corbit, 1974), so any such negative error signal may be delayed unless the animal is extensively trained (Solomon & Corbit, 1974). Interestingly, both types of error signals have been observed to coexist in primate BLA during an extensively trained (> 1,000 trials) aversive reversal task (Klavir, Genud-Gabai, & Paz, 2013). In this task, one cue was paired with an aversive outcome while another was non-reinforced. After successful learning, these contingencies were subsequently switched - the previously reinforced cue was no longer paired with the outcome whereas the previously non-reinforced cue was now reinforced, revealing both positive (non-reinforced to reinforced) and negative error (reinforced to non-reinforced) during different trials of the reversal phase. Klavir et al. (2013) observed amygdala cells that increased firing to both positive and negative error, as well as amygdala cells that changed their firing in opposite directions to the two signed error types. This finding suggests that both signed and unsigned error signals exist in the BLA. The latter is also consistent with observed attention processing in the BLA during appetitive associative conditioning (Roesch, Calu, Esber, & Schoenbaum, 2010; Roesch, Esber, Li, Daw, & Schoenbaum, 2013).

Other studies have tried to establish a causal role of BLA neurons in negative aversive prediction error. Optogenetic silencing of BLA PNs around time of shock omission augmented extinction (Sengupta et al., 2018), supporting the idea that BLA PNs signal a bidirectional prediction error. This is consistent with another finding that specifically isolated negative prediction error using an aversive overexpectation design (Sengupta et al., 2016), similar to that described earlier (Table 1: Overexpectation) but using shock as the reinforcer. Interestingly, chemogenetic excitation of BLA PNs prevented this overexpectation. That is, increasing activity of BLA PNs prevented negative error and prevented the loss of fear. Combined with the previously discussed observation that the same chemogenetic excitation of BLA PNs prevented blocking, this pattern of findings is uniquely consistent with BLA PNs learning in response to a signed, bidirectional prediction error.

Complexities within the BLA.

The evidence described above supports the idea that fear learning is dependent on error-modulated activity in BLA PNs. BLA PNs respond strongly to high positive error and this response is necessary to drive cue-outcome learning. When positive error is low, this activity is suppressed to restrict learning. Several outstanding questions remain. First, the focus here has been on BLA PNs, but the mechanisms involved in determining their activity remains unclear. Simply pairing a cue with optogenetic stimulation of BLA PNs is insufficient to mimic normal fear learning (Jasnow et al., 2013; Johansen et al., 2014), although it can support modest levels of fear (Johansen, Hamanaka, et al., 2010). Additional mechanisms, including outcome-induced noradrenaline release (Johansen et al., 2014) and/or release of BLA PNs from inhibition imposed by complex networks of local interneurons (Wolff et al., 2014) are both important for fear learning. How these additional mechanisms act to fine-tune BLA PN activity and instantiate prediction error remains poorly understood.

Secondly, another question that remains unanswered is whether individual or separate sets of BLA neurons code for positive and negative error. This is a likely possibility, given that

subsets of BLA PNs encoding for high fear (called ‘fear neurons’) and low fear states (called ‘extinction neurons’) have been observed. (Herry et al., 2008). Specific activation of this extinction neuron subset inhibits fear and enhances extinction (Jasnow et al., 2013), an effect that is not usually observed in BLA PNs. Additionally, fear and reward have also been found to be encoded in different subsets of BLA PNs (Gore et al., 2015; Kim, Pignatelli, Xu, Itohara, & Tonegawa, 2016; Namburi et al., 2015; Sangha, Chadick, & Janak, 2013) and reward encoding neurons also encode fear extinction (Zhang, Kim, & Tonegawa, 2020). Whether different subsets of BLA PNs also separately code for positive error and negative error awaits investigation.

Third, although the majority of neurons in the BLA are excitatory PNs, these PNs are part of intricate microcircuits within the BLA. These microcircuits consist of several different classes of local GABAergic interneurons that are densely interconnected with each other and to PNs and form a multi-layered inhibitory gating system that ultimately controls PN activity (Krabbe et al., 2019; Lee, Kim, Kwon, Lee, & Kim, 2013). The two major classes of interneurons, the parvalbumin (PV)-expressing and somatastatin (SOM)-expressing interneurons have been shown to have unique inhibitory control over PNs during fear learning (Wolff et al., 2014). Additionally, vasoactive intestinal peptide (VIP)-expressing interneurons exhibit similar patterns of activity to PNs across fear learning – decreased shock-evoked responses across trials (Krabbe et al., 2019). Like BLA PNs, unsignalled shocks also reinstate responses, suggesting that BLA VIP neurons are also modulated by expectancy. However, a better understanding of the relationship between activity in these microcircuits and learning in designs that explicitly isolate prediction error is required. Another critical question relates to the nature of learning itself. Learning is multifaceted. Prediction error is just one, albeit important, determinant of whether and how much is learned during conditioning. Learning is also influenced by an array of other factors, including stimulus salience and motivation. There is good evidence, from well-controlled behavioural experiments, that BLA PNs do act to maintain and control the salience of events during conditioning and that this role can be separate to a role in prediction error (Sengupta et al., 2018). Whether and how these multiple learning-related signals relate to each other in BLA (and elsewhere) remains to be determined (Yau & McNally, 2018). The section below discusses brain regions outside of the amygdala implicated in aversive prediction error.

