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Invited review

Neurocircuitry of drug reward

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ABSTRACT

In recent years, neuroscientists have produced profound conceptual and mechanistic advances on the neurocircuitry of reward and substance use disorders. Here, we will provide a brief review of intracranial drug self-administration and optogenetic self-stimulation studies that identified brain regions and neurotransmitter systems involved in drug- and reward-related behaviors. Also discussed is a theoretical framework that helps to understand the functional properties of the circuitry involved in these behaviors. The circuitry appears to be homeostatically regulated and mediate anticipatory processes that regulate behavioral interaction with the environment in response to salient stimuli. That is, abused drugs or, at least, some may act on basic motivation and mood processes, regulating behavior-environment interaction. Optogenetics and related technologies have begun to uncover detailed circuit mechanisms linking key brain regions in which abused drugs act for rewarding effects.

This article is part of a Special Issue entitled 'NIDA 40th Anniversary Issue'.

1. Introduction

Dopamine (DA) neurons localized in the midbrain projecting to the striatal complex, particularly the ventral tegmental area (VTA)-the ventral striatum (VStr) system, play a major role in mediating rewarding effects of drugs of abuse (Bowers et al., 2010; Fibiger and Phillips, 1986; Koob, 1992; Robbins and Everitt, 1996; Wise and Bozarth, 1987). The ascending DAergic system is thought to be a common pathway mediating response not only to psychomotor stimulant drugs but also to other drugs including ethanol and opioids (Pierce and Kumaresan, 2006; Wise and Bozarth, 1987). However, the DA system is not the sole mediator of this response because biological properties such as reward arise from the collective properties of many components (Ikemoto, 2010). To fully understand the large-scale circuitry underlying drug reward, it is necessary to identify all the key components and determine how they work together in relation to the DA systems. The aim of this paper is to review a theoretical background that helps us to understand the functional nature of "drug reward" circuitry and to outline related studies involving intracranial drug injections and optogenetics, as all together they help identify brain regions and neurotransmitter systems that are crucial components of this circuitry.

2. Theoretical framework: drug reward, motivation, and reinforcement

Before reviewing the brain regions and transmitters involved in drug self-administration, a theoretical framework is presented to help readers understand how detailed mechanisms can be put together as components of a system. After reviewing regions and transmitters that mediate reward, we will further elaborate key conceptual issues.

2.1. What is reward?

Although the VTA-VStr DA system has been identified as a key substrate for the rewarding effects of abused drugs, it has been questioned whether the DA system really mediates reward (Berridge and Robinson, 1998; Ikemoto and Panksepp, 1999; Salamone, 1994). This is in part because "reward" has not been uniformly defined. In addition, it is unclear how to integrate the

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role of DA in aversive situations (Salamone, 1994) and the lack of roles of DA in food consumption (Koob et al., 1978) and hedonic taste reaction (Berridge and Robinson, 1998). To tackle these issues, it is important to first define "reward". Rewards are things that have positive effects on behavior, attitude, relationships, etc., or in technical jargon, stimuli that reinforce behavior. In addition, reward is operationally defined, in this paper, as an *induced state that subsequently leads to conditioned approach behavior*. The latter definition is consistent with observations from manipulations of the VTA-VStr DA system (Ikemoto, 2007; Ikemoto and Panksepp, 1999). Although the roles of DA in aversive situations seem more complex than those in appetitive situations, this notion may even explain some effects of DA release or manipulations in aversive situations (Oleson et al., 2012), given that avoidance behavior is conceived as an approach behavior directed toward safety (Ikemoto and Panksepp, 1999). Moreover, this definition is not equal to or necessarily accompanied by positive conscious experience. Let us further elaborate on this.

Can activation of DA systems be accompanied by any feeling? It seems reasonable to speculate that the activation of DA systems initially alters sub-conscious processes, and then a cascade of actions, triggered by DA, eventually tap into the conscious mind and induces perceived positive changes in feelings. Based on the rewarding effects in humans of psychostimulants such as cocaine (Volkow et al., 1997), the activation of DA systems appears to be accompanied by positive emotional arousal characterized as "euphoria" rather than by hedonic sensory pleasure (Ikemoto, 2007, 2010). In any case, feelings accompanied by activation of DA systems are only the tip of the iceberg. Reward processes triggered by DA systems are mediated by an extensive set of brain structures and neurotransmitter systems (Ikemoto, 2010).

2.2. How do we study the neurocircuitry of drug reward?

It is reasonable to assume that the mammalian brain has never been selected for its capacity to take or seek drugs through its phylogeny (Nesse and Berridge, 1997). Drug reward seems to arise from brain's capacities that have already evolved to perform functions unrelated to drug taking or seeking. In addition, although the DA systems are key components of the circuitry, the entire circuitry is most likely much more complex and vast (Ikemoto, 2010). Thus, a key question is how we should begin to study the neurocircuitry responsible for drug reward. First, we briefly turn to rich scientific literature on laboratory animal behavior in appetitive and aversive conditions. These studies can provide insights and theoretical grounds on the functional system that abused drugs alter to elicit rewarding effects. Although it is not the focus of this review, it should be noted that while a common functional system appears to be involved in the rewarding effects of many drugs, each drug exerts additional unique actions not related to reward, which makes it difficult to identify the common substrates.

2.3. Coordinating processes of approach behavior

The distinction between hedonic sensation and emotional euphoria is rooted from the distinction in behavioral research between consummatory and approach behaviors. This distinction arose from the recognition that consummatory behavior (e.g., feeding) is regulated by different factors from approach behavior (e.g., instrumental behavior, which is guided by anticipatory processes) (Bindra, 1968; Konorski, 1967). While consummatory behavior is partly controlled by *proximal stimuli* (e.g., taste), approach behavior is largely guided by *distal stimuli* (e.g., visual cues), which allow organisms to anticipate what may happen and give time and space for behavioral action. Indeed, approach behavior can be dissociated from consummatory behavior by behavioral and neural manipulations. For example, rats that have been previously trained to approach and feed under a hungry state will seek out food regardless of being hungry or sated, if they have not experienced eating food under a sated state in the same context (Dickinson and Balleine, 1994). Approach and consummatory responses can also be dissociated by brain manipulations, for example, by the suppression of VTA-VStr DA system. Microinjections of GABA into the VTA or the DA receptor antagonist flupentixol into the VStr can selectively disrupt approach behavior without altering reward consumption (Ikemoto and Panksepp, 1996). These findings help us understand why systemic injections of amphetamine, which suppress food appetite, can increase responding previously reinforced by food if animals are tested without food (i.e., during an extinction phase) (Clark, 1966; Cohen, 1991; Herling et al., 1979; Olds, 1970).

Such anticipatory approach behaviors are conceived to arise from coordinating processes integrating sensory, perceptual, cognitive, motor, and visceral signals into a coherent whole (Ikemoto, 2010). In other words, the anticipatory coordinator integrates information from specialized processors to regulate *behavioral interaction with the environment in response to salient stimuli*, including novel stimuli and classical rewards.

Behavioral research over the past few decades has suggested that increase in approach behavior is associated with positive affect, while their suppression with negative affect (Dickinson and Pearce, 1977; Konorski, 1967; Mackintosh, 1983; Rescorla and Solomon, 1967). For example, approach responses rewarded by food are readily disrupted by the presentation of a distal cue associated with aversive footshock (Estes and Skinner, 1941). Conversely, the presentation of a cue signaling food disrupts avoidance behavior guided by another cue signaling footshock (Grossen et al., 1969). Strikingly, the presentation of cues signaling food appears to elicit the same affective quality as the omission of footshock, because simultaneous presentations of food-signaling cue and shock omission cue have additive effects on approach behavior (Grossen et al., 1969). Conversely, cues signaling the absence of food have the same affective quality as those signaling footshock, because simultaneous presentations of these cues have additive effects on avoidance (Grossen et al., 1969). These findings and many others led to the proposal that two affectively dichotomous processes are associated with the activation and suppression of approach behavior, respectively (Dickinson and Pearce, 1977; Konorski, 1967; Mackintosh, 1983; Rescorla and Solomon, 1967; Schneirla, 1959).

