Neuropsychopharmacology REVIEWS (2010) 35, 4–26

The Reward Circuit: Linking Primate Anatomy and Human Imaging

Suzanne N Haber*[,1] and Brian Knutson[2]

[1]*Department of Pharmacology and Physiology, University of Rochester School of Medicine, Rochester, NY, USA;* [2]*Department of Psychology, Stanford University, Stanford, CA, USA*

Although cells in many brain regions respond to reward, the cortical-basal ganglia circuit is at the heart of the reward system. The key structures in this network are the anterior cingulate cortex, the orbital prefrontal cortex, the ventral striatum, the ventral pallidum, and the midbrain dopamine neurons. In addition, other structures, including the dorsal prefrontal cortex, amygdala, hippocampus, thalamus, and lateral habenular nucleus, and specific brainstem structures such as the pedunculopontine nucleus, and the raphe nucleus, are key components in regulating the reward circuit. Connectivity between these areas forms a complex neural network that mediates different aspects of reward processing. Advances in neuroimaging techniques allow better spatial and temporal resolution. These studies now demonstrate that human functional and structural imaging results map increasingly close to primate anatomy.
Neuropsychopharmacology Reviews (2010) **35,** 4–26; doi:10.1038/npp.2009.129; published online 7 October 2009

Keywords: orbital prefrontal cortex; probability; reward anticipation; reward magnitude; substantia nigra; ventral medial prefrontal cortex; ventral striatum

INTRODUCTION

The demonstration by Olds and Milner that rats would work for electrical stimulation in specific brain sites led to the idea that there is an anatomically identifiable reward circuit (Olds and Milner, 1954). Support for the existence of such a circuit came with pharmacological manipulation of those sites, in particular intracranial injections of drugs of abuse (Carlezon and Wise, 1996; Carr and White, 1983; Phillips and Fibiger, 1978). Although several brain regions are part of this circuit, based on self-stimulation, pharmacological, physiological, and behavioral studies, the nucleus accumbens (NAcc) and the ventral tegmental area (VTA) dopamine neurons appear to be at the center (Hikosaka *et al*, 2008; Kelley and Berridge, 2002; Rolls, 2000; Schultz, 2000; Schultz *et al*, 2000; Stefani and Moghaddam, 2006; Wise, 2002). Recent studies have shown that the striatal and midbrain areas that are involved in the reward are more extensive than previously thought. They include the entire ventral striatum (VS) and the dopamine neurons of the substantia nigra (SN), respectively. The VS receives its main cortical input from the orbital frontal cortex (OFC) and anterior cingulate cortex (ACC) and a massive dopaminergic input from the midbrain. The VS projects to the ventral pallidum (VP) and to the VTA/SN, which, in turn, project back to the prefrontal cortex, via the medial dorsal (MD) nucleus of the thalamus. This circuit is an integral part of the cortico-basal ganglia system. In addition, other structures including the amygdala, hippocampus, lateral habenular (LHb) nucleus, and specific brainstem structures, such as the pedunculopontine nucleus and the raphe nuclei, are key components that regulate the reward circuit (Figure 1).

Reward is a central component for driving incentive-based learning, appropriate responses to stimuli, and the development of goal-directed behaviors. One of the main goals of animal and human studies is to understand how the different brain regions in the circuit work together to evaluate environmental stimuli and transform that information into actions. A key challenge is to translate what we know about reward from animal studies to the human brain. At the foundation of brain image analysis is anatomy, the identification of structures and their connectivities. While the basic anatomy of the structures and pathways of the reward circuit are now well established, new anatomical studies continue to add important data that shape our understanding of how its different components are related. In contrast to animal studies, human imaging work is relatively new. Nonetheless, there has been an

*Correspondence: Dr SN Haber, Department of Pharmacology and Physiology, University of Rochester School of Medicine, 601 Elmwood Avenue, Room 5-7425, Rochester, NY 14642, USA, Tel: +1 585 275 4538, Fax: +1 585 273 2652, E-mail: suzanne_haber@urmc.rochester.edu
Received 16 May 2009; revised 1 August 2009; accepted 4 August 2009

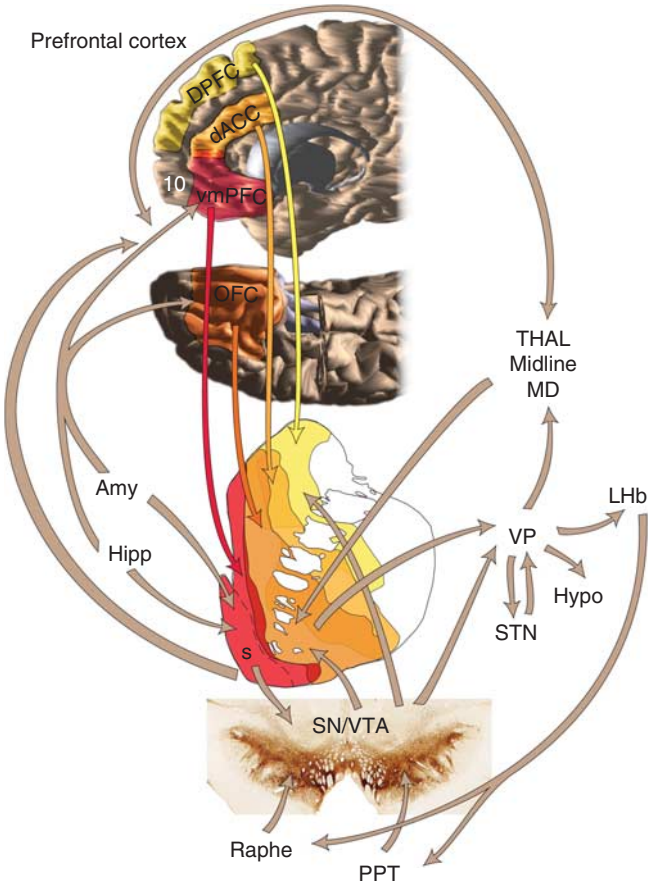

Figure 1. Schematic illustrating key structures and pathways of the reward circuit. Red arrow = input from the vmPFC; dark orange arrow = input from the OFC; light orange arrow = input from the dACC; yellow arrow = input form the dPFC; brown arrows other main connections of the reward circuit. Amy = amygdala; dACC = dorsal anterior cingulate cortex; dPFC = dorsal prefrontal cortex; Hipp = hippocampus; LHb = lateral habenula; hypo = hypothalamus; OFC = orbital frontal cortex; PPT = pedunculopontine nucleus; S = shell, SNc = substantia nigra, pars compacta; STN = subthalamic nucleus.; Thal = thalamus; VP = ventral pallidum; VTA = ventral tegmental area; vmPFC = ventral medial prefrontal cortex.

explosion of such studies that focus on the function of the prefrontal cortex and striatum in reward. These studies use different reward paradigms, methods of analysis, and technologies, creating a complex literature that is often difficult to synthesize. Thus, our goal here is not so much to exhaustively review that literature, but to highlight some promising lines of inquiry based on it. This chapter focuses first on the anatomy (primarily in monkeys). Second, we review functional activation of cortico-basal ganglia reward circuitry to explore points of convergence between primate anatomy studies and human functional MRI studies. Clearly, imaging methods to date do not have the resolution capabilities afforded by animal-tracing studies. Therefore, the anatomical specificity obtained through animal work is not currently possible using functional MRI. However, in each section, we link these studies when possible.

Reward and the Basal Ganglia

The reward circuit, now considered to be embedded within the cortico-basal ganglia network, is a central component for developing and monitoring motivated behaviors. Historically, however, the basal ganglia were best known for their relevance to motor functions, based both on the neuropathology of movement disorders and the idea that basal ganglia pathways return primarily to motor cortex (Nauta and Mehler, 1966). Our concept of basal ganglia function has dramatically changed in the last 30 years, from a purely motor or sensory-motor function to a more complex set of functions that mediate the full range of goal-directed behaviors, including emotions, motivation, and cognition. The change resulted from several lines of inquiry, but at the center was the demonstration that frontal cortical information passing through the basal ganglia returns to all of the frontal cortex, not only to motor cortex. This idea first arose in the late 1970s with the development of Heimer's classic concept of the VS and VP. The discovery added a separate functional loop, the limbic loop, within the basal ganglia (Heimer, 1978). Subsequently, the anatomical demonstration of this circuit (Haber *et al*, 1985; Heimer *et al*, 1982; Young III *et al*, 1984) provided the evidence for other functional loops (Alexander *et al*, 1990). The idea of separate cortical loops in the basal ganglia was expanded in primates to include several parallel and segregated circuits based on the finding that each general functional area of cortex (limbic, associative, and sensorimotor) is represented in specific regions in each basal ganglia structure (Alexander *et al*, 1990; Parent and Hazrati, 1995).

The concept of parallel and segregated functional pathways through the basal ganglia has dominated the field for the past 20 years. However, adaptive behaviors require a combination of reward evaluation, associative learning, and the ability to develop appropriate action plans and inhibit inappropriate choices on the basis of earlier experience. Thus, integration of different aspects of reward processing and interaction of reward circuits and brain regions involved in cognition and motor control are essential. Indeed, the idea of a motivation-to-movement interface through basal ganglia circuits was developed soon after the discovery of the limbic component to the basal ganglia (Heimer *et al*, 1982; Mogenson *et al*, 1980; Nauta, 1986). A relatively recent explosion of studies in rodents, monkeys, and humans supports the hypothesis of integration between functional circuits. Together, this literature shows the complexity of the cortico-basal ganglia network and the place of the reward circuit within it. Overall, there appears to be a dual organization that permits both parallel and integrative processing. Thus, the ventral cortico-basal ganglia network, while at the heart of reward processing, does not work in isolation (Belin and Everitt, 2008; Bevan *et al*, 1997; Brown *et al*, 1998; Draganski *et al*, 2008; Haber *et al*, 2000, 2006; Joel and Weiner, 1994; Kasanetz *et al*, 2008; Kolomiets *et al*, 2001; McFarland and Haber, 2002;

Mena-Segovia *et al*, 2005; Percheron and Filion, 1991). Indeed, within each station of the circuit, there are pathways that allow communication between different parts of the reward circuit and between the reward circuit and the associative circuit. In this chapter, we first describe the anatomical organization of each of the main structures and points of interaction between circuits before discussing their role in reward, as indicated from human imaging studies.

PREFRONTAL CORTEX

Organization of Prefrontal Cortex

Although cells throughout cortex fire in response to rewarding stimuli, the main cortical areas associated with reward are the anterior cingulate cortex and OFC. These are complex and heterogeneous regions, each of which is further divided into specific cortical areas: the anterior cingulate cortex includes areas 24, 25, and 32; the orbital cortex is divided into areas 11, 12, 13, and 14 (Barbas, 1992; Carmichael and Price, 1994; Fuster, 2001; Walker, 1940). Several homologies have been developed primarily based on cytoarchitectonics between monkey human prefrontal cortical areas (Brodmann, 1909; Fuster, 2001; Ongur and Price, 2000; Petrides and Pandya, 1994). Determining these homologies is a complex and difficult task due to the enormous expansion of prefrontal cortex through evolution. Nonetheless, there is reasonable agreement about which cortical areas can be considered homologous. However, cortical labeling in humans and monkeys can differ. Particularly relevant for this chapter is area 11 in the monkey, which is part of the OFC and does not reach the midline, whereas in the human PFC, area 11 does. In contrast, area 14 of the OFC lies on the ventral surface at the midline in monkeys, but may not be a designated area in some human maps. Area 32 occupies a somewhat different position in monkey and human maps. Since imaging studies cannot distinguish between these cortical divisions, they are, therefore, more broadly defined. These prefrontal regions include (1) a caudal, sensory region, which includes parts of both the OFC and insula cortex; (2) a rostral OFC, which includes parts of areas 11, 13, and 12; (3) a ventral, medial PFC (vmPFC), which includes primarily areas 11, 10, and 32 in humans and areas 25, 14, and subgenual area 32 in monkeys; and (4) the dorsal ACC (dACC), area 24. The vmPFC contains a subregion, the medial PFC (mPFC) that is limited to areas 10/32, and does not include medial OFC, area 11 (Knutson *et al*, 2003). Although some authors include the dACC in a general category of mPFC, others distinguish the dACC from subgenual medial areas (Averbeck and Seo, 2008; Botvinick *et al*, 1999b; Glascher *et al*, 2009; Haber *et al*, 2006; Knutson *et al*, 2003; Passingham *et al*, 2002; Petrides *et al*, 2002). For a more detailed anatomical discussion of these cortical regions, see Price and Drevets in this volume.