Beyond the amygdala

Positive aversive prediction error – the ventrolateral periaqueductal gray.

Multiple studies have implicated the ventrolateral periaqueductal gray (vlPAG) as a neural source of an aversive, positive prediction error (McNally, 2005; McNally et al., 2005; McNally et al., 2004). Direct, initial evidence came from blocking (Table 1; Kamin, 1969; McNally and Cole, 2006). In this variant of blocking, rats first received pairings of light → shock. In the next phase rats received compound pairings of light/tone → shock. Compared to control conditions, lesser learning was accrued to the tone in the blocked condition. In one interpretation, learning to the tone is ‘blocked’ because foot shock presentation during the compound trial resulted in a small prediction error. McNally and Cole (2006) found that blocking failed to occur when vlPAG μ-opioid receptors were antagonized (using CTAP)

during the compound phase. An identical effect was found in a single-trial version of blocking when μ-opioid receptors were antagonized systemically (Cole and McNally, 2007). That is, greater learning was accrued to the tone, indicating a stronger tone-shock association. These results, and those from a contemporary study (Cole and McNally, 2009), suggest that vlPAG μ-opioid receptors regulate positive prediction error signaling.

Yet infusion of CTAP – or any agonist/antagonist – would alter vlPAG activity for the duration of the conditioning session, including during cue presentation. The vlPAG has since been shown to be responsive to threat-predictive cues (Faull et al., 2016; Kveraga et al., 2015; Wright et al., 2019; Wright and McDannald, 2019). It is then possible that vlPAG agonism/antagonism disrupted prediction, rather than prediction error. If the vlPAG is a neural source of positive prediction error, a basic requirement would be differential activity to surprising and predicted foot shock.

Direct evidence of patterned vlPAG neural activity consistent with positive prediction error came from Johansen and colleagues (Johansen et al., 2010). VlPAG single-unit activity was recorded while rats received a single conditioning session in which a tone predicted eyelid shock. Consistent with positive prediction error signaling, single-units were maximally responsive to shock on first presentation. Shock-elicited activity declined with continued tone-shock pairings. Also consistent with positive prediction error signaling, vlPAG single-units were more responsive to unsignaled foot shock delivery than to cue-signaled shocks. The results demonstrate that in two settings, vlPAG activity was maximal to ‘surprising’ foot shock delivery and diminished when foot shock was ‘predicted’. The studies led by Cole and Johansen provided crucial pieces of evidence the vlPAG is a neural source for aversive, positive prediction error. The remaining puzzle piece was to demonstrate that vlPAG activity at the time of prediction error was necessary to strengthen a cue-shock association.

To provide this piece, Walker and colleagues devised a multi-cue fear discrimination procedure (Walker et al., 2018; Walker et al., 2019). Three cues predicted foot shock with unique probabilities: danger ($p = 1.00$), uncertainty ($p = 0.375$) and safety ($p = 0.00$). In this design, uncertainty trials should result in a positive error when foot shock is delivered, and a negative error when foot shock is omitted. The level of fear demonstrated to uncertainty would reflect a balance of positive and negative errors. First, vlPAG single-unit activity was recorded during multi-cue fear discrimination. As expected (Johansen et al., 2010), Walker and colleagues found that vlPAG neurons generally selected for foot shock-responsiveness were biased toward greater responding to ‘surprising’ shock delivery on uncertainty trials, compared to ‘predicted’ shock delivery on danger trials (Walker et al., 2019). That is, vlPAG activity signaled positive prediction error. Furthermore, single trials with greater positive error activity predicted enhanced fear on subsequent trials. Interestingly, shock-responsive vlPAG units did not signal negative prediction error, which would have manifested in firing inhibition below baseline during foot shock omission on uncertainty trials.