Our working hypothesis is that neural mechanisms that regulate approach behavior (i.e., anticipatory processes) are major substrates of rewarding effects of many drugs including psychomotor stimulant drugs. In other words, many abused drugs appear to alter the mechanisms in such a way to stimulate approach-behavioral processes, which are accompanied by positively affective states.

2.4. Reward, reinforcement and learning

Another issue that needs to be mentioned is that reward and anticipatory processes, either related to natural rewards or abused drugs such as cocaine, are intricately tied with synaptic and cellular mechanisms that are also shared by learning and memory processes (for reviews on this topic, see Bowers et al., 2010; Lüscher and Malenka, 2011). Drug use can alter many aspects of the nervous system, which will then influence how animals and humans act in future. Animals and humans will learn about the environmental stimuli associated with drug taking, which will help them predict the opportunity or occurrence of drug administration (so

called Pavlovian learning) and determine what actions are needed to make it happen (instrumental learning).

3. Drug reward circuitry

Psychoactive substances are administered through various routes: ingestion through the mouth, inhalation into the nose and lungs, and injection into the vein. Consumed drugs will then reach receptors at which drugs trigger reward. Whereabouts of brain regions containing such receptors can be investigated by intracranial drug self-administration (ICSA) procedures in rats (Ikemoto and Wise, 2004). ICSA involves instrumental responding that contingently delivers small volumes (50–100 nl) of neuroactive chemicals (or drugs) into discrete brain regions (Ikemoto and Sharpe, 2001), so that drugs do not travel far from injection sites for reward action. To address site specificity, well-executed studies of ICSA also examined various regions or sub-regions just outside of suspected regions for reward action (for methodological issues of ICSA, see Ikemoto and Wise, 2004). Because the actions of drugs are site-specific, we occasionally discover that drugs that are not rewarding via systemic administration are readily self-administered into discrete brain regions. For example, while systemically administered picrotoxin elicits anxiety and aversion (File, 1986) and thereby will not be self-administered by humans or animals, they are readily self-administered into the posterior hypothalamic area (Ikemoto, 2005). Similarly, while systemic administration of baclofen induces sedative effects, it elicits psychostimulant and rewarding effects when injected into the midbrain raphe nuclei (Shin and Ikemoto, 2010b; Vollrath-Smith et al., 2012). Thus ICSA can reveal the site-specific activities of drugs.

Before we review ICSA findings summarized in Fig. 1, we should mention the new research technology called optogenetics. Optogenetics integrates genetics and optics to selectively excite or inhibit specific neural populations and their specific projections down to the millisecond scale (Boyden et al., 2005; Britt et al., 2012b; Tye and Deisseroth, 2012; Yizhar et al., 2011; Zhang et al., 2010). Thus this technology helps to determine important links

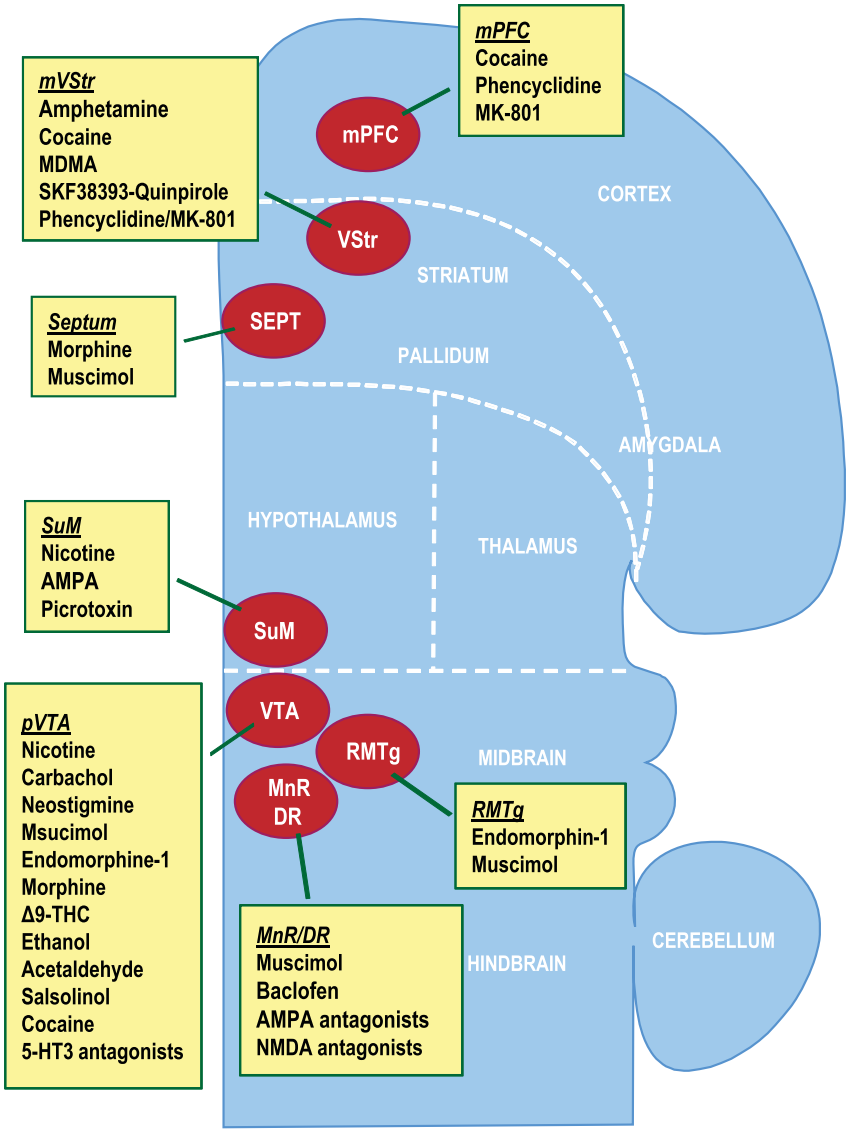

Fig. 1. Summary of intracranial self-administration studies. Previous studies showed that rats and mice self-administer various neuroactive chemicals (drugs) into discrete brain regions. Self-administered drugs are shown on a flat map modified from the one by Swanson (2004). Reference information is found in text. Abbreviations: mPFC, medial prefrontal cortex; MnR/DR, median and dorsal raphe nuclei; mVStr, medial ventral striatum; pVTA, posterior ventral tegmental area; RMTg, rostromedial tegmental nucleus; SEPT, septum; SuM, supramammillary nucleus.

among vast connectivity, including the key regions involved in reward as summarized in Fig. 2. That is, connectivity is not the same as functional circuitry, and key links need to be identified with respect to function of interest. We will mention relevant optogenetic studies as we review ICSA studies.

3.1. Ventral tegmental area and rostromedial tegmental nucleus

Tsai (1925) originally named this region as "nucleus tegmenti ventralis" (or "ventral tegmental nucleus"). However, researchers have subsequently referred to it as the ventral tegmental *area* (Nauta, 1958) because of its heterogeneous cytoarchitecture and lack of clear boundaries (for its history, see Ikemoto, 2007). Indeed, intracranial self-administration studies have revealed the functional heterogeneity within the VTA. The posterior VTA (Fig. 3B and C) mediates rewarding effects of many drugs more readily than the anterior VTA (Fig. 3A). The drugs that trigger reward from the posterior VTA include cholinergic agents (carbachol, neostigmine and nicotine) (Ikemoto et al., 2006; Ikemoto and Wise, 2002), opioids (endomorphin-1) (Zangen et al., 2002), cannabinoids ($^{\Delta 9}$THC) (Zangen et al., 2006), cocaine (Rodd et al., 2005a), alcohol-related chemicals (ethanol, acetaldehyde and salsolinol) (Rodd et al., 2005b, 2004, 2008), and serotonin-3 receptor agonists (Rodd et al., 2007). These drugs that are self-administered into the VTA most likely activate DA neurons. Recent optogenetic studies have demonstrated that rats and mice readily learn to instrumentally respond to obtain photostimulation that selectively excites VTA DA neurons, and that excitation of VTA DA neurons induces conditioned place preference (Kim et al., 2012; Tsai et al., 2009; Witten et al., 2011).

