Reward and Aversion

Hailan Hu[1,2]

[1]Interdisciplinary Institute of Neuroscience and Technology, Qiushi Academy for Advanced Studies, Zhejiang University, Hangzhou 310012, People's Republic of China; email: huhailan@zju.edu.cn

[2]Center for Neuroscience, School of Medicine, Zhejiang University, Hangzhou 310058, People's Republic of China

Annu. Rev. Neurosci. 2016. 39:297–324

First published online as a Review in Advance on April 21, 2016

The *Annual Review of Neuroscience* is online at neuro.annualreviews.org

This article's doi: 10.1146/annurev-neuro-070815-014106

Keywords

reward, aversion, dopamine, serotonin, VTA, NAc

Abstract

To benefit from opportunities and cope with challenges in the environment, animals must adapt their behavior to acquire rewards and to avoid punishments. Maladaptive changes in the neuromodulatory systems and neural circuits for reward and aversion can lead to manifestation of several prominent psychiatric disorders including addiction and depression. Recent progress is pushing the boundaries of knowledge on two major fronts in research on reward and aversion: First, new layers of complexity have been reported on the functions of dopamine (DA) and serotonin (5-HT) neuromodulatory systems in reward and aversion. Second, specific circuit components in the neural pathways that encode reward and aversion have begun to be identified. This review aims to outline historic perspectives and new insights into the functions of DA and 5-HT systems in coding the distinct components of rewards. It also highlights recent advances in neural circuit studies enabled by new technologies, such as cell-type-specific electrophysiology and tracing, and optogenetics-based behavioral manipulation. This knowledge may provide guidance for developing novel treatment strategies for neuropsychiatric diseases related to the malfunction of the reward system.

Contents

INTRODUCTION

> Now it is a universal law of human nature that nobody rejects what he judges to be good except through hope of a greater good or fear of greater loss, and that no one endures any evil except to avoid a greater evil or to gain a greater good. That is to say, everyone will choose of two goods that which he judges the greater, and of two evils that which seems to him the lesser.
>
> Benedictus de Spinoza

As elaborated by Benedictus de Spinoza in his *Tractatus Theologico-Politicus*, the pursuit of reward and the avoidance of punishment are two fundamental forces that drive human behavior. Philosophical matters aside, for any individual or species to survive and thrive, behaviors facilitating the acquisition of food, sex, and other natural rewards, as well as behaviors for avoiding predators and discomfort, must be selected through evolution. There is therefore an obvious biological need for the nervous system to create structures and mechanisms for adaptive behavior on the basis of reward and aversion.

Reward induces pleasurable feelings and generates approach and consummatory behaviors, eventually leading to behavioral reinforcement (Schultz 2010); reciprocally, aversive stimuli (or punishment) engage negative emotions, including dislike, disgust, and fear; cause avoidance; and reduce the likelihood of an associated behavior being expressed. The prospect of obtaining reward or avoiding punishment essentially drives decision making and motivates learning. Dysfunctions

in the brain's reward system contribute to prominent psychiatric disorders, including addiction and depression.

Since the seminal discovery made by Olds & Milner (1954) that electrical stimulation of certain brain areas causes approach behavior, positive reinforcement, and pleasure in rats, two essential questions have arisen: Which brain sites produce the rewarding effects? Which drugs block them? Attempts to address these questions have provided initial clues regarding the characteristics of neuromodulatory systems and neural circuits involved in reward (Wise 2004).

Enormous advances have since been made in understanding the neural mechanisms underlying reward and aversion. It is now understood that reward is not a unitary process but contains several psychological components: liking (pleasure, hedonic reaction to reward), wanting (desire, motivational process of incentive salience), and learning (Berridge & Kringelbach 2015). Dopamine (DA) was once considered almost synonymous with reward, but investigation of exactly which of the above components DA signals has just started. Furthermore, the field has begun to appreciate the huge degree of heterogeneity in the reward system in terms of functionality, cell composition, transmitter type, and neural connectivity. DA neurons are much more diverse than originally thought, transmitting not only positive reward but also aversive or alerting signals (Bromberg-Martin et al. 2010c). An emerging theme is that connectivity patterns play an essential role in determining these different functionalities (Lammel et al. 2014). Moreover, other neurotransmitter systems have also been brought under the spotlight. The serotonin (5-hydroxytryptamine; 5-HT) system, for example, was recently revealed to play a surprising role in the processing of reward and aversion (Luo et al. 2015). In addition, the discovery of the corelease of different neurotransmitters from the DA and 5-HT neurons brought up new possibilities of how different transmitter systems may cooperate to control reward behavior. Here, I review some important findings related to neuromodulatory systems and the neural circuits involved in the coding and processing of reward and aversion, with an emphasis on recent advances made with new technologies, including cell-type-specific electrophysiology and tracing, and optogenetics-based causality experiments. A better understanding of the neural mechanisms underlying reward and aversion may give new insights into the development of therapies for neuropsychiatric diseases, such as addiction and depression.

NEUROMODULATORY SYSTEMS IN REWARD AND AVERSION. I: THE DOPAMINERGIC SYSTEM

The first candidate neuromodulator implicated in reward was norepinephrine (NE) because drugs promoting NE release potentiated intracranial self-stimulation (ICSS) (see the sidebar titled Methods to Systematically Investigate the Neural Circuits of Reward and Aversion: I), whereas drugs depleting brain noradrenaline and those blocking noradrenergic receptors attenuated it (Olds & Travis 1960, Stein 1962). These observations prompted the hypothesis that the NE pathway may mediate reward function (Stein 1968). However, a more careful examination of the behavioral effects of NE drugs revealed that NE impaired performance capacity, e.g., by making animals sleepy (Roll 1970), rather than affecting the rewarding function itself.

Around the same period, evidence began to mount that DA is critical for processing reward information and learning approach behavior. The cell bodies of DA neurons are mainly located in several midbrain nuclei, including the substantia nigra pars compacta (SNc) and the ventral tegmental area (VTA). Anatomical mapping of ICSS sites shows that the boundaries of effective stimulation zones correspond best to the boundaries of these DA areas (Corbett & Wise 1980). DA receptor blockade and dopaminergic lesions reduce the rewarding impact of ICSS and attenuate the rewarding effects of drugs, including cocaine and amphetamine (Fouriezos & Wise 1976,

METHODS TO SYSTEMATICALLY INVESTIGATE THE NEURAL CIRCUITS OF REWARD AND AVERSION: I

The intracranial self-stimulation (ICSS) model is the most common classical method for studying brain stimulation reward (Olds & Milner 1954, Wise 1996) and can be applied either electrically or chemically (Ikemoto & Wise 2004). More than 50 brain sites with reinforcing properties, often reflected by an increase in bar pressing after self-stimulation, have been identified using this method. Many of these sites have also been classified as rewarding, a property commonly measured by conditioned place preference (CPP). The strongest effect has been found at the lateral hypothalamus, the medial forebrain bundle containing the most ascending dopaminergic pathways from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), the septal nuclei, and raphe. A potential problem of using electrodes for ICSS is that this results in the stimulation of both cell bodies and fibers of passage. The location of the source of brain activation therefore cannot be precisely determined, a problem that can now be overcome by optogenetic techniques combined with cell-type-specific promoters (Britt & Bonci 2013).

Positron emission tomography and fMRI neuroimaging are powerful empirical methods used mostly in human research to identify brain sites that respond to diverse reward categories (food, sex, addictive drugs, music, and art) and aversive stimuli (money loss, mild shock, and unpleasant odor or taste). Studies employing these brain imaging methods have revealed an overlapping brain reward network, composed of the NAc, ventral pallidum (VP), amygdala, and prefrontal cortical areas including the orbital frontal cortex (OFC), the insular cortex, and the anterior cingulate cortex (ACC) (Kringelbach & Berridge 2009). A challenge in these studies is to dissociate reward values from salience. This is often achieved by comparing the size and direction of response to appetitive, aversive, and neutral stimuli in the same task (Bissonette et al. 2014).

Wise & Rompre 1989). Furthermore, lesions to the nucleus accumbens (NAc), a major terminal field of DA neurons, disrupt cocaine self-administration (Roberts et al. 1977). However, despite the vast body of literature composed of ICSS, lesion, receptor blockade, and drug abuse studies, the consensus on the exact role of DA in reward has passed through many phases, as reflected by a multitude of expounded theories, which include the hedonia and anhedonia hypothesis, the incentive salience hypothesis, and the reward prediction error (RPE) hypothesis.

Three Major Hypotheses for Dopamine Function in Reward

The hedonia and anhedonia hypothesis of DA postulates that DA in the brain plays a critical role in the subjective pleasure associated with positive reward and that a reduction in DA results in a loss of pleasure (Wise 1978). This hypothesis has had a major impact on theories of reinforcement, motivation, and addiction, although several complications have arisen in the past two decades, opening these theories to reexamination and debate (Berridge & Kringelbach 2015, Wise 2008). Using stereotypic hedonic orofacial reactivity to taste as a readout, Berridge and colleagues found that, surprisingly, even after depleting 99% of DA neuron fibers in the NAc and neostriatum, the liking orofacial expression to sucrose as well as the disgust reaction to quinine remained intact (Berridge & Robinson 1998), although DA suppression did reduce appetitive seeking and cause aphagia, which is consistent with a lack of motivation (Wise & Raptis 1986). Parkinson's disease patients also retain normal hedonic ratings of liking a sweet taste despite extensive DA depletion (Sienkiewicz-Jarosz et al. 2013). On the basis of these observations, Berridge and coworkers (Berridge & Kringelbach 2015, Berridge & Robinson 1998) proposed that reward is not a unitary process but contains

distinct components of wanting and liking, which can be separately identified and behaviorally manipulated, and that DA mediates the wanting but not the liking component of reward.

According to this incentive salience hypothesis, the function of DA is not to mediate the pleasure of unconditioned incentives, such as food, sex, and drugs, but to convert the neural representations of conditioned stimuli into an attractive and desired incentive. Consistent with this hypothesis, DA is more strongly linked to the anticipatory, preparatory, and approach phases than to the consummatory phase of reward behavior, as reflected in the behavioral phenotypes of DA lesion and antagonism experiments (Berridge & Robinson 1998, Ikemoto & Panksepp 1999, Salamone 1996) and in the timing of DA neuron activation in relation to reward outcome (Schultz et al. 1997) (see the RPE hypothesis below).

The incentive salience hypothesis may explain how DA enables reward-seeking behavior, but it leaves unexplained how animals choose actions and optimize behavioral performance after the identification of a desirable goal (McClure et al. 2003). The RPE hypothesis of DA provides a simple and beautiful account of how DA may be involved in the learning and action selection aspect of reward behavior. It stems from one of the most influential discoveries of systems neuroscience made by Schultz and colleagues that midbrain DA neurons show highly characteristic activation to rewards associated with a variety of sensory stimuli (Schultz 1998; 2007a,b). Most notably, DA neurons show a rapid phasic firing increase only for unpredicted (in terms of occurrence, magnitude, and time) reward outcomes (positive prediction error) and suppress firing when reward is omitted (negative error) (**Figure 1*a***). The magnitude of response increases with reward size. Conversely, many DA neurons display decreased firing rates in response to aversive stimuli (**Figure 1*a***; Ungless et al. 2004). Therefore, DA neurons code the discrepancy of reward and its prediction bidirectionally, as shown in the following equation:

$$\text{Dopamine response} = \text{Reward occurred} - \text{Reward predicted}.$$

These features make DA an extremely attractive neural substrate for coding the teaching signal of learned reinforcement. The concept that a discrepancy between expectation and outcome is the major driving force of learning is at the very heart of modern learning theory. During the course of learning, the error signal can serve to modify synapses and neural circuitry, leading to changes in both predictions and behavior. These modifications are repeated until predictions match behavioral outcomes. The prediction error therefore becomes zero, and learning ceases. Through this process, DA-guided plasticity is proposed to guide animals in choosing the action that leads to an optimal reward (Schultz et al. 1997).

The RPE hypothesis has garnered considerable success owing to its strong explanatory power and is supported by extensive research data, including functional magnetic resonance imaging (fMRI) studies in humans (Chowdhury et al. 2013, D'Ardenne et al. 2008). However, in addition to the RPE signal, DA neurons can also encode more heterogeneous information.

Dopamine in Aversion and Alertness

A variety of aversive stimuli, such as a pinch, air puff, or mild electrical shock, can induce DA release in downstream brain structures as measured by microdialysis (Abercrombie et al. 1989, Doherty & Gratton 1992, Louilot et al. 1986, Young et al. 1993). Behavioral reactions to stress are also dramatically altered by DA agonists, antagonists, and lesions (Di Chiara 2002, Pezze & Feldon 2004, Salamone 1994).