Reward Processing in the Human Prefrontal Cortex

Initial metabolic PET and FMRI studies show that various types of rewards can recruit prefrontal cortical activity. These findings generally suggest that exposure to both primary rewards (eg, pleasant tastes, sounds, and sights) and secondary rewards (eg, monetary gains) increases activity in regions of frontal cortex in general and the vmPFC in particular (Aharon *et al*, 2001; Anderson *et al*, 2003; Blood and Zatorre, 2001; Breiter *et al*, 1997; Elliott *et al*, 2000b; Knutson *et al*, 2000; Kunig *et al*, 2000; Martin-Solch *et al*, 2001; O'Doherty *et al*, 2001; Rogers *et al*, 1999; Rolls *et al*, 2003; Small *et al*, 2001; Thut *et al*, 1997). Importantly, many of these studies control for confounds (eg, perceptual salience, arousal, motor demands), by contrasting neural responses to rewarding stimuli against those punishing stimuli of similar magnitude. Although all of these studies implicate the vmPFC in reward processing, some also implicate activation in dACC and dorsal prefrontal cortices (dPFC).

The region most often associated with reward in monkey physiology studies is the OFC (Padoa-Schioppa and Assad, 2006; Roesch and Olson, 2004; Rolls, 2000; Tremblay and Schultz, 2000; Wallis and Miller, 2003). Consistent with these studies and human lesion findings (Bechara *et al*, 1994), several neuroimaging studies suggest that sensory and abstract rewards can recruit the OFC. A meta-analysis of these findings uncovered two trends (Kringelbach and Rolls, 2004). First, sensory rewards (eg, juice) tend to activate more posterior OFC regions, whereas more abstract rewards (eg, money) tend to activate more anterior OFC regions. Second, rewards tend to activate medial regions of the OFC (eg, near the gyrus rectus), whereas punishments tend instead to activate more lateral regions of the OFC. Punishments, however, often inhibit ongoing motor responses, which also increases lateral OFC activation (O'Doherty *et al*, 2003a). More recent evidence suggests that activation in distinct but overlapping lateral OFC regions responds to punishment (more caudal and lateral, closer to the insula) *vs* motor inhibition (more rostromedial) (Elliott *et al*, 2000a). Together, these findings implicate the vmPFC in processing of diverse and abstract rewards compared with lateral OFC regions.

The improved temporal resolution of event-related FMRI (Buckner, 1998) allows tracking not only of where reward related activation occurs, but also when it occurs. This opens the possibility of separately examining neural activation during reward anticipation and in response to reward outcomes. For example, rewarding outcomes signaled by sensory cues, including cued pleasant odors (Gottfried *et al*, 2003) and attractive faces (Bray and O'Doherty, 2007), activate vmPFC. However, a number of studies using abstract rewards (ie, money), rather than sensory ones to measure gain outcomes, found that activation in the mPFC can be distinguished from the larger vmPFC area (Kim *et al*, 2006; Knutson *et al*, 2003, 2005; Kuhnen and Knutson, 2005; Yacubian *et al*, 2006). As

indicated above, this mPFC region occupies the middle frontal gyrus of the medial wall anterior to the genu of the corpus callosum (ie, at the confluence of Brodmann areas 10 and 32), but not the medial OFC or dACC. Specific responses in the mPFC to gain outcomes have been confirmed with human depth-electrode recordings in a gambling task (Oya *et al*, 2005). Taken together, these findings are consistent with the speculation that a subregion of vmPFC, specifically the mPFC, may preferentially respond to rewarding outcomes (Daw *et al*, 2006; Knutson *et al*, 2003).

Regions of the mPFC also respond to contextual aspects of reward during anticipation. For instance, in FMRI studies of expected value, mPFC activation correlate not only with the anticipated magnitude, but also with the anticipated probability of rewards (Knutson *et al*, 2005) (Figure 2) (Yacubian *et al*, 2006). mPFC activation may also weigh benefits against costs when people consider risky investments in the context of financial risk taking (Knutson *et al*, 2005; Preuschoff *et al*, 2006) and might do so by integrating input from the VS and insula (Bruguier *et al*, 2008). mPFC activation further correlates not only with anticipated magnitude of monetary gains, but also their immediacy in the context of temporal discounting (Ballard and Knutson, 2009; Kable and Glimcher, 2007; McClure *et al*, 2004a). Finally, mPFC activation correlates with the additional value of a product's price in the context of purchasing, consistent with the economic notion of 'consumer surplus' (Knutson *et al*, 2007; Plassmann *et al*, 2007). Interestingly, mPFC activation clearly tracks value rather than number, as its activation decreases in response to (undesirable) high prices in the context of buying, but increases in response to (desirable) high prices in the context of selling (De Martino *et al*, 2009; Knutson *et al*, 2008). Together, these findings suggest that mPFC activation may integrate value across different stimulus dimensions or different stimuli (Blair *et al*, 2006). This integrative account is consistent with responsiveness to reward outcomes, as these outcomes invoke a shift in the representation of reward probability after magnitude has been established. Although value integration can occur later, or even in the absence of choice, it can also occur before choice (Glascher *et al*, 2009; Knutson *et al*, 2007), thus carrying the potential to inform upcoming decisions.

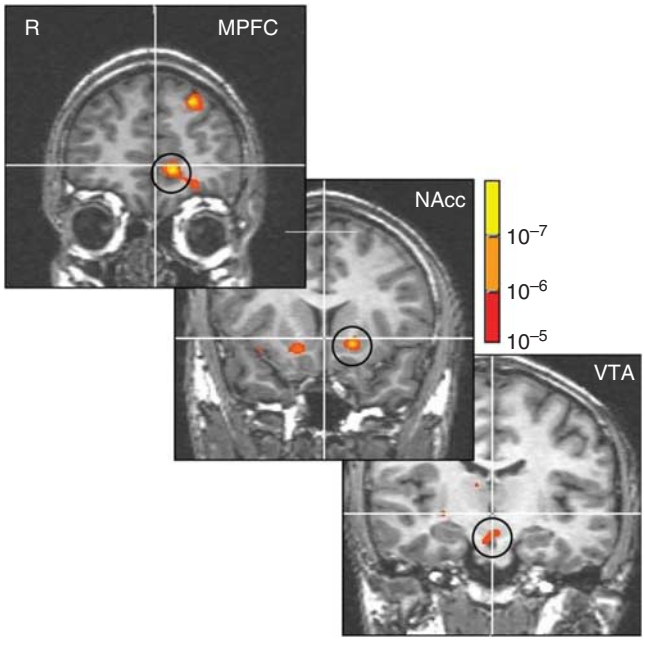

Figure 2. Expected value of monetary rewards activates the ventral cortico-basal ganglia circuit. Panels indicate activation significantly correlated with expected value in the mPFC (anterior = 45), NAcc (anterior = 12), and VTA (anterior = −15). Although the midbrain and VS are sensitive to anticipated reward magnitude, the MFPC is also sensitive to anticipated reward probability (not shown here; adapted from Knutson *et al*, 2005).

The dACC and dPFC also play important roles in reward processing, though not in ways that translate directly to valuation. The dACC is a unique part of frontal cortex. It contains a representation of diverse frontal lobe functions, including motivation, cognition, and motor control. This diversity is consistent with widespread connections with other affective, cognitive, and motor cortical areas. Despite this complexity, the overall function of the dACC seems to involve monitoring these functions in potential conflict situations (Botvinick *et al*, 1999a; Paus, 2001; Vogt *et al*, 2005; Walton *et al*, 2003). Conflict monitoring should prove important when comparing similarly valued options. In addition to the dACC and vmPFC, the dPFC (particularly areas 9 and 46) are engaged when working memory is required for monitoring incentive-based behavioral responses. Both lesion and neuroimaging findings implicate the dPFC in working memory (Fletcher and Henson, 2001), and this capacity should prove most critical when multiple options must be held in mind for evaluation, comparison, and selection. Thus, the dACC and dPFC may work together in a complementary manner to compare valued options, choose among them, and channel that choice into a course of action that promotes acquiring the most valuable option (MacDonald *et al*, 2000; Ridderinkhof *et al*, 2004). Indeed, this line of reasoning is consistent with the observation that consideration of highly valued options elicits increased dorsolateral prefrontal cortical activation in purchasing scenarios (Knutson *et al*, 2007; Plassmann *et al*, 2007). On the other hand, consideration of options that conflict on different dimensions (eg, high preference, but high price) increases dACC activation in investing and purchasing scenarios (without necessarily predicting choice) (Knutson *et al*, 2007; Kuhnen and Knutson, 2005).

VENTRAL STRIATUM

Organization of the VS

The concept of the VS was originally developed by Heimer in 1978 in the classic paper in which he describes the

relationship between the NAcc and the olfactory tubercle in rats (Heimer, 1978). The link between NAcc activity and reward had already been established as part of the self-stimulation circuit originally described by Olds and Milner (Olds and Milner, 1954). Since the identification of the VS, our concept of the striatal region associated with reward has evolved to include this extended region, expanding the traditional boundary of the NAcc. This entire region has been a focus for the study of reinforcement and the transition between drug use for a reward and as a habit (Bowman *et al*, 1996; Drevets *et al*, 2001; Jensen *et al*, 2003; Kalivas *et al*, 2005; Lyons *et al*, 1996; Parkinson *et al*, 2000; Schultz *et al*, 1992; Taha and Fields, 2006). In human and nonhuman primates, the VS includes the NAcc and the broad continuity between the caudate nucleus and the putamen ventral to the rostral internal capsule, the olfactory tubercle, and the rostrolateral portion of the anterior perforated space adjacent to the lateral olfactory tract (Haber and McFarland, 1999; Heimer *et al*, 1999). Importantly, however, neither cytoarchitectonic nor histochemistry distinctions mark a clear boundary between the VS and the dorsal striatum, which poses a problem for defining locations of activation in imaging and animal studies. Perhaps, the best way, therefore, to define the VS is by its afferent projections from cortical areas that mediate different aspects of reward and emotional processing, namely the vmPFC, OFC, dACC, and the medial temporal lobe, including the amygdala. Using these projections as a guide, the VS occupies over 20% of the striatum in nonhuman primates (Haber *et al*, 2006). As a subcomponent of the VS, the term NAcc is best described by a small ventromedial sector in the rostral striatum that receives input from specific cortical regions (see below).

Special features of the VS. Although the VS is similar to the dorsal striatum in most respects, there are also some unique features. Within the NAcc region of the VS, a subterritory, called the shell, has a particularly important function in the circuitry underlying goal-directed behaviors, behavioral sensitization, and changes in affective states (Carlezon and Wise, 1996; Ito *et al*, 2004). Although several transmitter and receptor distribution patterns distinguish the shell/core subterritories, calbindin is the most consistent marker for the shell across species (Alheid and Heimer, 1988; Ikemoto *et al*, 1995; Martin *et al*, 1993; Meredith *et al*, 1996; Sato *et al*, 1993). The shell has some unique connectivities that distinguish it from the rest of the VS (indicated below). However, while animal studies have distinguished the shell from the rest of the striatum, the spatial resolution in imaging studies is not yet sufficient to isolate this region in humans.

