Published in final edited form as:

Brain Res. 2019 June 15; 1713: 80–90. doi:10.1016/j.brainres.2018.10.008.

Dopamine signals related to appetitive and aversive events in paradigms that manipulate reward and avoidability

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Abstract

Using environmental cues to acquire good and avoid harmful things is critical for survival. Rewarding and aversive outcomes both drive behavior through reinforcement learning and sometimes occur together in the environment, but it remains unclear how these signals are encoded within the brain and if signals for positive and negative reinforcement are encoded similarly. Recent studies demonstrate that the dopaminergic system and interconnected brain regions process both positive and negative reinforcement necessary for approach and avoidance behaviors, respectively. Here, we review these data with a special focus on behavioral paradigms that manipulate both expected reward and the avoidability of aversive events to reveal neural correlates related to value, prediction error encoding, motivation, and salience.

Keywords

dopamine; appetitive; aversive; positive reinforcement; negative reinforcement; reward; rat; single neuron; fast scan cyclic voltammetry

Introduction

The ability to make beneficial choices is critical for normal, everyday behavior and, as a consequence, decision-making is a fundamental executive function across species (Calvert et al., 2011; Kalenscher and van Wingerden, 2011). Making good decisions is not always easy: it is a multifaceted process. To make a decision, an animal must weigh many possible outcomes against short- and long-term goals before deciding a course of action. By successfully monitoring environmental cues and predicting consequences, animals can select behaviors that facilitate the attainment of a chosen goal. When behaviors lead to the acquisition of a positive outcome (*i.e.*, *approach*) or the evasion of a negative outcome (*i.e.*, *avoidance*), these behaviors are reinforced, increasing the probability the same behavior will be selected again in the future when similar conditions are encountered. In this way, behavior can be shaped toward the good and away from the bad in one's environment.

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Conflict of Interest: The authors declare no biomedical financial interests or potential conflicts of interest.

Approach and avoidance behaviors are driven by *positive* and *negative* reinforcement, respectively. During positive reinforcement, a desirable unconditioned stimulus (US), a reward, is added to the environment contingent upon the subject's behavior; the acquisition of this reward increases the likelihood the subject will perform this behavior again in the future when faced with a predictive cue (*i.e.*, conditioned stimulus, CS). For example, if the delivery of a sucrose pellet is signaled by a cue (*e.g.*, light, auditory tone), an animal will learn to associate the cue preceding sucrose delivery with reward, and the cue itself will start to drive the appropriate behavioral response. This behavioral response would include an action or sequence of actions that must be performed in order to obtain the reward, such as pressing a lever and/or visiting a food receptacle. Generally, positive reinforcement is more often and more easily studied, as this is a fairly straightforward behavior for the animal to learn and perform. With that said, neural and psychological constructs during positive reinforcement paradigms are still complicated, evoking several different associative mechanisms (*e.g.*, stimulus-outcome, stimulus-response, response-outcome, attention, arousal, motivation, etc.)

During negative reinforcement, a noxious US (*e.g.*, foot shock) is removed from the environment contingent upon the subject's behavior; the removal of this threat acts to increase the probability the subject will repeat this behavior in the future. For example, if the delivery of the foot shock is first signaled by a cue (*e.g.*, light, auditory tone), an animal will learn to associate this cue with the impending shock, and the cue will start to drive the appropriate behavioral response to avoid or escape the shock threat, if possible. In contrast with positive reinforcement, tasks using negative reinforcement, such as active shock avoidance, can be difficult for the animal to learn and perform due to the formation of a Pavlovian response to the aversive cue, which is in conflict with actions that need to be performed to avoid the threat (Mowrer and Lamoreaux, 1946; Dayan et al., 2006; Maia, 2010). In negative reinforcement scenarios, it is thought that the predictive cue becomes aversive in itself after extensive training, and the animal will work to eliminate it even in the absence of a shock outcome (Mowrer and Lamoreaux, 1946; Parkinson et al., 1999; Everitt and Robbins, 2005; Balleine and O'Doherty, 2010; Budygin et al., 2012; Wenzel et al., 2015); at this stage, elimination of the aversive predictive cue becomes the reinforcing step in avoidance paradigms, which is likely driven by habit-like stimulus-response (S-R) encoding systems within the brain (LeDoux et al., 2017). This is supported by the fact that, with extensive training, avoidance behaviors remain immune to extinction, despite the recurrent uncoupling of the cue and the aversive outcome when the animal avoids shock (Solomon et al., 1953; Kamin et al., 1963; Rescorla and Solomon, 1967; Bolles, 1972). Due to these complications, the mechanisms underlying negative reinforcement have not been as thoroughly studied as positive reinforcement.

Here, it is important for us to note critical differences between negative reinforcement, punishment, and the non-contingent administration of an aversive stimulus. Prominent behaviorist B.F. Skinner defined punishment as the response-contingent presentation or removal of an aversive or appetitive reinforcer, respectively (Holland and Skinner, 1961; Sidman, 2006). Thus, while both punishment and negative reinforcement are dependent upon an animal's behavior, punishment would ideally decrease the probability of repeating an undesirable behavior, though this effect is often unreliable, temporary, and prone to

unpleasant side effects (Skinner, 1953; Holland and Skinner, 1961; Jean-Richard-Dit-Bressel et al., 2018; Wassum, 2018). During punishment, an aversive outcome is only likely to occur if a specific action is performed, leading to a response-outcome association (R-O; response punished by contingency); alternatively, during negative reinforcement, an aversive outcome is only likely to occur if a specific response is omitted (R-no O; response reinforced by contingency) (Jean-Richard-Dit-Bressel et al., 2018). While negative reinforcement is active avoidance (performing an action prevents the aversive event), punishment represents passive avoidance (withholding an action prevents the aversive event) (Wassum, 2018). Importantly, though fear conditioning studies are often framed in terms of punishment, these paradigms, which use Pavlovian conditioning to pair a tone with a shock irrespective of an animal's behavior, actually deliver a non-contingent aversive stimulus (stimulus-outcome association; S-O) (Jean-Richard-Dit-Bressel et al., 2018). We aim to be specific and consistent with our terminology throughout this review in order to prevent confusion as each of these manipulations lead to important differences in firing of dopamine (DA) neurons and DA release, providing insights to DA's contribution to processing appetitive and aversive events.

Although the neural mechanisms underlying approach/ positive reinforcement has been extensively studied, much less is known about avoidance/ negative reinforcement. This is true across brain circuits but is particularly true for the DA system. Further, in most studies, decisions and learning that involve appetitive and aversive events are often studied separately. This makes it difficult to determine if neural circuits critical for one component of learning are necessary for the other and/or if observed signals genuinely reflect aspects of positive and negative reinforcement or more generalized executive functions related to motivation, arousal, and attention (Bissonette et al., 2014; Bissonette and Roesch, 2015). In this review, we will first discuss the literature surrounding the role of DA in appetitive conditioning and unavoidable aversive events. We will then focus on work from our lab examining neural signals in the context of both approach and avoidance with a strong emphasis on the DA system and interconnected brain regions.

Dopamine neurons signal prediction errors or salience during positive reinforcement and unavoidable aversive events

The DA system has been studied extensively in the context of reinforcement learning and motivational control, specifically relating to reward approach. Within the midbrain lie the two major sources of DA neurons, the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), which send broad projections within the basal ganglia (striatum, pallidum, substantia nigra pars reticulata, subthalamic nucleus) and the prefrontal cortex (PFC) (Lavoie et al., 1989; Cragg et al., 2004; Björklund and Dunnett, 2007; Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010; Parker et al., 2016). Signals from these midbrain DA neurons have been shown to play a critical role in reinforcement learning by providing a physiological correlate to the well-studied prediction error (PE). Phasic bursts or pauses in DA neuron activity, together with resulting neurotransmitter release downstream, are thought to encode this PE signal, which guides goal-directed behavior by informing the system which aspects of the environment are appetitive or aversive and initiating actions to obtain the good and avoid the bad (Schultz, Dayan, & Montague, 1997). The PE signal

measures the difference between an expected outcome and the actual outcome to inform future behavior. A better-than-expected outcome activates DA neurons resulting in phasic neurotransmitter release (positive PE), while a worse-than-expected outcome induces a pause in DA neuron firing and neurotransmitter release downstream (negative PE). A fully predictable outcome elicits no change in firing of DA neurons or DA concentrations.

Based on the mismatch of expectation and consequence, the DA signal acts as a teaching mechanism, updating expectations and potential behavioral responses using feedback obtained from the environment. As the system continues to learn about the environment, the primary reinforcer (*i.e.*, the unconditioned stimulus; the outcome) will start to become more predictable and DA released in response to it will diminish over time; simultaneously, the DA signal will gradually shift to the outcome's first predictor (*e.g.*, related cues) (Schultz et al., 1997). Value signaling likely relies on DA to form associations between these stimuli and outcomes during learning and decision-making (Day, Roitman, Wightman, & Carelli, 2007; Schultz, 1998; Schultz et al., 1997).