Although DA neurons are excited primarily by rewarding stimuli, data suggest that some are also excited by aversive experience. Matsumoto & Hikosaka (2009b) examined the response of the

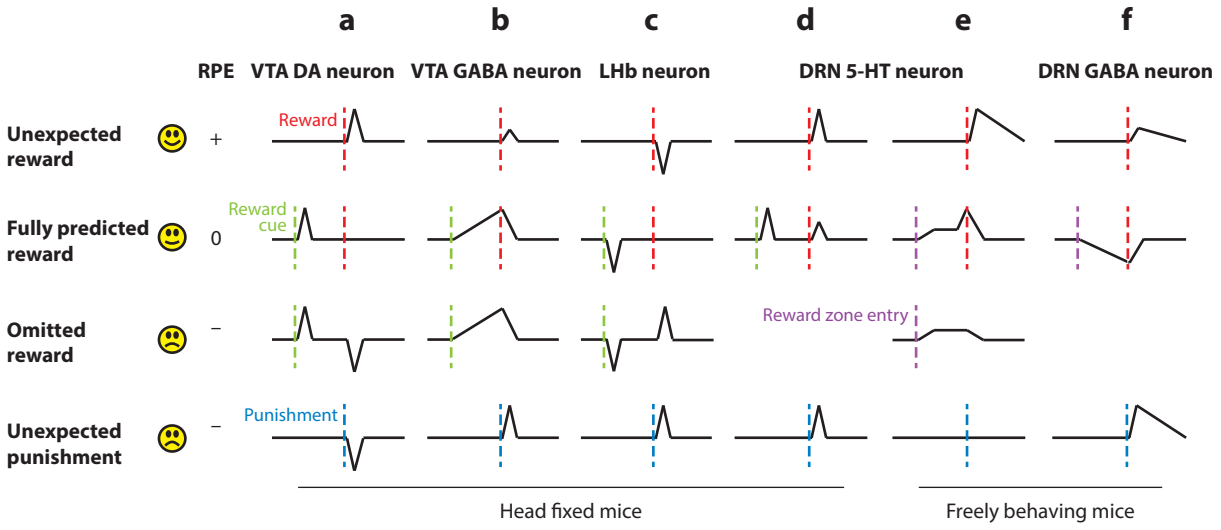

Figure 1

Characteristic response to reward and punishment by different neurons. (*a*) Ventral tegmental area (VTA) dopamine (DA) neurons encode reward prediction error (RPE) signals, showing excitatory responses only when the reward is not fully predicted (Cohen et al. 2012, Schultz 1998). (*b*) VTA GABA neurons encode reward expectation, contributing to RPE calculation by serving as a source of subtraction (Eshel et al. 2015). (*c*) Lateral habenula (LHb) neurons show mirror-inverted phasic responses to DA neurons, potentially providing a source of negative RPE signals (Matsumoto & Hikosaka 2009a). (*d*,*e*) Recordings from dorsal raphe nucleus (DRN) serotonergic (5-HT) neurons reveal diverse responses to reward and punishment, with a substantial subset showing excitatory responses to reward even when reward is predicted (Cohen et al. 2015, Li et al. 2016, Liu et al. 2014). (*f*) DRN GABA neurons are inhibited by reward seeking and activated by aversive stimuli. Green, red, and blue dashed lines indicate the timing of reward cue, reward delivery, and punishment delivery, respectively. Purple dashed lines indicate entry into a reward zone in a sucrose-foraging task. The responses of DRN 5-HT and GABA neurons to unexpected reward and punishment are derived from calcium-imaging fiber photometry experiments. All others are from single-unit electrophysiological recordings.

same set of DA neurons to both rewarding and aversive conditions in nonhuman primates and found that DA neurons can be divided into two categories: (*a*) a population excited by reward and inhibited by aversive stimuli (presumably encoding motional valence), and (*b*) another population excited by both reward and aversive events in a similar manner (presumably encoding motivational salience). Importantly, the distribution of the valence- and salience-coding DA populations appears to be segregated in space, with salience-coding neurons located more in the dorsolateral SNc and valence-coding DA neurons located more in the ventromedial SNc and lateral VTA. A similar segregation pattern has also been discovered in rodents, where DA neurons in the dorsal and ventral VTA were shown to encode valence and salience, respectively (Brischoux et al. 2009, Ungless et al. 2004).

In addition to rewarding and aversive events, the majority of DA neurons can also be activated phasically by the alerting signal, an umbrella term for any nonrewarding salient sensory stimuli that is surprising, novel, arousing, or attention-grabbing in nature (Bromberg-Martin et al. 2010c). The details of the neural circuitry that support this heterogeneous DA function are discussed in depth with the circuitry of reward described below in the section titled Ventral Tegmental Area and Substantia Nigra Pars Compacta.

Notably, the above-mentioned single-unit recordings identified putative DA neurons on their sensitivity to quinpirole (an agonist of the DA D2 autoreceptor) (Zweifel et al. 2011), electrophysiological signatures (Matsumoto & Hikosaka 2009b), or juxtacellular labeling (Brischoux et al.

2009)—which are not always accurate. The exact cell types of the aversion- or alert-coding putative DA neurons investigated in the above-mentioned studies requires further confirmation.

Recent Optogenetics-Based Electrophysiology Studies and Calculation of Reward Prediction Error

Aided by optogenetics-based cell-type tagging, Uchida and colleagues (Cohen et al. 2012, Eshel et al. 2015) precisely identified DA and GABAergic cell types recorded in the VTA while mice were engaged in classical conditioning. They show that the majority of DA neurons are phasically excited by reward and reward-predicting cues and are inhibited by aversive cues in a manner consistent with RPE coding. Furthermore, their work provides important insight into how the RPE signal is computed in the VTA. RPE is derived from the comparison of actual and expected reward. By comparing how different reward size and expectation influence DA neuron response, they found that DA neurons perform subtraction rather than division for the calculation of RPE. Interestingly, GABAergic neurons show persistent activation during the delay period between reward-predicting cues and reward delivery (**Figure 1*b***), providing a mechanism to signal reward expectation, which can be used by DA neurons to calculate RPE (Eshel et al. 2015).

In addition to VTA GABA neurons, other signal sources of reward expectation may also exist. Possible candidates include the neighboring GABAergic rostromedial tegmental nucleus (RMTg) (Jhou et al. 2009), dorsal striatum (Chuhma et al. 2011, Doya 1999, Suri 2002), the lateral hypothalamus (LHA) (Nakamura & Ono 1986), the pedunculopontine tegmental nucleus (Hong & Hikosaka 2014, Kobayashi & Okada 2007, Pan & Hyland 2005), and the orbital frontal cortex (OFC) (Takahashi et al. 2011, Tremblay & Schultz 1999). In addition to being generated locally within the VTA, the RPE signal itself can also be transmitted from brain loci outside the VTA, such as from the LHb (**Figure 1*c***) (Matsumoto & Hikosaka 2007, Tian & Uchida 2015). A more comprehensive review on computation of RPE in DA neurons can be found in Keiflin & Janak (2015).

Recent Optogenetics-Based Behavioral Studies

Recent optogenetics-based behavioral studies have extended previous work based on pharmacology, genetics, and lesions in testing the specific role of DA neurons in reward and aversion. It has been demonstrated that cell-type-specific optogenetic activation of VTA DA neurons is sufficient to drive CPP or facilitate positive reinforcement (Adamantidis et al. 2011, Tsai et al. 2009). The pattern of activation proves to be important, with only high-frequency phasic firing exhibiting effectiveness (Tsai et al. 2009). Conversely, optogenetic inhibition of VTA DA neurons causes conditioned place aversion (Tan et al. 2012). Likewise, optogenetic activation and inhibition of SNc DA neurons have the same effects as manipulating VTA DA neurons in operant place preference (Ilango et al. 2014). These results are consistent with the notion that DA neurons support the motivational drive for reward-seeking behavior. Optogenetic activation of VTA GABA neurons also causes conditioned place aversion (Tan et al. 2012) and disrupts reward consummatory behavior (van Zessen et al. 2012). Furthermore, consistent with the function in coding expected reward, as suggested by the physiology data, activation of VTA GABA neurons reduces anticipatory behavior in response to reward-predicting cues (Eshel et al. 2015).

To specifically address a causal role in signaling RPE and learning, Steinberg et al. (2013) used a classic behavioral paradigm called blocking based on the phenomenon that, if cue A already predicts an outcome, then concurrent presentation of cue A with a new cue B paired with the outcome will not establish a new association between cue B and the outcome, because there is

no prediction error, or surprise, to drive the new learning (Kamin 1968, Waelti et al. 2001). By activating the DA neurons briefly during reward outcome, Steinberg et al. (2013) were able to rescue the learning of the blocked cue B, suggesting that this brief pulse of DA release can mimic the effect of a positive RPE to cause learning.

The Issue of Corelease

Recent studies have also revealed the intriguing phenomenon that VTA DA neurons corelease glutamate (Stuber et al. 2010, Sulzer et al. 1998, Tecuapetla et al. 2010) or GABA (Tritsch et al. 2012) in downstream structures, such as the striatum and habenula. These coreleased transmitters can change membrane potentials, moving them between up and down states (Wilson & Kawaguchi 1996), or cause temporal summation of *N*-methyl-D-aspartate currents (Tecuapetla et al. 2010). Importantly, the coexistence of multiple transmitters in DA neurons indicates that manipulation of DA neurons is not equivalent to the manipulation of the DA transmitter system. In light of the intriguing recent finding that DRN neurons mediate reward mainly through glutamatergic transmission (Liu et al. 2014, McDevitt et al. 2014, Qi et al. 2014), we should not rule out the possibility that some functions previously assigned to DA through DA neuron manipulation studies may be mediated by other neurotransmitters released from DA neurons.

NEUROMODULATORY SYSTEMS IN REWARD AND AVERSION. II: THE SEROTONERGIC SYSTEM

The role of 5-HT in reward and aversion is even more elusive than that of DA. Forebrain-projecting 5-HT neurons reside mostly within the midbrain dorsal raphe nucleus (DRN) and median raphe nucleus (MRN), which also contain a number of other transmitter types including glutamate, GABA, DA, and acetylcholine (Hokfelt et al. 2000). DRN is also one of the most sensitive reward spots mapped in earlier ICSS studies (Simon et al. 1976).

For several decades, a prominent view, supported largely by data from pharmacological and lesion studies, was that 5-HT is linked to behavioral inhibition, reward suppression, and punishment through antagonizing the DA function (reviewed by Daw et al. 2002, Dayan & Huys 2008, Deakin & Graeff 1991, Tye et al. 1977). However, paradoxically, a large body of evidence points to a positive correlation between mood and 5-HT level (Perreau-Linck et al. 2007, Williams et al. 2006). For example, depression is commonly treated with selective serotonin reuptake inhibitors, which elevate synaptic levels of 5-HT (Hirschfeld 2000). Recently, an exciting new wave of results has emerged from behavioral manipulation, in vivo electrophysiological recordings and imaging studies, supporting a positive role for 5-HT in reward processing (Amo et al. 2014, Challis et al. 2013, Cohen et al. 2015, Fonseca et al. 2015, Li et al. 2016, Liu et al. 2014, Macoveanu 2014, Miyazaki et al. 2014, Schweimer & Ungless 2010, Seymour et al. 2012, Zhou et al. 2015).

Recent Optogenetics-Based Behavioral Studies

In a compelling set of experiments, Liu et al. (2014) demonstrated that optogenetic stimulation of DRN Pet-1+ neurons (consisting of 90% 5-HT neurons and 10% glutamatergic neurons) causes place preference, drives light self-stimulation, counters innate sucrose preference, and directs learning, demonstrating the strong appetitive role of DRN Pet-1 neurons. Surprisingly, analysis based on knockout mice for VGluT3 (the vesicular transporter for glutamatergic neurons in DRN) and Tph2 (tryptophan hydroxylase 2, the key enzyme for 5-HT synthesis) revealed that the rewarding effect was mediated primarily by glutamate, either released from the 10%

Pet-1+ glutamatergic neurons, or coreleased from 5-HT neurons. 5-HT displayed a minor contribution to the rewarding effect (Liu et al. 2014).

Two other optogenetic studies more specifically manipulated DRN 5-HT neurons, using more exclusive 5-HT promoters—Tph2 or SERT (serotonin transporter)—to drive ChR2 expression, and demonstrated that DRN 5-HT neuron activation promotes reward waiting (Fonseca et al. 2015, Miyazaki et al. 2011), which is consistent with a recent theory that 5-HT suppresses impulsivity and facilitates long-term optimal behaviors (Doya 2002). Intriguingly, these researchers did not find the same appetitive effects as with DRN Pet-1+ neuron activation. This discrepancy could potentially be explained by two other optogenetic studies, which found that DRN stimulation causes reinforcement primarily through non-5-HT neurons that send glutamatergic projections to the VTA (McDevitt et al. 2014) and that these DRN glutamatergic projections to the VTA can cause DA release in NAc, place preference, and instrumental reinforcement (Qi et al. 2014). Therefore, one plausible explanation consistent with most of these data is that the glutamatergic neural populations within Pet-1+ neurons are responsible for encoding rewarding and reinforcement effects, whereas 5-HT neurons are separately involved in impulse control. However, given that VGluT3 knockout animals still retain residual rewarding effects that can be abolished by 5-HT depletion, and given the potential differences in optogenetic stimulation patterns and locations of the viral injections (Luo et al. 2015), future experiments are needed to further dissect the potential roles of DRN 5-HT and glutamate neurons' functions in reward.