In addition to the shell compartment, several other characteristics are unique to the VS. The dopamine transporter (DAT) is relatively low in the VS compared to the dorsal striatum. This pattern is consistent with the fact that the dorsal tier dopamine neurons (which project to the VS) express relatively low levels of mRNA for the DAT compared to the ventral tier (which project to the dorsal striatum) (Counihan and Penney, 1998; Haber *et al*, 1995b; Harrington *et al*, 1996) (see section Amygdala). The VS has numerous smaller and more densely packed neurons; the dorsal striatum is more homogenous. The VS contains cell islands, including the islands of Calleja, which are thought to contain quiescent immature cells that remain in the adult brain (Bayer, 1985; Chronister *et al*, 1981; Meyer *et al*, 1989). The VS also contains many pallidal cells and their dendritic arbors that invade this ventral forebrain territory (see section Ventral pallidum). Finally, and of particular importance, is the fact that while both the dorsal and VS receive input from the cortex, thalamus, and brainstem, the VS alone receives a dense projection from the amygdala and hippocampus (Friedman *et al*, 2002; Fudge *et al*, 2002; Russchen *et al*, 1985).

Connections of the VS (Figure 3). Afferent projections to the VS, like those to the dorsal striatum are derived from three major sources: a massive, generally topographic glutamatergic input from cerebral cortex; a large glutamatergic input from the thalamus; and a smaller, but critical input from the brainstem, primarily from the midbrain dopaminergic cells. Although this section primarily focuses on the connections of the VS, it gives some attention to the dorsal striatum, especially the caudate nucleus, an area that is also involved in reward-based learning (Cromwell and Schultz, 2003; Kennerley and Wallis, 2009; Watanabe and Hikosaka, 2005). This region receives input from the dPFC.

Cortical projections. Cortico-striatal projections form dense, focal patches that can be visualized at low magnification. These terminal projections are organized in a functional topographic manner (Parent and Hazroti, 1995): the dorsolateral striatum receives cortical input from sensory-motor areas; the central striatum receives input from associative cortical areas; and the VS receives input from limbic areas. Within each general functional region (limbic, associative, and motor), terminals are also topographically organized. Thus, inputs from the vmPFC, OFC, and dACC terminate within subregions of the VS, and the dPFC terminates primarily in the caudate nucleus (Haber *et al*, 1995a; Selemon and Goldman-Rakic, 1985). The focal projection field from the vmPFC is the most limited. It is concentrated within the NAcc, including the shell (Figures 4a and 5). The vmPFC also projects to the medial wall of the caudate nucleus, adjacent to the ventricle. The densest input from agranular insular cortex also terminates in the NAcc and at the medial wall of the caudate (Chikama *et al*, 1997). Less data is available concerning the projections of area 10 to the VS, particularly medial area 10. However, tracer injections into dorsal and lateral area 10 project to the medial wall of the rostral caudate (overlapping with inputs from the vmPFC) (Ferry *et al*, 2000). Based on these data, one might assume that the medial and ventral area 10 (an area included in the mPFC in the imaging studies described above) would terminate in the NAcc. Thus, the NAcc in primates receives

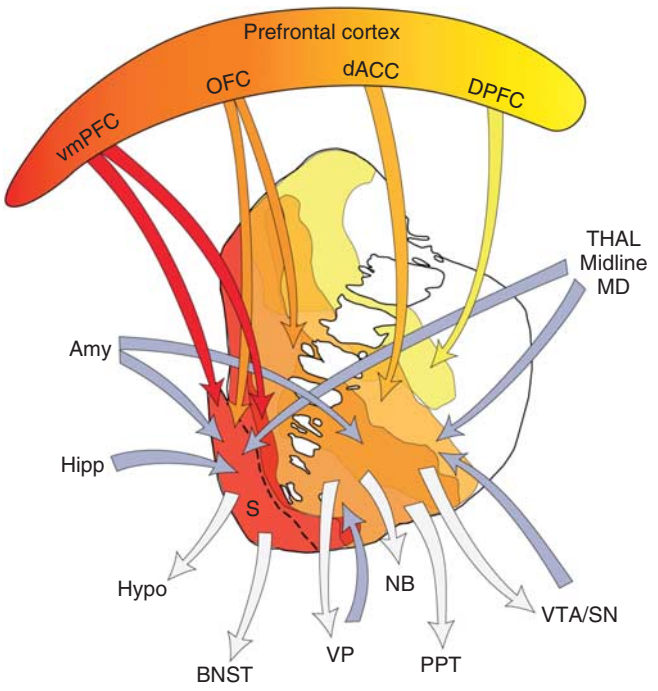

Figure 3. Schematic illustrating the connections of the VS. Blue arrows = inputs; gray arrows = outputs; Amy = amygdala; BNST = bed nucleus stria terminalis; dACC = dorsal anterior cingulate cortex; Hipp = hippocampus; hypo = hypothalamus; MD = medio-dorsal nucleus of the thalamus; OFC = orbital frontal cortex; PPT = pedunculopontine nucleus; S = shell; SNc = substantia nigra, pars compacta; STN = subthalamic nucleus; Thal = thalamus; VP = ventral pallidum; VS = ventral striatum; VTA = ventral tegmental area; vmPFC = ventral medial prefrontal cortex.

convergent input from the olfactory and visceral-associated insula, from the vmPFC, and most likely from area 10.

The dorsal and lateral parts of the VS (the ventral caudate nucleus and putamen) receive inputs from the OFC (Figures 4b and 5). These terminals also extend dorsally, along the medial caudate nucleus, but lateral to those derived from the vmPFC. The medial to lateral and rostral to caudal topographic organization of the OFC terminal fields is consistent with the positions of OFC regions in the PFC. That is, inputs from lateral parts of the OFC (ie, area 12) terminate lateral to those derived from more medial areas (area 13). For the most part, fibers from the OFC terminate lateral to the NAcc. Finally, projections from the dACC extend from the rostral pole of the striatum to the anterior commissure and are located in the rostral, central caudate nucleus and central putamen (Figures 4c and 5). These terminals primarily avoid the NAcc, terminating somewhat lateral to those from the OFC. Taken together, the vmPFC, OFC, and dACC project primarily to the rostral striatum, with the vmPFC projecting most medially (to the NAcc) and the dACC most laterally (Haber *et al*, 2006), with the OFC terminal fields positioned between them. In contrast, the dPFC projects throughout the rostrocaudal extent of the striatum, terminating primarily in the head of the caudate and in part of the rostral putamen (Figures 4d and 5),

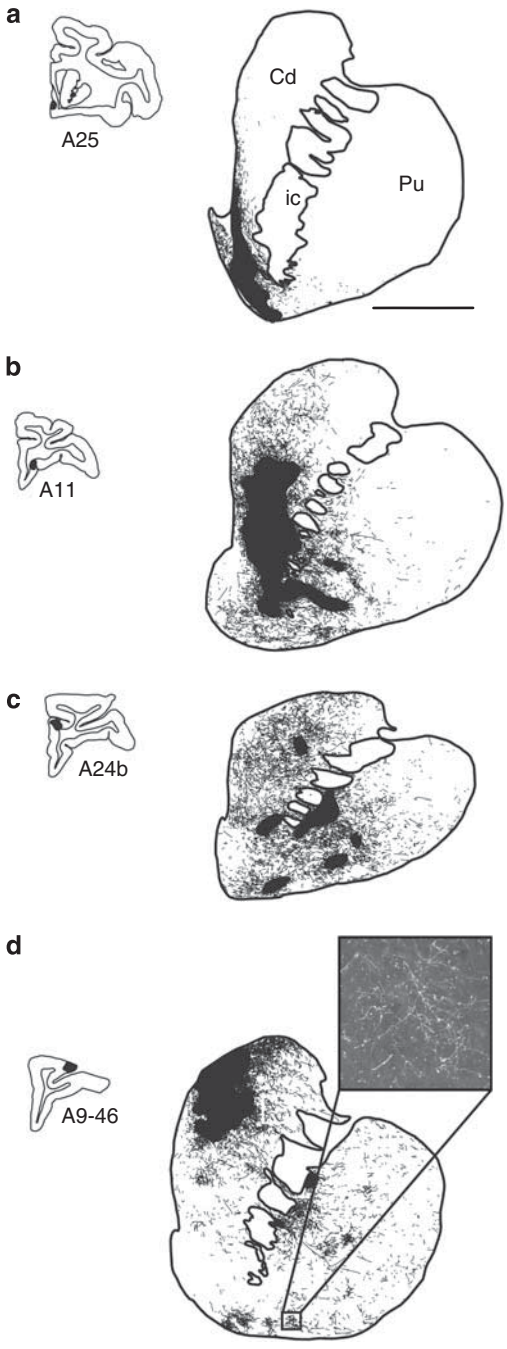

Figure 4. Schematic chartings of labeled fibers after injections into different prefrontal regions. (a) vmPFC injection site (area 25), (b) OFC injection site (area 11), (c) dACC, (d) dPFC injection site (area 9/46). The focal projection fields are indicated in large solid black shapes. Diffuse projection fibers are found outside of the focal projection fields (as illustrated in the photomicrograph in (d)).

but continuing into the caudal caudate nucleus. For the anatomical details concerning prefrontal corticostriatal projections, see Haber *et al* (1995a) and Selemon and Goldman-Rakic (1985).

Intergration between cortico-striatal projections. Although the topographic organization of cortico-striatal projections is well documented, there is increasing evidence for regions

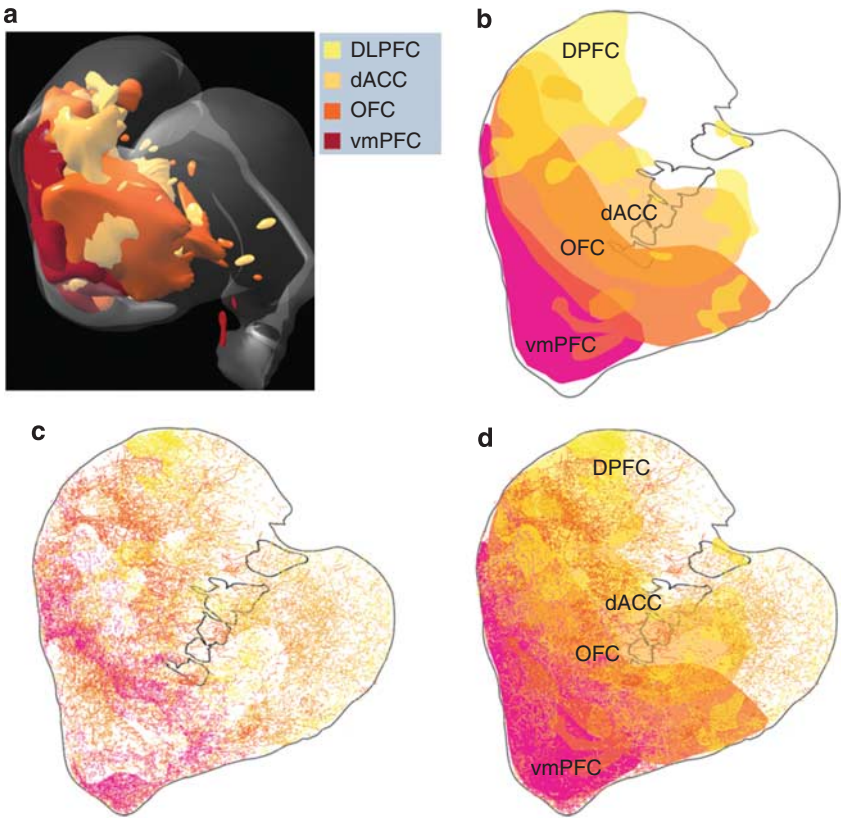

Figure 5. Schematics showing convergence of cortical projections from different reward-related regions and dorsal prefrontal areas. (a) Medio-frontal view of a 3D reconstruction illustrating convergence of inputs from PFC inputs. (b) 2D section through the striatum illustrating regions of convergence. (c) Distribution of diffuse fibers from different PFC regions. (d) Diffuse fibers are superimposed onto the focal projections, showing the interface between diffuse and focal projections. ACC = dorsal anterior cingulate cortex; dPFC = dorsal lateral prefrontal cortex; OFC = orbital prefrontal cortex; vmPFC = ventral medial prefrontal cortex. red = inputs from vmPFC; dark orange = inputs from OFC; light orange = inputs from dACC; yellow = inputs from dPFC.

of interface between terminals from different cortical areas, suggesting functional integration. For example, early studies showed that cortico-striatal terminals from sensory and motor cortex converge within the striatum (Flaherty and Graybiel, 1993). Here, axons from each area synapse onto single fast spiking GABAergic interneurons. Interestingly, these interneurons are more responsive to cortical input than the medium spiny cells (Charpier *et al*, 1999; Mallet *et al*, 2005; Ramanathan *et al*, 2002; Takada *et al*, 1998). This suggests a potentially critical role for interneurons to integrate information from different cortical areas before passing that information onto the medium spiny projection cells.