While DA activity within the mesolimbic pathway has been widely implicated in the construction of reward expectations, a growing literature has recently emerged investigating its role in aversive associative learning. Several studies have shown that aversive outcomes and their predictive cues decrease DA firing and release, while the omission or cessation of expected aversive stimuli results in an increased DA response (Roitman et al., 2008; Darvas et al., 2011; Badrinarayan et al., 2012; Budygin et al., 2012; Oleson et al., 2012; Oleson and Cheer, 2013; Volman et al., 2013). However, increased firing of DA neurons and increased DA release in the nucleus accumbens (NAc) core have also been shown to occur in direct response to aversive stimuli including tail pinch, foot shock, or air puff (Brischoux et al., 2009; Matsumoto and Hikosaka, 2009; Budygin et al., 2012). Additionally, activation of D1 and D2 receptors, specifically within the striatum, is necessary for the formation of fear memories (Fadok et al., 2009; Kishioka et al., 2009; Ikegami et al., 2014), and microdialysis studies have shown increased tonic DA and DA metabolite levels in response to aversive events within the NAc core (Abercrombie et al., 1989), including in fear conditioning paradigms (Young et al., 1993; Wilkinson et al., 1998). These seemingly contradictory findings have made it difficult to pinpoint the exact role of DA during administration of aversive stimuli, punishment, and negative reinforcement.

It has been suggested some of the heterogeneity previously seen in studies measuring the response of DA neurons to aversive stimuli is actually due to the mis-categorization of DA vs non-DA neurons (Ungless and Grace, 2012). For example, Ungless et al. found TH+ neurons in VTA inhibited by aversive tail pinch, while nearby TH- cells with similar waveforms were excited (Ungless et al., 2004). However, in a later study, they found that while DA neurons in the dorsal VTA were inhibited by aversive foot shock, DA neurons in the ventral portion of VTA were phasically excited by the same foot shock (Brischoux et al., 2009).

Further heterogeneity has been described in primates along the dorsoventral and mediolateral axis (Bromberg-Martin et al., 2010). In primates, more medial and ventral midbrain DA neurons signal reward PEs as described above, whereas cells that encode

motivational salience signals are more densely packed within the dorsolateral SNc (Matsumoto and Hikosaka, 2009; Bromberg-Martin et al., 2010). In experiments where visual stimuli predict delivery of either reward or an aversive air-puff, these motivational salience DA neurons fire more strongly for these outcomes and the cues that predict them compared to neutral trials where no reward or air-puff is delivered. It has been hypothesized that salience-encoding DA neurons might preferentially project to the PFC and the core of NAc, while reward-preferring or PE DA neurons project preferentially to the ventromedial PFC and the shell of NAc (Bromberg-Martin et al., 2010).

Heterogeneity of DA signals has also been described in mice. Following their own initial observations of a mix of increased and decreased DA neuron firing rates in response to aversive stimuli (Cohen, et al. 2012), the Uchida group published a series of experiments examining the heterogeneous responses of DA neurons. Importantly, in these studies DA neurons were identified optogenetically, which reduces contributions to response heterogeneity from mis-categorized neurons. Additionally, DA neuron responses to reward predictive cues, rewards, and reward omissions were also examined and found to conform to the PE hypothesis. Specifically, inhibitory responses to reward omission and modulation of response amplitude by predictability ensured that the observed DA neurons are involved in encoding PEs rather than salience (*cf.* Bromberg-Martin, et al., 2010), and eliminated this factor as a source of response heterogeneity.

Other reports from the Uchida lab have demonstrated that the firing of many DA neurons to air-puffs and cues that predict them were biphasic, suggesting that some of the reported excitatory DA neuron responses to aversive stimuli may be due to an initial excitatory response, followed by longer lasting decreases (Tian & Uchida, 2015). In a follow up study, the Uchida group examined DA activity in response to cues predicting aversive events in high vs. low reward context tasks (Matsumoto, et al., 2016). Both of these tasks interwove reward, neutral, and aversive trials. An air-puff with 90% probability followed the cue on aversive trials, and no stimulus was delivered after the neutral cue. The high reward context was established by delivering water with a 90% probability following the reward cue, and for the low reward context water was delivered with a 20% probability. Responses to the aversive cue in the high reward context matched those observed in the previous study, *i.e.*, the responses were biphasic (Tian & Uchida, 2015). In contrast, the DA neurons which responded to the aversive cue in the low reward context did so with monophasic inhibitions. In addition to examining responses to reward-related stimuli, the authors developed a separate, low reward context task which contained a fourth cue that was followed by an air-puff 75% of the time and followed by water 25% of the time. Importantly, while the firing rates were decreased in response to this mixed cue, they were in between the firing rates following the aversive only and reward only cues. This integration of positive and negative values together clearly points to PE signaling, rather than salience signaling, as the function of these neurons. Taken together these results establish variations in task design leading to high vs. low reward contexts as a primary contributor to response heterogeneity within PE signaling DA neurons.

Although task design has been established as a primary contributor to DA neuron response heterogeneity, heterogeneity of DA neuron function also likely plays a role in many studies.

Arguments about whether mesolimbic DA functions to signal PEs, or salience have been ongoing for many years, and it has even been suggested that DA neurons take PE as an input, transform the information, and signal salience as an output (Berridge, 2007). It has also been suggested that differences in DA innervation and kinetics across striatal regions result in a segregation of function, with PEs signaled by more rapid DA signals in the dorsal striatum and salience signaled by slower DA signals in the ventral striatum (Wickens, et al., 2007). More recent support for regional segregation of these two types of signals comes from FSCV which has revealed heterogeneity in the function of DA signals in different subregions of the ventral striatum with PE signals in the core of the NAc and salience signals in the medial shell (Saddoris, et al., 2015).

The discussion about whether DA signals PEs or salience has been further complicated by recent observations that changes in NAc DA can be dissociated from changes in DA neuron action potential firing. During a two-armed bandit task for rats, DA neuron electrophysiological responses appear to match PEs, *i.e.*, they are excited by delivery of unexpected rewards with modulation of the response by predictability, and they are inhibited by the omission of expected rewards (Mohebi, et al., 2018). However, NAc DA signals recorded during the same task exhibit ramping, or gradual increases over the course of a trial (Hamid, et al., 2016). These DA ramps are thought to result from presynaptic control of DA release, and they are more correlated with state values, the temporally discounted estimate of future reward (Berke, 2018; Hamid, et al., 2016). It has been hypothesized that these DA encoded value signals underlie both PEs and salience (Berke, 2018). In the former case PEs are mathematically defined as the moment to moment differences in state value, while in the latter case these value signals contain the information necessary to regulate proper levels of motivation, *i.e.*, state value increases as rewards become larger and/or more imminent. Thus, state values could signal PEs to neurons that are sensitive to rapid changes in DA while signaling salience to neurons that are more sensitive to the absolute DA level. In confirmation of this dual role for DA, optogenetically enhancing NAc DA signals at the start of a trial enhanced the animals' motivation while optogenetically enhancing these signals at reward delivery improved learning (Hamid, et al., 2016). Taken one step further, it has been suggested that throughout the striatum DA has a unitary, value-signaling function that influences various behaviors depending on the circuits that are receiving the signal (Berke, 2018).

Further support for a role of presynaptic regulation in sculpting DA signals comes from a study using fiber photometry to record GCaMP reported Ca^{++} influx into DA neuron terminals in various regions of the striatum (Menegas, et al., 2017). The results indicate that these Ca^{++} signals match the PE hypothesis for both appetitive and aversive related stimuli in the ventral striatum, but in the posterior tail of the striatum these Ca^{++} signals appeared to encode novelty and salience. Additionally, Ca^{++} signals in both the dorsomedial and dorsolateral striatum were not as clear cut appearing more similar to PE signals for reward-related stimuli and more similar to salience signals for punishment-related stimuli. Of course, a recently demonstrated dissociation between Ca^{++} influx into DA terminals and DA vesicle exocytosis complicates interpretation of these signals, but further highlights the importance of presynaptic control of DA release (Pereira, et al., 2016).

It appears that variations in the task design and the function of DA neurons are primary contributors to the observed heterogeneity of DA neuron responses to aversive stimuli. Furthermore, these two factors may be related as different tasks can be reasonably expected to differentially recruit circuits subserving PEs and salience. Moving forward, it seems likely that more functions for DA will be identified, because some published experiments have reported results that cannot be parsimoniously explained by either PE or salience. Consider for example the ambiguous Ca^{++} signals observed in the dorsal striatum (Menegas, et al., 2017), the experience dependent heterogeneity in DA release to unexpected rewards in the dorsomedial striatum (Brown et al., 2011), or the rostral-caudal appetitive-aversive gradient of function observed within the medial shell itself (Faure, et al., 2008; Hurley, et al., 2017). If striatal DA signals have a unitary function, then examining these signals in more complex behavioral paradigms should help to reveal what that is.

Dopamine's role in avoidance

As described above, avoidance is a complex behavioral paradigm that should prove particularly useful in defining the function of DA signals (Lloyd & Dayan, 2016). In a typical avoidance paradigm an animal is presented with a warning cue (*e.g.*, tone) which precedes an aversive outcome (*e.g.*, shock) unless a required operant response (*e.g.*, lever press) is emitted. This type of behavior has long been thought to rely on both Pavlovian and instrumental learning as formalized by two-factor theory. Two-factor theory posits that initially the animal forms a Pavlovian association between the cue and the aversive outcome; thus, the cue evokes a state of fear in the animal. Then the instrumental lever pressing contingency is reinforced by the relief associated with the reduction in fear that comes from terminating the warning cue.