In addition, one of the midline DAergic structures clearly implicated in reward is the central (or caudal) linear nucleus raphe (Fig. 3C). This structure contains both DA (Swanson, 1982) and 5-HT neurons (Halliday and Tork, 1989; Steinbusch, 1981) and appears to mediate the rewarding effects of nicotine (Ikemoto et al., 2006) and muscimol (Ikemoto et al., 1998b).

Recent research has suggested that some of these drugs, especially opioids, exert their rewarding actions at the posterior tip of the VTA (Fig. 3C), which is traditionally considered to be part of the VTA, but hardly contains DA neurons (Ikemoto, 2007). This zone appears to be part of a newly identified nucleus that has been named as the tail of the VTA (Kaufling et al., 2009) or the rostromedial tegmental nucleus (RMTg) (Jhou et al., 2009). The RMTg extends posteriorly beyond the traditional VTA boundary (Fig. 4). It contains predominantly GABAergic neurons, whose major projections target DAergic neurons in the VTA and substantia nigra pars compacta. Stimulation of the RMTg has been shown to inhibit over 90% of DA neurons (Hong et al., 2011). Because GABAergic neurons of the RMTg are tonically active and express μ-opioid receptors (Jhou et al., 2009), we hypothesized that intra-RMTg injections of μ-opioid receptor agonists would be rewarding by inhibiting RMTg GABA neurons, which may tonically inhibit midbrain DA neurons, leading to disinhibition of DA neurons. We found that rats readily self-administer the μ-opioid receptor agonist endomorphin-1 into the RMTg, but not into the regions dorsal, ventral, or lateral to it (Jhou et al., 2012). Rats appear to self-administer endomorphin-1 into the RMTg more vigorously than into the VTA filled with DA neurons. In addition, we found that the GABA receptor agonist muscimol is self-administered into the RMTg. Consistently, recent studies have found that application of μ-opioid agonists into the RMTg disinhibit VTA DA neurons (Jalabert et al., 2011; Lecca et al., 2012; Matsui and Williams, 2011). It has not yet been investigated whether other drugs found to trigger reward from the posterior VTA also trigger reward from the RMTg.

3.2. Ventral striatum

VTA DA neurons robustly project to the VStr, consisting of the nucleus accumbens and the striatal part of the olfactory tubercle (OT_{Str}). The OT_{Str} has received little research attention; however, recent studies have suggested that the OT_{Str} plays an important role in the rewarding effects of psychostimulant drugs. The OT_{Str} is anatomically continuous with the nucleus accumbens shell (Heimer, 1978). First, the OT_{Str} contains medial spiny GABAergic neurons and other cellular features similar to the nucleus accumbens. Second, although the OT_{Str} of rats and mice are separated from the nucleus accumbens shell by the medial forebrain bundle, the primate OT_{Str} is not separated from the shell by such fiber tract. In addition, the afferents and efferents of the OT_{Str} are very similar to those of the shell of nucleus accumbens. Both regions receive, in addition to DAergic afferents from the VTA, glutamatergic afferents from the midline thalamus and limbic cortices including the prefrontal area, basolateral amygdala, and ventral subiculum (Heimer, 1978; Heimer and Wilson, 1975), although there are projections unique to each of them. Because the two structures seem to be continuous in many ways, common afferents and efferents between the medial accumbens shell and medial OT_{Str} are shown in Fig. 2D as the mVStr.

Rats readily learn to self-administer DAergic drugs into the VStr. In general, self-administration mediated by the medial shell or medial OT_{Str} is more reliable than that by the core or other striatal regions; however, the most effective zone within the striatum appears to differ depending on the drug. Cocaine, amphetamine, nomifensine and D_1/D_2 receptor agonists are self-administered into the medial shell of the nucleus accumbens more vigorously than the accumbens core (Carlezon et al., 1995; Ikemoto et al., 1997, 2005; Rodd-Henricks et al., 2002). Studies that examined subregions of ventral and dorsal striatum suggested that the medial OT_{Str} robustly mediates self-administration effects of cocaine or amphetamine more than any other ventral or dorsal striatal regions (Ikemoto, 2003; Ikemoto et al., 2005). However, MDMA is readily self-administered into the medial shell and core, but not into the medial OT_{Str} (Shin et al., 2008). Although MDMA has similar properties as D-amphetamine and cocaine on DA mechanisms, it alters serotonergic systems and increases extracellular serotonin levels much more potently than amphetamine or cocaine (Green et al., 2003). This property of MDMA may interfere with DA reward mediated through the medial OT_{Str}, which may have stronger serotonergic innervations than the nucleus accumbens.

The differential effects among MDMA, amphetamine and cocaine shed light on understanding drug actions on reward. Even within discrete brain regions, the property of the drugs to alter neural activities other than DAergic ones may significantly influence the rewarding effects of drugs. In addition, although previous studies emphasized the role of the medial VStr (medial shell and medial OT_{Str}) in reward, the core can also mediate reward. However, reward mediated through the core does not seem to be as robust as that mediated through the medial shell or medial OT_{Str}.

In addition, non-DAergic drugs are self-administered into the shell. Rats self-administer the cannabinoid $^{\Delta 9}$THC into the medial shell, but not the core (Zangen et al., 2006). Within the medial shell, the posterior rather than the anterior medial shell appears to mediate $^{\Delta 9}$THC reward. Effects of opioids are not consistent among reports. Goeders et al. (1984) found that rats self-administer methionine-enkephalin into the accumbens. However, Zangen et al. (2002) failed to detect conditioned place preference effects of the μ-receptor selective agonist endomorphin-1 when injected into the nucleus accumbens, even though the same concentrations of endomorphin-1 injected into the VTA induce conditioned place preference.