Recent studies reveal that projections from the OFC, vmPFC, and dACC also converge in specific regions within the VS. Thus, focal terminal fields from the vmPFC, OFC, and dACC show a complex interweaving and convergence, providing an anatomical substrate for modulation between these circuits (Haber *et al*, 2006) (Figure 5a and b). For example, in certain regions, the vmPFC projection field converges with that from the OFC. Moreover, projections from the dACC and OFC regions do not occupy completely separate territories in any part of the striatum, but converge most extensively at rostral levels. In addition, projections from dACC and OFC also converge with inputs from the dPFC, particularly at the most rostral striatal levels. A similar pattern of both topographic and integrative connectivity of cortico-striatal projections has been demonstrated in the human brain using diffusion tensor imaging (DTI). These data show a similar overall organization of the different cortical regions and the striatum, providing a strong correlation between monkey anatomical-tracing studies and human DTI studies (Draganski *et al*, 2008). Taken together, a coordinated activation of dPFC, dACC, and/or OFC terminals in these subregions could produce a unique combinatorial activation at the specific sites for channeling reward-based incentive drive in selecting between different valued options. Functional imaging studies do not, at this time, have the resolution to specifically detect these convergence zones. Nonetheless, the fact that these areas exist may help explain complex activation patterns following different reward-related paradigms described below.

In addition to focal projection fields described above, the cortex also has a diffuse projection system to the striatum. Based on intracellular tracer injections into individual neurons, cortico-striatal axons have been shown to travel some distance (Parent and Parent, 2006; Zheng and Wilson,

2002), invading striatal regions that receive their focal input from other prefrontal cortex areas (Figure 4). Collectively, the diffuse projections from each cortical area consist of clusters of terminal fibers that are widely distributed throughout the striatum, not only expanding the borders of the focal terminal fields, but also extending throughout other regions of the striatum (Haber *et al*, 2006). For example, the diffuse projection from the vmPFC extends lateral and dorsal to its focal projection field. The diffuse OFC fibers extend deep into the dorsal caudate, central caudate, and putamen, with extensive convergence with both focal and diffuse projections from the dACC and the dPFC (Figure 4b). Finally, clusters of dPFC fibers terminate throughout the rostral striatum, including the VS. Thus, the diffuse fiber system constitutes a large population of axons invading each focal projection field. Under certain conditions, if collectively activated, they may provide the recruitment strength necessary to modulate striatal activity by broadly disseminating cortical information. This relatively low level of modulation may provide an anatomical substrate for cross-encoding information to influence the future firing of medium spiny neurons (Kasanetz *et al*, 2008), playing an important role in the temporal activation of different striatal regions during learning. Taken together, the fronto-striatal network constitutes a dual system comprising both topographically organized terminal fields and subregions that contain convergent pathways derived from functionally discrete cortical areas (Draganski *et al*, 2008; Haber *et al*, 2006).

The amygdala and hippocampal projections to the VS. Overall, the basal nucleus and the magnocellular division of the accessory basal nucleus are the main source of inputs to the VS (Fudge *et al*, 2002; Russchen *et al*, 1985). The lateral nucleus has a relatively minor input to the VS. The amygdala has few inputs to the dorsal striatum in primates. Although the basal and accessory basal nuclei innervate both the NAcc and the larger regions of the VS striatum, the densest projection appears to be within the NAcc. The shell of the NAcc, however, is set apart from the rest of the VS by a specific set of connections derived from the medial part of the central nucleus (CeM), periamygdaloid cortex, and the medial nucleus of the amygdala. In contrast to the amygdala, the hippocampal formation projects to a more limited region of the VS, primarily derived not only from the subiculum, but also from the parasubiculum and part of CA1 (Friedman *et al*, 2002). The main terminal field is located in the most medial and ventral parts of the VS and is essentially confined to the NAcc shell. Here, these inputs overlap with those from the amygdala and from the vmPFC. Taken together, the existence of convergent fibers from cortex within the VS, along with hippocampal and amygdalo-striatal projections, places the VS as a key entry port for processing emotional and motivational information that, in turn, drives basal ganglia action output (see Sesack and Grace in this volume). Within the VS, the NAcc receives the densest innervation from the amygdala, hippocampus, and the vmPFC.

Thalamic projections to the VS. The midline and medial intralaminar thalamic nuclei project to medial prefrontal areas, the amygdala, and hippocampus. As such, they are referred to as the limbic-related thalamic nuclear groups (Akert and Hartmann-von Monakow, 1980; Yakovlev *et al*, 1960). These nuclei also project to the VS (Berendse and Groenewegen, 1990; Giménez-Amaya *et al*, 1995). As seen with the cortical projections, the NAcc receives the most limited input, which is derived almost exclusively from the midline nuclei. The medial wall of the caudate nucleus receives projections, not only from the midline and the medial intralaminar nuclei, but also from the central superior lateral nucleus. In contrast, the lateral part of the VS receives a limited projection from the midline thalamic nuclei. Its input is mainly from the intraliminar nuclei (the parafascicular nucleus and the central superior lateral nucleus). In addition to the midline and intralaminar thalamo-striatal projections, in primates, there is a large input from the 'specific' thalamic-basal ganglia relay nuclei, the MD, ventral anterior, and ventral lateral nuclei (McFarland and Haber, 2001). The VS receives this input from the medial MD nucleus and a limited projection from the magnocellular subdivision of the ventral anterior nucleus.

Efferent projections from the VS. The VS, like those to the dorsal striatum, projects primarily to the pallidum and midbrain (Haber *et al*, 1990a; Hedreen and DeLong, 1991; Parent *et al*, 1997) (Figure 3). Specifically, fibers terminate topographically in the subcommissural VP, the rostral pole of the external segment, and the rostromedial portion of the internal segment (see section Ventral pallidum). The more central and caudal portions of the globus pallidus do not receive this input. Fibers from the VS projecting to the midbrain are not as confined to as specific a region as those projecting to the pallidum. Although the densest terminal fields are in the medial portion (VTA and medial SN), numerous fibers also extend laterally to innervate the entire dorsal tier of the midbrain dopaminergic neurons (see section Midbrain Dopamine Neurons for a more detailed discussion on the SN). Projections from the medial part of the VS continue more caudally, terminating in the pedunculopontine nucleus. In addition to these projections, the VS also terminates in nonbasal ganglia regions (Haber *et al*, 1990a; Zahm and Heimer, 1993). The shell sends fibers caudally and medially into the lateral hypothalamus and, to some extent, in the periaqueductal gray. Axons from the medial VS (including the shell) also terminate in the bed nucleus of the stria terminalis, indicating a direct striatal influence on the extended amygdala (see Davis and Grillon in this volume). Finally, axons from ventral regions of the VS terminate in the nucleus basalis. This connection has been demonstrated at the light microscopic level in monkeys and verified at the

EM level in rodents (Beach *et al*, 1987; Chang *et al*, 1987; Haber, 1987; Martinez-Murillo *et al*, 1988; Zaborszky and Cullinan, 1992). A projection to the nucleus basalis in the basal forebrain is of particular interest, since this is the main source of cholinergic fibers to the cerebral cortex and the amygdala. These data indicate that the VS may influence cortex directly, without going through the pallidal and thalamic circuit. This may provide a route through which reward circuit has access to a wider region of frontal cortex than via the more confined ventral cortico-basal ganglia circuit.

Reward Processing in the Human VS

To localize striatal activation, researchers have devised structural schemes that distinguish ventral from dorsal striatum in the case of PET or NAcc from caudate and putamen in the case of FMRI (Breiter *et al*, 1997; Drevets *et al*, 2001; Mawlawi *et al*, 2001) (Figure 6). These schemes are based on anatomical landmarks that define more restricted areas than the patterns of connectivity described above. For instance, based on the primate anatomy reviewed above, inputs to the region labeled as VS (upper panel) likely come from the vmPFC, amygdala, and the hippocampus, and some, but not all, from OFC regions (particularly the more lateral OFC areas). The region labeled as the NAcc (lower panel) is smaller and likely receives a more limited subset of inputs from the vmPFC and amygdala. However, it receives most of its input from the mPFC and hippocampus. Connectivity studies (as indicated above) suggest that the VS encompasses a larger region, which includes the medial caudate nucleus and rostroventral putamen along with the NAcc. Thus, here the term VS refers the NAcc, the ventral medial caudate, and the rostroventral putamen. Mention of any of these subcomponents alone implies a more specific focus on activation in that region, but does not exclude the possibility of activation in other ventral striatal subcomponents.

Both metabolic and ligand-based PET studies have shown recruitment of striatal regions during reward processing. For instance, metabolic PET studies suggest that exposure to both primary (ie, pleasant tastes and sounds) and secondary rewards (ie, monetary gambles) can increase striatal activity (Blood and Zatorre, 2001; Kunig *et al*, 2000; Martin-Solch *et al*, 2001; Small *et al*, 2001). Similarly, initial FMRI studies of reward processing have also shown that both primary (ie, pleasant tastes, smells, sights, sounds, and touch) and secondary (ie, monetary gain) rewards could increase striatal activation, consistent with the notion that striatal activation does not depend on sensory modality (Aharon *et al*, 2001; Anderson *et al*, 2003; Delgado *et al*, 2000; Elliott *et al*, 2000b; Gottfried *et al*, 2002; Knutson *et al*, 2000; Menon and Levitin, 2005; Mobbs *et al*, 2003; O'Doherty *et al*, 2001; Rolls *et al*, 2003). As with studies of the frontal cortex, many of these studies also included unpleasant and neutral stimuli, thus controlling for arousal and other confounds (eg, perceptual and behavioral demands). Owing to either reduced temporal resolution or temporally nonspecific questions, however, these studies did not establish when neural activation occurred during reward processing.

Although it has similar spatial resolution and less temporal resolution than metabolic PET (ie, on the order of hours), ligand-based PET confers a unique advantage of supporting inference about dopamine release in the striatum. Relative to placebo injection, amphetamine injection robustly increases striatal dopamine (inferred from radioactive ligand displacement), and these increases can correlate with positive and arousing affective experience (eg, feelings of 'euphoria') (Drevets *et al*, 2001; Leyton *et al*, 2002; Martinez *et al*, 2003; Volkow *et al*, 1999). Consumption of alcohol and cocaine also increase dopamine release in the VS (Boileau *et al*, 2003; Cox *et al*, 2009). Secondary rewards such as playing videogame and gambling may also

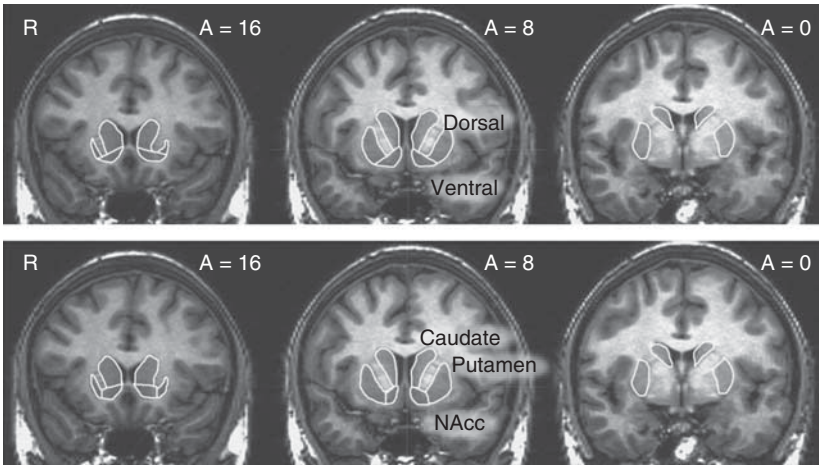

Figure 6. Anatomical schemes for parcellating the striatum based on structural landmarks. Top: Ventral and dorsal striatum (adapted from Mawlawi *et al*, 2001); Bottom: nucleus NAcc, caudate, and putamen (adapted from Breiter *et al*, 2001).

increase dopamine release in parts of the striatum, albeit less consistently and robustly (Koepp *et al*, 1998; Pappata *et al*, 2002; Zald *et al*, 2004).