While DA is known to play a major role in reward approach, its role in the avoidance of aversive stimuli is just beginning to be defined. Early studies from the late 20th century used a variety of strategies to show that DA is likely important in the learning and initiation of avoidance behaviors. Lesioning midbrain DA neurons or DA terminals of the striatum, specifically within the NAc, using 6-hydroxydopamine prevented animals from acquiring active avoidance behaviors, which was then completely rescued by systemic administration of a low dose of the DA precursor L-DOPA (Cooper et al., 1973; Fibiger et al., 1974; Zis et al., 1974; Amalric and Koob, 1987; McCullough et al., 1993). Tonic DA levels, measured by microdialysis probes, tend to be higher in the striatum during both the acquisition and maintenance of avoidance behavior (McCullough et al., 1993; Dombrowski et al., 2013). Interestingly, DA does not appear to be necessary for escape behaviors; broadly inhibiting DA using the antipsychotic haloperidol or other DA antagonists prevent animals from acquiring avoidance behavior, while leaving escape behaviors intact (Fibiger et al., 1975; Arnt, 1982; Wadenberg et al., 1990). It is likely that the effectiveness of antipsychotics in disrupting avoidance stems from their ability to block D2-type receptors, whose activation is thought to promote active defense behaviors (Beninger et al., 1980; Beninger, 1983, 1989; Kapur, 2003; Smith et al., 2005; Lloyd and Dayan, 2016). Specifically, D2 receptors within the ventral striatum are thought to be essential to the learning and expression of conditioned instrumental avoidance (Wadenberg et al., 1990; Wadenberg and Hicks, 1999). Increased freezing in response to shock and impaired retention of fear conditioning extinction

memories have been shown after systemic, intracerebroventricular, and accumbal D2 receptor blockade (Blackburn and Phillips, 1990; Blackburn et al., 1992; Holtzman-Assif et al., 2010; Mueller et al., 2010) and selective optogenetic activation of striatal D2-receptor expressing neurons (Kravitz et al., 2010).

While tonic DA and D2 receptor activation are thought to be important for fear extinction and the execution of active defense behaviors, phasic DA release and D1 receptor activation are thought to help acquire the CS-US contingency between cue and shock (Beninger and Miller, 1998; Eyny and Horvitz, 2003; Dalley et al., 2005). NAc lesions (6-hydroxydopamine, quinolinic acid, electrolytic) have been shown to disrupt avoidance learning (Cooper et al., 1974; McCullough et al., 1993). More specifically, D1 receptor antagonists have been shown to disrupt fear and avoidance learning (Beninger et al., 1980; Inoue et al., 2000; Fadok et al., 2009), and D1-knockout mice, not D2-knockouts, show impaired acquisition of fear conditioning and fear extinction (Ikegami et al., 2014). Importantly, these effects appear to be time-sensitive to the acquisition of new fear-related CS-US contingencies, since injections of D1-receptor antagonists after fear conditioning has been acquired have no effect on behavior (Inoue et al., 2000).

These studies all suggest that DA increases during avoidance, consistent with its function as a motivational signal driving the animal to avoid aversive stimuli. However, if DA increases then does it still signal PEs, and if it does then how do animals learn that the stimuli are aversive? A partial answer to these questions arose from a computational model of the two-factor theory of avoidance (Dayan 2012). In this model positive PEs are generated when aversive events are successfully avoided, because the value of the outcome (no shock) is referenced to the estimated value (shock). In other words, a positive PE is generated even though no rewards are ever delivered, because the outcome is better than expected. For this model DA is conceptualized as signaling the relief that reinforces the two-factor theory's instrumental learning, while aversive outcomes are signaled by an additional neurotransmitter, serotonin. The answer to the questions according to this model is that animals learn the stimuli are aversive by the actions of serotonin, but they learn to lever press in order to avoid punishment by the actions of DA. Thus, the PE function of DA signals can theoretically result in increased DA during punishment avoidance provided that serotonin, or some other circuit not involved in traditional DA PE signaling, is responsible for signaling aversive events. Importantly, the model predicted increased DA at the presentation of a warning cue for a trained animal, because of the relief the animal expects to experience following a successful lever press.

At the time this computational model was being developed, no study had been reported that directly measured phasic DA release in response to cues predicting avoidable shock. However, Oleson and colleagues were in the process of determining how DA neurons respond to aversive stimuli. A 2012 study by Oleson and colleagues tackled this question by using fast-scan cyclic voltammetry (FSCV) to measure phasic DA release within the NAc core during cued active avoidance (Oleson et al., 2012). In this task, a warning cue (light + tone) was presented above a response lever for 2 s, termed the "warning period". If the rat pressed the lever during this 2 s warning period, he would completely avoid shock and progress into a 20 s safety period, cued by a separate tone; this was categorized as an

avoidance response. If the rat failed to press during this 2 s warning period, shock commenced. The rat could then press the lever to terminate shock delivery and, thus, progress into a 20 s signaled safety period; this was categorized as an escape response. There were two discrete cues in this task: the warning cue, which signaled that an aversive event could potentially occur, and a safety cue, which signaled the aversive event was no longer a threat. Even though rats were well-trained on the task (50% avoidance criterion), they found most rats exhibited a mixture of these two responses.

Interestingly, DA release increased to the warning cue only when animals subsequently avoided shock. No increases in DA release were present to cues that were followed by escape responses or failed presses, in fact there was a significant decrease in DA between the cue presentation and lever press during escape responses. They also saw increased DA release to the cued safety period, though these increases in DA release were not predictive of the animal's behavioral choice, as increases were seen during the safety period whether the animal escaped or avoided shock (Oleson and Cheer, 2013). It is possible, then, that increases in phasic DA release to shock avoidance cues and to the receipt of safety could be analogous to cues predicting reward and reward delivery.

Additionally, Oleson and colleagues wondered if escape responses, when shock is experienced and then terminated, are encoded similarly by DA compared with inescapable shock experienced during fear conditioning experiments. To test this, they measured phasic DA release using FSCV during a standard fear conditioning task (Monfils et al., 2009). Similar to what was seen during escape responses, a pause in DA transients occurred during the presentation of cues that had previously predicted unavoidable shock. This effect diminished over time, as the association between the cue and the unavoidable shock became weaker, similar to extinction seen to fear conditioning cues.

Together, this suggests that the warning signal may gain predictive power as avoidable responses are executed more often. Oleson et al. extended the two-factor theory by hypothesizing that initially during avoidance training, a decrease in DA release is seen to the warning cue likely due to initial Pavlovian fear generated by the cue related to the prediction of shock and behavioral uncertainty; in the beginning, this inhibits avoidance by promoting passive defensive strategies, *i.e.*, freezing. Over time, as the animal begins to press the lever the warning signal becomes more heavily associated with safety, the fear/freezing response begins to dissipate, and animals can now overcome this response to press and avoid. The cue is now encoded as the first predictor of safety through a positive PE—when the animal presses the lever, the expected shock is omitted, and this is better than expected. The warning signal now predicts safety and this is encoded through increased phasic DA release as predicted by the computational model (Dayan, 2012).

Thus, in rats performing an instrumental escape-avoidance paradigm, phasic DA activity to the cue presentation can foretell if rats will successfully avoid an upcoming foot shock (Oleson, Gentry, Chioma, & Cheer, 2012). In this task, successful avoidance behavior was predicted by DA release time-locked to the warning cue; DA release was also seen in response to cues signaling the safety period, once shock had been successfully avoided. Importantly, DA release was not present to cues predicting escape responses during the

avoidance paradigm or unavoidable shock in a fear conditioning paradigm; here, the DA was uninformative in that the animal could do nothing to avoid the shocks. Combined, these results align with results from recent studies suggesting increased cue-evoked DA release in the NAc predicts shock avoidance, whereas a pause in DA transients occurs during the presentation of unavoidable aversive stimuli across modalities (Roitman et al., 2008; Darvas et al., 2011; Badrinarayan et al., 2012; Oleson and Cheer, 2013; Volman et al., 2013).

Although there is now a body of literature that has studied neural systems involved in both reward approach and active avoidance, very few have set out to explicitly study how these neural systems directly reconcile appetitive and aversive neural signals in a single task. Even fewer have addressed questions related to individual differences that arise during approach and avoidance tasks. Our work followed up and expanded upon Oleson's 2012 study and aimed to answer these questions by investigating phasic DA release using FSCV during a combined approach avoidance task (Gentry et al., 2016).

In the task we developed, animals experienced three separate cues predicting the possibility for reward, the possibility for shock, or no change in the environment (Fig 1A–C). These cues and outcomes were pseudorandomly interleaved within a session and counterbalanced across rats. At the onset of each trial, a cue light and one of three discriminatory auditory cues (tone, white noise or clicker) were activated. After 5 s, an operant lever was extended into the chamber, which rats could press to produce one of three outcomes (dependent on the auditory cue identity): delivery of a food reward (a sucrose pellet; positive reinforcement behavior), prevention of foot shock (0.42 mV; negative reinforcement behavior), or no consequence (neutral). If the rat failed to press the lever within a 10 s period, no food reward was delivered, foot shock commenced, or there was no consequence. However, rats were able to press the lever at any time to escape the foot shock once it commenced; if rats failed to press the lever, foot shock automatically terminated after 15 s. After response or termination of the trial, an unsignaled intertrial interval of 20 s was initiated. Animals were very well trained on this task, completing at least 30 sessions and displaying greater than 60% avoidance responses for three consecutive sessions before FSCV recordings began.