Recent Optogenetics-Based Electrophysiology and Fiber Photometry Studies

Early recordings of DRN activity revealed diverse response patterns to sensory cues, motor responses, and rewarding or aversive events (Bromberg-Martin et al. 2010a, Hayashi et al. 2015, Inaba et al. 2013, Kim et al. 2004, Li et al. 2013b, Miyazaki et al. 2011, Nakamura et al. 2008, Ranade & Mainen 2009, Schweimer & Ungless 2010), presumably reflecting the considerable heterogeneity in DRN neuron transmitter types and functions. Some of these studies were dependent on electrophysiological properties (wide spike shapes and low firing rates) for the identification of 5-HT neurons, which could have false hits. Three recent studies used a more precise optogenetic tagging method to identify and record DRN 5-HT neurons during a conditioned learning task (Cohen et al. 2015, Li et al. 2016, Liu et al. 2014). These studies found that unlike DA neurons, a substantial number of DRN 5-HT neurons are excited even when a reward is predicted (**Figure 1*d***). In particular, Cohen et al. (2015) found that a large fraction of 5-HT neurons change their baseline tonic activity on the basis of reward value, showing greater activity in blocks of reward than in blocks of punishment, an attractive feature that could allow 5-HT neurons to track global reward states (Niv et al. 2006, Seymour et al. 2012) and modulate mood (Savitz et al. 2009). Similar findings have also been reported for DRN neurons in nonhuman primates (Hayashi et al. 2015).

Most recently, Luo and colleagues combined fiber photometry (see the sidebar titled Methods to Systematically Investigate the Neural Circuits of Reward and Aversion: II; **Figure 2**) with single-unit recording on SERT+ DRN 5-HT neurons for the first time in freely behaving mice and demonstrated that a majority of DRN 5-HT neurons fire tonically during waiting and phasically on acquisition of a variety of rewards, including sex and social interaction, which may nicely settle recent debates on whether 5-HT neurons function before or after reward acquisition (**Figure 1*e***) (Li et al. 2016). They also reported complementary responses from DRN GABA neurons, which were activated by aversive stimuli and were inhibited during reward seeking (**Figure 1*f***).

METHODS TO SYSTEMATICALLY INVESTIGATE THE NEURAL CIRCUITS OF REWARD AND AVERSION: II

Another strategy to map the causal generator of pleasure in the rodent brain is based on localized neurochemical application: the identification of hedonic hot or cold spots that can enhance or suppress emotional response (Berridge & Kringelbach 2015). This approach has identified an affective network that includes the NAc and connected VP, as well as the limbic areas of the prefrontal cortex (PFC, including OFC and insular cortex) (**Figure 2*a***). Within the NAc, there is an affective "keyboard" pattern arranged rostrocaudally, which is linked to positive and negative valence (Berridge & Kringelbach 2015).

Admittedly, spatial resolution is an issue for most of the abovementioned methods. The size of the hedonic spots, for example, is typically one cubic millimeter in volume, still containing millions of neurons. Furthermore, many brain regions are involved in both reward and aversion [e.g., VTA, NAc, hypothalamus, and basolateral amygdala (BLA)] (see the review by Namburi et al. 2015a). To resolve whether neurons in these areas encode emotional valence or salience, investigators need to determine at the single-cell level how neurons respond to both reward and aversion. To address this issue, new molecular imaging tools are being developed that can report neural activity in response to both reward and aversion at the cellular level and in the same brain preparation. Lin et al. (2011) studied the activation patterns induced by mating and aggression, two behaviors of opposite valence, using a technique called cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) that is based on the differential subcellular localization of immediate early gene c-fos mRNA at different time points after neural activation. A recent study by Xiu et al. (2014) used tyramide-amplified immunohistochemistry–FISH (TAI-FISH), employing the differential time course of c-fos mRNA and protein expression to simultaneously visualize the neural representations of two stimuli of contrasting emotional valence, morphine and foot shock, across the limbic forebrain (**Figure 2*b***).

Furthermore, dynamic activity mapping at high resolution in freely behaving animals can be achieved now by cutting-edge calcium imaging technology that is based on a genetically encoded fluorescent Ca^{2+} indicator and that detects real-time intracellular Ca^{2+} transients, which is a proxy for certain neural activities (Akerboom et al. 2012). It can report neural activity at single-cell resolution with the help of an endoscope (Ziv et al. 2013) and activity changes in axonal fibers of a population of neurons of the same genetic identity through fiber photometry (Gunaydin et al. 2014).

Finally, powerful viral genetic methods that are based on rabies virus–mediated trans-synaptic tracing, including TRIO (tracing the relationship between input and output) and cTRIO (cell-type-specific TRIO), have been developed to map the connectivity of reward circuitry (Callaway & Luo 2015). TRIO utilizes the axonal uptake of CAV-Cre, a canine adenovirus expressing Cre recombinase that can transduce the axonal terminals from the output targets to cell bodies. By further combining a Cre-dependent Flp recombinase, cTRIO provides an even more refined cell-type- and output-specific input analyses (Callaway & Luo 2015).

KEY BRAIN REGIONS IN THE NEURAL CIRCUITS OF REWARD AND AVERSION

Below, I discuss some of the key brain areas in reward circuitry, mostly in light of recent circuit mapping data, and the function of these connections as indicated by optogenetic manipulations.

Ventral Tegmental Area and Substantia Nigra Pars Compacta

The VTA and SNc are heterogeneous structures containing DA, GABA, and glutamatergic neurons. Recent studies using rabies virus–based circuit tracing tools have permitted high-resolution,

systematic mapping of monosynaptic inputs, as well as input-output relationships of VTA neurons on the basis of the location, cell type, and axonal projections of starter cells (Beier et al. 2015, Lerner et al. 2015, Menegas et al. 2015, Watabe-Uchida et al. 2012). These mapping analyses unraveled several key characteristics of the circuit architecture of DA systems in mice as summarized below.

First, cell-type-specific mapping has allowed whole-brain-level comparison of inputs to the two major neuron types—DA and GABA neurons—in VTA/SNc, showing that VTA DA and VTA GABA neurons receive generally similar patterns of input from diverse brain regions and cell types (Beier et al. 2015). One observed difference is in the striatum: Neurons in patch compartments project to DA neurons, whereas neurons in matrix compartments project to GABA neurons (Watabe-Uchida et al. 2012). The striatal patch and matrix compartments define distinct connection pathways, receiving preferential input from the prelimbic (PL) and ACC part of the medial prefrontal cortex (mPFC), respectively, in rodents (Gerfen 1992). This segregation may therefore provide the anatomical specificity needed to compute reward output.

Second, the comparison of VTA and SNc input circuits, as well as subcircuits within the SNc, has revealed differential wiring that could potentially account for the heterogeneous functions of DA neurons in salience versus valence coding. Watabe-Uchida et al. (2012) found that VTA and SNc DA neurons receive distinct inputs from largely segregated areas: the former from the lateral hypothalamus, which may signal subjective values (Nakamura & Ono 1986), and the latter from the somatosensory/motor cortices, subthalamic nucleus, and central amygdala, which may convey salience signals. Overall, VTA inputs tend to localize in more ventral and medial areas in relation to SNc inputs. Within the SNc, there is also a highly organized subcircuit following the same medial-lateral topography. By applying fiber photometry in freely behaving mice, Lerner et al. (2015) found that, although both medial and lateral SNc populations were excited by rewards, only the lateral SNc neurons projecting to dorsolateral striatum were excited by aversive foot shocks, concordant with the spatial distribution of valence- and salience-coding neurons reported in the monkey SNc (Matsumoto & Hikosaka 2009b).

Finally, input-output analysis using recently developed TRIO and cTRIO techniques (Schwarz et al. 2015) has permitted dissection of the VTA DA circuits based on their output targets (Beier et al. 2015). Malenka and colleagues (Lammel et al. 2011, 2012) demonstrated previously that VTA DA neurons signal different reward values on the basis of their input and output circuits, delineating a pathway from the laterodorsal tegmentum → VTA-DA → NAc lateral shell (NAcLat), which primarily signals reward, and a pathway from the lateral habenula (LHb) → VTA-DA → mPFC, which signals aversion (**Figure 3**). Expanding on this, high-sensitivity cTRIO analysis uncovered several previously unidentified circuits, including a pathway from the mPFC → VTA-DA → NAcLat (Beier et al. 2015) (**Figure 3**), exemplifying a direct top-down executive control from mPFC. Furthermore, Menegas et al. (2015) reported that DA neurons projecting to various targets (with the exception of posterior striatum) share similar input sources, suggesting that this top-down control may be a more general theme for the VTA DA system.

Dorsal Raphe Nucleus and Median Raphe Nucleus

The majority of forebrain-projecting 5-HT neurons are located in the DRN and MRN, which have different pharmacological sensitivity (Judge & Gartside 2006) and connectivity patterns (Dayan & Huys 2009). Using the same strategy as for the DA system, several teams mapped whole-brain monosynaptic inputs into DRN and MRN 5-HT neurons (Ogawa et al. 2014, Pollak Dorocic et al. 2014, Weissbourd et al. 2014). Previously unknown direct inputs to 5-HT neurons from PFC, LHb, and basal ganglia circuits were identified (Pollak Dorocic et al. 2014).