Event-related FMRI enabled researchers to track changes in striatal activity during different phases of reward processing. This increased temporal specificity coincided with an increase in the number of FMRI studies documenting ventral striatal activation. For instance, in the case of primary rewards, anticipation of a pleasant (but not an unpleasant) taste elicits ventral striatal and OFC activation, whereas the pleasant taste itself elicits only OFC activation (O'Doherty *et al*, (2002). In the case of secondary rewards, anticipation of uncertain monetary rewards (but not punishments) increases NAcc activation, whereas obtaining (*vs* not obtaining) rewards increased MPFC activation and kept putamen activation from decreasing (Breiter *et al*, 2001; Knutson *et al*, 2001b, 2003).

Anticipated reward can vary along many dimensions, including magnitude, probability, uncertainty, delay, and effort. NAcc activation in these and other imaging studies clearly increases proportional to the magnitude of anticipated monetary reward (Knutson *et al*, 2001a; Yacubian *et al*, 2006) (Figure 2). Although medial caudate and MD thalamic activation also increases proportional to the magnitude of anticipated reward, they additionally increased proportional to the magnitude of anticipated punishment. A recent meta-analysis of over 20 similar FMRI studies has confirmed preferential activation of the NAcc during anticipation of monetary gains, but not during anticipation of losses (Knutson and Greer, 2008). Depth-electrode recordings of epileptic patients gambling have also shown that NAcc activity increases proportional to the magnitude of anticipated reward (Cohen *et al*, 2009a). This proportional response to anticipated reward magnitude provided an anchor for exploring the impact of varying other attributes of anticipated reward. An increasing number of subsequent studies have focused on whether other aspects of anticipated reward besides magnitude might increase NAcc activation (eg, probability, uncertainty, delay and effort).

Probability refers to the likelihood that an anticipated reward will occur, and individuals usually value rewards with high probabilities. Probability can be related to uncertainty, as moderate ranges of probability can imply maximum uncertainty about an outcome (eg, 50% probability is least informative about whether a given outcome will occur or not occur). During reward anticipation, ventral striatal activation has been reported to track uncertainty in some studies, but probability in other studies. For instance, some studies find that VS activation peaks at intermediate probability levels, consistent with maximal uncertainty (Cooper and Knutson, 2008; Dreher *et al*, 2006; Knutson *et al*, 2005; Preuschoff *et al*, 2006). Other studies, however, have reported linear effects of anticipated reward probability on VS activation (Abler *et al*, 2006; Hsu *et al*, 2009; Tobler *et al*, 2008; Yacubian *et al*, 2006). A large subsequent study investigated the possibility that different subcomponents within the VS showed greater sensitivity to anticipated reward magnitude *vs* probability (Yacubian *et al*, 2007). Although peak responsiveness to magnitude occupied the NAcc and medial caudate, peak responsiveness to probability occupied the rostroventral putamen, suggesting differential sensitivity to anticipated reward magnitude *vs* probability in different VS subcomponents (see also Preuschoff *et al*, 2006; Tobler *et al*, 2007).

Delay refers to the amount of time until an anticipated reward can be obtained, and individuals usually devalue or 'discount' rewards with long delays. Initial FMRI studies found evidence that VS activation increased when immediate *vs* delayed rewards were considered and decreased with the delay of future rewards (Kable and Glimcher, 2007; McClure *et al*, 2007; McClure *et al*, 2004a). A subsequent study separately examined VS responses to information about the magnitude and delay of future rewards and found that while NAcc activation alone increased with the magnitude of a future rewards, activation in frontal regions (eg, mPFC and dPFC) instead showed sensitivity to the delay of future rewards (Ballard and Knutson, 2009).

Effort refers to how much an individual must work to get an anticipated reward, and individuals usually devalue rewards that require substantial effort. Investigators have also examined the influence of anticipated effort on VS activation. They found that while anticipated reward magnitude increased NAcc and medial caudate activation, anticipated reward effort decreased activation in a partially overlapping region of the rostroventral putamen (Croxson *et al*, 2009) (see also Botvinick *et al*, 2009). Together, these studies raise the possibility that while anticipated reward magnitude consistently increases NAcc and medial caudate activation, other aspects of anticipated value (eg, anticipated probability and effort) may elicit more pronounced activation in the rostroventral putamen subcomponent of the VS.

Within the VS, overlap between these regions may combine distinct aspects of anticipated reward. The findings also raise the possibility of a temporal flow of information through the VS to the dorsal striatum. If the NAcc is recruited early during reward prediction, it may respond to relatively basic information about reward magnitude, whereas other considerations may influence reward processing as activation moves dorsolaterally through the striatum, perhaps as a function of integration of information from prefrontal circuits (Figure 7). Such a dynamic flow of information might occur either through cortico-striatal connections as described in the earlier section or through striato-nigral-striatal connections (described below) or both.

Other research has focused on neural responses to reward outcomes (ie, when potential, but uncertain rewards are obtained or lost). Several studies have associated activation of the medial caudate portion of the VS with rewarding (*vs* nonrewarding) outcomes (Delgado *et al*, 2003, 2000). The medial caudate likely receives inputs from a combination of vmPFC, OFC, dACC, and possibly dPFC. This region

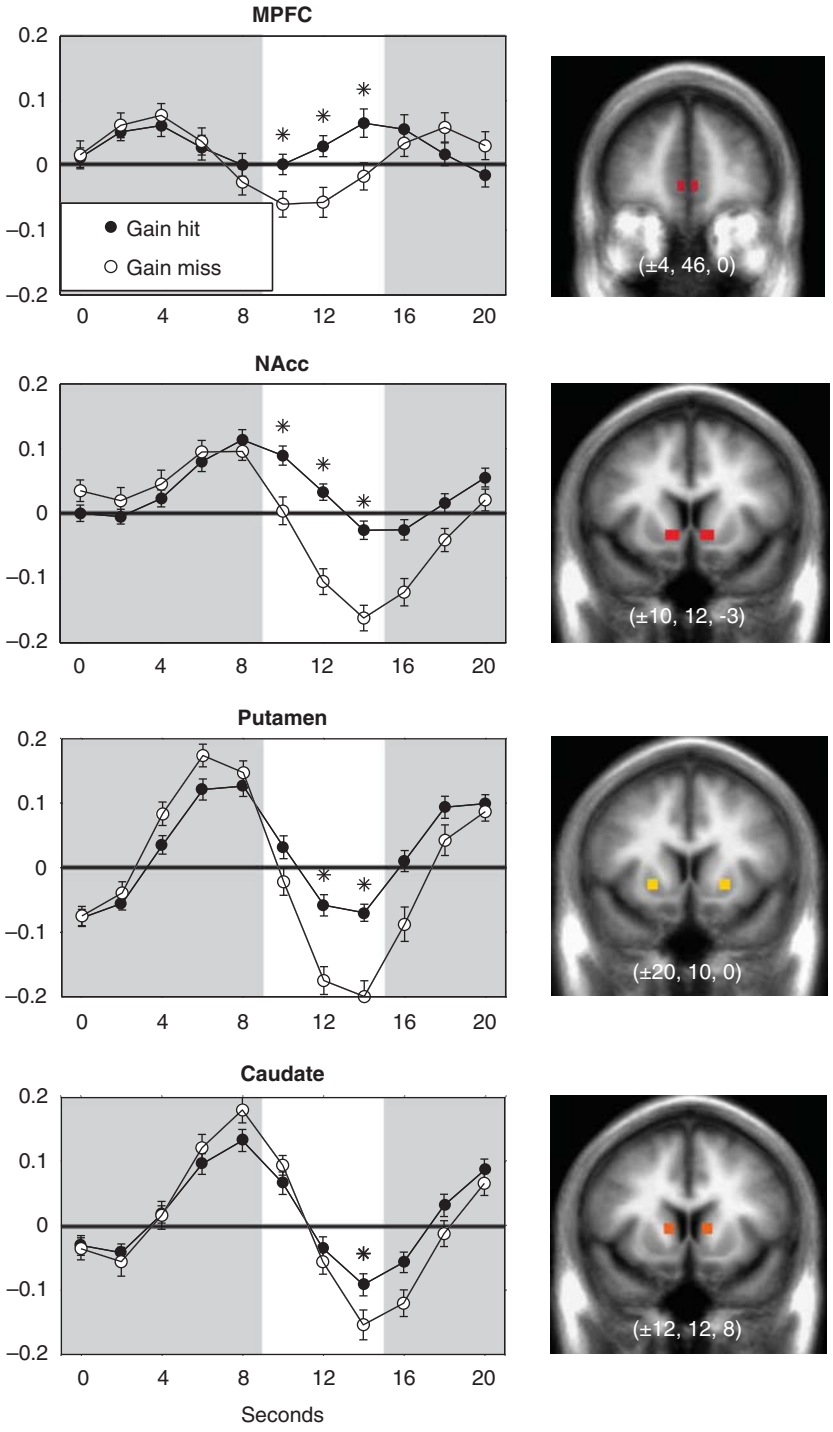

Figure 7. Propagation of gain prediction error from rostral to dorsal striatal regions over time. Lines depict neural responses to gain (+$5.00; black) *vs* nongain (+$0.00; gray) outcomes during trials in which subjects had earlier anticipated winning an uncertain large gain (ie, $5.00 with 66% chance of hitting) in the monetary incentive delay task (Knutson *et al*, 2003). The white band indicates the onset of gain *vs* nongain feedback (lagged by 4 s to account for the hemodynamic delay). Stars indicate a significant difference between activation for gain *vs* nongain feedback ($p<0.01$). Note that gain prediction error differences appear in the mPFC and NAcc immediately, but not in the dorsomedial caudate until 2 s later, and not in the putamen until 4 s later ($n=40$ subjects, unpublished data).

responds to relative as well as absolute reward outcomes (ie, when an individual compares what she received to what she might have, but did not receive) (Kuhnen and Knutson, 2005; Lohrenz *et al*, 2007; Nieuwenhuis *et al*, 2005). These findings share similarities to an earlier literature suggesting that 'cognitive' feedback can elicit caudate activation (Elliott *et al*, 1997; Poldrack *et al*, 1999). Moreover, it establishes that rewards can enhance this activation (Tricomi *et al*,

2006). Outcome-elicited medial caudate activation may promote choice of the next best action, as it is most prominent when reward feedback informs subsequent actions (O'Doherty *et al*, 2004) and decreases as action requirements become more predictable (Delgado *et al*, 2005). Taken together, the anatomy and imaging data supports the idea that the medial caudate may integrate information from reward and cognitive cortical areas in the development of strategic action planning.