We found that, overall, DA release within the NAc increased to both reward approach and shock avoidance cues compared to neutral cues, and these changes occurred within the same microdomain of the NAc. This is shown in figure 1D–F. Increases in DA release were observed shortly after cue onset and were higher for reward (blue) and shock (red) cues compared to neutral (yellow). Further, we found significant positive correlations between DA release on reward and shock trials relative to neutral trials during the cue epoch (5s of cue presentation) and lever epoch (1 s after lever extension), indicating that increases in DA release to reward cues occurred in the same session and, hence, the same microdomain as increases in DA release to shock cues during avoidance trials (Fig 1E–F). This work confirms that, at least within the NAc core, local DA release can signal the need for approach or avoidance behavior and keeps track of the value of each cue. This result coincides with prior results from Oleson et al. showing that DA release in NAc core predicts successful avoidance and is inhibited by unavoidable shock (Oleson et al., 2012).

Additionally, we uncovered intriguing individual differences in behavioral responses and NAc DA release within our group of animals. Behaviorally, animals that were good at avoiding shock responded quickly and at a high rate for all predictive cues; in contrast, animals who were worse at avoiding shock responded slower and less reliably for neutral and shock cues compared to reward cues. We hypothesized that these behavioral differences could be due to differences in freezing behavior and would also likely be reflected in accumbal DA release. Indeed, we found that poor avoiders froze more to cues predicting avoidable shock, both when they pressed and failed to press to avoid; importantly, good avoiders still occasionally froze during shock avoidance cues but were able to overcome this freezing response to avoid more often. Thus, while poor avoiders were focused on the negative outcome and behavior was negatively affected, it seems good avoiders were able to respond without being deterred by the potential negative outcome of shock trials, as if they were responding habitually (Gentry et al., 2016). Interestingly, it was only in good avoiders that DA release to cues clearly delineated the value; in poor avoiders, DA release did not significantly differ between reward, neutral and avoidance cues. We did not observe a decrease in DA following the punishment cue for poor avoiders, as might be expected based on previous work (Oleson, et al., 2012). However, this discrepancy is easily explained as the inclusion of reward trials in our paradigm results in a high reward context, which leads to a biphasic DA neuron response to aversive stimuli, and would be expected to increase DA due to the initial excitatory phase (Tian & Uchida, 2015).

This work is in line with previous research suggesting that good avoiders develop habit-like strategies. Stress can lead animals to develop an insensitivity toward shifting reinforcement values and reduce explicit knowledge of action-outcome contingencies (Dias-Ferreira et al., 2009; Schwabe and Wolf, 2009, 2011; Soares et al., 2012; Taylor et al., 2014). Both goal-directed and habitual processes are thought to be involved in successful avoidance learning and maintenance, and we speculate that the behavioral pattern of good avoiders could reflect the utilization of a proactive habitual strategy under the control of dorsal lateral striatum (DLS; habit center) in order to maximally obtain reward and avoid shock (Seymour et al., 2007).

Additionally, behavioral differences between good and poor avoiders could arise from differences in instrumental incentive for haste versus sloth within the task. A model created by Dayan and colleagues postulates that state-action values for punishment encourage slow-pressing, compared to reward where fast-pressing is encouraged (Dayan, 2012). While waiting too long to press the lever (*i.e.*, sloth) could result in a shock on the current trial, acting quickly (*i.e.*, haste) would safely avoid the immediate aversive outcome but would also progress the task, potentially leading to another shock trial (Dayan and Huys, 2008; Cools et al., 2010; Boureau and Dayan, 2011; Dayan, 2012). As mentioned previously, good avoiders on our task responded quickly and at a high rate for all predictive cues, while poor avoiders responded slower and less reliably for neutral and shock cues compared to reward cues. This supports the idea that, in our combined approach and avoidance task, the threat of shock has more of an effect on the behavior of poor avoiders than good avoiders.

A complementary explanation of these behavioral differences as it specifically relates to DA release and behavior on our tasks comes from two computational models reported by Lloyd

and Dayan in this special issue (Lloyd & Dayan, 2018). One model was designed to capture the behavior and DA signals of our high performers and the other model was for the low performers. The model for the high performers involved purely instrumental learning processes with an implementation of the two-factor theory of avoidance learning similar to the avoidance model discussed previously (Dayan 2012). Additionally, the model captures the results of neutral trials by including an opportunity cost of time. The opportunity cost of time causes the neutral cue to acquire negative value, which results in decreased DA when it is presented. This opportunity cost also results in pressing on neutral trials, because this action ends the trial more quickly and hastens the next reward trial. The model for the low performers required two modifications. First, the outcome on punishment trials was made more negative, as though the shock is subjectively more aversive to poor performers. This has the effect of producing a negative average reward rate, which means the neutral cue will acquire positive value and increase DA, because it is not followed by punishment. Second, value-based Pavlovian influences over behavior had to be modeled in addition to the instrumental influences. This Pavlovian influence speeds responding to positively valued cues while slowing responding to negatively valued cues which accounts for the failure to lever press on punishment trials.

Together, these models place the results squarely within a two-factor learning theory framework (Lloyd & Dayan, 2018). The good performers have reached a state where the instrumental contingency (lever pressing to terminate the cue and avoid shock) has overcome the Pavlovian contingency (fear/freezing to the warning cue). While the poor performers, perhaps due to their subjective experience of the shock, are still influenced by the Pavlovian contingency. Although freezing wasn't specifically modeled, one would be hard-pressed to argue that the freezing observed in the actual experiment was not a Pavlovian fear response that slowed responding. Thus, we hypothesize that good performers rely on habitual, stimulus-response associative processes involving the DLS while poor performers are unduly influenced by Pavlovian, stimulus-outcome associative processes involving the NAc core (Ikemoto 2007). What remains to be determined is if phenotypic differences render the poor avoiders unable to overcome Pavlovian influences, or if poor performance is acquired through experience, *e.g.*, learned helplessness resulting from stochastic differences early during training.

The work described above clearly indicates that, at least in good avoiders, cues that predict the ability to avoid shock increase DA to levels associated with cues that predict reward. Recent work has further demonstrated that DA computes the value associated with negative reinforcement by measuring DA release using FSCV during a behavioral economics task where the price to avoid shock increased progressively over the course of a session (Pultorak et al., 2018). They found an inverse relationship between DA amplitude at avoidance-predictive cues and the effort needed in order to avoid. They also artificially shifted the value of avoidance cues by optically manipulating VTA DA neurons showing that optically increasing DA release to avoidance cues made rats more sensitive to price by inducing a negative PE, and that increasing DA release when the animal successfully avoided made them less sensitive to price by inducing a positive PE.

Other recent work has supported and extended these findings. A study conducted by Wenzel et al. provides further evidence supporting DA's role in avoidance (Wenzel et al., 2018). By mimicking a physiologically-relevant pattern of DA release seen prior to successful avoidance, Wenzel demonstrates bidirectional control over avoidance behavior. They found that optically stimulating DA neurons enhanced avoidance, while optogenetic inhibition of these cells impaired avoidance behavior. Additionally, optically stimulating DA neurons during conditioned fear accelerates extinction of conditioned fear and associated freezing responses to cue presentation. Taken together, these data suggest that DA indeed represents the economic value of avoidance, much like it has been shown to represent the value of reward approach.

Summary and the larger circuit

Conditioned stimuli that predict reward and aversive events set into motion several functions that are highly interrelated but can be distinguished via task design. Although DA signals are not selective for the identity of appetitive and aversive stimuli (*i.e.*, sucrose versus water; shock versus quinine; etc.), it is clear that the DA system reports errors in reward prediction during both positive and negative reinforcement, punishment, and cues that predict unavoidable shock. That is, the firing of DA neurons and DA release are modulated by factors that reflect the value of appetitive and aversive stimuli, as they respond oppositely for appetitive and aversive events (*e.g.*, increase to reward and avoided shock, and decrease to punishment or unavoidable aversive events). Other DA neurons (located more laterally) seem to encode salience in that they increase to both appetitive and aversive events. That is, DA activity is modulated by factors that vary with the strength of both appetitive and aversive stimuli, in that activity was similar for appetitive and aversive trials. A final signal that arises from the DA system is one where cues predicting reward or avoidable aversive outcomes could both be construed as high value. Here, the avoidability of the aversive event is highly relevant. Cues that predict unavoidable aversive events would be salient, attention-grabbing, and arousing, but they would not have a high value since no action could be taken to prevent it; conversely, cues signaling reward or avoidable aversive events would also have value, since action could be taken to acquire the reward or avoid the unwanted consequence, respectively.

Thus, DA neurons in VTA are clearly important for signaling the PEs associated with both positive and negative events, value, and associated stimuli, increasing and decreasing firing for cues that predict avoidable and unavoidable events, respectively, as well as increasing and decreasing to events related to the presence and absence of reward. Of course, DA neurons don't perform these computations on their own and don't directly drive behavior in these contexts. Like the work that has characterized DA firing and release, work has started to uncover correlates in other interconnected brain areas (Fig. 2) involved in modifying behaviors associated with both positive and negative reinforcement. We have extensively reviewed these studies elsewhere (Bissonette et al., 2014; Bissonette and Roesch, 2015). Here we summarize those results.