Walker and colleagues used optogenetic inhibition to determine a necessary role for vlPAG positive prediction error activity to strengthen a cue shock-association. Using the same multi-cue discrimination procedure, vlPAG activity was specifically inhibited around foot shock delivery on danger and uncertainty trials. If vlPAG activity reflects positive error,

optogenetic inhibition around ‘predicted’ foot shock should have no effect on subsequent fear to the danger cue. By contrast, vlPAG optogenetic inhibition around ‘surprising’ foot shock should reduce subsequent fear to the uncertainty cue. Consistent with vlPAG positive prediction error signalling, only inhibition around ‘surprising’ foot shock delivery reduced subsequent fear to its predictive cue. This result is somewhat at odds with a previous study reporting that vlPAG optogenetic inhibition at the precise time of foot shock facilitated – rather than impaired – the acquisition of freezing to a shock-associated cue (Assareh et al., 2017). Though methodological differences may contribute to the differing results of Walker et al and Assareh et al, a theoretical account is perhaps likely. Prediction error is a comparison of predicted and received shock, and prediction error activity can only be observed following shock receipt. Inhibiting vlPAG activity only during shock (as was done by Assareh and colleagues) may abolish incoming prediction signals, enhancing the prediction-outcome discrepancy to augment prediction error. Inhibiting vlPAG activity during and following foot shock may abolish the prediction error signal itself. The combined results (Johansen et al., 2010; McNally and Cole, 2006; Walker et al., 2019) provide evidence for the vlPAG as a neural source of positive prediction error in aversive settings (McNally et al., 2011).

Positive aversive prediction error – brain wide correlates.

Although there is greatest evidence for the vlPAG as a neural source of aversive positive prediction error, additional brain regions have been implicated. Matsumoto and Hikosaka found that putative VTA dopamine neurons signaling positive reward prediction error through firing increases signal positive aversive prediction error through firing decreases (Matsumoto & Hikosaka 2009a). Utilizing the same task, Matsumoto and Hikosaka observed firing increases consistent with positive aversive prediction error by lateral habenula neurons (Matsumoto & Hikosaka 2009b). Human functional magnetic resonance imaging (fMRI) has implicated many more brain regions. Two studies in particular utilized fear/pain procedures to reveal fMRI BOLD signals consistent with positive prediction error (Ploghaus et al., 2000; Spoormaker et al., 2011). Ploghaus and colleagues observed increased fMRI signal intensity in the hippocampus, superior parietal gyrus, superior frontal gyrus, and cerebellum specifically when heat stimulation of the left hand was more painful than expected (Ploghaus et al., 2000). Spoormaker and colleagues paired visual stimuli with probabilistic shock and observed increased fMRI signal intensity in the insular cortex, supplementary motor area, brain stem and visual cortex following shock delivery (Spoormaker et al., 2011).

The spatial and temporal resolution of fMRI may contribute to these widespread activations. For example, ‘brain stem’ and ‘visual cortex’ activations must be summing over distinct subregions and cortical layers. Nevertheless, a widespread activation pattern would conform to expectations of a neural implementation of prediction error. Positive prediction error can only strengthen a cue-outcome association if it is broadcasted to brain regions that store/signal the strength of the cue-shock association. Brain regions showing activation patterns consistent with prediction error may utilize error to update a cue-outcome association, rather than compute error *de novo*. Of interest, threat-predictive cues elicit BOLD responses in nearly all regions in which positive prediction error signals have been reported:

hippocampus (Knight et al., 2004b), superior frontal gyrus (LaBar et al., 1998), cerebellum (Fullana et al. 2015), insular cortex (Fullana et al. 2015), supplemental motor area (Knight et al., 2004a), brain stem (Kveraga et al., 2015; Mobbs et al., 2010) and visual cortex (Tabbert et al., 2005).

Negative aversive prediction error – ventral tegmental area and hippocampus.

Neural sources of aversive, negative prediction error signaling have received less research attention than their positive counterparts. This is unfortunate because stress and anxiety disorders are characterized by excessive fear, and negative prediction error provides a means to weaken the associative strength of threat-predictive cues. Nevertheless, brain regions utilizing and perhaps generating negative prediction error have been put forward. Expanding its role beyond reward prediction error, Salinas-Hernandez and colleagues revealed a role for VTA dopamine in negative prediction error. (Salinas-Hernandez et al., 2018). To do this, they used a cued fear extinction procedure combined with single-unit recording and fiber photometry, calcium imaging of VTA-dopamine neurons in mice. They found that VTA dopamine neurons were selectively excited when expected foot shock was omitted during the extinction session – a neural correlate expected of a negative prediction error. Using an optogenetic approach, they showed that blocking VTA dopamine activity at the time of omission impaired fear extinction. Conversely, driving VTA dopamine activity at the time of omission facilitated fear extinction. Luo and colleagues found an equivalent result in rats – inhibiting VTA dopamine neurons at the time of shock omission impaired fear extinction (Luo et al., 2018).