Reward outcomes can also influence VS activation. Specifically, several studies indicate that omission (*vs* delivery) of expected rewards can decrease VS activation (Berns *et al*, 2001; Knutson *et al*, 2001b; Ramnani *et al*, 2004). Given that reward anticipation can increase, and nonreward outcomes can decrease, VS activation, theorists have proposed that VS activity tracks a reward prediction error (or the difference between expected and obtained rewards) (McClure *et al*, 2007; Montague *et al*, 1996; Schultz *et al*, 1997). Indeed, computational modeling of brain activity during reward learning indicates that a reward prediction error term correlates with activity in the rostroventral putamen (McClure *et al*, 2003; O'Doherty *et al*, 2003b). As the NAcc and medial caudate subcomponents robustly activate during reward anticipation, and the rostroventral putamen most reliably deactivates in response to nonreward delivery, it remains to be established whether common or distinct subcomponents of the VS respond to both events. One meta-analysis of monetary incentive delay studies suggests that the NAcc and medial caudate may respond more robustly during reward anticipation, but the rostroventral putamen in response to reward outcomes. However, these subcomponents may prove more difficult to dissociate in dynamic studies that involve learning. If different phases of reward-processing recruit distinct VS subcomponents, further enhancements in the spatial and temporal resolution of FMRI may help to test these hypotheses and yield new insights.

AMYGDALA

The amygdala is a prominent limbic structure that plays a key role in emotional coding of environmental stimuli. It provides contextual information used for adjusting motivational level. The amygdala has an important role in reward processing, in part through the critical interactions between it and VS for stimulus-reward associations (Baxter and Murray, 2002; Cador *et al*, 1989; Everitt *et al*, 1989, 1999; Murray, 2007; Ramirez and Savage, 2007). As indicated above, those connections terminate most densely in the NAcc, but extend throughout much of the VS. However, relative to VS activation, amygdalar activation appears less frequently in neuroimaging studies of reward. Although the amygdala has been prominently implicated in fear learning in animal studies (LeDoux, 2000), other animal studies have also implicated the amygdala in reward processing—particularly when previously rewarding stimuli are devalued (Baxter and Murray, 2002). Metabolic PET studies have reported amygdalar activation in contexts involving potential rewards (particularly related to drug craving), but overall have reported more reliable amygdalar activity in contexts involving potential punishment (see Zald, 2003 for a review).

FMRI studies, too, have reported amygdalar activation in the context of potential reward (McClure *et al*, 2004b). Controlling for arousal, however, direct comparison of amygdalar responses to rewarding *vs* punishing stimuli often reveals no significant differences, leading researchers to infer that the amygdalar signal in FMRI responds more to stimulus arousal than value (ie, positive or negative) (Anderson *et al*, 2003; Small *et al*, 2003). This inference is consistent with the commonly observed rapid habituation of amygdalar activation to emotional stimuli in FMRI studies (Breiter *et al*, 1996), which stands in contrast to the relative constancy of VS activation to reward cues over time. For example, one study illustrated temporal dynamics of amygdalar signal by tracking both amygdalar and NAcc activation over time as people learned to associate cues with rewarding or punishing odors (Gottfried *et al*, 2003). Although amygdalar responses to the rewarding cue decreased over time, NAcc responses to the rewarding cue increased over time. Despite suggesting a less direct function than the VS in reward processing, in line with animal findings, FMRI studies have documented that amygdalar activation decreases with reward devaluation (Gottfried *et al*, 2003).

VENTRAL PALLIDUM (Figure 8)

The VP is an important component of the reward circuit in that cells in this forebrain region respond specifically during the learning and performance of reward-incentive behaviors. It, like the VS, is an area of focus in the study of addictive behaviors (Mitrovic and Napier, 2002; Smith and Berridge, 2007; Tindell *et al*, 2006). The term VP was first used to describe, in rats, the forebrain region below the anterior commissure, extending into the anterior perforated space that contained pallidal-like cells. This area was included as part of the pallidum based both on histological criteria and the fact that it received its input from the VS (Heimer, 1978). Pallidal neurons have a distinct morphology, which is nicely outlined using immunohistochemistry for the peptides, enkephalin, and substance P. Staining for these peptides was particularly useful for determining the boundaries of the VP (DiFiglia *et al*, 1982; Fox *et al*, 1974; Haber and Nauta, 1983; Haber and Watson, 1985; Mai *et al*, 1986; Reiner *et al*, 1999). Based on these staining patterns and its input from the VS, the VP is now considered to encompass not only the subcommissural regions, but also the rostral pole of the external segment and the medial rostral internal segment of the globus pallidus. The VP also reaches rostrally to invade the rostral and ventral portions of the VS. In the human brain, the VP

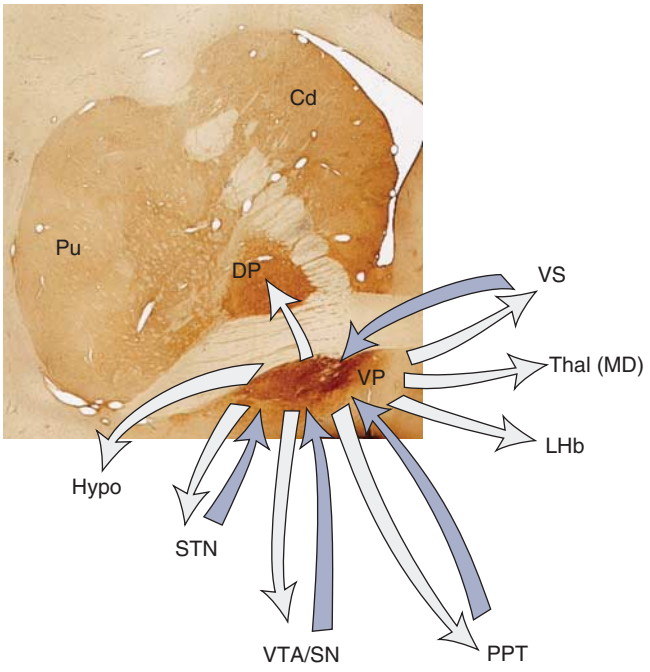

Figure 8. Schematic illustrating the connections of the VP. Blue arrows = inputs; gray arrows = outputs; DP = dorsal pallidum; hypo = hypothalamus; LHb = lateral habenula; MD = medio-dorsal nucleus of the thalamus; PPT = pedunculopontine nucleus; SN = substantia nigra; STN = subthalamic nucleus; Thal = thalamus; VP = ventral pallidum; VTA = ventral tegmental area.

extends far into the anterior perforated space, where the structure is broken up into an interconnected lacework of pallidal areas, interdigitating with islands of Calleja (Heimer and Alheid, 1991). The identification of the VS and VP simplified the structural analysis of ventral forebrain. It demonstrated that a large part of the area referred to as 'substantia innominata' is actually an extension of the reward-related striatopallidal complex (Alheid and Heimer, 1988). In addition to receiving VS input, the VP also receives a glutamatergic input from the subthalamic nucleus (STN) and a dopaminergic input from the midbrain (Klitenick *et al*, 1992; Turner *et al*, 2001) (Figure 8).

The VP projects topographically to the STN and adjacent hypothalamus (Figure 8). Axons also continue to the midbrain, terminating medially in the substantia nigra pars compacta (SNc), pars reticulata (SNr), and VTA (Haber *et al*, 1993, 1990b; Parent *et al*, 1997). These fibers are less topographically organized compared with those that project to the STN. Here, terminals from the VP interface with those from other basal ganglia circuits (Bevan *et al*, 1996). Fibers continue caudally to innervate the pedunculopontine nucleus. Cells of the VP that receive substance P striatal input project to the MD thalamic nucleus (Haber *et al*, 1993; Parent *et al*, 1999; Sidibe *et al*, 1997). The VP also projects to both the internal and external segments of the dorsal pallidum. This is a unique projection, in that the dorsal pallidum does not seem to project ventrally. Parts of the VP (along with the dorsal pallidum) project to the LHb, a structure now considered to be part of the reward circuit (Matsumoto and Hikosaka, 2007; Morissette and Boye, 2008; Ullsperger and von Cramon, 2003); Haber *et al*, 1993 #554; Parent, 1981 #12010 (see section below for a discussion of the habenular nucleus). Finally, part of the VP (as with the external segment of the pallidum) also projects to the striatum (Spooren *et al*, 1996). This pallidostriatal pathway is extensive and more widespread than reciprocal striatopallidal projection. In summary, the complexity of the VP circuitry coupled with its central position in the reward circuit indicates that this structure is likely to be activated during imaging studies. Many neuroimaging studies that document ventral striatal activation also document overlapping ventral pallidal activation. However, these methods lack sufficient spatial resolution to distinguish the VP from the VS. Therefore, these imaging studies are not reviewed separately here.

MIDBRAIN DOPAMINE NEURONS

Organization of the Dopamine Neurons

The central function of the dopamine neurons in the reward circuit is now well established (Schultz, 2002; Wise, 2002). Behavioral and pharmacological studies of dopamine pathways have lead to the association of the mesolimbic pathway with reward processing and nigro-striatal pathway with motor activity. However, more recently both of these projections have been associated with reward (Schultz, 2002). We first review the organization of the midbrain dopamine cells, and then turn to a discussion of their projections and associated functions.

Dopamine cell groups. The midbrain dopamine neurons are classically divided into the SNc, the VTA, and the retrorubral cell groups (Hokfelt *et al*, 1984). In human and nonhuman primates, the SNc is further divided into three groups: a dorsal group (α or pars dorsalis), a densocellular region (the ß group), and the cell columns (the γ group) (Francois *et al*, 1985; Haber *et al*, 1995b; Halliday and Tork, 1986; Olszewski and Baxter, 1982; Poirier *et al*, 1983). The dorsal group is composed of loosely arranged cells, extending dorsolaterally circumventing the ventral and lateral superior cerebellar peduncle and the red nucleus. These neurons, which form a continuous band with the VTA, are oriented horizontally and do not extend into the ventral parts of the SNc or into the SNr. Calbindin, a calcium binding protein, is an important phenotypic marker for both the VTA and the dorsal SNc and illustrates the continuity of these two cell groups (Haber *et al*, 1995b; Lavoie and Parent, 1991; McRitchie and Halliday, 1995). In contrast, the dendritic arbors of the ventral cell groups are oriented ventrally and extend deep into the SNr. The interweaving of dopamine cells and dendrites in the SNr is particularly prominent in human and nonhuman primates. These ventral cell groups are calbindin negative, but have

high expression levels for DAT and for the D2 receptor mRNAs (Ciliax *et al*, 1995; Counihan and Penney, 1998; Haber *et al*, 1995b; Hersch *et al*, 1997). Based on these and other characteristics, the midbrain dopamine neurons are divided into two tiers: a dorsal tier (the dorsal SNc and the contiguous VTA) that is calbindin-positive, has relatively low expression levels for DAT and the D2R mRNAs, and is selectively spared from neurodegeneration; and a ventral tier (the densocellular region and the cell columns) that is calbindin-negative, has relatively high levels of neuromelanin and expression of DAT and the D2 receptor mRNA, and is selectively vulnerable to neurodegeneration (Burns *et al*, 1983; German *et al*, 1992; Haber *et al*, 1995b; Parent and Lavoie, 1993) (Figure 9a). Connection of the dopamine neurons have been extensively studied for several species. Below, we briefly review those pathways, focusing on primate studies.