Firing in orbitofrontal cortex (OFC) represents value expectancies and task structure necessary for guiding decision-making and learning. These signals are informed by

basolateral amygdala (ABL), which represents associative information as well as the intensity or salience of behavioral outcomes (Saddoris et al., 2005; Belova et al., 2007; Shabel and Janak, 2009; Roesch et al., 2010; Tye et al., 2010; Lichtenberg et al., 2017). Although both regions carry associative information about the identity of future reward, OFC seems to be better tuned to value of appetitive and aversive events, whereas ABL might better reflect salience (Pickens et al., 2003; Schoenbaum et al., 2003; Padoa-Schioppa and Assad, 2006). In OFC, neurons increase firing to cues that predict reward but decrease firing to cues that predict the possibility of punishment (Roesch and Olson, 2004). At the single neuron level, ABL is modulated by the predictability of both appetitive and aversive events (*i.e.*, quinine, air puff), specifically when expectancies are violated (Belova et al., 2007; Calu et al., 2010; M. R. Roesch, Calu, Esber, & Schoenbaum, 2010; Tye et al., 2010). These signals, possibly generated in OFC and ABL, in turn, are thought to inform neurons in NAc and DA neurons (Takahashi, Stalnaker, Roesch, & Schoenbaum, 2017). PE and salience signals generated by DA neurons provide feed-forward information to more dorsal-medial and dorsal-lateral regions in striatum, which are critical for goal-directed and habitual behaviors, respectively (O'Doherty et al., 2004). These regions receive specific inputs from cortex consistent with these roles. The medial regions of striatum receive dense projections from the medial prefrontal cortex (mPFC) and the anterior cingulate cortex (ACC), while the DLS is densely innervated by sensorimotor cortex (SMC), but also receives projections from mPFC and ACC (Haber and Knutson, 2010).

In addition to impacting behavior via dorsal striatum, these regions feed into NAc. Remarkably, different populations of NAc neurons encode value and motivation, thus making predictions about the value of future rewards and also carrying signals that might motivate behavior (Bromberg-Martin et al., 2010). Similar to OFC, It has been shown, that VTA DA neuronal PE responses depend on signals from NAc (Schultz, 2000; Stefani and Moghaddam, 2006). Notably, these regions not only inform the DA system but are critical for updating value representations during learning and when outcome contingencies change. Lastly, parietal cortex and ACC likely increase attentional control to ensure that neural processes are prioritized depending on expected actions and unsigned errors in reward prediction (Bryden et al., 2011; Hayden et al., 2011; Leathers and Olson, 2012).

Another critical cortical component within this circuit, which has been underexplored in avoidance contexts when it comes to single neuron recordings is the ventromedial prefrontal cortex (vmPFC). In humans, the vmPFC is presumed to be the functional homolog of the infralimbic (IL) and dorsopeduncular (DP) regions of the mPFC in non-human primates and rodents (Milad et al., 2007; Öngür, Ferry, & Price, 2003; Peters, Pattij, & De Vries, 2013). The vmPFC is well-connected to many other areas involved in appetitive and aversive processing, with IL receiving inputs from ABL, hippocampus, thalamus and sending projections to basomedial amygdala (BMA), the lateral central nucleus of the amygdala (CeA), and the striatum (McDonald et al., 1996; McDonald, 1998; Vertes, 2004). Optogenetic studies have revealed intra-mPFC connections between IL and its dorsal neighbor prelimbic mPFC (PL), with IL activation shown to have inhibitory effects on PL activity (Ji & Neugebauer, 2012). It has also been shown that, compared with PL and other prefrontal regions, IL has a particularly high D2 receptor density, specifically in its Layer V

cortical output neurons to amygdala, and is heavily innervated by DA projections from VTA (Swanson, 1982; Vincent et al., 1993; Lidow et al., 1998; Mueller et al., 2010).

Taking these connections into account, the vmPFC has been implicated in a variety of seemingly contradictory functions, such as fear suppression, habit, and extinction; these varied results have recently been reconciled into an overarching IL theory of behavioral flexibility, which can be applied across appetitive and aversive contexts. While the vmPFC has been extensively implicated in fear extinction and more recently in appetitive contexts, few studies have recorded from vmPFC during tasks that present the opportunity for both appetitive and aversive outcomes. Recently, we have recorded from single neurons while rats performed our previously outlined combined approach and avoidance task (Gentry and Roesch, 2018). Surprisingly, we found that cues predicting reward significantly modulated firing rates of vmPFC cells, but cues predicting avoidable shock did not (Fig. 3). These results suggest that vmPFC does not signal for avoidance, as it does for reward approach, at least in well trained animals.

However, it is possible that we did not find many vmPFC cells related to shock simply due to the layout of our task. While avoidance and reward opportunities occurred separately during our task, studies combining reward and avoidance decisions within the same trial had markedly different results. In a task where rats were forced to choose between a small, “safe” (low shock probability) reward and a large, “risky” (high shock probability) reward, inactivation of mPFC shifted decisions in favor of the more risky option across changing contingencies (Orsini et al., 2018). Further, it seems that mPFC to NAc, but not mPFC to VTA, connections are diminished when taking risky action, and specific subsets of these mPFC to NAc connections (layer 5a) encode information regarding prior aversive outcomes and help to suppress high-risk actions (Kim et al., 2017). Thus, future work should continue to focus on investigating the specific involvement of prefrontal subregions and projections in shock avoidance and the conflict between reward and avoidance, as it still remains unclear the extent to which vmPFC controls avoidance processing.

In conclusion, many (but not all) brain areas have been shown to be modulated by expected appetitive and aversive outcomes. Combining appetitive and aversive features into behavioral paradigms, as well as manipulating the avoidability of aversive outcomes has uncovered specific brain area functions related to value signaling, PE encoding, motivation, and salience, all of which appear to be encoded in one form or another by the DA system and interconnected brain regions (Fig. 2) in both positive and negative reinforcement contexts. Future work is necessary to dissect the necessity of connections and their causal relationship to approach and avoidance.

Acknowledgements:

This work was supported by grants from the NIH (R01DA031695, R01MH112504).

References

- Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ (1989) Differential Effect of Stress on In Vivo Dopamine Release in Striatum, Nucleus Accumbens, and Medial Frontal Cortex. *J Neurochem* 52:1655–1658. [PubMed: 2709017]
- Amalric M, Koob GF (1987) Depletion of dopamine in the caudate nucleus but not in nucleus accumbens impairs reaction-time performance in rats. *J Neurosci* 7:2129–2134. [PubMed: 3112323]
- Arnt J (1982) Pharmacological specificity of conditioned avoidance response inhibition in rats: inhibition by neuroleptics and correlation to dopamine receptor blockade. *Acta Pharmacol Toxicol (Copenh)* 51:321–329. [PubMed: 6129770]
- Badrinarayan A, Wescott SA, Vander Weele CM, Saunders BT, Couturier BE, Maren S, Aragona BJ (2012) Aversive Stimuli Differentially Modulate Real-Time Dopamine Transmission Dynamics within the Nucleus Accumbens Core and Shell. *J Neurosci* 32:15779–15790. [PubMed: 23136417]
- Balleine BW, O'Doherty JP (2010) Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35:48–69. [PubMed: 19776734]
- Belova MA, Paton JJ, Morrison SE, Salzman CD (2007) Expectation modulates neural responses to pleasant and aversive stimuli in primate amygdala. *Neuron* 55:970–984. [PubMed: 17880899]
- Beninger RJ (1983) The role of dopamine in locomotor activity and learning. *Brain Res* 287:173–196. [PubMed: 6357357]
- Beninger RJ (1989) The role of serotonin and dopamine in learning to avoid aversive stimuli In: Aversion, avoidance, and anxiety: Perspectives on aversively motivated behavior (Archer T, Nilsson LG, eds), pp 265–284. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.
- Beninger RJ, Mason ST, Phillips AG, Fibiger HC (1980) The Use of Conditioned Suppression to Evaluate the Nature of Neuroleptic-Induced Avoidance Deficits. *J Pharmacol Exp Ther* 213:623–627. [PubMed: 6110768]
- Beninger RJ, Miller R (1998) Dopamine D1-like receptors and reward-related incentive learning. *Neurosci Biobehav Rev* 22:335–345. [PubMed: 9579323]
- Berke JD (2018) What does dopamine mean? *Nat Neurosci* 1:787–793.
- Berridge KC (2007) The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* 191:391–431. [PubMed: 17072591]
- Bissonette GB, Gentry RN, Padmala S, Pessoa L, Roesch MR (2014) Impact of appetitive and aversive outcomes on brain responses: linking the animal and human literatures. *Front Syst Neurosci* 8:24. [PubMed: 24624062]
- Bissonette GB, Roesch MR (2015) Neurophysiology of Reward-Guided Behavior: Correlates Related to Predictions, Value, Motivation, Errors, Attention, and Action Prediction error.
- Björklund A, Dunnett SB (2007) Dopamine neuron systems in the brain: an update. *Trends Neurosci* 30:194–202. [PubMed: 17408759]
- Blackburn JR, Pfau JG, Phillips AG (1992) Dopamine functions in appetitive and defensive behaviours. *Prog Neurobiol* 39:247–279. [PubMed: 1502338]
- Blackburn JR, Phillips AG (1990) Enhancement of freezing behaviour by metoclopramide: implications for neuroleptic-induced avoidance deficits. *Pharmacol Biochem Behav* 35:685–691. [PubMed: 1971114]
- Bolles RC (1972) The Avoidance Learning Problem. *Psychol Learn Motiv* 6:97–145.
- Boureau Y-L, Dayan P (2011) Opponency revisited: competition and cooperation between dopamine and serotonin. *Neuropsychopharmacology* 36:74–97. [PubMed: 20881948]
- Brischoux F, Chakraborty S, Brierley DI, Ungless MA (2009) Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *Proc Natl Acad Sci U S A* 106:4894–4899. [PubMed: 19261850]
- Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010) Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron* 68:815–834. [PubMed: 21144997]