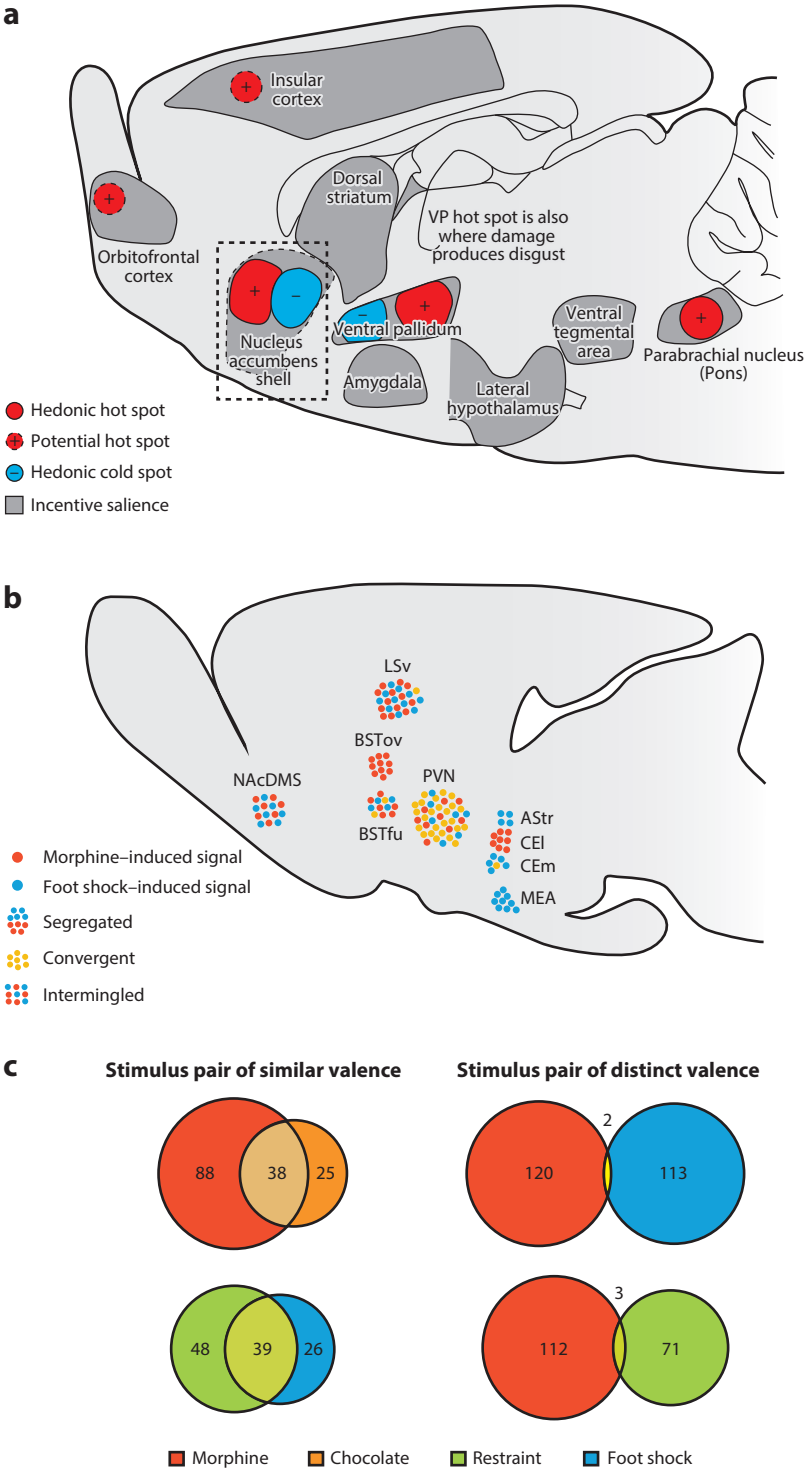

Figure 2

Whole-brain mapping of emotional valence in the rodent brain. (*a*) Hedonic hot spots or cold spots in rat brain, identified by enhancement (*red*) or suppression (*blue*) of liking taste reactivity to sucrose after localized infusion of an opioid agonist. Panel adapted with permission from Berridge & Kringelbach (2015). (*b*) The TAI-FISH technique reveals segregated (in central amygdala), convergent (in the PVN), and intermingled (in NAc and LSv) patterns of interaction between neural representations of morphine and foot shock in the limbic forebrain. (*c*) Scaled Venn diagram summarizing the interaction of multiple positive and negative emotion representations in the NAcDMS. The number of c-fos-positive neurons in response to each stimulus condition is indicated. Note that stimuli of similar emotional valences excite neuron ensembles with much larger overlaps than those of opposite valences. Panels *b* and *c* were adapted with permission from Xiu et al. (2014). Abbreviations: AStr, amygdalostriatal transition area; BSTfu, fusiform nucleus of bed nucleus of the stria terminalis; BSTov, oval nucleus of BST; CEl, lateral division of central amygdala; CEm, medial division of central amygdala; LSv, ventral lateral septum; MEA, medial amygdala; NAc, nucleus accumbens; NAcDMS, dorsomedial shell of the NAc; PVN, paraventricular nucleus of hypothalamus; TAI-FISH, tyramide-amplified immunohistochemistry fluorescence in situ hybridization.

Cell-type-specific mapping found that DRN 5-HT and GABA neurons receive inputs from generally similar sources; however, DRN-GABA neurons are more likely innervated by inputs from the central amygdala, whereas DRN 5-HT neurons receive more inputs from the anterior neocortex (Weissbourd et al. 2014).

Importantly, Ogawa et al. (2014) compared the connection patterns with those of VTA/SNc DA neurons, identified three main input streams along the medial-lateral axis, and found a remarkable similarity between inputs to the DRN and VTA, which both receive the most input from

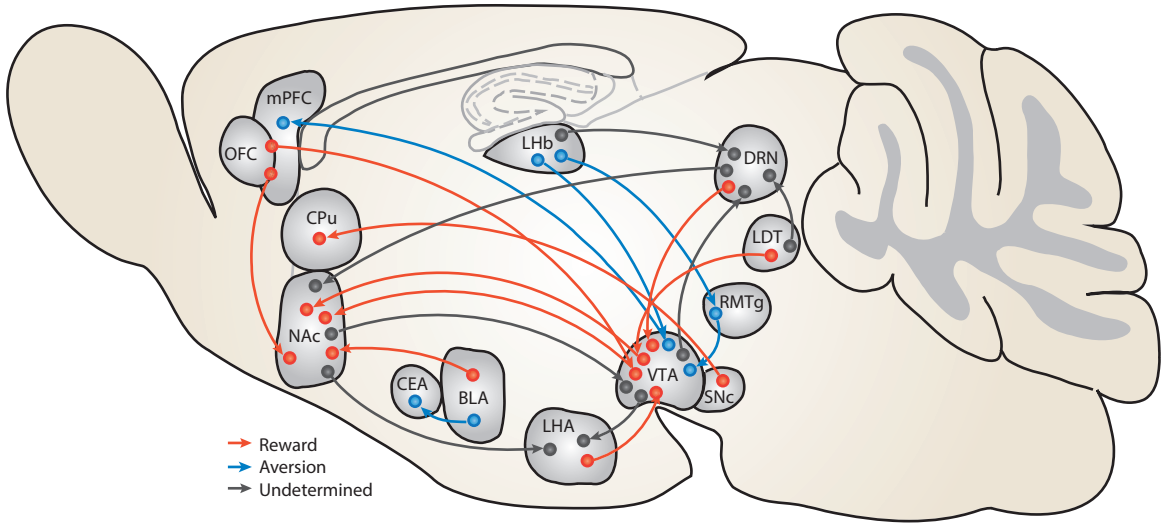

Figure 3

A simplified schematic summarizing the reward-mediating (*red*) and aversion-mediating (*blue*) neural pathways that have been verified by recent optogenetics-based behavioral studies. Prominent pathways that are implicated but unverified in reward and aversion are also delineated (*gray*) (Beier et al. 2015; Britt et al. 2012; Humphries & Prescott 2010; Kirouac et al. 2004; Lammel et al. 2012; Lerner et al. 2015; Liu et al. 2014; Luo et al. 2015; McDevitt et al. 2014; Namburi et al. 2015a,b; Nieh et al. 2015; Qi et al. 2014; Sesack & Grace 2010; Stuber & Wise 2016; Stuber et al. 2011). Abbreviations: BLA, basolateral amygdala; CEA, central amygdala; CPu, caudate putamen; DRN, dorsal raphe nucleus; LDT, laterodorsal tegmental nucleus; LHA, lateral hypothalamus; LHb, lateral habenula; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; OFC, orbitofrontal cortex; RMTg, rostromedial tegmental nucleus; SNc, substantia nigra pars compacta; VTA, ventral tegmental area.

LHA. In addition, there are also heavy reciprocal projections, either directly or indirectly, between the 5-HT and DA systems. VTA DA neurons receive a large number of inputs from DRN 5-HT neurons; DRN 5-HT neurons also receive direct inputs from VTA but mostly from its GABAergic population (Kirouac et al. 2004; Ogawa et al. 2014). Interestingly, although striatum receive inputs from both VTA DA and DRN 5-HT neurons, it sends back a lot more projections to VTA DA than to the DRN 5-HT system, suggesting a hierarchical organization (Ogawa et al. 2014). These results provide an anatomical basis for the intimate interactions between the DA and 5-HT systems.

Nucleus Accumbens

Located in the ventral striatum, NAc is a prominent downstream target of the VTA DA system and the DRN 5-HT neurons. It has been clearly implicated in reward processing and drug addiction, as well as in aversion and depression (Carlezon & Thomas 2009, Roberts & Zito 1987, Roitman et al. 2005, Russo et al. 2010, Salamone 1994). Just as in the remainder of the striatum, the principal cell types in the NAc are projecting GABAergic medium spiny neurons (MSNs), divided into two groups on the basis of the type of DA receptor expressed (D1 or D2 type) and the projection target (direct or indirect to the midbrain) (Gerfen & Surmeier 2011, but see Kupchik et al. 2015).

Partly owing to its neuroanatomical connectivity pattern, NAc has been proposed to act as a limbic-motor interface, integrating mnemonic, affective, and cognitive signals from the limbic system and turning them into action via output to the VP and other motor effector areas (Floresco 2015). Several upstream glutamatergic inputs, including the hippocampus, BLA, PFC, and thalamus, send reward-related information to NAc (Sesack & Grace 2010). DA released from VTA is thought to modulate the saliency attributed to this information by modifying the synaptic properties of these glutamatergic inputs and the excitability of NAc MSN neurons (Goto & Grace 2008, Nicola et al. 2000, Tritsch et al. 2012). As such, changes in these glutamatergic inputs may be translated to motivationally relevant motor patterns (approach or avoidance) through NAc (Britt et al. 2012, Stuber et al. 2011). GABA neurons in the VTA also project to NAc and synapse on the cholinergic interneurons. Activation of this pathway enhances associative learning (Brown et al. 2012). Another source of NAc input comes from the raphe. A recent study (Dolen et al. 2013) illustrated how 5-HT and the neural peptide oxytocin systems interact at the NAc to mediate social reward.

On the output side, both the D1- and D2-MSNs in NAc project to VP and the hypothalamus, but only D1-MSNs directly target the VTA and SNc (Humphries & Prescott 2010, Kupchik et al. 2015, Sesack & Grace 2010). D1-MSNs were also recently reported to directly synapse onto DRN 5-HT neurons (Pollak Dorocic et al. 2014). The distinct projection patterns of the two MSN types in the striatum suggest that they may antagonize each other in regulating motor planning and action selection (Kravitz et al. 2010). Indeed, this hypothesis has been supported by a series of recent optogenetic experiments. For example, selective optogenetic activation of the D1-type MSNs in the dorsal striatum promoted locomotion and induced persistent reinforcement; by contrast, activation of the D2-type MSNs suppressed locomotion and induced transient punishment (Kravitz et al. 2010, 2012). Transient optogenetic stimulation of these two MSN types also induced opposite bias in goal-directed action selection (Tai et al. 2012). When selective activation of D1- or D2-MSNs was restricted to the NAc part of the striatum, it was insufficient to elicit place preference or aversion on its own but was able to promote or suppress cocaine-induced place preference, respectively (Lobo et al. 2010).

These optogenetic and additional pharmacological manipulation studies clearly implicate NAc function in both reward and aversion, although they do not explain how rewarding and aversive

stimuli are encoded in NAc neurons. A recent study based on the TAI-FISH technique (see the sidebar titled Methods to Systematically Investigate the Neural Circuits of Reward and Aversion: II) compared activation patterns of multiple pairs of rewarding and aversive stimuli and found that morphine predominantly activated D1-MSNs in the NAc, whereas foot shock preferentially activated D2-MSNs (Xiu et al. 2014). Furthermore, stimuli of the same valence activated largely overlapping neural populations in the dorsomedial shell of the NAc, whereas stimuli of opposite valence recruited intermingled but nonoverlapping cell populations (**Figure 2*c***). These results suggest the existence of a valence map, which partially, but not completely, coincides with the mosaic distribution of D1 and D2 neurons in the NAc. Considering that D1-MSNs define the Go pathway that facilitates action and D2-MSNs define the NoGo pathway that suppresses action, the distribution of such a valence map provides an intuitive picture of how reward leads to approach behavior and how aversive stimulus causes avoidance. However, the same rule may not apply to the ventral shell of the NAc, where activation of dynorphin neurons, which largely overlap with D1-MSNs, leads to aversion (Al-Hasani et al. 2015).

The VTA-NAc circuit is the most prominent target of drugs of abuse, which are thought to hijack the brain's reward system by causing maladaptive changes in synaptic circuit properties (Koya & Hope 2011, Lüscher & Malenka 2011, Pignatelli & Bonci 2015). Addictive drugs induce DA-dependent potentiation of glutamatergic synapses in VTA DA neurons (Chen et al. 2008, Saal et al. 2003, Ungless et al. 2001) as well as in NAc MSN neurons (Bocklisch et al. 2013, Lee et al. 2013, Mameli et al. 2009) and so does addictive DA neuron self-stimulation (Pascoli et al. 2015). GABAergic synapses in the VTA-NAc circuit are also subjected to modification by addictive drugs. For example, after recurrent in vivo cocaine administration, GABAergic synapses from NAc D1-MSNs to VTA GABA neurons undergo potentiation, causing disinhibition of VTA DA neurons (Bocklisch et al. 2013). Reversal of some of these synaptic changes by optogenetic means is effective in treating drug-induced behavioral sensitization (Britt & Bonci 2013, Pascoli et al. 2012, Stefanik et al. 2013), corroborating the idea that the VTA-NAc circuit is a crucial target for the treatment of drug abuse disorders. In addition to the VTA-NAc circuit, a pathway from the paraventricular nucleus of the thalamus to NAc was recently reported to mediate negative symptoms during drug withdrawal (Zhu et al. 2016).

Abnormalities in the VTA-NAc circuit are also heavily implicated in mood disorders such as depression (Russo & Nestler 2013). Exposure to stress also induces α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) potentiation in the VTA DA synapses (Saal et al. 2003) and functional changes in NAc MSN synapses (Khibnik et al. 2015). Chronic stress can act through a hypothalamus-released neuropeptide, melanocortin, to decrease the excitatory synaptic strength of D1-MSNs in the NAc, which is critical for the specific induction of the anhedonia aspect of depression-like behavior (Lim et al. 2012). Intriguingly, optogenetically induced phasic firing of VTA DA neurons was shown to produce seemingly opposite effects on depressive-like behaviors: It was an antidepressant for mice experiencing chronic mild stress (Tye et al. 2013) and a prodepressant for mice exposed to a subthreshold social defeat paradigm (Chaudhury et al. 2013), both involving the VTA-DA → NAc circuit. Future studies are needed to resolve this contradiction. A possible explanation may be that NAc-projecting VTA DA neurons manipulated in these two studies were of different subpopulations mediating different reward valence (Ikemoto 2007, Lammel et al. 2012).