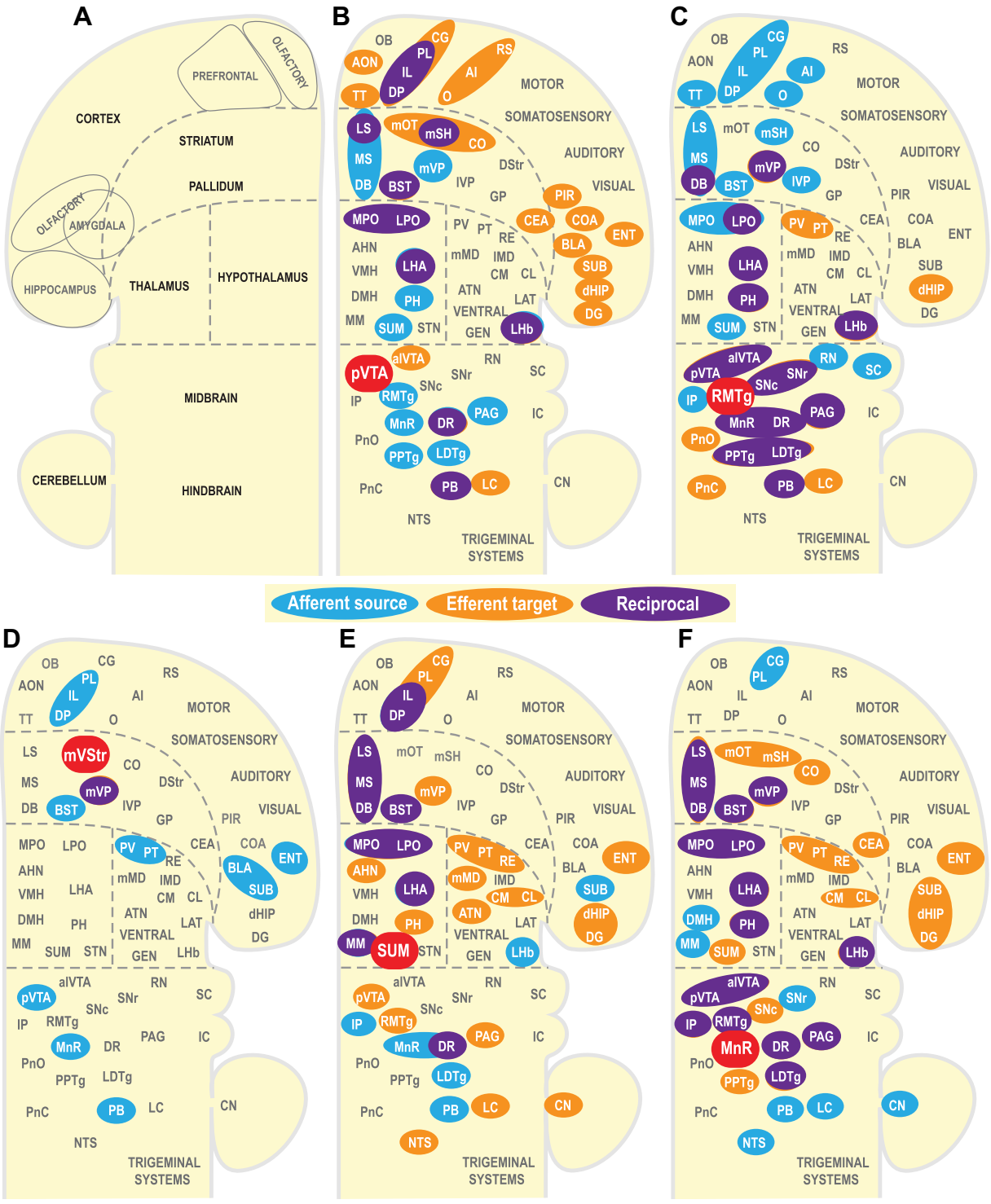

Fig. 2. Afferents to and efferents from the trigger zones. (A) Schematic drawing shows a flat map adopted and modified from Swanson (2004). (B–F) Afferent, efferent, and reciprocal projections of the region of interest (red-filled circle) are indicated by different colors: blue, orange and purple, respectively. Shown here are generally clear projections, except VTA afferents to the cortical regions, which are sparse (for references, see Ikemoto, 2010) Abbreviations: AHN, anterior hypothalamic nucleus; AI, agranular insular cortex; alVTA, anterolateral ventral tegmental area; ATN, anterior nuclei, dorsal thalamus; BLA, basolateral amygdalar nucleus; BST, bed nucleus of stria terminalis; CEA, central amygdalar nucleus; CG, cingulate cortex; CL, centrolateral thalamic nucleus; CM, central medial thalamic nucleus; CN, cerebellar nuclei; CO, core of the nucleus accumbens; COA, cortical amygdalar nucleus; DB, diagonal band of Broca; dHIP, dorsal hippocampus; DG, dentate gyrus; DMH, dorsomedial hypothalamic nucleus; DP, dorsal peduncular cortex; DR, dorsal raphe nucleus; DS, dorsal striatum; ENT, entorhinal area; GEN, geniculate thalamic nuclei; GP, globus pallidus; IC, inferior colliculus; IL, infralimbic cortex; IMD, intermediodorsal thalamic nucleus; IP, interpeduncular nucleus; IVP, lateral ventral pallidum; LAT, lateral nuclei, dorsal thalamus; LC, locus coeruleus; LDTg, laterodorsal tegmental nucleus; LHA, lateral hypothalamic area; LHb, lateral habenular nucleus; LPO, lateral preoptic area; LS, lateral septal area; MM, medial mammillary nucleus; mMD, medial mediodorsal thalamic nucleus; MPO, medial preoptic area; MnR, median raphe nucleus; MS, medial septal area; mSH, medial shell of the nucleus accumbens; mOT, medial olfactory tubercle; mVP, medial ventral pallidum; mVStr, medial ventral striatum; NTS, nucleus of the solitary tract; O, orbital area; PAG, periaqueductal gray; PB, parabrachical nucleus; PIR, piriform cortex; PH, posterior hypothalamic nucleus; PL, prelimbic cortex; PnC, pontine reticular nucleus, caudal part; PnO, pontine reticular nucleus, oral part; PPTg, pedunculopontine tegmental nucleus; PT, paratenial thalamic nucleus; PV, paraventricular thalamic nucleus; pVTA, posterior ventral tegmental area; RE, reuniens thalamic nucleus; RMTg, reostromedial tegmental nucleus; RN, red nucleus; RS, retrosplenial cortex; SNr, substantia nigra, reticular part; SNc, substantia nigra, compact part; STN, subthalamic nucleus; SUB, subiculum; SuM, supramammillary nucleus; SC, superior colliculus; TT, tenia tecta; VMH, ventromedial hypothalamic nucleus. Modified from Fig. 8 of Ikemoto (2010).

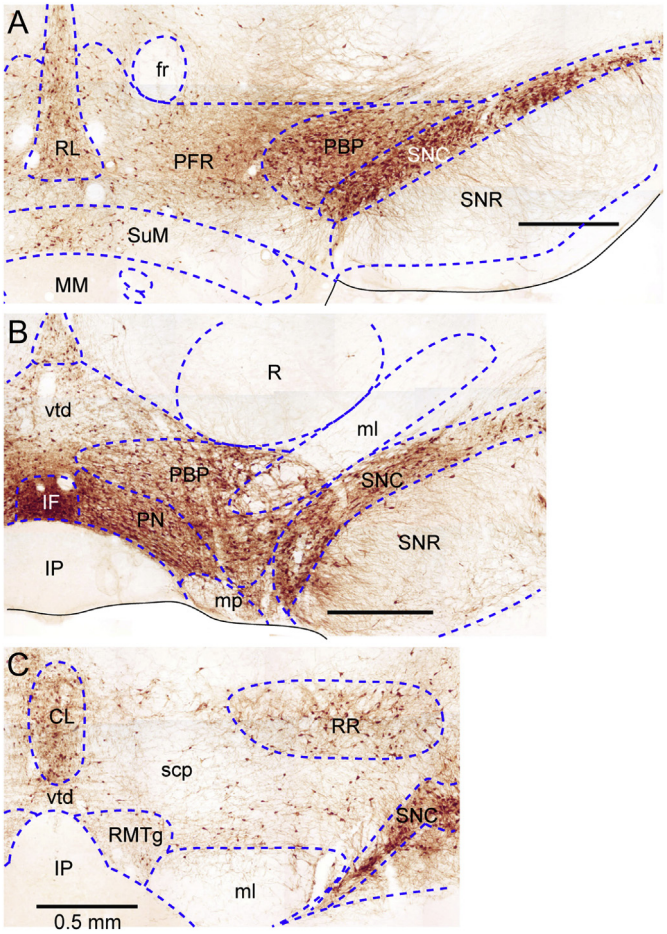

Fig. 3. Coronal sections of the ventral tegmental area of the rat brain. Three sections from the anterior to posterior (A, B and C) are shown to illustrate the differential cytoarchitectonic features within the ventral tegmental area. Sections are stained with tyrosine hydroxylase, which indicates dopaminergic neurons in this area of the brain. Abbreviations: CL, central (or caudal) linear nucleus raphe; fr, fasciculus retroflexus; IF, interfascicular nucleus; IP, interpeduncular nucleus; ml, medial lemniscus; PBP, parabrachial pigmented area; PFR, parafasciculus retroflexus area; PN, paranigral nucleus; R, red nucleus; RL, rostral linear nucleus raphe; RMTg, rostromedial tegmental nucleus; RR, retrorubral nucleus; scp, superior cerebellar peduncle; SNC, substantia nigra compact part; SNR, substantia nigra reticular part; SuM, supramammillary nucleus; vtd, ventral tegmental decussation. Modified from Figs. 5, 6 and 8 in Ikemoto (2007).