If VTA dopamine neurons signal negative prediction error, then what regions may utilize error to reduce the associative strength of cue-shock associations? One candidate is the hippocampus, which receives modest VTA inputs (Swanson, 1982). A compelling series of studies have shown that – using contextual fear conditioning – hippocampal Erk signaling is specifically upregulated during contextual fear extinction (Fischer et al., 2007; Huh et al., 2009; Radulovic and Tronson, 2010; Tronson et al., 2009). Hippocampal Erk upregulation is necessary for normal contextual fear extinction (Fischer et al., 2007). These results suggest that negative prediction error may recruit hippocampus function, which in turn reduces the associative strength of context-shock associations. The hippocampus may adjust the associative strength of cue-shock associations as well. Amadi and colleagues observed that auditory cues associated with random foot shock delivery timing produce greater freezing than auditory cues associated with fixed timing. Optogenetically inhibiting dorsal hippocampus activity at the time of shock omission led to reduced freezing in a subsequent test (Amadi et al., 2017; Goosens, 2011). Of course, inhibiting activity during the cue may also disrupt prediction. This is particularly relevant, as hippocampal neurons acquire responding to places and cues associated with foot shock (Moita et al., 2003, 2004). Nevertheless, these results suggest a role for the hippocampus in utilizing error to adjust cue-shock associations.

Negative aversive prediction error – brain wide correlates.

Additional brain regions have been implicated in the production or use of negative error. Neurotoxic lesions of the dorsal raphe selectively increase fear to uncertain predictors of

foot shock (Berg et al., 2014) – consistent with impaired negative error signaling. However, this could equally be due to inflated positive error signaling. In addition, these lesions ablated all neuron types and the dorsal raphe is highly heterogeneous (Huang et al., 2019; Okaty et al., 2020). Although neural correlates of negative error have not been observed in the vlPAG (Walker et al., 2019), it may nonetheless contribute to negative prediction error. Antagonizing vlPAG opioid receptors impairs fear extinction (McNally et al., 2004), while agonizing opioid receptors facilitates extinction (McNally, 2005) – consistent with manipulating the use of negative prediction error. More recently it has been shown that DREADD-inhibiting the vlPAG also impairs fear extinction (Arico et al., 2017). Many more brain regions have been revealed with fMRI. Spoormaker and colleagues uncovered BOLD responses in the ventromedial prefrontal cortex, dorsolateral prefrontal cortex, lateral orbital gyrus, temporal gyri, angular gyri and visual cortex (Spoormaker et al., 2011). Dunsmoor and Labar report negative error BOLD activations in the anterior cingulate cortex, parietal cortex, insula, and striatum (Dunsmoor and LaBar, 2012). Using ERP, which provides superior temporal resolution, Garofalo and colleagues found a negative prediction error-related response centered in mediofrontal cortex (Garofalo et al., 2014).

Clear from these studies is that patterned activity consistent with negative error is observed in many brain regions. As was the case for positive error, most of the brain regions showing BOLD activation consistent with negative error also show activation to threat-predictive cues: ventromedial prefrontal cortex (Fullana et al., 2016), dorsolateral prefrontal cortex, lateral orbital gyrus (Fullana et al., 2016), angular gyri (Fullana et al., 2016), visual cortex (Tabbert et al., 2005), anterior cingulate cortex (Milad et al., 2007), parietal cortex (Armony and Dolan, 2001), insular cortex (Knight et al., 2005), and striatum (Pohlack et al., 2012).

Fully signed error.

A somewhat unexpected feature of aversive prediction error is that single brain regions often show one type of error (positive, for example), but not the other (negative). Yet, a hallmark of VTA dopamine reward prediction error is that it is fully signed. Single VTA dopamine neurons respond to positive error with firing increases, and negative error with firing decreases. Like the VTA reward prediction error, neural correlates of a fully signed aversive prediction error have been identified in the vlPAG (Roy et al., 2014), VTA dopamine neurons projecting to the tail of the striatum (Menegas et al., 2018), dorsal anterior cingulate (Klavir et al., 2013), bilateral lateral orbitofrontal cortex and genual anterior cingulate cortex (Seymour et al., 2005), nucleus accumbens (Delgado et al., 2008; Li et al., 2011; Schiller et al., 2008; Seymour et al., 2004) and the anterior subdivision of the insular cortex (Fazeli and Büchel, 2018).Yet most of these studies measured activity with the fMRI BOLD response. So although positive and negative error may be observed in the same region, they may originate from different neuronal populations. Moreover, the brain regions reported to contain a fully-signed error in some studies have been reported to contain uni-directional error in other studies: ventrolateral periaqueductal gray (positive error, negative error & signed error), anterior cingulate cortex (negative error & signed error), insular cortex (positive error, negative error & signed error) and orbitofrontal cortex (negative error & signed error).