In the NAc, the manipulation of several molecular players involved in neural plasticity, including ΔFosB (Nestler 2015), P11 (Svenningsson et al. 2006), TrkB (Lobo et al. 2010), and β-catenin (Dias et al. 2014), has proven these molecules to be crucial in addictive- and depressive-like behaviors, providing molecular targets for the treatment of these disorders.

Lateral Habenula

The LHb has recently attracted considerable attention owing to the postulation that it could be a source of negative motivational value signals to the DA and 5-HT systems (Hikosaka 2010, Proulx et al. 2014). Many LHb neurons exhibit mirror-inverted phasic responses to DA neurons, activated by negative RPE and inhibited by positive RPE (**Figure 1*c***) (Bromberg-Martin et al. 2010b, 2010d; Matsumoto & Hikosaka 2007, 2009a). Lesion studies and measurement of response latency indicated that the LHb acts upstream of the VTA and SNc to control DA neuron activity (Gao et al. 1990, Matsumoto & Hikosaka 2007). A recent study tested how the habenula contributes to RPE signals of VTA DA neurons, showing that habenular lesions specifically diminish the negative RPE of VTA DA neurons caused by reward omission, but not that caused by aversive stimuli (Tian & Uchida 2015).

Anatomically, the habenula is positioned as a node to relay information from the limbic forebrain to the midbrain areas, including VTA, SNc, DRN, and MRN (Herkenham & Nauta 1979). The LHb sends a direct projection into both these aminergic nuclei and a prominent indirect pathway, mediated by the GABAergic RMTg, through which the LHb can negatively influence DA and 5-HT systems (Jhou et al. 2009). Optogenetic activation of the direct or indirect pathway produces conditioned place aversion (Lammel et al. 2012, Stamatakis & Stuber 2012). Activation of the presynaptic input to LHb from the basal ganglia also causes avoidance behaviors (Shabel et al. 2012).

Given that LHb neurons are activated predominantly by aversive stimuli and disappointment (absence of reward), it is not surprising that LHb hyperactivity is strongly associated with depression and negative symptoms in addiction (Li et al. 2011, Morris et al. 1999, Shumake et al. 2003, Tost et al. 2015). Both presynaptic and postsynaptic changes occur in LHb in rodent models of depression: Postsynaptically, upregulation in the expression of β-calcium/calmodulin-dependent protein kinase II (β-CaMKII in LHb neurons) enhances synaptic efficacy and spike output (Li et al. 2013a); presynaptically, a decrease in the ratio of coreleased GABA/glutamate from presynaptic input into the LHb causes a net increase in the depolarizing drive to the LHb (Shabel et al. 2014).

Lateral Hypothalamus

The LHA is another prominent input area for both VTA and DRN (Ogawa et al. 2014). It is one of the most sensitive ICSS sites (Wise & Rompre 1989) and is involved in a variety of behaviors related to reward and motivation, especially in feeding, the most studied form of reward (Sternson et al. 2013, Stuber & Wise 2016). Several recent optogenetic studies dissected the cell-type- and pathway-specific functions of diverse LHA neuron groups in reward and feeding and revealed a reciprocal projection loop back from the VTA transmitting the RPE signal to LHA neurons (Jennings et al. 2015, Nieh et al. 2015).

Amygdala

Although the amygdala is most famous for fear-related learning in acquiring a threat response, it also mediates the acquisition of positive memories (Janak & Tye 2015, Nader et al. 2000). Rewards, punishments, and the cues that predict them all elicit responses in the BLA and central amygdala (Shabel & Janak 2009, Winston et al. 2005) and are represented by distinct neural populations (Gore et al. 2015, Paton et al. 2006, Salzman et al. 2007).

A possible way in which BLA neurons could be differentially associated with reward or punishment is by virtue of distinct input or output connections. Indeed, BLA → NAc and

BLA → centromedial amygdala pathways were recently shown to differentially code positive and negative valence, respectively (Namburi et al. 2015b). This hardwired connectivity pattern explains why valence coding in the BLA appears to be fixed and cannot be switched to an opposite valence as it can be in the hippocampal dentate gyrus (DG) network (Redondo et al. 2014). Strikingly, depression-related behaviors can be rescued by optogenetic activation of a DG → BLA → NAc pathway activated previously during a rewarding experience (Ramirez et al. 2015).

Cortex

The frontal cortical areas (including the OFC, mPFC, ACC, and insular cortex) have strong reciprocal connections with the subcortical reward network, not only allowing for top-down cortical control of emotional behaviors but also supporting cost-benefit decision making on the basis of rewarding and aversive values.

The OFC is a site that appears especially linked to pleasure in neuroimaging studies (Kringelbach 2005). Remarkably, OFC activity follows sensory satiety, declining together with subjective pleasantness over repeated exposure to reward (Gottfried et al. 2003, Kringelbach et al. 2003). Similar satiety-sensitive responses have also been found in the NAc (Krause et al. 2010, Roitman et al. 2010), amygdala (Yan & Scott 1996), and VP (Tindell et al. 2006). Single-unit recordings in rhesus monkeys and rats have demonstrated that OFC neurons encode a spectrum of features of expected reward, including magnitude, probability, economic value, reward type, and temporal delay (Padoa-Schioppa & Assad 2006, Roesch & Olson 2004, Roesch et al. 2006, Tremblay & Schultz 1999, van Duuren et al. 2009). Furthermore, the signaling of reward prediction by OFC neurons is related to that of VTA DA neurons, as contralateral inactivation of the VTA and OFC disrupts learning driven by unexpected outcomes, similar to bilateral inactivation of the VTA (Takahashi et al. 2009).

Recordings in rhesus monkeys show that neurons in the mPFC (including parts of ACC) are excited by both positive and negative prediction errors of action values (Matsumoto et al. 2007). Distinct subregions in the ventromedial PFC contribute differently to the processing of valence, with the ventral part more active in the rewarding block and the dorsal part more active in the punishment block (Monosov & Hikosaka 2012). Correspondingly in rodents, the dorsal PL and ventral infralimbic portions of the mPFC also appear to be involved in processes of opposite valence, e.g., fear retrieval versus fear extinction and reward seeking versus extinction (Moorman & Aston-Jones 2015, Morgan & LeDoux 1995, Quirk & Beer 2006, Rudebeck et al. 2006). This may explain some conflicting effects of mPFC activation on reward-related behavior (Covington et al. 2010, Ferenczi et al. 2016, Yizhar et al. 2011). Interestingly, a specific mPFC PL → striatal patch pathway has been identified as causally required for decision making in conflict situations, where both rewards and aversive stimuli are provided and a cost-benefit analysis must be made (Friedman et al. 2015).

It has been hypothesized that the ACC receives prediction error signals from DA neurons (Holroyd & Coles 2002). Using optogenetic tagging, Kvitsiani et al. (2013) recorded specific interneuron types in the ACC and observed that a subtype of somatostatin interneurons responded selectively at reward approach, whereas parvalbumin interneurons responded at reward exit.

Optogenetic studies also revealed interesting properties of sensory cortexes in reward-related behavior, demonstrating that some sensory perception (such as taste in the gustatory cortex) is hardwired to an appetitive or aversive network, whereas other perceptions (such as odor in the piriform cortex) can only be afforded valence upon experience (Choi et al. 2011, Peng et al. 2015).

CONCLUSIONS AND FUTURE DIRECTIONS

We have witnessed tremendous progress in identifying crucial neuromodulatory systems and brain network interactions involved in the coding and processing of reward and aversion with the aid of contemporary recording, tracing, and manipulation technologies. Owing to limited space, this article does not cover details for some brain regions (e.g., septum and VP) and neurotransmitter systems (e.g., endogenous opioids and endocannabinoids), which are closely related to reward and aversion, but relevant reviews can be found elsewhere (Berridge & Kringelbach 2015, Hyman et al. 2006, Le Merrer et al. 2009, Sheehan et al. 2004). Below I highlight several areas in which further work is needed to deepen our understanding.

First, to clarify the function of DA and DA neurons in reward, a clean loss-of-function study with temporal precision and cell-type specificity remains warranted. Although a recent series of optogenetic experiments has strongly established the sufficiency of acute DA neuron activation in CPP, reinforcement, and reward learning, experiments establishing proof of necessity are still needed. It remains to be examined whether acute inactivation of DA neurons affects reinforcement and CPP that are induced by natural and drug rewards. Furthermore, to specifically dissect functions in motivation and learning, it is necessary to resolve whether transient inactivation of DA neurons concurrent to the RPE signal abolishes associative learning. The lack of such studies is perhaps due to the difficulty in achieving complete inhibition of DA neuron function in a temporally precise manner. Application of a light-sensitive inhibitory channel, NphR or Arch, or activation of local GABA neurons may be feasible. Another difficulty lies in the lack of a specific tactic to only inactivate a phasic response without affecting tonic firing of DA neurons. For this, it will be helpful to identify a specific input responsible for the phasic DA response.

Regarding DA-RPE-driven learning, another unsolved hallmark phenomenon is the gradual transfer of DA neuron activation from reward itself to cues predicting the reward. It will be fascinating to unravel the plasticity mechanism underlying the synaptic or circuit changes during this transfer process.

Second, the function of the DRN 5-HT system, and its interaction with the VTA DA system in reward and aversion, is a new exciting frontier that awaits further investigation. Although emerging evidence suggests a positive role of DRN 5-HT neurons in reward coding, the degree of heterogeneity, the role of different transmitter systems, and whether there is any spatial segregation of 5-HT neurons of different valences remain to be resolved. As the response of 5-HT neurons seems to point to a function in reward consumption and pleasure, it would be interesting to examine 5-HT neuron function in the hedonic taste reactivity assay with optogenetics, e.g., testing whether pairing a neutral taste with transient activation of 5-HT neurons can induce a liking type of orofacial reactivity and, more importantly, whether transient inactivation of 5-HT neurons reduces liking taste reactivity to sucrose.

Regarding the relationship between the DA and 5-HT systems, the outstanding questions are: How does acute manipulation of the 5-HT system affect the activity of DA neurons, and vice versa? Given that many DRN 5-HT neurons show excitation to actual reward regardless of the reward being predicted or not, could they contribute to the signal of actual reward value to VTA DA neurons for the computation of RPE? At the behavioral level, do the 5-HT and DA systems play parallel or redundant roles? There is indeed some evidence suggesting that the combination of DA and 5-HT is important for certain aspects of reward-related behaviors: Depression is often accompanied by changes in both neuromodulatory systems; antidepressant and euphoric drugs target both systems; the knockout of the DA transporter DAT or SERT does not disrupt cocaine-induced CPP, but the knockout of both does (Sora et al. 2001), suggesting that cocaine reward/reinforcement may be supported by either one of the two systems. Therefore to address

a potential redundant role of the two systems, it would be necessary to test dual inactivation of both systems in more reward-related assays.

Finally, cell-type- and output-specific whole-brain mapping has revealed unprecedented information. However, the input analyses of VTA DA versus VTA GABA neurons, and DRN 5-HT versus DRN GABA neurons, have so far revealed little difference both in terms of input brain regions and input cell types, although these cells clearly have distinct or even opposite functions. It would be useful to develop tools to simultaneously map the inputs of two cell types, e.g., VTA DA and VTA GABA, using multiple colors in the same mouse brain to examine whether there are unique spatial patterns embedded in their input maps. Furthermore, in addition to cell-type and projection-based whole-brain tracing, it would be especially useful to systematically trace the inputs on the basis of the functionality of neural groups to answer questions, such as where do inputs originate for the reward- and aversion-coding neurons within different sites of reward circuitry? The incorporation of activity markers such as the immediate early gene in the tracing system holds promise.

DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The author thanks Jihua Wang, Qi Zhang, Yiyan Dong, Hong Zhu, Kristina Zeljic, and Qiye He for assistance with figure and manuscript preparation, as well as Drs. Naoshiga Uchida, Minmin Luo, Qijing Li, Haohong Li and the anonymous reviewer for their insightful discussions and advice. The literature on the subject is huge, and the author apologizes for omissions of references to relevant papers. This review was supported in part by grants from the National Natural Science Foundation of China (91432108, 31225010, and 81527901).