- Brown HD, McCutcheon JE, Cone JJ, Ragozzino ME, Roitman MF (2011) Primary food reward and reward-predictive stimuli evoke different patterns of phasic dopamine signaling throughout the striatum. *Eur J Neurosci* 34:1997–2006. [PubMed: 22122410]
- Bryden DW, Johnson EE, Tobia SC, Kashtelyan V, Roesch MR (2011) Attention for Learning Signals in Anterior Cingulate Cortex. *J Neurosci* 31:18266–18274. [PubMed: 22171031]
- Budygin EA, Park J, Bass CEE, Grinevich VPP, Bonin KDD, Wightman RMM, Wightman ARM (2012) Aversive stimulus differentially triggers subsecond dopamine release in reward regions. *Neuroscience* 201:331–337. [PubMed: 22108611]
- Calu DJ, Roesch MR, Haney RZ, Holland PC, Schoenbaum G (2010) Neural correlates of variations in event processing during learning in central nucleus of amygdala. *Neuron* 68:991–1001. [PubMed: 21145010]
- Calvert AL, Green L, Myerson J (2011) Discounting in Pigeons When the Choice is between Two Delayed Rewards: Implications for Species Comparisons. *Front Neurosci* 5:96. [PubMed: 21887130]
- Cools R, Nakamura K, Daw ND (2010) Serotonin and Dopamine: Unifying Affective, Activational, and Decision Functions. *Neuropsychopharmacology* 36:98–113. [PubMed: 20736991]
- Cooper BR, Breese GR, Grant LD, Howard JL (1973) Effects of 6-hydroxydopamine treatments on active avoidance responding: evidence for involvement of brain dopamine. *J Pharmacol Exp Ther* 185:358–370. [PubMed: 4703827]
- Cooper BR, Howard JL, Grant LD, Smith RD, Breese GR (1974) Alteration of avoidance and ingestive behavior after destruction of central catecholamine pathways with 6-hydroxydopamine. *Pharmacol Biochem Behav* 2:639–649. [PubMed: 4610593]
- Cohen JY, Haesler S, Vong L, Lowell BB, Uchida N (2012) Neuron-type-specific signals for reward and punishment in the ventral tegmental area. *Nature* 482:85–88. [PubMed: 22258508]
- Cragg SJ, Baufreton J, Xue Y, Bolam JP, Bevan MD (2004) Synaptic release of dopamine in the subthalamic nucleus. *Eur J Neurosci* 20:1788–1802. [PubMed: 15380000]
- Dalley JW, Lääne K, Theobald DEH, Armstrong HC, Corlett PR, Chudasama Y, Robbins TW (2005) Time-limited modulation of appetitive Pavlovian memory by D1 and NMDA receptors in the nucleus accumbens. *Proc Natl Acad Sci U S A* 102:6189–6194. [PubMed: 15833811]
- Darvas M, Fadok JP, Palmiter RD (2011) Requirement of dopamine signaling in the amygdala and striatum for learning and maintenance of a conditioned avoidance response. *Learn Mem* 18:136–143. [PubMed: 21325435]
- Day JJ, Roitman MF, Wightman RM, Carelli RM (2007) Associative learning mediates dynamic shifts in dopamine signaling in the nucleus accumbens. *Nat Neurosci* 10:1020–1028. [PubMed: 17603481]
- Dayan P (2012) Instrumental vigour in punishment and reward. *Eur J Neurosci* 35:1152–1168. [PubMed: 22487044]
- Dayan P, Huys QJM (2008) Serotonin, Inhibition, and Negative Mood. *PLoS Comput Biol* 4:e4. [PubMed: 18248087]
- Dayan P, Niv Y, Seymour B, Daw N D (2006) The misbehavior of value and the discipline of the will. *Neural Networks* 19:1153–1160. [PubMed: 16938432]
- Dias-Ferreira E, Sousa JC, Melo I, Morgado P, Mesquita AR, Cerqueira JJ, Costa RM, Sousa N (2009) Chronic stress causes frontostriatal reorganization and affects decision-making. *Science* (80-) 325:621–625.
- Dombrowski PA, Maia TV, Boschen SL, Bortolanza M, Wendler E, Schwarting RKW, Brandão ML, Winn P, Blaha CD, Da Cunha C (2013) Evidence that conditioned avoidance responses are reinforced by positive prediction errors signaled by tonic striatal dopamine. *Behav Brain Res* 241:112–119. [PubMed: 22771418]
- Everitt BJ, Robbins TW (2005) Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci* 8:1481–1489. [PubMed: 16251991]
- Eyny YS, Horvitz JC (2003) Opposing Roles of D 1 and D 2 Receptors in Appetitive Conditioning.
- Fadok JP, Dickerson TMK, Palmiter RD (2009) Dopamine is necessary for cue-dependent fear conditioning. *J Neurosci* 29:11089–11097. [PubMed: 19741115]

- Faure A, Reynolds SM, Richard JM, Berridge KC (2008) Mesolimbic dopamine in desire and dread: enabling motivation to be generated by localized glutamate disruptions in nucleus accumbens. *J Neurosci* 28:7184–7192. [PubMed: 18614688]
- Fibiger HC, Phillips AG, Zis AP (1974) Deficits in instrumental responding after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection. *Pharmacol Biochem Behav* 2:87–96. [PubMed: 4151316]
- Fibiger HC, Zis AP, Phillips AG (1975) Haloperidol-induced disruption of conditioned avoidance responding: attenuation by prior training or by anticholinergic drugs. *Eur J Pharmacol* 30:309–314. [PubMed: 1126366]
- Gentry RN, Lee B, Roesch MR (2016) Phasic dopamine release in the rat nucleus accumbens predicts approach and avoidance performance. *Nat Commun* 7:13154. [PubMed: 27786172]
- Gentry RN, Roesch MR (2018) Neural Activity in Ventral Medial Prefrontal Cortex Is Modulated More Before Approach Than Avoidance During Reinforced and Extinction Trial Blocks. *J Neurosci* 38:4584–4597. [PubMed: 29661965]
- Haber SN, Knutson B (2010) The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* 35:4–26. [PubMed: 19812543]
- Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, Kennedy RT, Aragona BJ, Berke JD (2016) Mesolimbic dopamine signals the value of work. *Nat Neurosci* 19:117–126. [PubMed: 26595651]
- Hayden BY, Heilbronner SR, Pearson JM, Platt ML (2011) Surprise signals in anterior cingulate cortex: neuronal encoding of unsigned reward prediction errors driving adjustment in behavior. *J Neurosci* 31:4178–4187. [PubMed: 21411658]
- Hurley SW, West EA, Carelli RM (2017) Opposing roles of rapid dopamine signaling across the rostral–caudal axis of the nucleus accumbens shell in drug-induced negative affect. *Biol Psychiatry* 82:839–846. [PubMed: 28624112]
- Holland JG, Skinner BF (1961) *The analysis of behavior: A program for self-instruction*. New York, NY: McGraw-Hill.
- Holtzman-Assif O, Laurent V, Westbrook RF (2010) Blockade of dopamine activity in the nucleus accumbens impairs learning extinction of conditioned fear. *Learn Mem* 17:71–75. [PubMed: 20154351]
- Ikegami M, Uemura T, Kishioka A, Sakimura K, Mishina M (2014) Striatal dopamine D1 receptor is essential for contextual fear conditioning. *Sci Rep* 4:3976. [PubMed: 24496082]
- Ikemoto S (2007) Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens–olfactory tubercle complex. *Brain Res Rev* 56:27–78. [PubMed: 17574681]
- Inoue T, Izumi T, Maki Y, Muraki I, Koyama T (2000) Effect of the dopamine D(1/5) antagonist SCH 23390 on the acquisition of conditioned fear. *Pharmacol Biochem Behav* 66:573–578. [PubMed: 10899372]
- Jean-Richard-Dit-Bressel P, Killcross S, McNally GP (2018) Behavioral and neurobiological mechanisms of punishment: implications for psychiatric disorders. *Neuropsychopharmacology* 43:1639–1650. [PubMed: 29703994]
- Ji G, Neugebauer V (2012) Modulation of medial prefrontal cortical activity using in vivo recordings and optogenetics. *Mol Brain* 5:36. [PubMed: 23044043]
- Kalenscher T, van Wingerden M (2011) Why We Should Use Animals to Study Economic Decision Making – A Perspective. *Front Neurosci* 5:82. [PubMed: 21731558]
- Kamin LJ, Brimer CJ, Black AH (1963) Conditioned suppression as a monitor of fear of the CS in the course of avoidance training. *J Comp Physiol Psychol* 56:497–501. [PubMed: 13962088]
- Kapur S (2003) Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry* 160:13–23. [PubMed: 12505794]
- Kim CK, Ye L, Jennings JH, Pichamoorthy N, Tang DD, Yoo ACW, Ramakrishnan C, Deisseroth K (2017) Molecular and Circuit-Dynamical Identification of Top-Down Neural Mechanisms for Restraint of Reward Seeking. *Cell* 170:1013–1027.e14. [PubMed: 28823561]