Aversive prediction error engages a brain-wide network. However, the specific function performed by each region within this network has not been resolved. This is because the majority of studies reviewed examine the phenomenon of prediction error - differential activity to surprising versus predicted aversive outcome - but do not examine the function of prediction error to update a cue-outcome association. Even more, many studies cannot differentiate a brain region's contribution to prediction, prediction error and cue-outcome updating. The associative learning procedures outlined in Tables 1–3 will be essential to delineate the function of each brain region within the network and to identify new brain regions. The serial blocking paradigm may be especially useful, as this procedure separates prediction (predictive cue activity), prediction error (outcome activity) and cue-outcome updating (to-be-conditioned cue activity). Recording single-unit activity, or monitoring BOLD activation, during serial blocking will allow for correlates of prediction, prediction error and cue-outcome updating to be observed. Disrupting neural activity during specific periods (predictive cue vs. outcome vs. to-be-conditioned cue) with optogenetic inhibition or continuous theta-burst stimulation (Howard et al. 2020) will establish specific, causal roles for each region in the generation and use of aversive prediction error.

Like in aversive settings, negative prediction error has also received lesser research attention than its positive counterpart in appetitive settings. The next section outlines negative prediction error contribution to extinction, with a special role for the noradrenergic system.

A focused look at extinction and noradrenaline

As articulated above, prediction error does not only encourage the acquisition of new associations but can also update previous learning when environmental conditions change, and the organism's predictions about impending events are no longer accurate. Extinction is a specific case of learning driven by negative prediction error where error is introduced by the omission of an expected reinforcer. Extinction is studied widely in the context of fear, reward, addiction, habits, trauma etc. As a result of its popularity, we will review research examining the importance of prediction error for extinction and the contribution of noradrenaline to this form of learning.

In a typical example of extinction, initially, a stimulus, such as a light, is followed by a reinforcing event, such as food delivery leading to relevant behavioural responses elicited by the stimulus; approach, salivation and ingestion. Thereafter, the same stimulus is no longer followed by the reinforcer and the previously acquired behaviours decrease or *extinguish* over trials. Current views of extinction argue that the observed decrease in behaviour is not simply the result of forgetting or unlearning because evidence of the original learning can be revealed in a number of ways. For example, re-exposure to the original reinforcer, a change in environment or context, or the simple passage of time can all lead to recovery of conditioned responding suggesting the original learning remains intact at least to some degree (e.g., Bouton et al., 2006). These restoration phenomena are particularly useful in examining whether behaviour or neural manipulations can strengthen extinction learning.

Prediction error and extinction.

If learning is driven by prediction error, it follows that the amount of learning should relate to the size of the error. Evidence that this is the case for extinction, just like other forms of learning, comes from demonstrations that increasing the magnitude of prediction error improves extinction learning (Rescorla, 2000; 2006; Janak & Corbit, 2011). Several experiments have manipulated the size of the error by examining the effects of additional stimuli present during extinction of other stimuli or responses (Reberg, 1972). The logic here is that the concurrent presence of an excitatory stimulus should increase expectation of reinforcement and when this occurs at a time when a response or other stimulus is nonreinforced this should result in a particularly large prediction error and hence should enhance extinction when the reinforcer does not occur. In line with this type of prediction, Rescorla (2000; Table 2: Concurrent Excitor) demonstrated that extinguishing a response in the presence of an additional previously reinforced stimulus resulted in significantly less subsequent responding in a test conducted the following day than extinguishing the response either alone or in the presence of a control stimulus that had never been reinforced (controlling for novelty of the situation but adding no additional error). This suggests that the extinction was more effective in the presence of the additional excitatory stimulus where negative prediction error is hypothesized to be particularly high.

A related study examined the effects of presenting stimuli together, or in compound during extinction. Rescorla (2006; Table 2: Compound Extinction) reported that nonreinforcement of a compound of previously reinforced stimuli augmented extinction when the components were later tested alone. In that experiment, rats received training in which three separate stimuli signaled the availability of a common reinforcer. After training, all of the stimuli underwent the same amount of extinction training; the critical difference was that following initial extinction of each stimulus alone, two of the stimuli were presented together (compound) during further extinction trials, whereas the remaining stimulus continued to be presented alone during further extinction trials. At test, rats responded less in the presence of a single stimulus that had been extinguished in compound than when presented with a stimulus that had only been extinguished alone, suggesting that nonreinforcement of a compound stimulus further engaged learning mechanisms at the time of nonreinforcement, and, thus, deepened the resultant extinction learning. This effect has been observed in Pavlovian and instrumental learning paradigms, with aversive and appetitive reinforcers, with food and drug rewards, and with different species including rats, pigeons and humans, suggesting it is a general phenomenon and providing clear evidence that the magnitude of prediction error contributes to the strength and longevity of extinction learning (Rescorla, 2000; 2006; Janak & Corbit, 2011; Janak et al., 2012; Kearns et al., 2012; Coelho et a., 2015; Culver et al., 2015; Furlong et al., 2015; Leung & Corbit, 2017).