LITERATURE CITED

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.* 52:1655–58

Adamantidis AR, Tsai HC, Boutrel B, Zhang F, Stuber GD, et al. 2011. Optogenetic interrogation of dopaminergic modulation of the multiple phases of reward-seeking behavior. *J. Neurosci.* 31:10829–35

Akerboom J, Chen TW, Wardill TJ, Tian L, Marvin JS, et al. 2012. Optimization of a GCaMP calcium indicator for neural activity imaging. *J. Neurosci.* 32:13819–40

Al-Hasani R, McCall JG, Shin G, Gomez AM, Schmitz GP, et al. 2015. Distinct subpopulations of nucleus accumbens dynorphin neurons drive aversion and reward. *Neuron* 87:1063–77

Amo R, Fredes F, Kinoshita M, Aoki R, Aizawa H, et al. 2014. The habenulo-raphe serotonergic circuit encodes an aversive expectation value essential for adaptive active avoidance of danger. *Neuron* 84:1034–48

Beier KT, Steinberg EE, DeLoach KE, Xie S, Miyamichi K, et al. 2015. Circuit architecture of VTA dopamine neurons revealed by systematic input-output mapping. *Cell* 162:622–34

Berridge KC, Kringelbach ML. 2015. Pleasure systems in the brain. *Neuron* 86:646–64

Berridge KC, Robinson TE. 1998. What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience? *Brain Res. Brain Res. Rev.* 28:309–69

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

Bocklisch C, Pascoli V, Wong JC, House DR, Yvon C, et al. 2013. Cocaine disinhibits dopamine neurons by potentiation of GABA transmission in the ventral tegmental area. *Science* 341:1521–25

Brischoux F, Chakraborty S, Brierley DI, Ungless MA. 2009. Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *PNAS* 106:4894–99

Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. 2012. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* 76:790–803

Britt JP, Bonci A. 2013. Optogenetic interrogations of the neural circuits underlying addiction. *Curr. Opin. Neurobiol.* 23:539–45

Bromberg-Martin ES, Hikosaka O, Nakamura K. 2010a. Coding of task reward value in the dorsal raphe nucleus. *J. Neurosci.* 30:6262–72

Bromberg-Martin ES, Matsumoto M, Hikosaka O. 2010b. Distinct tonic and phasic anticipatory activity in lateral habenula and dopamine neurons. *Neuron* 67:144–55

Bromberg-Martin ES, Matsumoto M, Hikosaka O. 2010c. Dopamine in motivational control: rewarding, aversive, and alerting. *Neuron* 68:815–34

Bromberg-Martin ES, Matsumoto M, Nakahara H, Hikosaka O. 2010d. Multiple timescales of memory in lateral habenula and dopamine neurons. *Neuron* 67:499–510

Brown MT, Tan KR, O'Connor EC, Nikonenko I, Muller D, Lüscher C. 2012. Ventral tegmental area GABA projections pause accumbal cholinergic interneurons to enhance associative learning. *Nature* 492:452–56

Callaway EM, Luo L. 2015. Monosynaptic circuit tracing with glycoprotein-deleted rabies viruses. *J. Neurosci.* 35:8979–85

Carlezon WA Jr, Thomas MJ. 2009. Biological substrates of reward and aversion: a nucleus accumbens activity hypothesis. *Neuropharmacology* 56(Suppl. 1):122–32

Challis C, Boulden J, Veerakumar A, Espallergues J, Vassoler FM, et al. 2013. Raphe GABAergic neurons mediate the acquisition of avoidance after social defeat. *J. Neurosci.* 33:13978–88

Chaudhury D, Walsh JJ, Friedman AK, Juarez B, Ku SM, et al. 2013. Rapid regulation of depression-related behaviours by control of midbrain dopamine neurons. *Nature* 493:532–36

Chen BT, Bowers MS, Martin M, Hopf FW, Guillory AM, et al. 2008. Cocaine but not natural reward self-administration nor passive cocaine infusion produces persistent LTP in the VTA. *Neuron* 59:288–97

Choi GB, Stettler DD, Kallman BR, Bhaskar ST, Fleischmann A, Axel R. 2011. Driving opposing behaviors with ensembles of piriform neurons. *Cell* 146:1004–15

Chowdhury R, Guitart-Masip M, Lambert C, Dayan P, Huys Q, et al. 2013. Dopamine restores reward prediction errors in old age. *Nat. Neurosci.* 16:648–53

Chuhma N, Tanaka KF, Hen R, Rayport S. 2011. Functional connectome of the striatal medium spiny neuron. *J. Neurosci.* 31:1183–92

Cohen JY, Amoroso MW, Uchida N. 2015. Serotonergic neurons signal reward and punishment on multiple timescales. *eLife* 4:e06346

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

Corbett D, Wise RA. 1980. Intracranial self-stimulation in relation to the ascending dopaminergic systems of the midbrain: a moveable electrode mapping study. *Brain Res.* 185:1–15

Covington HE 3rd, Lobo MK, Maze I, Vialou V, Hyman JM, et al. 2010. Antidepressant effect of optogenetic stimulation of the medial prefrontal cortex. *J. Neurosci.* 30:16082–90

D'Ardenne K, McClure SM, Nystrom LE, Cohen JD. 2008. BOLD responses reflecting dopaminergic signals in the human ventral tegmental area. *Science* 319:1264–67

Daw ND, Kakade S, Dayan P. 2002. Opponent interactions between serotonin and dopamine. *Neural Netw.* 15:603–16

Dayan P, Huys QJ. 2008. Serotonin, inhibition, and negative mood. *PLOS Comput. Biol.* 4:e4

Dayan P, Huys QJ. 2009. Serotonin in affective control. *Annu. Rev. Neurosci.* 32:95–126

Deakin JF, Graeff FG. 1991. 5-HT and mechanisms of defence. *J. Psychopharmacol.* 5:305–15

Di Chiara G. 2002. Nucleus accumbens shell and core dopamine: differential role in behavior and addiction. *Behav. Brain Res.* 137:75–114

Dias C, Feng J, Sun H, Shao NY, Mazei-Robison MS, et al. 2014. β-Catenin mediates stress resilience through Dicer1/microRNA regulation. *Nature* 516:51–55

Doherty MD, Gratton A. 1992. High-speed chronoamperometric measurements of mesolimbic and nigrostriatal dopamine release associated with repeated daily stress. *Brain Res.* 586:295–302
Dolen G, Darvishzadeh A, Huang KW, Malenka RC. 2013. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. *Nature* 501:179–84
Doya K. 1999. What are the computations of the cerebellum, the basal ganglia and the cerebral cortex? *Neural Netw.* 12:961–74
Doya K. 2002. Metalearning and neuromodulation. *Neural Netw.* 15:495–506
Eshel N, Bukwich M, Rao V, Hemmelder V, Tian J, Uchida N. 2015. Arithmetic and local circuitry underlying dopamine prediction errors. *Nature* 525:243–46
Ferenczi EA, Zalocusky KA, Liston C, Grosenick L, Warden MR, et al. 2016. Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. *Science* 351:aac9698
Floresco SB. 2015. The nucleus accumbens: an interface between cognition, emotion, and action. *Annu. Rev. Psychol.* 66:25–52
Fonseca MS, Murakami M, Mainen ZF. 2015. Activation of dorsal raphe serotonergic neurons promotes waiting but is not reinforcing. *Curr. Biol.* 25:306–15
Fouriezos G, Wise RA. 1976. Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. *Brain Res.* 103:377–80
Friedman A, Homma D, Gibb LG, Amemori K, Rubin SJ, et al. 2015. A corticostriatal path targeting striosomes controls decision-making under conflict. *Cell* 161:1320–33
Gao DM, Jeaugey L, Pollak P, Benabid AL. 1990. Intensity-dependent nociceptive responses from presumed dopaminergic neurons of the substantia nigra, pars compacta in the rat and their modification by lateral habenula inputs. *Brain Res.* 529:315–19
Gerfen CR. 1992. The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci.* 15:133–39
Gerfen CR, Surmeier DJ. 2011. Modulation of striatal projection systems by dopamine. *Annu. Rev. Neurosci.* 34:441–66
Gore F, Schwartz EC, Brangers BC, Aladi S, Stujenske JM, et al. 2015. Neural representations of unconditioned stimuli in basolateral amygdala mediate innate and learned responses. *Cell* 162:134–45
Goto Y, Grace AA. 2008. Limbic and cortical information processing in the nucleus accumbens. *Trends Neurosci.* 31:552–58
Gottfried JA, O'Doherty J, Dolan RJ. 2003. Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 301:1104–7
Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, et al. 2014. Natural neural projection dynamics underlying social behavior. *Cell* 157:1535–51
Hayashi K, Nakao K, Nakamura K. 2015. Appetitive and aversive information coding in the primate dorsal raphe nucleus. *J. Neurosci.* 35:6195–208
Herkenham M, Nauta WJ. 1979. Efferent connections of the habenular nuclei in the rat. *J. Comp. Neurol.* 187:19–47
Hikosaka O. 2010. The habenula: from stress evasion to value-based decision-making. *Nat. Rev. Neurosci.* 11:503–13
Hirschfeld RM. 2000. History and evolution of the monoamine hypothesis of depression. *J. Clin. Psychiatry* 61(Suppl. 6):4–6
Hokfelt T, Arvidsson U, Cullheim S, Millhorn D, Nicholas AP, et al. 2000. Multiple messengers in descending serotonin neurons: localization and functional implications. *J. Chem. Neuroanat.* 18:75–86
Holroyd CB, Coles MG. 2002. The neural basis of human error processing: reinforcement learning, dopamine, and the error-related negativity. *Psychol. Rev.* 109:679–709
Hong S, Hikosaka O. 2014. Pedunculopontine tegmental nucleus neurons provide reward, sensorimotor, and alerting signals to midbrain dopamine neurons. *Neuroscience* 282C:139–55
Humphries MD, Prescott TJ. 2010. The ventral basal ganglia, a selection mechanism at the crossroads of space, strategy, and reward. *Prog. Neurobiol.* 90:385–417
Hyman SE, Malenka RC, Nestler EJ. 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. *Annu. Rev. Neurosci.* 29:565–98

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

Ikemoto S, Panksepp J. 1999. The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking. *Brain Res. Brain Res. Rev.* 31:6–41

Ikemoto S, Wise RA. 2004. Mapping of chemical trigger zones for reward. *Neuropharmacology* 47(Suppl. 1):190–201

Ilango A, Kesner AJ, Keller KL, Stuber GD, Bonci A, Ikemoto S. 2014. Similar roles of substantia nigra and ventral tegmental dopamine neurons in reward and aversion. *J. Neurosci.* 34:817–22

Inaba K, Mizuhiki T, Setogawa T, Toda K, Richmond BJ, Shidara M. 2013. Neurons in monkey dorsal raphe nucleus code beginning and progress of step-by-step schedule, reward expectation, and amount of reward outcome in the reward schedule task. *J. Neurosci.* 33:3477–91

Janak PH, Tye KM. 2015. From circuits to behaviour in the amygdala. *Nature* 517:284–92

Jennings JH, Ung RL, Resendez SL, Stamatakis AM, Taylor JG, et al. 2015. Visualizing hypothalamic network dynamics for appetitive and consummatory behaviors. *Cell* 160:516–27

Jhou TC, Geisler S, Marinelli M, Degarmo BA, Zahm DS. 2009. The mesopontine rostromedial tegmental nucleus: a structure targeted by the lateral habenula that projects to the ventral tegmental area of Tsai and substantia nigra compacta. *J. Comp. Neurol.* 513:566–96

Judge SJ, Gartside SE. 2006. Firing of 5-HT neurones in the dorsal and median raphe nucleus in vitro shows differential α_1-adrenoceptor and 5-HT_{1A} receptor modulation. *Neurochem. Int.* 48:100–7

Kamin LJ. 1968. Predictability, surprise, attention, and conditioning. In *Punishment and Aversive Behavior*, ed. BA Campbell, RM Church, pp. 279–96. New York: Appleton-Century-Crofts

Keiflin R, Janak PH. 2015. Dopamine prediction errors in reward learning and addiction: from theory to neural circuitry. *Neuron* 88:247–63

Khibnik LA, Beaumont M, Doyle M, Heshmati M, Slesinger PA, et al. 2015. Stress and cocaine trigger divergent and cell type-specific regulation of synaptic transmission at single spines in nucleus accumbens. *Biol. Psychiatry.* In press. doi: 10.1016/j.biopsych.2015.05.022

Kim MA, Lee HS, Lee BY, Waterhouse BD. 2004. Reciprocal connections between subdivisions of the dorsal raphe and the nuclear core of the locus coeruleus in the rat. *Brain Res.* 1026:56–67

Kirouac GJ, Li S, Mabrouk G. 2004. GABAergic projection from the ventral tegmental area and substantia nigra to the periaqueductal gray region and the dorsal raphe nucleus. *J. Comp. Neurol.* 469:170–84

Kobayashi Y, Okada K. 2007. Reward prediction error computation in the pedunculopontine tegmental nucleus neurons. *Ann. N.Y. Acad. Sci.* 1104:310–23

Koya E, Hope BT. 2011. Cocaine and synaptic alterations in the nucleus accumbens. *Biol. Psychiatry* 69:1013–14

Krause M, German PW, Taha SA, Fields HL. 2010. A pause in nucleus accumbens neuron firing is required to initiate and maintain feeding. *J. Neurosci.* 30:4746–56

Kravitz AV, Freeze BS, Parker PR, Kay K, Thwin MT, et al. 2010. Regulation of parkinsonian motor behaviours by optogenetic control of basal ganglia circuitry. *Nature* 466:622–26