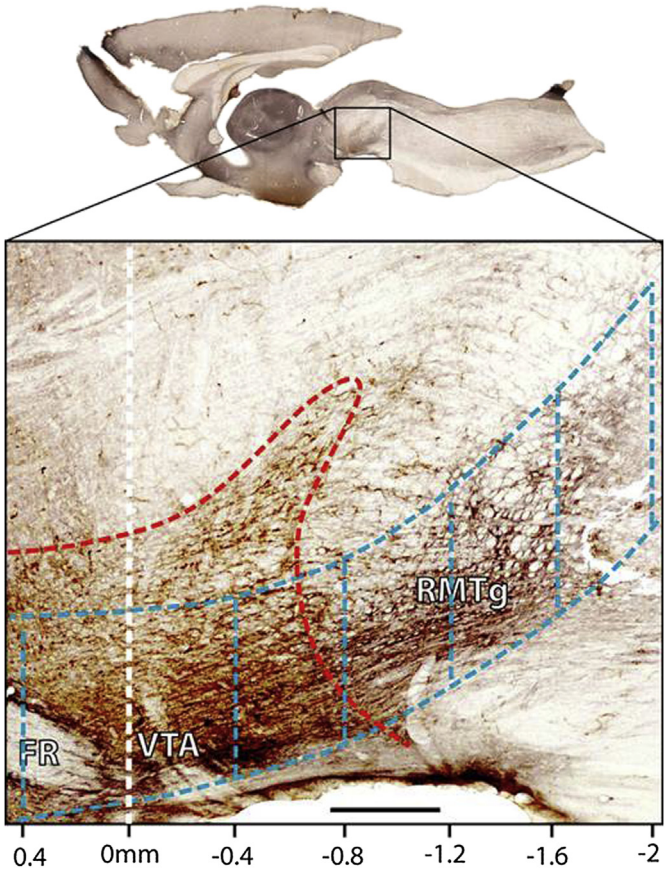

Fig. 4. A parasagittal rat brain section showing the rostromedial tegmental nucleus. Tyrosine hydroxylase immunostaining (red brown outlined with red dashed line) indicates dopamine neurons, while immunostaining of μ-opioid receptors (bluish black) indicates the RMTg region. Bottom panel is magnified from top. Numbers at the bottom indicate anterior-posterior (AP) distance relative to a plane (vertical dashed line) passing through the rostral tip of the interpeduncular nucleus (not visible in this section). Blue dotted lines delineate a series of 0.4 mm thick slabs stacked anteroposteriorly, forming a column of tissue passing through the VTA, RMTg, and sites immediately posterior. Scalebar in bottom panel is 400 μm. Adopted from Fig. 2 in Jhou et al. (2012).

Carlezon and Wise (1996) found that rats self-administer NMDA receptor antagonists into the shell, but not the core, a finding that led to the hypothesis that inhibition of GABAergic medium spiny projection neurons (MSNs) is rewarding (Carlezon and Thomas, 2009). However, this hypothesis is not supported by recent optogenetic findings. Photostimulation of glutamate afferents that impinge on accumbens MSNs appears to be rewarding. Optogenetic studies revealed that selective stimulation of any of the afferents from the basolateral amygdala, ventral subiculum or medial prefrontal cortex to the VStr can support self-stimulation (Britt et al., 2012a; Stuber et al., 2011). Moreover, mice learn to instrumentally respond to obtain optogenetic stimulation of MSNs in the nucleus accumbens (Britt et al., 2012a). The apparent discrepancy between the pharmacological and optogenetic studies may be resolved if NMDA receptor antagonists in fact excite MSNs rather than inhibit them. The blockade of NMDA receptors in the medial prefrontal cortex has been shown to increase extracellular glutamate concentration (Ceglia et al., 2004; Pozzi et al., 2011). If the blockade of NMDA receptors in the accumbens does the same, increased glutamate could excite MSNs via other glutamate receptors including AMPA receptors.

Similarly, selective stimulation of MSNs in the dorsomedial striatum that express D_1 receptors and project to the midbrain (i.e., "direct pathway") has been shown to induce reward (Kravitz et al., 2012). This study not only supports the idea that excitation of MSNs is rewarding, but also offers additional information that MSNs localized in the dorsomedial striatum mediate reward. This is a novel finding since pharmacological studies failed to find the role of dorsomedial striatum in reward. Especially, DAergic drugs may not have rewarding effects in the dorsomedial striatum, because microinjections of amphetamine into the region do not induce psychostimulant effects, a correlate of reward (Shin et al., 2010). The rewarding effect of activating the direct pathway originating from the dorsomedial striatum seems to be consistent with the electrical self-stimulation study that showed that stimulation of the striosomes/patches rather than the matrixes in the dorsomedial striatum is rewarding (White and Hiroi, 1998). The striosomes/patches largely contain D_1-expressing MSNs (Crittenden and Graybiel, 2011). Thus, both the Kravitz et al. study and White and Hiroi study suggest that activation of the direct pathway (i.e., D_1-expressing MSNs) in the dorsomedial striatum induces reward.

Contrary to the dorsal striatum, the direct pathway does not seem to play a major role in VStr reward. First of all, the nucleus accumbens core, which has a similar direct- and indirect-pathway

organization of MSNs as the dorsal striatum, mediates little drug reward as reviewed above. In addition, the medial OT_{Str}, which mediates robust rewarding effects of cocaine and amphetamine (Ikemoto, 2003; Ikemoto et al., 2005), only project to the ventral pallidum, but not the midbrain or any other region (Heimer et al., 1987; Ikemoto, unpublished observation). That is, the OT_{Str} does not have the direct pathway, but solely the indirect pathway. This raises the question of how the indirect pathway mediates reward. Kravitz et al. (2012) found that optogenetic stimulation of the indirect pathway in the dorsomedial striatum is punishing. As discussed below (section 4.2), the reward circuitry appears to be homeostatically regulated; therefore, the opposite of positive and negative manipulations often induces negative and positive affective effects, respectively. In this light, it can be hypothesized that injections of DAergic drugs into the OT_{Str} are rewarding because they inhibit local MSNs, thereby, the indirect pathway. On the contrary, the notion that the OT_{Str} is an extension of the nucleus accumbens leads to the hypothesis that excitation of OT_{Str} MSNs is rewarding. This issue needs to be addressed by future research. In any case, the ventral pallidum appears to play a pivotal role in OT_{Str} DA reward as the sole downstream structure.

Activity of MSNs is not only modulated by DA and glutamate, but also acetylcholine. The source of acetylcholine in the VStr is its local interneurons. While cholinergic interneurons constitute less than 1% of the total VStr neurons, they can readily modulate activity of MSNs. Optogenetic stimulation of cholinergic interneurons inhibits about 80% of MSNs and excites the rest (Witten et al., 2010). Interestingly, systemic injections of cocaine activate cholinergic interneurons, and optogenetic inhibition of these interneurons disrupts the acquisition of conditioned place preference induced by cocaine (Witten et al., 2010). In addition, optogenetic stimulation of cholinergic interneurons evokes DA release (Cachope et al., 2012; Threlfell et al., 2012). Moreover, rats can learn to self-administer the cholinergic receptor agonist carbachol into the nucleus accumbens (Ikemoto et al., 1998a). Therefore, rewarding effects of cocaine may depend, at least in part, on VStr cholinergic activity.