Noradrenaline and Extinction.

While error correction models focus on the conditions under which learning will occur, they do not specify the biological mechanism(s). A substantial literature, some of which is reviewed above, implicates dopamine in signaling reward prediction errors including accumulating evidence that dopamine signals errors related to aversive reinforcers and contributes to negative error signals (e.g., Chang et al., 2016, 2017, Iordanova et al., 2006,

Iordanova, 2010; Luo et al., 2018). Noradrenaline (NA) is another catecholamine, manufactured from dopamine, and activation of its receptors can initiate similar intracellular signaling cascades involved in cellular plasticity needed for long-term learning and memory. The locus coeruleus (LC), while comprised of only approximately 1500 neurons in the rat, or 15000 neurons in humans, projects broadly and diffusely throughout almost the entire forebrain as well as having descending projections to the brainstem and spinal cord. These projections provide the primary source of NA to forebrain regions and as such, the LC has been the focus of much research into the role of NA in learning and memory. The widespread projections to forebrain structures responsible for decision making and higher cognitive functions can likely account for the broad range of functions ascribed to NA and the LC. These include arousal, determination of sensory salience and attention, pain, learning and decision making (Berridge & Waterhouse 2003; Aston-Jones & Cohen 2005; Arnsten 2009; Sara, 2009; Chandler et al, 2019).

Here we review evidence that NA contributes to extinction learning.

Electrophysiological recording studies have demonstrated that LC neurons respond to both reward and punishment as well as stimuli from multiple modalities that predict these events (Foote et al., 1980; Sara & Segal, 1991) suggesting that the LC responds to and facilitates the processing of salient or significant events. The phasic LC response is transient, fading across trials under stable conditions but the LC response reappears in response to contingency changes including reversals or shifts from rewarded to extinction conditions (Sara et al., 1994; Aston-Jones et al. 1997; Usher et al. 1999; Bouret & Sara, 2004). Changes in contingencies and poor task performance are accompanied by an increase in tonic firing rate and the changes in LC activity observed in early extinction may be critical for signaling a prediction error and a shift to exploratory behaviour needed for identifying more successful responses and ultimately producing behavioural change (Aston-Jones & Cohen, 2005).

Although electrophysiological data are correlative, lesion and pharmacological studies also implicate NA and the LC in extinction. For example, NA-depleting lesions produced with 6-hydroxydopamine left animals able to learn a simple runway task, but slowed their ability to inhibit that behaviour under extinction conditions. Similar impairments have been reported following NA depletion in the amygdala or infralimbic cortex and across a range of behavioural tasks (Ellis, 1984; Mason & Fibiger, 1979). Microdialysis studies suggest that mPFC NA levels are high during extinction (Hugues et al., 2007) and voltammetry data have demonstrated that there is a surge of NA release coincident with omission of an expected reward (Park et al., 2013) consistent with an active signal for negative error when an expected outcome is omitted. Consistent with this, NA infusion into the BLA, or activation of NA b receptors within the infralimbic cortex improve extinction (Berlau & McGaugh, 2006; Mueller et al., 2008). It is important to note that high levels of NA mimic stress responses and augmenting NA levels in regions such as the amygdala during conditioning with a weak aversive outcome such as shock produces learning typically observed following conditioning with a strong outcome (e.g., Hatfield & McGaugh, 1999; Uematsu et al., 2017). Such findings make it all the more interesting that manipulations of NA can also enhance extinction of conditioned fear. For example, while yohimbine, a a2 antagonist that increases

synaptic NA, at high doses can produce a stress response sufficient to produce reinstatement (Ghitza et al., 2006), yohimbine has also been shown to promote extinction of conditioned fear (Cain et al., 2004; Morris & Bouton, 2007; Powers et al., 2009; but see also Mueller et al., 2009). Specifically, when injected with yohimbine prior to presentation of the shock-associated cue in extinction, mice showed reduced fear response to the cue when tested drug-free the following day relative to controls. Additionally, while control mice did show extinction given enough trials, those treated with yohimbine showed extinction after fewer nonreinforced trials (Cain et al., 2004). Similar results have been found in an appetitive extinction paradigm where rats were trained to respond for food reward during a discriminative stimulus. When yohimbine was administered prior to extinction training, spontaneous recovery was reduced compared to a control group that had received saline suggesting improved extinction (Janak & Corbit, 2011).