Kravitz AV, Tye LD, Kreitzer AC. 2012. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat. Neurosci.* 15:816–18

Kringelbach ML. 2005. The human orbitofrontal cortex: linking reward to hedonic experience. *Nat. Rev. Neurosci.* 6:691–702

Kringelbach ML, Berridge KC. 2009. Towards a functional neuroanatomy of pleasure and happiness. *Trends Cogn. Sci.* 13:479–87

Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. 2003. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. *Cereb. Cortex* 13:1064–71

Kupchik YM, Brown RM, Heinsbroek JA, Lobo MK, Schwartz DJ, Kalivas PW. 2015. Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections. *Nat. Neurosci.* 18:1230–32

Kvitsiani D, Ranade S, Hangya B, Taniguchi H, Huang JZ, Kepecs A. 2013. Distinct behavioural and network correlates of two interneuron types in prefrontal cortex. *Nature* 498:363–66

Lammel S, Ion DI, Roeper J, Malenka RC. 2011. Projection-specific modulation of dopamine neuron synapses by aversive and rewarding stimuli. *Neuron* 70:855–62

Lammel S, Lim BK, Malenka RC. 2014. Reward and aversion in a heterogeneous midbrain dopamine system. *Neuropharmacology* 76(Part B):351–59
Lammel S, Lim BK, Ran C, Huang KW, Betley MJ, et al. 2012. Input-specific control of reward and aversion in the ventral tegmental area. *Nature* 491:212–17
Le Merrer J, Becker JA, Befort K, Kieffer BL. 2009. Reward processing by the opioid system in the brain. *Physiol. Rev.* 89:1379–412
Lee BR, Ma YY, Huang YH, Wang X, Otaka M, et al. 2013. Maturation of silent synapses in amygdala-accumbens projection contributes to incubation of cocaine craving. *Nat. Neurosci.* 16:1644–51
Lerner TN, Shilyansky C, Davidson TJ, Evans KE, Beier KT, et al. 2015. Intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits. *Cell* 162:635–47
Li B, Piriz J, Mirrione M, Chung C, Proulx CD, et al. 2011. Synaptic potentiation onto habenula neurons in the learned helplessness model of depression. *Nature* 470:535–39
Li K, Zhou T, Liao L, Yang Z, Wong C, et al. 2013a. βCaMKII in lateral habenula mediates core symptoms of depression. *Science* 341:1016–20
Li Y, Dalphin N, Hyland BI. 2013b. Association with reward negatively modulates short latency phasic conditioned responses of dorsal raphe nucleus neurons in freely moving rats. *J. Neurosci.* 33:5065–78
Li Y, Zhong W, Wang D, Feng Q, Liu Z, et al. 2016. Serotonin neurons in the dorsal raphe nucleus encode reward signals. *Nat. Commun.* 7:10503
Lim BK, Huang KW, Grueter BA, Rothwell PE, Malenka RC. 2012. Anhedonia requires MC4R-mediated synaptic adaptations in nucleus accumbens. *Nature* 487:183–89
Lin D, Boyle MP, Dollar P, Lee H, Lein ES, et al. 2011. Functional identification of an aggression locus in the mouse hypothalamus. *Nature* 470:221–26
Liu Z, Zhou J, Li Y, Hu F, Lu Y, et al. 2014. Dorsal raphe neurons signal reward through 5-HT and glutamate. *Neuron* 81:1360–74
Lobo MK, Covington HE 3rd, Chaudhury D, Friedman AK, Sun H, et al. 2010. Cell type specific loss of BDNF signaling mimics optogenetic control of cocaine reward. *Science* 330:385–90
Louilot A, Le Moal M, Simon H. 1986. Differential reactivity of dopaminergic neurons in the nucleus accumbens in response to different behavioral situations. An in vivo voltammetric study in free moving rats. *Brain Res.* 397:395–400
Luo M, Zhou J, Liu Z. 2015. Reward processing by the dorsal raphe nucleus: 5-HT and beyond. *Learn. Mem.* 22:452–60
Lüscher C, Malenka RC. 2011. Drug-evoked synaptic plasticity in addiction: from molecular changes to circuit remodeling. *Neuron* 69:650–63
Macoveanu J. 2014. Serotonergic modulation of reward and punishment: evidence from pharmacological fMRI studies. *Brain Res.* 1556:19–27
Mameli M, Halbout B, Creton C, Engblom D, Parkitna JR, et al. 2009. Cocaine-evoked synaptic plasticity: Persistence in the VTA triggers adaptations in the NAc. *Nat. Neurosci.* 12:1036–41
Matsumoto M, Hikosaka O. 2007. Lateral habenula as a source of negative reward signals in dopamine neurons. *Nature* 447:1111–15
Matsumoto M, Hikosaka O. 2009a. Representation of negative motivational value in the primate lateral habenula. *Nat. Neurosci.* 12:77–84
Matsumoto M, Hikosaka O. 2009b. Two types of dopamine neuron distinctly convey positive and negative motivational signals. *Nature* 459:837–41
Matsumoto M, Matsumoto K, Abe H, Tanaka K. 2007. Medial prefrontal cell activity signaling prediction errors of action values. *Nat. Neurosci.* 10:647–56
McClure SM, Daw ND, Montague PR. 2003. A computational substrate for incentive salience. *Trends Neurosci.* 26:423–28
McDevitt RA, Tiran-Cappello A, Shen H, Balderas I, Britt JP, et al. 2014. Serotonergic versus nonserotonergic dorsal raphe projection neurons: differential participation in reward circuitry. *Cell Rep.* 8:1857–69
Menegas W, Bergan JF, Ogawa SK, Isogai Y, Umadevi Venkataraju K, et al. 2015. Dopamine neurons projecting to the posterior striatum form an anatomically distinct subclass. *eLife* 4:e10032
Miyazaki K, Miyazaki KW, Doya K. 2011. Activation of dorsal raphe serotonin neurons underlies waiting for delayed rewards. *J. Neurosci.* 31:469–79

Miyazaki KW, Miyazaki K, Tanaka KF, Yamanaka A, Takahashi A, et al. 2014. Optogenetic activation of dorsal raphe serotonin neurons enhances patience for future rewards. *Curr. Biol.* 24:2033–40
Monosov IE, Hikosaka O. 2012. Regionally distinct processing of rewards and punishments by the primate ventromedial prefrontal cortex. *J. Neurosci.* 32:10318–30
Moorman DE, Aston-Jones G. 2015. Prefrontal neurons encode context-based response execution and inhibition in reward seeking and extinction. *PNAS* 112:9472–77
Morgan MA, LeDoux JE. 1995. Differential contribution of dorsal and ventral medial prefrontal cortex to the acquisition and extinction of conditioned fear in rats. *Behav. Neurosci.* 109:681–88
Morris JS, Smith KA, Cowen PJ, Friston KJ, Dolan RJ. 1999. Covariation of activity in habenula and dorsal raphe nuclei following tryptophan depletion. *NeuroImage* 10:163–72
Nader K, Schafe GE, LeDoux JE. 2000. The labile nature of consolidation theory. *Nat. Rev. Neurosci.* 1:216–19
Nakamura K, Matsumoto M, Hikosaka O. 2008. Reward-dependent modulation of neuronal activity in the primate dorsal raphe nucleus. *J. Neurosci.* 28:5331–43
Nakamura K, Ono T. 1986. Lateral hypothalamus neuron involvement in integration of natural and artificial rewards and cue signals. *J. Neurophysiol.* 55:163–81
Namburi P, Al-Hasani R, Calhoon GG, Bruchas MR, Tye KM. 2015a. Architectural representation of valence in the limbic system. *Neuropsychopharmacology.* In press. doi: 10.1038/npp.2015.358
Namburi P, Beyeler A, Yorozu S, Calhoon GG, Halbert SA, et al. 2015b. A circuit mechanism for differentiating positive and negative associations. *Nature* 520:675–78
Nestler EJ. 2015. ΔFosB: a transcriptional regulator of stress and antidepressant responses. *Eur. J. Pharmacol.* 753:66–72
Nicola SM, Surmeier J, Malenka RC. 2000. Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. *Annu. Rev. Neurosci.* 23:185–215
Nieh EH, Matthews GA, Allsop SA, Presbrey KN, Leppla CA, et al. 2015. Decoding neural circuits that control compulsive sucrose seeking. *Cell* 160:528–41
Niv Y, Joel D, Dayan P. 2006. A normative perspective on motivation. *Trends Cogn. Sci.* 10:375–81
Ogawa SK, Cohen JY, Hwang D, Uchida N, Watabe-Uchida M. 2014. Organization of monosynaptic inputs to the serotonin and dopamine neuromodulatory systems. *Cell Rep.* 8:1105–18
Olds J, Milner P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* 47:419–27
Olds J, Travis RP. 1960. Effects of chlorpromazine, meprobamate, pentobarbital and morphine on self-stimulation. *J. Pharmacol. Exp. Ther.* 128:397–404
Padoa-Schioppa C, Assad JA. 2006. Neurons in the orbitofrontal cortex encode economic value. *Nature* 441:223–26
Pan WX, Hyland BI. 2005. Pedunculopontine tegmental nucleus controls conditioned responses of midbrain dopamine neurons in behaving rats. *J. Neurosci.* 25:4725–32
Pascoli V, Terrier J, Hiver A, Lüscher C. 2015. Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. *Neuron* 88:1054–66
Pascoli V, Turiault M, Lüscher C. 2012. Reversal of cocaine-evoked synaptic potentiation resets drug-induced adaptive behaviour. *Nature* 481:71–75
Paton JJ, Belova MA, Morrison SE, Salzman CD. 2006. The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* 439:865–70
Peng Y, Gillis-Smith S, Jin H, Trankner D, Ryba NJ, Zuker CS. 2015. Sweet and bitter taste in the brain of awake behaving animals. *Nature* 527:512–15
Perreau-Linck E, Beauregard M, Gravel P, Paquette V, Soucy JP, et al. 2007. In vivo measurements of brain trapping of C-labelled α-methyl-L-tryptophan during acute changes in mood states. *J. Psychiatry Neurosci.* 32:430–34
Pezze MA, Feldon J. 2004. Mesolimbic dopaminergic pathways in fear conditioning. *Prog. Neurobiol.* 74:301–20
Pignatelli M, Bonci A. 2015. Role of dopamine neurons in reward and aversion: a synaptic plasticity perspective. *Neuron* 86:1145–57
Pollak Dorocic I, Furth D, Xuan Y, Johansson Y, Pozzi L, et al. 2014. A whole-brain atlas of inputs to serotonergic neurons of the dorsal and median raphe nuclei. *Neuron* 83:663–78

Proulx CD, Hikosaka O, Malinow R. 2014. Reward processing by the lateral habenula in normal and depressive behaviors. *Nat. Neurosci.* 17:1146–52
Qi J, Zhang S, Wang HL, Wang H, de Jesus Aceves Buendia J, et al. 2014. A glutamatergic reward input from the dorsal raphe to ventral tegmental area dopamine neurons. *Nat. Commun.* 5:5390
Quirk GJ, Beer JS. 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr. Opin. Neurobiol.* 16:723–27
Ramirez S, Liu X, MacDonald CJ, Moffa A, Zhou J, et al. 2015. Activating positive memory engrams suppresses depression-like behaviour. *Nature* 522:335–39
Ranade SP, Mainen ZF. 2009. Transient firing of dorsal raphe neurons encodes diverse and specific sensory, motor, and reward events. *J. Neurophysiol.* 102:3026–37
Redondo RL, Kim J, Arons AL, Ramirez S, Liu X, Tonegawa S. 2014. Bidirectional switch of the valence associated with a hippocampal contextual memory engram. *Nature* 513:426–30
Roberts D, Zito K. 1987. Interpretation of lesion effects on stimulant self-administration. In *Methods of Assessing the Reinforcing Properties of Abused Drugs*, ed. MA Bozarth, pp. 87–103. Berlin: Springer
Roberts DC, Corcoran ME, Fibiger HC. 1977. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol. Biochem. Behav.* 6:615–20
Roesch MR, Olson CR. 2004. Neuronal activity related to reward value and motivation in primate frontal cortex. *Science* 304:307–10
Roesch MR, Taylor AR, Schoenbaum G. 2006. Encoding of time-discounted rewards in orbitofrontal cortex is independent of value representation. *Neuron* 51:509–20
Roitman MF, Wheeler RA, Carelli RM. 2005. Nucleus accumbens neurons are innately tuned for rewarding and aversive taste stimuli, encode their predictors, and are linked to motor output. *Neuron* 45:587–97
Roitman MF, Wheeler RA, Tiesinga PH, Roitman JD, Carelli RM. 2010. Hedonic and nucleus accumbens neural responses to a natural reward are regulated by aversive conditioning. *Learn. Mem.* 17:539–46
Roll SK. 1970. Intracranial self-stimulation and wakefulness: Effect of manipulating ambient brain catecholamines. *Science* 168:1370–72
Rudebeck PH, Walton ME, Smyth AN, Bannerman DM, Rushworth MF. 2006. Separate neural pathways process different decision costs. *Nat. Neurosci.* 9:1161–68
Russo SJ, Dietz DM, Dumitriu D, Morrison JH, Malenka RC, Nestler EJ. 2010. The addicted synapse: mechanisms of synaptic and structural plasticity in nucleus accumbens. *Trends Neurosci.* 33:267–76
Russo SJ, Nestler EJ. 2013. The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 14:609–25
Saal D, Dong Y, Bonci A, Malenka RC. 2003. Drugs of abuse and stress trigger a common synaptic adaptation in dopamine neurons. *Neuron* 37:577–82
Salamone JD. 1994. The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behav. Brain Res.* 61:117–33
Salamone JD. 1996. The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *J. Neurosci. Methods* 64:137–49
Salzman CD, Paton JJ, Belova MA, Morrison SE. 2007. Flexible neural representations of value in the primate brain. *Ann. N.Y. Acad. Sci.* 1121:336–54
Savitz J, Lucki I, Drevets WC. 2009. 5-HT_{1A} receptor function in major depressive disorder. *Prog. Neurobiol.* 88:17–31
Schultz W. 1998. Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80:1–27
Schultz W. 2007a. Behavioral dopamine signals. *Trends Neurosci.* 30:203–10
Schultz W. 2007b. Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* 30:259–88
Schultz W. 2010. Dopamine signals for reward value and risk: basic and recent data. *Behav. Brain Funct.* 6:24
Schultz W, Dayan P, Montague PR. 1997. A neural substrate of prediction and reward. *Science* 275:1593–99
Schwarz LA, Miyamichi K, Gao XJ, Beier KT, Weissbourd B, et al. 2015. Viral-genetic tracing of the input-output organization of a central noradrenaline circuit. *Nature* 524:88–92
Schweimer JV, Ungless MA. 2010. Phasic responses in dorsal raphe serotonin neurons to noxious stimuli. *Neuroscience* 171:1209–15
Sesack SR, Grace AA. 2010. Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology* 35:27–47