3.3. The medial prefrontal cortex

The medial prefrontal cortex receives DAergic afferents from the VTA and glutamate afferents from other cortical regions. DAergic and NMDA receptor antagonists are self-administered into the medial prefrontal cortex, in addition to the nucleus accumbens shell. Rats learn to self-administer cocaine (Goeders et al., 1986; Goeders and Smith, 1983) and NMDA receptor antagonists – phencyclidine, MK-801, and 3-((±)2-carboxypiperazin-4yl)propryl-1-phosphate (Carlezon and Wise, 1996) – into the vicinity of the prelimbic area.

3.4. The supramammillary nucleus

The supramammillary nucleus (SuM) is localized in the posterior hypothalamic area, which is anterior to the VTA and dorsal to the mammillary bodies. Along its midline, some DA neurons are found, although DA or other neurons of the SuM do not project to any part of ventral or dorsal striatum. The SuM robustly projects to the entire septo-hippocampus formation (Vertes, 1992). Because of its connectivity, the SuM has been studied with respect to its role in hippocampal theta rhythm and memory (Pan and McNaughton, 2004).

ICSA studies have now established that the SuM participates in reward processes. Administration of $GABA_A$ receptor antagonists into the SuM is one of the most effective manipulations that support ICSA (Ikemoto, 2005). Rats not only administer $GABA_A$ receptor antagonist picrotoxin at relatively faster rates for ICSA, but also progressively increase responding when response requirement for an infusion of picrotoxin increases. In addition, the SuM mediates reward triggered by administration of nicotine (Ikemoto et al., 2006) or the glutamate receptor agonist AMPA (Ikemoto et al., 2004). These drugs are not self-administered into the anterior VTA, while AMPA injections into the anterior VTA induce aversive effects (Ikemoto et al., 2004), demonstrating site specificity of drug actions.

The SuM appears to reciprocally interact with the VTA-VStr DA system in reward. AMPA administration into the SuM, which induces reward, increases extracellular DA concentrations in the medial VStr as measured by microdialysis (Ikemoto et al., 2004). In addition, self-administration of AMPA or picrotoxin into the SuM is readily disrupted by a low dose of systemic administration of DA receptor antagonists. The administration of the cholinergic agent carbachol into the posterior VTA, which stimulates DA neurons (Westerink et al., 1996) and induces reward (Ikemoto and Wise, 2002), markedly increases expression of the transcription factor c-Fos in SuM neurons (Ikemoto et al., 2003). Moreover, c-Fos expression in SuM is positively correlated with the locomotor activity increased by VTA carbachol administration. These findings suggest that the SuM closely interacts with the VTA-VStr DA system in reward, but the underlying mechanism for this interaction has yet to be determined.

3.5. Midbrain raphe nuclei

Because the median (MnR) and dorsal (DR) raphe nuclei contains ascending serotonergic neurons, it is of interest to determine what extent serotonergic neurons are involved in affective processes. Electrical stimulation applied at vicinity of the MnR and DR can be very rewarding, since rats learn to self-stimulate at very fast rates (Deakin, 1980; Miliaressis et al., 1975; Rompré and Miliaressis, 1985). However, stimulation applied at the DR, and possibly at MnR, can also be aversive (Houdouin et al., 1991). The discrepancy probably depends on the stimulation parameter, in addition to the exact site of application. Intracranial drug injection studies found that the inhibition, rather than stimulation, of midbrain raphe neurons is rewarding. Fletcher and colleagues found that microinjections of the 5-HT_{1A} receptor agonist 8-OH-DPAT into the MnR or DR, manipulations that inhibit serotonergic neurons, induce conditioned place preference (Fletcher et al., 1993) and facilitate lateral hypothalamic self-stimulation (Fletcher et al., 1995). Our group provided further evidence that the inhibition of neurons in the MnR and DR is rewarding through studies administering GABAergic receptor agonists and glutamatergic receptor antagonists into these nuclei. We found that rats readily learn to self-administer the $GABA_A$ receptor agonist muscimol or the $GABA_B$ receptor agonist baclofen into the MnR or DR (Liu and Ikemoto, 2007; Shin and Ikemoto, 2010b). We also found that rats learn to self-administer AMPA or NMDA receptor antagonists ZK-200775 or AP-5 into these regions (Webb et al., 2012). Overall, the self-administration data suggest that inhibition of midbrain raphe neurons is rewarding.

While compelling evidence has not yet been accumulated, reward mediated through the MnR may depend on the activity of DA systems. The rewarding effects of muscimol or baclofen into the MnR depend on intact DA transmission, since self-administration is readily disrupted by a low dose of systemic administration of DA receptor antagonists. Consistently, muscimol injections into the MnR increase the ratios of DOPAC or HVA to DA in post mortem accumbens tissues (Wirtshafter and Trifunovic, 1992), suggesting that these manipulations increase extracellular DA levels in the nucleus accumbens.

Available evidence suggests the role of non-serotonergic MnR neurons in reward. While stimulation of $GABA_A$ receptors in the MnR

or DR can inhibit serotonergic neurons and reduce extracellular serotonin in the forebrain (Judge et al., 2004; Shim et al., 1997), serotonin depletion caused by the serotonin synthesis inhibitor PCPA does not reduce DA metabolism potentiated by intra-MnR muscimol injections (Wirtshafter and Trifunovic, 1992). Moreover, selective lesions of serotonergic cells using 5,7-dihydroxytryptamine do not reduce locomotion potentiated by intra-MnR muscimol injections (Paris and Lorens, 1987; Wirtshafter et al., 1987). Hence, non-serotonin neurons in the vicinity of the MnR appear to be involved in facilitating mesolimbic DA transmission, locomotor activity, and possibly reward.

3.6. Other trigger zones

Reward can be triggered by drugs from other regions: the septum, lateral hypothalamus and periaqueductal gray. Rats and mice are found to self-administer morphine or muscimol into the septal area (Cazala et al., 1998; Gavello-Baudy et al., 2008; Stein and Olds, 1977). Opiates appear to be also self-administered into the lateral hypothalamic area (Cazala et al., 1987; Olds, 1979) and periaqueductal gray (David and Cazala, 1994).

In summary, trigger regions identified by ICSA for reward include the VTA, RMTg, SuM and MnR. They are extensively linked with other brain regions including the parabrachial nucleus, locus coeruleus, laterodorsal tegmental nucleus, lateral habenula, posterior and lateral hypothalamic areas, preoptic areas, septal area, bed nucleus of stria terminalis, medial ventral pallidum and medial prefrontal cortex (Fig. 2). Accumulating evidence supports that these brain regions interact with the VTA-VStr DA system in motivated behavior, although it is beyond the scope of the present paper.

4. How do we bring them together?

The section above summarized trigger regions for reward and reward-trigger drugs. These findings raise questions as to whether these different regions and neurotransmitters form common functional circuitry. If so, how do these components interact and regulate with each other and other regions for common functions? These questions can be partly addressed by optogenetic procedures, which have already begun to do so. Another approach is to address the functional nature of the circuitry and to examine whether the reward manipulations from different brain regions induce common functional effects that are predicted by the theoretical framework discussed in section 2.

4.1. Potentiation of approach-behavioral processes

According to the theoretical framework, activation of the DA system facilitates approach-behavioral processes by promoting interactions between extended brain structures. If, for example, reward manipulations of the MnR stimulate the same circuitry as that of the VTA-VStr DA system, reward manipulations of the MnR should therefore induce behavioral and physiological effects related to anticipatory processes similar to those of the VTA-VStr DA system. Indeed, similar behavioral and physiological effects are observed between reward manipulations of the VTA-VStr DA system and those of other regions (Ikemoto, 2010). The behavioral effects of rewarding drug manipulations are discussed below and summarized in Table 1.