Afferent projections. Input to the midbrain dopamine neurons comes primarily from the striatum, from both the external segment of the globus pallidus and the VP, and from the brainstem (Figure 9b). In addition, there are

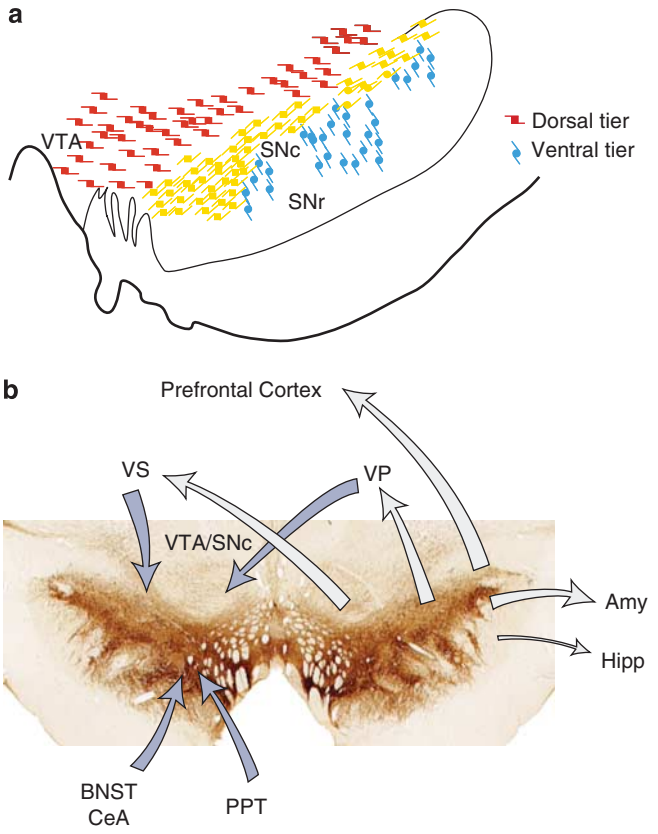

Figure 9. Schematic illustrating the organization (a) and connections (b) of the midbrain dopamine cells. Red cells = connections with VS regions; yellow cells = connections with dorsal caudate nucleus; blue cells = connections with motor control striatal areas. BNST = bed nucleus stria terminalis; CeA = central amygdala nucleus; Amy = amygdala; Hipp = hippocampus; PPT = Pedunculopontine nucleus; SNc = substantia nigra, pars compacta; VP = ventral pallidum; VTA = ventral tegmental area.

projections to the dorsal tier from the bed nucleus of the stria terminalis, from the sublenticular substantia innominata, and the extended amygdala (the bed nucleus of the stria terminalis and the central amygdala nucleus). The striatonigral projection is a massive projection to the midbrain dopamine cells and terminates in both the VTA/SNc and the SNr. There is medial/lateral topography and inverse ventral/dorsal topography to these projections, such that the dorsal striatonigral inputs are concentrated in the ventral midbrain and the ventral striatal projects to the dorsal midbrain. In particular, the ventral striatum terminates in the dorsal tier, the dorsal part of the ventral tier, and in the medial and dorsal SNr (Haber *et al*, 2000; Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994a; Szabo, 1979). Projections from the pallidum follow a similar inverse dorsal/ventral organization as the striatonigral projection. Thus, the VP projects dorsally, primarily to the dorsal tier and dorsal SNc (Haber *et al*, 1993; Parent *et al*, 1984).

Descending projections from the extended amgydala also terminate in a wide medio-lateral region, but are limited primarily to the dorsal tier cells (Fudge and Haber, 2000; Fudge and Haber, 2001). The pedunculopontine nucleus sends a major glutamatergic input to the dopaminergic cells bodies (Lavoie and Parent, 1994a) and there is a serotonergic innervation from the dorsal raphe nucleus (Corvaja *et al*, 1993; Gervais and Rouillard, 2000; Mori *et al*, 1987). Other brainstem inputs to the dopamine neurons include those from the superior colliculus (May *et al*, 2009). This input raises the interesting possibility that dopamine cells receive a direct sensory projection. The collicular input has been suggested to be responsible for the short latency, burst-firing activity of the dopamine cells in response to a salient or rewarding stimuli (Dommett *et al*, 2005). Finally, in primates, there is a small and relatively limited projection from the PFC to the midbrain DA neurons in primates. These fibers terminate in both the VTA and SNc (Frankle *et al*, 2006).

Efferent projections. The midbrain dopamine neurons project massively to the striatum (Hedreen and DeLong, 1991; Lynd-Balta and Haber, 1994b; Selemon and Goldman-Rakic, 1990; Szabo, 1979) (Figure 9b). As with the descending striatonigral pathway, there is a medio-lateral and an inverse dorsoventral topography arrangement to the projection. Thus, the ventral SNc neurons project to the dorsal striatum and the dorsal tier dopamine neurons project to the VS. The shell region of the NAcc receives the most limited midbrain input, primarily derived from the medial VTA (Lynd-Balta and Haber, 1994c). The rest of the VS receives input from the dorsal tier and from the medial and dorsal part SNc. In contrast to the VS, the central striatal area (the region innervated by the dPFC) receives input from a wide region of the SNc. The dorsolateral (motor-related) striatum receives the largest midbrain projection from cells throughout the ventral tier and the VS receives the most limited dopamine cell input. Thus, in addition to an inverse topography, there is also a

differential ratio of dopamine projections to the different striatal areas (Haber *et al*, 2000). These characteristics are important when considering how information flows between different functional striatal regions through their projection to the midbrain (see below).

In addition to striatal input, the dorsal tier cells also project widely throughout the primate cortex. Tyrosine hydroxylase-positive fibers are found not only in granular frontal cortex, but also in agranular frontal regions, parietal cortex, temporal cortex, and albeit sparsely, in occipital cortex (Gaspar *et al*, 1992; Lidow *et al*, 1991). The dopamine cells that project to these functionally diverse cortical regions are intermingled with each other. Moreover, individual neurons often send collateral axons to different cortical regions. Thus, the nigrocortical projection is a more diffuse system compared with the more topographically organized nigro-striatal system. Dopamine fibers are located in superficial layers in primate cortex, including a prominent projection throughout layer I and are also found in the deep layers in specific cortical areas (Goldman-Rakic *et al*, 1999; Lewis, 1992; Williams and Goldman-Rakic, 1993). Finally, dopamine neurons, in particular the dorsal tier, project to the wide range of midline structures, including the hypothalamus, periaqueductal gray, the bed nucleus of the stria terminalis, and to the amygdala and hippocampus.

Striato-nigro-striatal network. The idea that VS can influence the dorsal striatum through the midbrain dopamine cells originated in rodent studies, which demonstrated (both at the light and electron microscopy levels) projections from the NAcc to the dorsal striatum, through the SN (Nauta *et al*, 1978b; Somogyi *et al*, 1981). Through this pathway, therefore, limbic regions could impact on the motor regions of the basal ganglia (Nauta and Domesick, 1978a). The concept of transferring information through different functional regions of the striatum was later expanded, taking into account the functional diversity of the striatum in monkeys (Haber *et al*, 2000). In monkeys, projections from the striatum to the midbrain and from the midbrain to the striatum each create a loose topographic organization. The VTA and medial SN are associated with limbic regions, and the central and ventrolateral SN are associated with the associative and motor striatal regions, respectively. However, as indicated above, each functional region differs in their proportional projections. The VS receives a limited midbrain input, but projects to a large region. In contrast, the dorsolateral striatum receives a wide input, but projects to a limited region. In other words, the VS influences a wide range of dopamine neurons, but is itself influenced by a relatively limited group of dopamine cells. On the other hand, the dorsolateral striatum influences a limited midbrain region, but is affected by a relatively large midbrain region.

Thus, while the main efferent projection from the VS to the midbrain is to the dorsal tier, this projection field extends beyond the tight VS/dorsal tier/VS circuit. Indeed, the VS also terminates in the ventral tier, in a position to influence more dorsal striatal regions, particularly those that receive input from associative cortical regions (dPFC). This part of the ventral tier is reciprocally connected to the central (or associative) striatum. The central striatum also projects to a more ventral region than it receives input from. This region, in turn, projects to the dorsolateral (or motor) striatum. Taken together, the interface between different striatal regions through the midbrain DA cells is organized in an ascending spiral interconnecting different functional regions of the striatum and creating a feed forward organization from reward-related regions of the striatum to cognitive and motor areas (Figure 10).

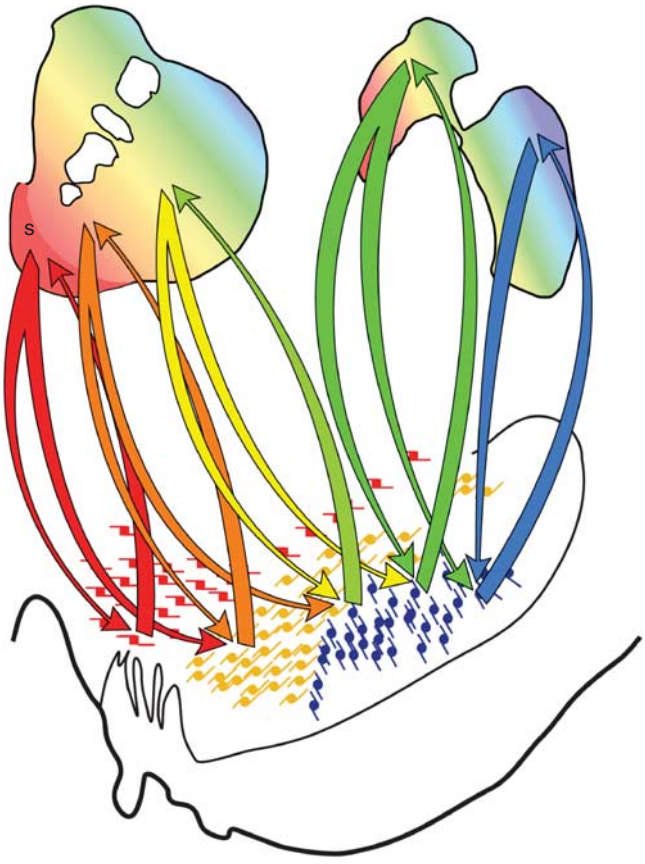

Figure 10. Schematic illustrating the complex connections between the striatum and SN. The arrows illustrate how the VS can influence the dorsal striatum through the midbrain dopamine cells. Colors indicate functional regions of the striatum based on cortical inputs. Midbrain projections from the shell target both the VTA and ventromedial SNc. Projections from the VTA to the shell form a 'closed,' reciprocal loop, but also project more laterally to impact on dopamine cells that project to the rest of the VS, forming the first part of a feed forward loop (or spiral). The spiral continues through the striato-nigro-striatal projections through which the VS impacts cognitive and motor striatal areas through the midbrain dopamine cells; red = inputs from the vmPFC; orange = inputs from the OFC and dACC; yellow = inputs from the dPFC; green and blue = inputs from motor control areas.

Although the short latency burst-firing activity of dopamine that signals immediate reinforcement is likely to be triggered from brainstem nuclei (Dommett *et al*, 2005), the cortico-striato-midbrain pathway is in the position to influence dopamine cells to distinguish rewards and modify responses to incoming salient stimuli over time. This pathway is further reinforced through the nigro-striatal pathway, placing the striato-nigro-striatal pathway in a pivotal position for transferring information from the VS to the dorsal striatum during learning and habit formation. Indeed, cells in the dorsal striatum are progressively recruited during different types of learning from simple motor tasks to drug self-administration (Everitt and Robbins, 2005; Lehericy *et al*, 2005; Pasupathy and Miller, 2005; Porrino *et al*, 2004; Volkow *et al*, 2006). Moreover, when the striato-nigro-striatal circuit is interrupted, information transfer from classical to instrumental learning does not take place (Belin and Everitt, 2008).

Reward Processing in the Human Midbrain

Event-related FMRI currently offers sufficient spatial resolution to allow investigators to visualize changes in the activity of specific midbrain nuclei (Duzel *et al*, 2009). After electrophysiological evidence that reward prediction and prediction errors alter the firing of midbrain dopamine neurons in monkeys (Schultz, 2002), a growing body of FMRI research has begun to examine midbrain activity during reward processing in human beings. Less neuroimaging work research has focused on midbrain regions than on striatal and prefrontal regions, however, because the midbrain suffers from artifacts related to inhomogeneity (because of its nearness to tissue boundaries), endogenous motion (because of its proximity to the carotid artery), and partial voluming (because of its small size). In addition, while the VTA is difficult to visualize on structural FMRI scans, the SN is not (because of its dark appearance), but investigators can localize the VTA with respect to the SN and other landmarks (including the midline of the brain).

FMRI researchers have reported increased midbrain activation during anticipation of pleasant tastes (D'Ardenne *et al*, 2008; O'Doherty *et al*, 2002), anticipation of monetary gains (Knutson *et al*, 2005), and during exposure to visual stimuli that evoke romantic love (Aron *et al*, 2005). Interestingly, in neither the juice nor monetary reward studies did midbrain activation appreciably decrease when anticipated rewards failed to occur (consistent with a reward prediction, but not necessarily a prediction error signal). In addition, midbrain increases in activation have been reported in response to reward-predicting cues (Adcock *et al*, 2006; Wittmann *et al*, 2005), and this activation, in concert with medial temporal lobe activation, predicts subsequent enhancements in memory for associated stimuli. In summary, FMRI research suggests that midbrain regions near dorsal tier dopamine neurons, including the VTA, show increased activation in response to stimuli that predict reward. The responsiveness of these regions to other incentive features (eg, punishment, arousal) has received less characterization (Bunzeck and Duzel, 2006).