Seymour B, Daw ND, Roiser JP, Dayan P, Dolan R. 2012. Serotonin selectively modulates reward value in human decision-making. *J. Neurosci.* 32:5833–42
Shabel SJ, Janak PH. 2009. Substantial similarity in amygdala neuronal activity during conditioned appetitive and aversive emotional arousal. *PNAS* 106:15031–36
Shabel SJ, Proulx CD, Piriz J, Malinow R. 2014. Mood regulation. GABA/glutamate co-release controls habenula output and is modified by antidepressant treatment. *Science* 345:1494–98
Shabel SJ, Proulx CD, Trias A, Murphy RT, Malinow R. 2012. Input to the lateral habenula from the basal ganglia is excitatory, aversive, and suppressed by serotonin. *Neuron* 74:475–81
Sheehan TP, Chambers RA, Russell DS. 2004. Regulation of affect by the lateral septum: implications for neuropsychiatry. *Brain Res. Brain Res. Rev.* 46:71–117
Shumake J, Edwards E, Gonzalez-Lima F. 2003. Opposite metabolic changes in the habenula and ventral tegmental area of a genetic model of helpless behavior. *Brain Res.* 963:274–81
Sienkiewicz-Jarosz H, Scinska A, Swiecicki L, Lipczynska-Lojkowska W, Kuran W, et al. 2013. Sweet liking in patients with Parkinson's disease. *J. Neurol. Sci.* 329:17–22
Simon H, Le Moal M, Cardo B. 1976. Intracranial self-stimulation from the dorsal raphe nucleus of the rat: effects of the injection of para-chlorophenylalanine and of alpha-methylparatyrosine. *Behav. Biol.* 16:353–64
Sora I, Hall FS, Andrews AM, Itokawa M, Li XF, et al. 2001. Molecular mechanisms of cocaine reward: Combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. *PNAS* 98:5300–5
Stamatakis AM, Stuber GD. 2012. Activation of lateral habenula inputs to the ventral midbrain promotes behavioral avoidance. *Nat. Neurosci.* 15:1105–7
Stefanik MT, Moussawi K, Kupchik YM, Smith KC, Miller RL, et al. 2013. Optogenetic inhibition of cocaine seeking in rats. *Addict. Biol.* 18:50–53
Stein L. 1962. Effects and interactions of imipramine, chlorpromazine, reserpine and amphetamine on self-stimulation: possible neurophysiological basis of depression. In *Recent Advances in Biological Psychiatry*, Vol. IV, ed. J Wortis, 4:288–309. New York: Plenum
Stein L. 1968. Chemistry of reward and punishment. In *Psychopharmacology: A Review of Progress, 1957–1967*, ed. DH Efron, pp. 105–23. Washington, DC: Am. Coll. Neuropsychopharmacol.
Steinberg EE, Keiflin R, Boivin JR, Witten IB, Deisseroth K, Janak PH. 2013. A causal link between prediction errors, dopamine neurons and learning. *Nat. Neurosci.* 16:966–73
Sternson SM, Nicholas Betley J, Cao ZF. 2013. Neural circuits and motivational processes for hunger. *Curr. Opin. Neurobiol.* 23:353–60
Stuber GD, Hnasko TS, Britt JP, Edwards RH, Bonci A. 2010. Dopaminergic terminals in the nucleus accumbens but not the dorsal striatum corelease glutamate. *J. Neurosci.* 30:8229–33
Stuber GD, Sparta DR, Stamatakis AM, van Leeuwen WA, Hardjoprajitno JE, et al. 2011. Excitatory transmission from the amygdala to nucleus accumbens facilitates reward seeking. *Nature* 475:377–80
Stuber GD, Wise RA. 2016. Lateral hypothalamic circuits for feeding and reward. *Nat. Neurosci.* 19:198–205
Sulzer D, Joyce MP, Lin L, Geldwert D, Haber SN, et al. 1998. Dopamine neurons make glutamatergic synapses in vitro. *J. Neurosci.* 18:4588–602
Suri RE. 2002. TD models of reward predictive responses in dopamine neurons. *Neural Netw.* 15:523–33
Svenningsson P, Chergui K, Rachleff I, Flajolet M, Zhang X, et al. 2006. Alterations in 5-HT_{1B} receptor function by p11 in depression-like states. *Science* 311:77–80
Tai LH, Lee AM, Benavidez N, Bonci A, Wilbrecht L. 2012. Transient stimulation of distinct subpopulations of striatal neurons mimics changes in action value. *Nat. Neurosci.* 15:1281–89
Takahashi YK, Roesch MR, Stalnaker TA, Haney RZ, Calu DJ, et al. 2009. The orbitofrontal cortex and ventral tegmental area are necessary for learning from unexpected outcomes. *Neuron* 62:269–80
Takahashi YK, Roesch MR, Wilson RC, Toreson K, O'Donnell P, et al. 2011. Expectancy-related changes in firing of dopamine neurons depend on orbitofrontal cortex. *Nat. Neurosci.* 14:1590–97
Tan KR, Yvon C, Turiault M, Mirzabekov JJ, Doehner J, et al. 2012. GABA neurons of the VTA drive conditioned place aversion. *Neuron* 73:1173–83
Tecuapetla F, Patel JC, Xenias H, English D, Tadros I, et al. 2010. Glutamatergic signaling by mesolimbic dopamine neurons in the nucleus accumbens. *J. Neurosci.* 30:7105–10

Tian J, Uchida N. 2015. Habenula lesions reveal that multiple mechanisms underlie dopamine prediction errors. *Neuron* 87:1304–16
Tindell AJ, Smith KS, Pecina S, Berridge KC, Aldridge JW. 2006. Ventral pallidum firing codes hedonic reward: When a bad taste turns good. *J. Neurophysiol.* 96:2399–409
Tost H, Champagne FA, Meyer-Lindenberg A. 2015. Environmental influence in the brain, human welfare and mental health. *Nat. Neurosci.* 18:1421–31
Tremblay L, Schultz W. 1999. Relative reward preference in primate orbitofrontal cortex. *Nature* 398:704–8
Tritsch NX, Ding JB, Sabatini BL. 2012. Dopaminergic neurons inhibit striatal output through non-canonical release of GABA. *Nature* 490:262–66
Tsai HC, Zhang F, Adamantidis A, Stuber GD, Bonci A, et al. 2009. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science* 324:1080–84
Tye KM, Mirzabekov JJ, Warden MR, Ferenczi EA, Tsai HC, et al. 2013. Dopamine neurons modulate neural encoding and expression of depression-related behaviour. *Nature* 493:537–41
Tye NC, Everitt BJ, Iversen SD. 1977. 5-Hydroxytryptamine and punishment. *Nature* 268:741–43
Ungless MA, Magill PJ, Bolam JP. 2004. Uniform inhibition of dopamine neurons in the ventral tegmental area by aversive stimuli. *Science* 303:2040–42
Ungless MA, Whistler JL, Malenka RC, Bonci A. 2001. Single cocaine exposure in vivo induces long-term potentiation in dopamine neurons. *Nature* 411:583–87
van Duuren E, van der Plasse G, Lankelma J, Joosten RN, Feenstra MG, Pennartz CM. 2009. Single-cell and population coding of expected reward probability in the orbitofrontal cortex of the rat. *J. Neurosci.* 29:8965–76
van Zessen R, Phillips JL, Budygin EA, Stuber GD. 2012. Activation of VTA GABA neurons disrupts reward consumption. *Neuron* 73:1184–94
Waelti P, Dickinson A, Schultz W. 2001. Dopamine responses comply with basic assumptions of formal learning theory. *Nature* 412:43–48
Watabe-Uchida M, Zhu L, Ogawa SK, Vamanrao A, Uchida N. 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* 74:858–73
Weissbourd B, Ren J, DeLoach KE, Guenthner CJ, Miyamichi K, Luo L. 2014. Presynaptic partners of dorsal raphe serotonergic and GABAergic neurons. *Neuron* 83:645–62
Williams E, Stewart-Knox B, Helander A, McConville C, Bradbury I, Rowland I. 2006. Associations between whole-blood serotonin and subjective mood in healthy male volunteers. *Biol. Psychol.* 71:171–74
Wilson CJ, Kawaguchi Y. 1996. The origins of two-state spontaneous membrane potential fluctuations of neostriatal spiny neurons. *J. Neurosci.* 16:2397–410
Winston JS, Gottfried JA, Kilner JM, Dolan RJ. 2005. Integrated neural representations of odor intensity and affective valence in human amygdala. *J. Neurosci.* 25:8903–7
Wise RA. 1978. Catecholamine theories of reward: a critical review. *Brain Res.* 152:215–47
Wise RA. 1996. Addictive drugs and brain stimulation reward. *Annu. Rev. Neurosci.* 19:319–40
Wise RA. 2004. Dopamine, learning and motivation. *Nat. Rev. Neurosci.* 5:483–94
Wise RA. 2008. Dopamine and reward: the anhedonia hypothesis 30 years on. *Neurotoxicity Res.* 14:169–83
Wise RA, Raptis L. 1986. Effects of naloxone and pimozide on initiation and maintenance measures of free feeding. *Brain Res.* 368:62–68
Wise RA, Rompre PP. 1989. Brain dopamine and reward. *Annu. Rev. Psychol.* 40:191–225
Xiu J, Zhang Q, Zhou T, Zhou TT, Chen Y, Hu H. 2014. Visualizing an emotional valence map in the limbic forebrain by TAI-FISH. *Nat. Neurosci.* 17:1552–59
Yan J, Scott TR. 1996. The effect of satiety on responses of gustatory neurons in the amygdala of alert cynomolgus macaques. *Brain Res.* 740:193–200
Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, et al. 2011. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature* 477:171–78
Young AM, Joseph MH, Gray JA. 1993. Latent inhibition of conditioned dopamine release in rat nucleus accumbens. *Neuroscience* 54:5–9
Zhou J, Jia C, Feng Q, Bao J, Luo M. 2015. Prospective coding of dorsal raphe reward signals by the orbitofrontal cortex. *J. Neurosci.* 35:2717–30

Zhu Y, Wienecke CF, Nachtrab G, Chen X. 2016. A thalamic input to the nucleus accumbens mediates opiate dependence. *Nature* 530:219–22

Ziv Y, Burns LD, Cocker ED, Hamel EO, Ghosh KK, et al. 2013. Long-term dynamics of CA1 hippocampal place codes. *Nat. Neurosci.* 16:264–66

Zweifel LS, Fadok JP, Argilli E, Garelick MG, Jones GL, et al. 2011. Activation of dopamine neurons is critical for aversive conditioning and prevention of generalized anxiety. *Nat. Neurosci.* 14:620–26

Annual Review of Neuroscience

Volume 39, 2016

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Neuroscience* articles may be found at http://www.annualreviews.org/errata/neuro