4.1.1. Locomotor activity

The increase in locomotor activity of rodents after activation of the VTA-VStr DA system is a well-documented effect. In their seminal paper, Wise and Bozarth (1987) argued that administration of many abused drugs including opioids and ethanol can increase locomotor activity in rats, an effect that indicates activation of the VTA-VStr DA system, which is a common substrate of the rewarding effects of abused drugs. Indeed, microdialysis studies have shown that administration of many abused drugs including psychomotor stimulants, opioids and ethanol increases extracellular DA levels in the VStr (Di Chiara and Imperato, 1988). In addition, locomotor activity is a key component of approach behavior. Therefore, it is consistent with the theoretical framework that systemic administration of abused drugs generally recruits processes involved in approach behavior.

Consistent with systemic administration, reward manipulations of different brain regions increase locomotor activity (Table 1). Injections of DAergic drugs into the VStr increase locomotor activity (Kelley et al., 1989). The effective zones within the VStr for locomotor effects (Ikemoto, 2002) appear to roughly correspond to effective zones for intracranial self-administration (Ikemoto, 2003; Ikemoto et al., 2005). Similarly, locomotor activity is facilitated by other rewarding manipulations: picrotoxin injections into the SuM (Shin and Ikemoto, 2010a), injections of carbachol, endomorphin-1, or $^{\Delta 9}$THC into the posterior VTA (Ikemoto et al., 2003; Zangen et al., 2002, 2006), and injections of muscimol, baclofen or excitatory amino acid receptor antagonists into the MnR or DR (Fink and Morgenstern, 1986; Przewlocka et al., 1979; Wirtshafter et al., 1993, 1989).

However, locomotor activity does not clearly indicate what underlying processes are and may simply reflect “general” arousal or hyperactivity instead of approach-behavioral processes. Thus locomotor activity does not serve as a strong measurement model to index coordinating processes of approach behavior. It is necessary to have behavioral measures that unequivocally index approach-behavioral processes.

4.1.2. Visual sensation seeking

Our group adopted a behavioral model, which is referred to as visual sensation (VS) seeking to index approach-behavioral

Table 1
Reward manipulations increase approach-behavioral processes.

Reward manipulation		Action @ receptor	Presumed neural effect	Behavioral effect	
Region	Trigger			Locomotion	VS seeking
VStr	Amphetamine or Cocaine	Increase in DA, then DA-R stimulation	Stimulation of GABA N activity	↑	↑
VTA	Carbachol Nicotine	Muscarinic or nicotinic R stimulation	DA N excitation	↑	?
	Morphine, Endomorphin-1, Optogenetic stimulation of GABA N	Stimulation of GABA N			
RMTg	Endomorphin-1	Mu-R stimulation	Inhibition of GABA neurons	↑	?
SuM	AMPA	AMPA-R stimulation	Excitation of local N	↑	↑
	Picrotoxin	$GABA_A$-R blockade		↑	?
MnR	Baclofen	$GABA_B$-R stimulation	Inhibition of local N	↑	↑
	ZK 200775	AMPA-R inhibition		↑	↑

Note: ↑, increase; ?, has not yet been investigated; Abbreviation: N, neuron; R, receptor.

processes. Rats that *have not been trained to lever-press for any classical rewards* (e.g., food) readily learn to lever-press for visual sensation (VS) such as a flash of light (Kish, 1966; Stewart and Hurwitz, 1958). That is, VS seeking is shorthand of instrumentally conditioned responding with VS. It is easily quantified and stable over many days. However, it remains unclear why rats work at all for VS, since the presentation of VS does not seem to directly contribute to homeostasis. The phenotypic trait to seek VS may have given its host a survival advantage by increasing probability for homeostatic opportunities. In any case, VS seeking can be used as a practical measurement model that unequivocally indicates approach-behavioral processes.

The effects of any manipulations on VS seeking should be attributed to approach coordinating processes after careful considerations of experimental conditions, since VS seeking depends on visuoperceptual, cognitive and motor processes. The manipulations described below most likely alter coordinating processes rather than visuoperception, cognition, or movement, since (1) they are not known to alter visual sensation or perception, (2) the cognitive requirement to perform task is minimal and constant across testing and (3) hyperactivity is ruled out by control tests.

We have shown that VS seeking is markedly increased by activation of the VTA-VStr DA system. More specifically, noncontingent administration of amphetamine into the VStr especially the medial OT_{Str} increases VStr seeking (Shin et al., 2010). Increased lever-pressing is not due to an increase in general movement, because the same amount of amphetamine injected into the same site fails to increase lever-pressing that is not reinforced by VS. That is, intra-VStr amphetamine increases locomotor activity with or without VS, while marked increase in lever-pressing depends on VS plus amphetamine. VStr seeking stimulated by intra-VStr amphetamine depends on DA mechanisms, since co-administration of DA receptor antagonists (D_1 or D_2) diminishes amphetamine-induced VS seeking. This study, in summary, confirms that VS seeking can be used as a measurement model to quantify coordinating processes involved in approach behavior.

We then examined whether reward manipulations of the MnR can increase VS seeking just like intra-VStr amphetamine. As discussed above, stimulation of $GABA_B$ receptors in the MnR induces a DA-dependent reward suggesting that MnR neurons expressing $GABA_B$ receptors appear to tonically suppress reward processes (Shin and Ikemoto, 2010b). Therefore, we reasoned that if baclofen reward in the MnR depends on the same circuitry as the VTA-VStr DA system, intra-MnR baclofen should increase VS seeking just like intra-VStr amphetamine. We found that noncontingent administration of baclofen into the MnR increases VS seeking (Vollrath-Smith et al., 2012). Fig. 5 shows a synergistic (i.e., supra-additive) interaction between noncontingent injections of intra-MnR baclofen and contingent presentation of VS on approach behavior. The levels of lever-presses are low when VS and baclofen are absent. Noncontingent injections of intra-MnR baclofen (BAC) insignificantly increase lever-pressing in the absence of VS (SEEKING $_{BAC}$). The presentation of VS without baclofen (SEEKING $_{VS}$) slightly increases active lever-presses. The presentation of VS with noncontingent intra-MnR baclofen (SEEKING $_{BAC+VS}$) markedly increases lever-pressing (i.e., SEEKING $_{BAC+VS}$ > SEEKING $_{BAC}$ + SEEKING $_{VS}$). These results suggest that intra-MnR baclofen selectively disinhibits approach-behavioral processes by inhibiting $GABA_B$ expressing neurons and that *MnR neurons expressing $GABA_B$* receptors do not merely suppress movements of any kind, but tonically suppress coordinating processes involved in approach behavior.

A similar effect on VS seeking is also observed with AMPA receptor blockade in the MnR. Rats readily learn to self-administer the AMPA receptor antagonist ZK 200775 (ZK) into the MnR (Webb et al., 2012). We observed intra-MnR ZK and VS synergistically potentiate approach responding (i.e., SEEKING $_{ZK+VS}$ > SEEKING $_{ZK}$ + SEEKING $_{VS}$) (Webb et al., 2012) similar to what we observed with intra-MnR baclofen. These results suggest that glutamatergic afferents to the MnR tonically suppress reward and approach-behavioral processes.

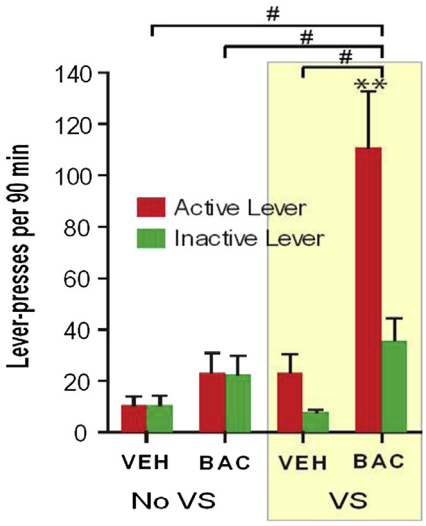

Fig. 5. Visual sensation (VS) seeking potentiated by noncontingent injections of intra-MnR baclofen. The data are means with SEM. A combination of VS and baclofen (BAC) injections increased lever-pressing more effectively than either manipulation alone ($N = 8$). $^{\#}P < 0.01$, the BAC + VS condition induced significantly greater lever-presses than other conditions. Both active lever-presses in the BAC-VS condition were significantly greater than any active or inactive lever responding in other conditions ($^{**}P < 0.01$). Abbreviations: VEH, vehicle. Modified from Fig. 3B in Vollrath-Smith et al. (2012).