- Kishioka A, Fukushima F, Ito T, Kataoka H, Mori H, Ikeda T, Itohara S, Sakimura K, Mishina M (2009) A novel form of memory for auditory fear conditioning at a low-intensity unconditioned stimulus. *PLoS One* 4.
- Kravitz AV, Freeze BS, Parker PRL, Kay K, Thwin MT, Deisseroth K, Kreitzer AC (2010) Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. *Nature* 466:622–626. [PubMed: 20613723]
- Lavoie B, Smith Y, Parent A (1989) Dopaminergic innervation of the basal ganglia in the squirrel monkey as revealed by tyrosine hydroxylase immunohistochemistry. *J Comp Neurol* 289:36–52. [PubMed: 2572613]
- Leathers ML, Olson CR (2012) In monkeys making value-based decisions, LIP neurons encode cue salience and not action value. *Science* 338:132–135. [PubMed: 23042897]
- LeDoux JE, Moscarello J, Sears R, Campese V (2017) The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm. *Mol Psychiatry* 22:24–36. [PubMed: 27752080]
- Lichtenberg NT, Pennington ZT, Holley SM, Greenfield VY, Cepeda C, Levine MS, Wassum KM (2017) Basolateral amygdala to orbitofrontal cortex projections enable cue-triggered reward expectations. *J Neurosci* 37:0486–17.
- Lidow MS, Wang F, Cao Y, Goldman-Rakic PS (1998) Layer V neurons bear the majority of mRNAs encoding the five distinct dopamine receptor subtypes in the primate prefrontal cortex. *Synapse* 28:10–20. [PubMed: 9414013]
- Lloyd K, Dayan P (2016) Safety out of control: dopamine and defence. *Behav Brain Funct* 12:15. [PubMed: 27216176]
- Lloyd K, Dayan P (2018) Pavlovian-instrumental interactions in active avoidance: Do neutral trials bark? This issue of *Brain Res*.
- Maia TV (2010) Two-factor theory, the actor--critic model, and conditioned avoidance. *Learn Behav* 38:50–67. [PubMed: 20065349]
- Matsumoto M, Hikosaka O (2009) How do dopamine neurons represent positive and negative motivational events? *Nature* 459:837–841. [PubMed: 19448610]
- Matsumoto H, Tian J, Uchida N, Watabe-Uchida M (2016) Midbrain dopamine neurons signal aversion in a reward-context-dependent manner. *Elife* 5:e17328. [PubMed: 27760002]
- McCullough LD, Sokolowski JD, Salamone JD (1993) A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. *Neuroscience* 52:919–925. [PubMed: 8450978]
- McDonald AJ (1998) Cortical pathways to the mammalian amygdala. *Prog Neurobiol* 55:257–332. [PubMed: 9643556]
- Menegas W, Babayan BM, Uchida N, Watabe-Uchida M (2017) Opposite initialization to novel cues in dopamine signaling in ventral and posterior striatum in mice. *Elife* 6:e21886. [PubMed: 28054919]
- McDonald AJ, Mascagni F, Guo L (1996) Projections of the medial and lateral prefrontal cortices to the amygdala: a Phaseolus vulgaris leucoagglutinin study in the rat. *Neuroscience* 71:55–75. [PubMed: 8834392]
- Milad MR, Wright CI, Orr SP, Pitman RK, Quirk GJ, Rauch SL (2007) Recall of Fear Extinction in Humans Activates the Ventromedial Prefrontal Cortex and Hippocampus in Concert. *Biol Psychiatry* 62:446–454. [PubMed: 17217927]
- Mohebi A, Pettibone J, Hamid A, Wong JM, Kennedy R, Berke J (2018) Forebrain dopamine value signals arise independently from midbrain dopamine cell firing. *bioRxiv*, 334060.
- Monfils MH, Cowansage KK, Klann E, LeDoux JE (2009) Extinction-reconsolidation boundaries: key to persistent attenuation of fear memories. *Science* 324:951–955. [PubMed: 19342552]
- Mowrer OH, Lamoreaux RR (1946) Fear as an intervening variable in avoidance conditioning. *J Comp Psychol* 39:29–50. [PubMed: 21018303]
- Mueller D, Bravo-Rivera C, Quirk GJ (2010) Infralimbic D2 receptors are necessary for fear extinction and extinction-related tone responses.
- O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ (2004) Dissociable Roles of Ventral and Dorsal Striatum in Instrumental Conditioning. *Science* (80-) 304:452–454.

- Oleson EB, Cheer JF (2013) On the role of subsecond dopamine release in conditioned avoidance. *Front Neurosci* 7:1–9. [PubMed: 23386807]
- Oleson EB, Gentry RN, Chioma VC, Cheer JF (2012) Subsecond Dopamine Release in the Nucleus Accumbens Predicts Conditioned Punishment and Its Successful Avoidance. *J Neurosci* 32:14804–14808. [PubMed: 23077064]
- Öngür D, Ferry AT, Price JL (2003) Architectonic subdivision of the human orbital and medial prefrontal cortex. *J Comp Neurol* 460:425–449. [PubMed: 12692859]
- Orsini CA, Heshmati SC, Garman TS, Wall SC, Bizon JL, Setlow B (2018) Contributions of medial prefrontal cortex to decision making involving risk of punishment. *Neuropharmacology* 139:205–216. [PubMed: 30009836]
- Padoa-Schioppa C, Assad JA (2006) Neurons in the orbitofrontal cortex encode economic value. *Nature* 441:223–226. [PubMed: 16633341]
- Parker NF, Cameron CM, Taliaferro JP, Lee J, Choi JY, Davidson TJ, Daw ND, Witten IB (2016) Reward and choice encoding in terminals of midbrain dopamine neurons depends on striatal target. *Nat Neurosci* 19:845–854. [PubMed: 27110917]
- Parkinson JA, Olmstead MC, Burns LH, Robbins TW, Everitt BJ (1999) Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by D-amphetamine. *J Neurosci* 19:2401–2411. [PubMed: 10066290]
- Paxinos G, Watson C (2007) *The Rat Brain in Stereotaxic Coordinates*, 6th ed Burlington, MA: Elsevier Inc.
- Peters J, Pattij T, De Vries TJ (2013) Targeting cocaine versus heroin memories: divergent roles within ventromedial prefrontal cortex. *Trends Pharmacol Sci* 34:689–695. [PubMed: 24182624]
- Pereira DB, Schmitz Y, Mészáros J, Merchant P, Hu G, Li S, Henke A, Lizardi-Ortiz JE, Karpowicz RJ, Morgenstern TJ, Sonders MS, Kanter E, Rodriguez PC, Moharov EV, Sames D, Sulzer D (2016) Fluorescent false neurotransmitter reveals functionally silent dopamine vesicle clusters in the striatum. *Nat Neurosci* 19:578–586. [PubMed: 26900925]
- Pickens CL, Saddoris MP, Setlow B, Gallagher M, Holland PC, Schoenbaum G (2003) Different roles for orbitofrontal cortex and basolateral amygdala in a reinforcer devaluation task. *J Neurosci* 23:11078–11084. [PubMed: 14657165]
- Pultorak KJ, Schelp SA, Isaacs DP, Krzystyniak G, Oleson EB (2018) A Transient Dopamine Signal Represents Avoidance Value and Causally Influences the Demand to Avoid. *eneuro:ENEURO*. 0058–18.2018.
- Rescorla RA, Solomon RL (1967) Two-process learning theory: relationships between Pavlovian conditioning and instrumental training. *Psychol Rev*:151–183. [PubMed: 5342881]
- Roesch MR, Calu DJ, Esber GR, Schoenbaum G (2010) Neural Correlates of Variations in Event Processing during Learning in Basolateral Amygdala. *J Neurosci* 30:2464–2471. [PubMed: 20164330]
- Roesch MR, Olson CR (2004) Neuronal activity related to reward value and motivation in primate frontal cortex. *Science* 304:307–310. [PubMed: 15073380]
- Roitman MF, Wheeler RA, Wightman RM, Carelli RM (2008) Real-time chemical responses in the nucleus accumbens differentiate rewarding and aversive stimuli. *Nat Neurosci* 11:1376–1377. [PubMed: 18978779]
- Saddoris MP, Cacciapaglia F, Wightman RM, Carelli RM (2015) Differential dopamine release dynamics in the nucleus accumbens core and shell reveal complementary signals for error prediction and incentive motivation. *J Neurosci* 35:11572–11582. [PubMed: 26290234]
- Saddoris MP, Gallagher M, Schoenbaum G (2005) Rapid Associative Encoding in Basolateral Amygdala Depends on Connections with Orbitofrontal Cortex. *Neuron* 46:321–331. [PubMed: 15848809]
- Schoenbaum G, Setlow B, Saddoris MP, Gallagher M (2003) Encoding predicted outcome and acquired value in orbitofrontal cortex during cue sampling depends upon input from basolateral amygdala. *Neuron* 39:855–867. [PubMed: 12948451]
- Schultz W (2000) Multiple reward signals in the brain. *Nat Rev Neurosci* 1:199–207. [PubMed: 11257908]

- Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. *Science* 275:1593–1599. [PubMed: 9054347]
- Schultz W, Sakamoto M, Usui S, Noll DC, Fiez JA (1998) Predictive reward signal of dopamine neurons. *J Neurophysiol* 80:1–27. [PubMed: 9658025]
- Schwabe L, Wolf OT (2009) Stress prompts habit behavior in humans. *J Neurosci* 29:7191–7198. [PubMed: 19494141]
- Schwabe L, Wolf OT (2011) Stress-induced modulation of instrumental behavior: From goal-directed to habitual control of action. *Behav Brain Res* 219:321–328. [PubMed: 21219935]
- Seymour B, Singer T, Dolan R (2007) The neurobiology of punishment. *Nat Rev Neurosci* 8:300–311. [PubMed: 17375042]
- Shabel SJ, Janak PH (2009) Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *Proc Natl Acad Sci U S A* 106:15031–15036. [PubMed: 19706473]
- Sidman M (2006) The distinction between positive and negative reinforcement: some additional considerations. *Behav Anal* 29:135–139. [PubMed: 22478460]
- Skinner BF (Burroughs F) (1953) *Science and human behavior*. Simon and Schuster.
- Smith AJ, Becker S, Kapur S (2005) A computational model of the functional role of the ventral-striatal D2 receptor in the expression of previously acquired behaviors. *Neural Comput* 17:361–395. [PubMed: 15720772]
- Soares JM, Sampaio A, Ferreira LM, Santos NC, Marques F, Palha J, Cerqueira JJ, Sousa N (2012) Stress-induced changes in human decision-making are reversible. *Transl Psychiatry* 2:e131. [PubMed: 22760555]
- Solomon RL, Kamin LJ, Wynne LC (1953) Traumatic avoidance learning: the outcomes of several extinction procedures with dogs. *J Abnorm Soc Psychol* 48:291–302.
- Stefani MR, Moghaddam B (2006) Rule learning and reward contingency are associated with dissociable patterns of dopamine activation in the rat prefrontal cortex, nucleus accumbens, and dorsal striatum. *J Neurosci* 26:8810–8818. [PubMed: 16928870]
- Swanson LW (1982) The projections of the ventral tegmental area and adjacent regions: A combined fluorescent retrograde tracer and immunofluorescence study in the rat. *Brain Res Bull* 9:321–353. [PubMed: 6816390]
- Takahashi YK, Stalnaker TA, Roesch MR, Schoenbaum G (2017) Effects of inference on dopaminergic prediction errors depend on orbitofrontal processing. *Behav Neurosci* 131:127–134. [PubMed: 28301188]
- Taylor SB, Anglin JM, Paode PR, Riggert a. G, Olive MF, Conrad CD (2014) Chronic stress may facilitate the recruitment of habit- and addiction-related neurocircuits through neuronal restructuring of the striatum. *Neuroscience* 280:231–242. [PubMed: 25242641]
- Tian J, Uchida N (2015) Habenula lesions reveal that multiple mechanisms underlie dopamine prediction errors. *Neuron* 87:1304–1316. [PubMed: 26365765]
- Tye KM, Cone JJ, Schairer WW, Janak PH (2010) Amygdala Neural Encoding of the Absence of Reward during Extinction. *J Neurosci* 30:116–125. [PubMed: 20053894]
- Ungless MA, Grace AA (2012) Are you or aren't you? Challenges associated with physiologically identifying dopamine neurons. *Trends Neurosci* 35:422–430. [PubMed: 22459161]
- Ungless MA, Magill PJ, Bolam JP (2004) Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 303:2040–2042. [PubMed: 15044807]
- Vertes RP (2004) Differential Projections of the Infralimbic and Prelimbic Cortex in the Rat. *Synapse* 51:32–58. [PubMed: 14579424]
- Vincent SL, Khan Y, Benes FM (1993) Cellular distribution of dopamine D1 and D2 receptors in rat medial prefrontal cortex. *J Neurosci* 13:2551–2564. [PubMed: 8501521]
- Volman SF, Lammel S, Margolis EB, Kim Y, Richard JM, Roitman MF, Lobo MK (2013) New insights into the specificity and plasticity of reward and aversion encoding in the mesolimbic system. *J Neurosci* 33:17569–17576. [PubMed: 24198347]

- Wadenberg ML, Ericson E, Magnusson O, Ahlenius S (1990) Suppression of conditioned avoidance behavior by the local application of (-)-sulpiride into the ventral, but not the dorsal, striatum of the rat. *Biol Psychiatry* 28:297–307. [PubMed: 2144458]
- Wadenberg ML, Hicks PB (1999) The conditioned avoidance response test re-evaluated: is it a sensitive test for the detection of potentially atypical antipsychotics? *Neurosci Biobehav Rev* 23:851–862. [PubMed: 10541060]
- Wassum KM (2018) Clarifying punishment. *Neuropsychopharmacology* 43:1633–1634. [PubMed: 29728646]
- Wenzel JM, Oleson EB, Gove WN, Patel S, Lupica CR, Cheer Correspondence JF, Cole AB, Gyawali U, Dantrassy HM, Bluett RJ, Dryanovski DI, Stuber GD, Deisseroth K, Mathur BN, Cheer JF (2018) Phasic Dopamine Signals in the Nucleus Accumbens that Cause Active Avoidance Require Endocannabinoid Mobilization in the Midbrain.
- Wenzel JM, Rauscher NA, Cheer JF, Oleson EB (2015) A role for phasic dopamine release within the nucleus accumbens in encoding aversion: A review of the neurochemical literature. *ACS Chem Neurosci* 6:16–26. [PubMed: 25491156]
- Wickens JR, Budd CS, Hyland BI, Arbuthnott GW (2007) Striatal contributions to reward and decision making. *Ann N Y Acad Sci* 1104:192–212. [PubMed: 17416920]
- Wilkinson LSS, Humby T, Killcross ASS, Torres EMM, Everitt BJ, Robbins TWW (1998) Dissociations in dopamine release in medial prefrontal cortex and ventral striatum during the acquisition and extinction of classical aversive conditioning in the rat. *Eur J Neurosci* 10:1019–1026. [PubMed: 9753169]
- Young AM, Joseph MH, Gray JA (1993) Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience* 54:5–9. [PubMed: 8515846]
- Zis AP, Fibiger HC, Phillips AG (1974) Reversal by L-dopa of impaired learning due to destruction of the dopaminergic nigro-neostriatal projection. *Science* 185:960–962. [PubMed: 4471715]

Figure 1.

Task design and population behavioral results. **A-C**, Sessions consisted of 3 trial types: reward (**a**), neutral (**b**), and shock (**c**), which could be identified by their unique auditory cue. At the beginning of each trial, rats were presented with a light cue and trial-specific sound cue 5s before lever extension and then had a maximum of 10s to press the lever before it was retracted. If rats pressed the lever, they could receive a sucrose pellet reward, avoid an impending foot shock (0.42 mV), or experience no consequence, depending on the identity of the sound cue. If rats failed to press the lever within 10s after its extension into the chamber, they would alternatively receive no sucrose reward, receive continuous foot shock (0.42 mV), or experience no consequence depending on the identity of the sound cue. Once shock commenced, it could be terminated by lever press. After each consequence, the trial progressed into a 20s ITI. Trial types were pseudo-randomly interleaved within each session (~60 min) and sound cue identity was counterbalanced across rats. (**D**) Dopamine release (nM) across time for reward (blue), neutral (yellow), and shock (red) trials. Dopamine release is baseline (5s before light onset to light onset) subtracted. (**E-F**) Correlation between shock and reward trials normalized over neutral trials (shock minus neutral; reward minus neutral) for both cue epoch (5 s after cue onset) and lever epoch (1 s after lever extension). Adapted from Gentry et al, 2016.

Figure 2.

Circuit diagram demonstrating connectivity between brain regions involved in reward-guided decision-making. Arrows represent direction of information flow where single headed arrows are unidirectional and double headed arrows are reciprocal. Words in shaded box specify functions and shading of box provides a general idea of the role that nearby anatomical labels play in the strength of these functions. Orbitofrontal Cortex – OFC, Dorsal Lateral Prefrontal Cortex – PFC, Basolateral Amygdala – ABL, Anterior Cingulate Cortex – ACC, Parietal Cortex – Parietal, Premotor Cortex – PM, Nucleus Accumbens – NA, Dorsal Medial Striatum – DMS, Dorsal Lateral Striatum – DLS, Ventral Tegmental Area – VTA, Dopamine – DA, Substantia Nigra compacta – SNc, GP – Globus Pallidus, Thalamus – Thal, Substantia Nigra reticulata – SNr, Prediction error – PE. Adapted from Bissonette et al 2014 and Burton et al 2014.

Figure 3:

vmPFC neurons were strongly and weakly modulated during reward and shock cues, respectively, and very few were modulated by both reward and shock cues. **A**, Location of recording sites based on histology (Paxinos and Watson 2007; PL: prelimbic cortex, IL: infralimbic cortex, DP: dorsopeduncular region). Each symbol represents the location of neurons that showed differential firing (Wilcoxon; $p < 0.05$) in the analyses described in the text (See Results) and shown in the table in B. Dark blue = Reward > Neutral; Light blue = Neutral > Reward; Dark red = Shock > Neutral; Light red = Neutral > Shock; '-' = decreasing-cells; '+' = increasing cells. **B**, Bar graph quantifying numbers and percentages of cells that were Reward > Neutral, Neutral > Reward, Shock > Neutral, Neutral > Reward, or none of the above. Adapted from Gentry et al, 2018.