Drugs that block reuptake of NA are currently used for treatment of depression and attention deficit hyperactivity disorder (ADHD; e.g. venlafaxine and atomoxetine). One advantage of these drugs compared to direct agonists is that they should amplify any NA signal by blocking reuptake in locations where it is released in relation to the behavioral task. This is important given recent evidence of a modular organization of LC neurons and potentially opposing effects of different efferent pathways (Uematsu et al., 2017; Chandler et al., 2019). Atomoxetine, given prior to extinction training, while having no observable effect on behaviour during extinction itself, reduces spontaneous recovery of responding suggesting improved extinction learning (Janak & Corbit, 2011; Janak et al. 2012; Furlong et al., 2015; Leung & Corbit, 2017).

A problem for interpreting the effects of pharmacologically manipulating NA activity is that any effects on learning may relate to changes in attention or other processes attributed to NA other than error. Here, sophisticated designs from the associative learning literature, such as those of Rescorla (2000; 2006) reviewed above, can help isolate the role of prediction error from other processes. Several studies now show that the effects of compound stimulus presentation (Table 2; Compound extinction) and corresponding negative prediction error on extinction learning can be blocked if the NA antagonist propranolol is administered prior to extinction sessions where the compound trials and corresponding error are introduced without affecting extinction of a single stimulus (Janak & Corbit, 2011; see also Janak et al. 2012; Leung & Corbit, 2017). This suggests that the surprising combination of stimuli evokes NA release which then augments extinction learning related to these stimuli. However, further work specifically manipulating both NA activity and error is needed to establish a direct causal relationship.

A well-known limitation of pharmacological treatments is their coarse timescale. This is important for isolating any effects on signaling or detecting error from effects on arousal, attention, or memory consolidation processes. Optogenetic methods that permit far greater temporal precision can reduce this problem. Furthermore, while previously viewed as a singular nucleus, with the advent of optogenetic and related tools that allow targeting of specific populations of cells, the longstanding view that the LC is a homogeneous structure and that its neurons fire as a population has been called into question (Chandler et al., 2019). Distinct roles for LC cells projecting to different forebrain regions are starting to emerge.

For example, Uematsu et al. (2017) found that optogenetic inhibition of the LC coinciding with shock delivery during training impaired fear conditioning. Interestingly, they also found that inhibition of the LC during cue presentations during extinction, impaired extinction learning. However, when they used optogenetic methods to selectively target LC-BLA and LC-mPFC pathways, they found that stimulation of the LC-BLA pathway enhanced otherwise weak fear conditioning whereas inhibition of the LC-mPFC pathway during extinction impaired retention of extinction training. Each of these effects was more pronounced with pathway-specific manipulation than with manipulation of the LC as a whole suggesting that universal LC activation may produce activity in subpopulations of cells that serve antagonistic functions. Electrophysiological recordings confirmed that distinct populations of cells responded to the cue during fear conditioning or after extinction training, while a far greater and overlapping population of cells responded to a strong noxious stimulus (shock) which helps reconcile these results with previous findings that have argued for a more homogenous response based on experiments with highly salient stimuli. Finally, it is important to note that some other more unexpected effects were also observed in this study; inhibition of the LC-BLA pathway during extinction enhanced extinction and stimulating the LC-mPFC pathway during extinction reduced long-term expression of extinction, an effect that could be blocked with an $\alpha 1$ adrenergic receptor antagonist. These types of results echo findings in pharmacological studies which suggest that an optimal level of NA is needed for memory enhancement and too much or too little can have deleterious effects. This may be particularly true in fear conditioning paradigms where high levels of NA may promote amygdala processing and fear, whereas lower levels may promote cortical processing and extinction (McCall et al., 2017; Giustino & Maren, 2018).

While there is a substantial literature that establishes the importance of noradrenaline to learning and memory, there remains debate regarding its precise function. With regards to prediction error, several important questions remain. Although electrophysiological recording studies demonstrate that LC neurons respond to surprising events, more work is needed to pinpoint any specific role in signaling prediction error apart from known contribution to signaling novelty, salience and related phenomena. Future experiments with appropriate behavioural controls allowing separation of error from novelty and/or arousal will help address this question. Further, while recent pharmacological studies suggest that NA can augment extinction, whether NA plays a broader role in signaling negative error or in error-driven learning more generally has not been systematically addressed.