COMPLETING THE CORTICO-BASAL GANGLIA REWARD CIRCUIT

In addition to the PFC, VS, VP, and amygdala, other key components of the circuit include the thalamus, the LHb, the raphe nuclei, and the pedunculopontine tegmental nuclei. Each of these structures has complex connectivities with multiple brain regions and their direct associations with the cortico-basal ganglia reward system have been discussed. However, below, we add a few additional important points with respect to their role in the reward circuitry.

Thalamus

The medial MD nucleus projects to the frontal cortex, and is the final link in the reward circuit. (Haber *et al*, 1993; Ray and Price, 1993). These connections, however, are bidirectional (Erickson and Lewis, 2004; McFarland and Haber, 2002; Zikopoulos and Barbas, 2007). Moreover, while cortico-thalamic projections of the specific thalamic relay nuclei follow a general rule of reciprocity, the cortical projections to these thalamic nuclei are more extensive than their projections back to cortex (as seen in other thalamocortical systems) (Darian-Smith *et al*, 1999; McFarland and Haber, 2002; Sherman and Guillery, 1996). Importantly, in addition to the reciprocal connection, there is a nonreciprocal cortico-thalamic component. Thus, while the MD nucleus completes the reward circuit back to cortex, there is a nonreciprocal cortical input to the MD nucleus that is derived from functionally distinct frontal cortical areas. For example, the central MD has not only a reciprocal projections with the OFC, but also a nonreciprocal input from vmPFC. Similarly, more lateral MD areas are not only reciprocally connected to the dPFC, but also have a nonreciprocal input from the OFC (McFarland and Haber, 2002). Therefore, similar to the striato-nigro-striatal projection system, the thalamic relay nuclei from the basal ganglia also seem to integrate information flow from reward and higher cortical 'association' areas of the prefrontal cortex. A recent DTI study indicates that integration between these cortical areas in the thalamus is also likely to exist in humans (Draganski *et al*, 2008).

Both PET and FMRI findings suggest that primary and secondary rewards (*vs* nonrewards) can increase thalamic activation (Aharon *et al*, 2001; Anderson *et al*, 2003; Blood and Zatorre, 2001; Knutson *et al*, 2000; Martin-Solch *et al*, 2001; Rogers *et al*, 1999; Rolls *et al*, 2003; Small *et al*, 2001; Thut *et al*, 1997). Moreover, a meta-analysis of over 20 event-related FMRI studies using monetary incentive delay tasks indicated that anticipation of reward *vs* anticipation of punishment did not clearly elicit differential dorsomedial thalamic activation. On the other hand, anticipation of

reward did clearly elicit more dorsomedial thalamic activation than did reward outcomes (Knutson and Greer, 2008). Together, these findings are consistent with the notion that dorsomedial thalamic activation reflects general arousal to a greater extent than value (ie, either rewarding or punishing).

The Lateral Habenula, Pedunculopontine Tegmental Nucleus, and the Raphe Serotonergic Systems

Recent studies have emphasized the potential importance of the LHb in regulating the dopamine reward signal (Morissette and Boye, 2008). Experiments show that stimulation of the LHb nuclei in primates results in a negative reward-related signal in SNc. (Matsumoto and Hikosaka, 2007). LHb cells are inhibited by a reward-predicting stimulus, but fire following a nonreward signal. This stimulation of the LHb directly, or following a non-reward signal inhibits dopamine cells (Ji and Shepard, 2007; Matsumoto and Hikosaka, 2007). An event-related FMRI study featuring adequate spatial and temporal resolution to visualize habenular activity indicated that negative but not positive feedback can activate the habenular complex, consistent with findings from primate electrophysiology (Ullsperger and von Cramon, 2003). Interestingly, few fibers from the LHb directly reach the SNc in the primates, indicating an indirect regulation of the dopamine signal. There are several possible routes by which the LHb might influence midbrain dopamine firing. In addition to an input from the globus pallidus and VP, other connections include the basal forebrain, preoptic area of hypothalamus, interpeduncular nucleus, pedunculopontine nucleus, raphe nucleus, superior colliculus, pretectal area, central gray, VTA, and reticular formation (Araki *et al*, 1988; Haber *et al*, 1993; Herkenham and Nauta, 1977; Parent *et al*, 1981).

The pedunculopontine tegmental nucleus is connected to multiple basal ganglia structures and provides one of the strongest excitatory inputs to the midbrain dopamine cells (Blaha *et al*, 1996; Lavoie and Parent, 1994b). Moreover, the cells in this brainstem area receive input from the LHb. Anatomical and physiological studies, coupled with the central function of dopamine for reward prediction error, led to studies that support the hypothesis that PPT may have a function in this reward signal (Kobayashi and Okada, 2007). The brainstem serotonergic system may also play a role in reinforcement behaviors by encoding expected and received rewards (Nakamura *et al*, 2008). This reward signal could arise from a number of brain regions, but perhaps the strongest candidates include inputs derived from the OFC and vmPFC, the amygdala, the SN, and the LHb (Peyron *et al*, 1998).

SUMMARY AND CONCLUSIONS

The reward circuit comprises several cortical and subcortical regions forming a complex network that mediates different aspects of incentive-based learning, leading to adaptive behaviors. To develop an appropriate behavioral response to external environmental stimuli, information about motivation and reward needs to be combined with a strategy and an action plan for obtaining goals. For example, to win at a card game, desire is not sufficient. One has to understand the rules of the game, remember the cards played, and so forth, before executing the play. In addition, there is a complex interaction between the desire to put cards in play and the inhibition of impulse to play them too early. Thus, action plans developed toward obtaining a goal require a combination of reward processing, cognitive planning, and motor control.

Reward, therefore, does not work in isolation, but its pathways interface with circuits that mediate cognitive function to affect motor planning. The pathways and connections reviewed in this chapter clearly show that there are dual cortico-basal ganglia systems permitting both parallel and integrative processing (Figure 11). Thus, within each of the cortico-basal ganglia structures, there are convergence zones that can link the reward pathway with those associated with cognitive function. Through these interactive networks, information about reward can be channeled through cognitive circuits to influence motor

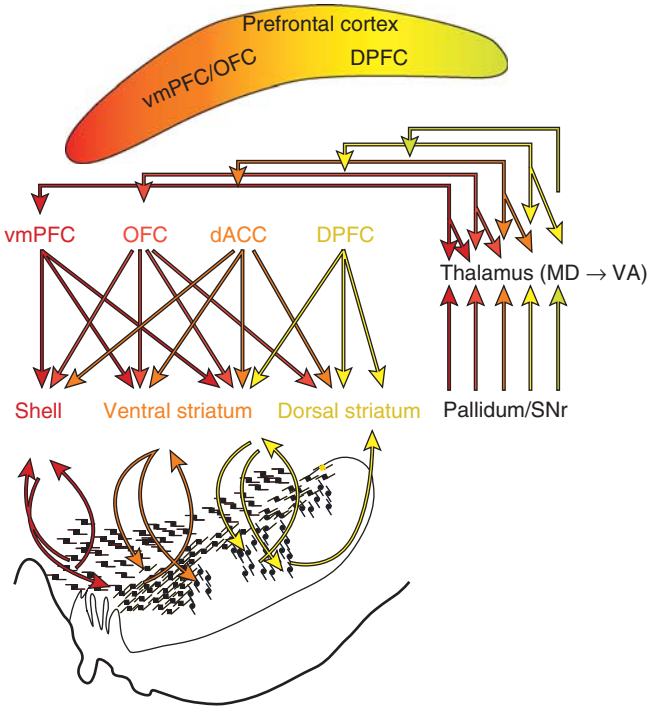

Figure 11. Three networks of integration through cortico-basal ganglia pathways. (1) Fibers from different prefrontal areas converge within subregions of the striatum. (2) Through the organization of striato-nigro-striatal (SNS) projections, the VS can influence the dorsal striatum. (3) The nonreciprocal cortico-thalamic projection carries information from reward-related regions, through cognitive, and motor controls. dACC = dorsal anterior cingulate cortex; dPFC = dorsal prefrontal cortex; OFC = orbital frontal cortex; vmPFC = ventral medial prefrontal cortex. Red = vmPFC pathways; dark orange = OFC pathways; light orange = dACC pathways; yellow = dPFC pathways; green = output to motor control areas.

control circuits. DTI studies support the idea that interactive networks exist also in the human brain (Draganski *et al*, 2008). Moreover, fMRI studies provide evidence for functional interactions. For example, while reward anticipation tends to co-activate NAcc and midbrain, reward outcomes subsequently recruit the medial caudate and putamen, followed by the dorsal caudate, including the supplementary motor area. The idea that this recruitment is likely to involve the dopamine pathways through the striato-nigro-striatal spiral is supported by animal behavioral studies (Belin and Everitt, 2008; Porrino *et al*, 2004). Alternatively, several striatal areas may be co-activated, as in the case for anticipation of reward, by a convergence of different cortico-striatal projections. For example, as indicated above, reward outcomes increased vmPFC and putamen activation, areas that do not appear to have a direct connection. However, within the striatum, the vmPFC projections do converge with those from the OFC in parts of the rostral putamen. Thus, an understanding from animal studies of where these networks interface results in better interpretations of neuroimaging findings in which seemingly unconnected structures can be activated simultaneously. As we learn more about the complexities of circuits, we can hypothesize how other brain regions may be co-activated. Moreover, we are able to better predict where co-activation should occur. This chapter brings together a unique monkey to human translational review that emphasizes the importance of drawing on anatomical constructs developed from primate anatomy to interpret and extend findings from human imaging studies.

The circuitry reviewed in this chapter implies that information flows from ventral to dorsolateral cortico-basal ganglia circuits. Thus, sequentially over time, this suggests a mechanism through which activity occurs across reward-processing episodes during the course of learning (Tanaka *et al*, 2004). Sequential activation also occurs within a single reward-processing episode (eg, from anticipation to outcome). Consistent with this notion, gain prediction error in a typical cued response task occurs first in the mPFC and NAcc, and subsequently appears in the dorsomedial caudate and putamen parts of the VS seconds later (see Figure 7). The ability to visualize neural activity related to expected value raises the exciting possibility of going beyond correlating brain activation with behavior. It may be possible to use activation to predict behavior. For example, evidence suggests that anticipatory activation in the NAcc and in the mPFC can independently predict approach, whereas anticipatory activation in the connected insular cortex can predict avoidance in financial risk taking, gambling, and purchasing scenarios.

FUTURE DIRECTIONS

Linking anatomical studies in animals and human imaging is a powerful way to gain insight into brain regions associated with different aspects of reward processing and cognition that lead to appropriate choices. As imaging techniques are refined, we will be able to use results from those studies to explore in depth the underpinnings of co-activation or temporal activation of structures that appear unrelated. One important outcome from these linkages is the validation of imaging results based on what is anatomically well established. As such, neuroimaging has now demonstrated human functional results that map increasingly close to primate anatomy. For example, the adoption of event-related FMRI has generated a proliferation of new results that highlight anticipatory activation in related cortical and striatal regions. Moreover, in the case of neural correlates of expected value, these patterns of activation mapped more closely onto the connected mPFC, VS, and VTA implied by anatomical studies than did earlier functional results. An emerging set of DTI tools for visualizing connectivity in humans promises to further bridge the gap between primate structure and human function (Cohen *et al*, 2009b; Draganski *et al*, 2008; Lehericy *et al*, 2004).

DISCLOSURE

Dr Haber has received honoraria fees from Lilly and consultation fees from Medtronic. Dr Knutson has no conflicts of interest to declare.

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