In addition, our preliminary data suggest that the SuM can also mediate potentiation of VS seeking. While stimulation of AMPA receptors in the SuM is rewarding in rats (Ikemoto et al., 2004), noncontingent injections of AMPA into the SuM potentiate VS seeking (see Fig. 7C of Ikemoto, 2010).

These findings suggest that although the potentiation of approach behavior is thought to be a hallmark function of VStr DA, this function can be mimicked by manipulations of other brain regions including the MnR or SuM. Therefore, these findings are consistent with the view that the MnR and SuM are structural components of the circuitry in which the VTA-VStr DA system participates, and they coordinate processes of approach behavior.

4.2. Evidence for homeostatic regulation of reward processes

Accumulating evidence suggests that the coordinating processes involved in reward and approach behavior are homeostatically regulated. This notion is partly supported by the findings showing that the opposite of reward manipulations can suppress ongoing approach behavior and induce aversion (Table 2). We believe that this is an important notion for understanding how drugs of abuse alter the brain for reward. Consistently, Koob and Le Moal (2008) have used the notion of homeostatic regulation to understand drug addiction. We first present evidence supporting that the VTA-VStr DA system is homeostatically regulated in affective function.

Electrophysiological studies have shown that midbrain DA neurons constantly fire even if there is no salient stimulus available in the environment. Such activity of midbrain DA neurons must be involved in homeostatic regulation of some functions. The first report that explicitly addressed this issue was conducted by Liu et al. (2008), who found that injections of the D_2 receptor agonist

Table 2
Opposite manipulations of reward manipulations in the respective regions induce opposite behavioral effects, such as disruption in approach behavior and aversion.

Manipulation		Immediate action	Presumed neural effect	Behavioral effect	
Region	Trigger			Freezing/inactivity	CPA
VStr	SCH 23390 (1)	D_1-R blockade	Inhibition of GABA N	↑	↑
VTA	Quinpirole (2)	D_2-R stimulation	Inhibition of DA N	↑	↑
	Optogenetic excitation of GABA N (3)	Excitation of GABA N			
RMTg	Optogenetic stimulation (4)	Excitation of GABA N	Inhibition of midbrain DA N	?	↑
	AMPA (5)	AMPA-R stimulation			
SuM	Muscimol (6)	$GABA_A$-R stimulation	Inhibition of local N	↑	?
MnR	Kainate (7)	Kainate-R stimulation	Excitation of local N	↑	?

Note: ↑, increase; ?, has not yet been investigated; Abbreviation: N, neuron; R, receptor.
Reference information: (1) Baldo et al., 2002; Shippenberg et al., 1991; (2) Liu et al., 2008; (3) Lammel et al., 2012; Tan et al., 2012; (4) Stamatakis and Stuber, 2012; (5) Jhou et al., 2013; (6) Ma and Leung, 2007; (7) dos Santos et al., 2005.

quinpirole into the VTA, which reduce basal DA levels in the VStr, induce conditioned place aversion and reduce general activity level. Similarly, a recent optogenetic study found that inhibition of VTA DA neurons reduces struggles triggered by aversive stimuli (Tye et al., 2012). These findings are consistent with the view that reduction in tonic activity of VTA DA neurons induces a negative affective state, accompanied by the lack of motivation to interact with the environment.

The notion that tonic activity of the VTA-VStr DA system regulates motivation and mood is consistent with the finding that injections of the D_1 receptor antagonist SCH 23390 into the VStr induce aversion (Shippenberg et al., 1991), presumably by blocking tonic DA transmission. It also helps to explain how cocaine administration induces reward. Cocaine's rewarding effects partly depend on its action in the medial VStr (Ikemoto and Wise, 2002), which receive DA afferents from the VTA. Cocaine does not stimulate DA release, but merely blocks uptake of already released DA into the cytoplasm. Thus cocaine's reward action, at least initially, depends on the homeostatic regulation of the VTA-VStr DA system, and cocaine dysregulates it in an opposite manner that DA receptor antagonists do. This also means that effects of cocaine are significantly influenced by the homeostatic state of organisms. This notion is consistent with the finding that rats learn to acquire cocaine self-administration at lower doses in novel environments than in home environments (Caprioli et al., 2007).

Rewarding effects of some non-DAergic drugs can be attributed to mechanisms involved in the homeostatic regulation of the VTA-VStr DA system. While tonic activity of VTA DA neurons is partly intrinsic and displayed without afferent inputs, cholinergic afferents to DA neurons appear to contribute to tonic activity of DA neurons. As discussed above, stimulation of cholinergic receptors in the VTA activates DA neurons and induces reward, and rats readily learn to self-administer cholinergic agents including carbachol, nicotine and neostigmine into the posterior VTA (Ikemoto et al., 2006; Ikemoto and Wise, 2002). Neostigmine is an acetylcholinesterase inhibitor, which interferes with the breakdown of acetylcholine, thereby it can increase the extracellular levels of acetylcholine when it is tonically released. The finding that rats self-administer neostigmine into the VTA suggests that acetylcholine is tonically released in the VTA and that acetylcholine in the VTA participates in the homeostatic regulation of DA neurons, which modulates mood processes.

In addition, the homeostatic regulation of the DA system appears to be a key process for the rewarding effects of opioids administered into the posterior VTA and RMTg. As discussed above, stimulation of opioid receptors in the RMTg and posterior VTA inhibits local GABA neurons, an effect that appears to remove tonic inhibition over DA neurons (Jalabert et al., 2011; Lecca et al., 2012; Matsui and Williams, 2011), which then induces reward (Jhou et al., 2012). Recent optogenetic study suggests that the afferent inputs coming from the lateral habenula or bed nucleus of stria terminalis provide aversive signals to the RMTg and VTA by exciting local GABA neurons (Jennings et al., 2013; Jhou et al., 2013; Lammel et al., 2012; Stamatakis and Stuber, 2012). Therefore, certain afferents appear to provide tonic excitatory inputs to RMTg and VTA GABA neurons, which then tonically inhibit midbrain DA neurons.

There are other brain structures that appear to play important roles in homeostatic regulation of motivation and mood. As discussed above, rats vigorously self-administer the $GABA_A$ receptor antagonist picrotoxin or bicuculline into the SuM (Ikemoto, 2005). This observation suggests that GABAergic afferents tonically inhibit SuM neurons, and thereby imposing tonic inhibition over positive mood and motivation states. Thus GABA transmission via $GABA_A$ receptors in the SuM is involved in the homeostatic regulation of mood and motivation processes, and consequently, mere blockade of $GABA_A$ receptors induces reward. Similarly, MnR neurons appear to be involved in homeostatic regulation of mood and motivation processes. Rats readily learn to self-administer the AMPA receptor antagonist ZK 200775 or the NMDA receptor antagonist AP-5 into the MnR (Webb et al., 2012). This observation suggests that glutamate afferents tonically excite MnR neurons that suppress positive mood and motivational state. In summary, accumulating evidence supports the view that the circuitry that mediates drug reward is homeostatically regulated.

5. Conclusions

Past research conducted on psycho-behavioral mechanisms of appetitive and avoidance behavior in laboratory animals offers a theoretical framework to understand why certain neuroactive chemicals can induce reward. ICSA and related studies have provided information on brain regions and neurotransmitters involved in reward and homeostatic regulation of mood and motivation. In addition, emerging technologies such as optogenetics and DREADDs appears to be useful in elucidating the circuits of drug reward in detail.

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