A blueprint for research progress

Here we have reviewed neural substrates for the production and use of prediction error in the appetitive and aversive domains. Neural sources of prediction error have now been identified for signed, unsigned, positive and negative error for each setting. Further, neural networks that utilize prediction error to update stimulus-outcome associations are emerging. Yet, complete neural circuits for the production and use of prediction error have not been described for any error type in appetitive or aversive settings. In our opinion, there is no replacement for an associative learning approach. Embracing procedures that isolate the ability of prediction errors to alter associative relations (Summarized in Tables 1 & 2) would

be the backbone to any impactful, informative investigations into the neural basis of prediction error. These approaches can isolate key components of the error signal such as prediction, novelty, outcome specificity, and error itself. Progress requires the dissociation of each of these constructs in order to elucidate brain function. Even in standard associative learning paradigms these events can overlap in time. Variants of associative learning procedures that temporally isolate these events will be particularly valuable. For example, a variant of blocking using serial cue-cue-outcome (prediction-learned cue-error) has recently been described (Mahmud et al., 2019).

The importance of dissociating behavioural constructs is key to establishing sound animal models of disease states. For example, failure to flexibly control behaviour and modify previously learned responses is central to a number of neuropsychiatric diseases including dementia, depression, drug addiction and attention deficit hyperactivity disorder (ADHD). To understand pathology of this kind requires insight into the neural bases of learning, attention and their constituents in the healthy brain. Many commonly prescribed medications, ranging from β-blockers or antipsychotics to antidepressant and ADHD medications, directly alter DA and NA activity despite lack of a complete understanding of the role of these transmitters in learning processes or the implications of modifying activity in these systems. Moving towards more targeted approaches to treatment requires such insight.

We are at an exceptional time in science when advances in the development of neuroscientific techniques and analyses is making tremendous progress. Joining the forces of this new development with the old behavioural knowledge is a recipe for growth and advancement. For example, using controlled associative learning designs with temporally specific manipulation of neuronal populations or circuits can dissociate the distinct behavioural constructs mentioned earlier that support learning. Armed with this approach, the field is sure to make great strides.

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Highlights

- Prediction error is fundamental to associative learning
- Prediction error signals have been reported across the brain
- Phasic firing of dopamine neurons has been linked to reward prediction error
- The amygdala and related circuitry have been linked to aversive prediction error
- The locus coeruleus and norepinephrine regulate negative prediction error in extinction.

Table 1.

Common associative learning paradigms using an appetitive outcome (sucrose). Identical or similar paradigms use an aversive outcome (e.g. footshock). and denote visual stimuli (e.g. steady and flashing light). denotes an auditory stimulus (e.g. tone). denotes omiss ion of an expected outcome.

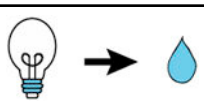
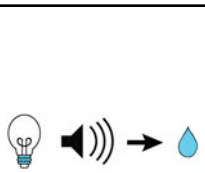
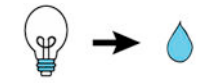
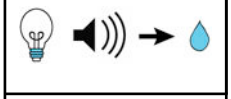
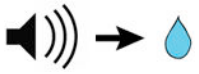
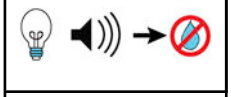
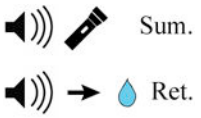
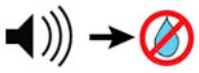
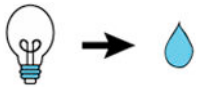
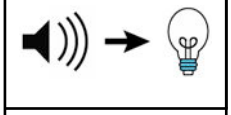
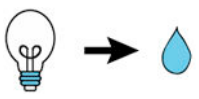
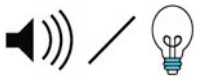
Paradigm	Group	Phase 1	Phase 2	Test
Blocking	Block			
	Control			
	Unblock			
Extinction	Extinction			
	Control			
Over Expectation	Over-Expectc			
	Control			
Conditioned Inhibition	Cond-Inh			
	Control			
Second-Order Conditining	Second-Order			
	Control			
Sensory Pre-Conditioning	Sensory-Pre			
	Control			

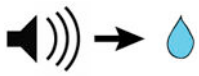
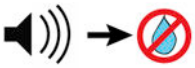
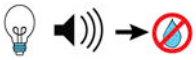
Table 2.

Serial occasion setting paradigms using an appetitive outcome (sucrose 💧). Identical or similar paradigms use an aversive outcome (e.g. footshock). 💡 denotes a visual stimulus (e.g. steady and flashing light). 🔊 denotes an auditory stimulus (e.g . tone).

Paradigm	Group	
Serial Occasion Setting	Feature Positive	
	Feature Negative	

Table 3.

Common associative learning paradigms using an appetitive outcome (sucrose 💧). Identical or similar paradigms use an aversive outcome (e.g. footshock). 💡 and ✏ denote visual stimuli (e.g. steady and flashing light). 🔊 denotes an auditory stimulus (e.g. tone).

Paradigm	Group	Phase 1	Phase 2	Test
Concurrent Excitor	Extinction			
	Excitor			
	Control			
Compound Extinction