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Dorsal and ventral streams: The distinct role of striatal subregions in the acquisition and performance of goal-directed actions

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Abstract

Considerable evidence suggests that distinct neural processes mediate the acquisition and performance of goal-directed instrumental actions. Whereas a cortical-dorsomedial striatal circuit appears critical for the acquisition of goal-directed actions, a cortical-ventral striatal circuit appears to mediate instrumental performance, particularly the motivational control of performance. Here we review evidence that these distinct mechanisms of learning and performance constitute two distinct ‘streams’ controlling instrumental conditioning. From this perspective, the regulation of the interaction between these ‘streams’ becomes a matter of considerable importance. We describe evidence that the basolateral amygdala, which is heavily interconnected with both the dorsal and ventral subregions of the striatum, coordinates this interaction providing input to the final common path to action as a critical component of the limbic-motor interface.

Keywords

instrumental conditioning; goal-directed action; outcome devaluation; pavlovian instrumental transfer; striatum; nucleus accumbens; prelimbic cortex; amygdala

Introduction

Research on instrumental conditioning is concerned with the acquisition and performance of actions that control the environment to gain access to commodities of motivational significance. The learning processes associated with the acquisition of instrumental actions have been divided into those mediating goal-directed actions and those controlling habits and although, with regard to performance, these are redundant (both can control actions with broadly similar topographies), psychologically they reflect the operation of functionally distinct associative processes governed by different learning rules. In this review we will be

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primarily concerned with goal-directed actions, which are flexible, rapidly acquired actions the acquisition and performance of which is mediated by the formation of action-outcome associations (cf. Dickinson & Balleine, 1994; Balleine, 2001).

Although, from a behavioral perspective, learning and performance are clearly distinct processes – learning doesn't necessarily result in performance and, as noted above, performance can be mediated by more than one kind of learning – it has been research into the neural bases of goal-directed action that has demonstrated that they are not only distinct functionally but also structurally. Historically, two apparently independent networks have been proposed to control goal-directed action, one centered on the dorsal and the other on the ventral striatum, and, as a consequence, one might wonder whether there is widespread redundancy in the brain with regard to this capacity or whether perhaps some larger organizing principle can be established. We will argue the latter; that whereas a dorsal cortico-basal ganglia network centered on the dorsomedial striatum mediates the acquisition of goal-directed actions, a parallel ventral network centered on the nucleus accumbens controls their performance (cf. Figure 1). There is an analogy in this dorsal and ventral division to research in the visual system in which visual information is processed by distinct dorsal and ventral 'streams' within the mammalian brain (e.g. Ungerleider & Mishkin, 1982; Mishkin, Ungerleider & Macko, 1983; Goodale & Milner, 1992; Creem & Proffitt, 2001), the 'dorsal stream' guiding actions based on an object's spatial location, and the 'ventral stream' mediating object recognition and form representation (Kravitz, Saleem, Baker & Mishkin, 2011). With regard to research on the neural basis of goal-directed action we propose that analogous dorsal and ventral 'streams' can be discerned, although in this case mediating 'learning what to do' and 'deciding when and where to do it', respectively.

In what follows we will discuss the evidence for this division and elaborate on the neural circuits or 'streams' that subserve these distinct functions. In doing so, we will rely heavily on earlier anatomical studies describing connections between various parts of these networks. Where such studies are ambiguous or incomplete with respect to specific projections we add illustrations from recent tracing studies conducted in our lab using a uniform experimental procedure. Before turning to the circuitry, however, we begin with a brief discussion of behavioral evidence that has emerged regarding the nature of the learning and performance factors subserving goal-directed actions to structure the discussion of the neural bases that follows.

The behavioral determinants of goal-directed action

Goal-directed learning

The ability to perform flexible, goal-directed actions requires the ability to encode both the contingency between a specific action and its consequences or outcome, and the current value of the outcome (Balleine & Dickinson, 1998a). Perhaps the easiest way to demonstrate the importance of, and the interaction between, the contingency and evaluative components of goal-directed action has been using the outcome devaluation procedure, a tool that probes the contents of the learning underlying instrumental performance. The logic of this test is straightforward: If, in instrumental conditioning, animals encode the action–outcome association and use that association to guide performance then changes in the value of the

outcome should alter their tendency to perform the action. Devaluation is usually conducted in one of two ways; either by pairing an outcome with illness (Adams & Dickinson, 1981; Colwill & Rescorla, 1985; Dickinson & Balleine, 1994), or by allowing the animals to consume the outcome to satiety (Balleine & Dickinson, 1998b). Performance of the action previously paired with the now 'devalued' outcome is then measured in extinction (i.e. in the absence of the outcome). This rate of responding can be compared within-subjects to the propensity to make an alternative response that had been paired with another, non-devalued outcome. This "choice" paradigm allows a distinction to be drawn between the overall rates of responding and bias in responding, hence it can disambiguate performance effects due to alternative factors, such as different rates of extinction or lower baseline responding. Alternatively, responding can be compared between-subjects to the rate of responding of an animal that had been pre-fed with a different outcome. In either case, in order to selectively reduce the response associated with a now devalued outcome, animals must combine knowledge acquired during training about the response-outcome contingency (R-O) with updated information about the current value of the outcome. As such, successful devaluation provides one source of evidence that animals acquire and are able to integrate these sources of information.

Another means of measuring an animal's ability to encode the R-O association is to manipulate the contingency between a given response and its outcome; i.e. the difference between the probability of earning a specific outcome given a response and the probability of earning that outcome given no response (Hammond, 1980). There is now evidence that rats also make these contingency-based comparisons when selecting between responses in choice situations (Balleine & Dickinson, 1998a). In a contingency degradation procedure, the contingency between one response (R1) and its outcome (O1) is degraded via 'free' deliveries of O1 in the absence of R1. The result of such degradation is that the probability of the outcome (O1) given R1 becomes closer to the probability of O1 given no R1. The behavioral consequence of this degradation is that rats selectively reduce R1 whilst maintaining their performance of a response (R2) whose contingency with its outcome is unchanged. Once again, in order to select the response with the higher contingency, animals must be able to detect and encode the current contingency and flexibly alter their responding accordingly.

Goal-directed performance

Factors influencing performance modulate the impact of action-outcome associations on motor output. There are a number of factors that can influence performance in this way but only two primary categories: (i) the experienced value of a specific instrumental outcome and (ii) the predicted value based on the presence of Pavlovian cues that predict the occurrence of a specific outcome. These performance factors are traditionally referred to as incentive processes: experienced value is an instrumental incentive process whereas predicted value is a Pavlovian incentive process. Although both incentive processes utilize a representation of the outcome to bias choice, there are now several lines of evidence to suggest that the representation utilized by these two processes differs (Corbit, et al., 2001; Corbit & Balleine, 2003a). Furthermore, recent research has identified at least two forms of Pavlovian incentive process, one that influences actions based on anticipation of the general

affective properties of the outcome, i.e. whether it is appetitive or aversive, and a second based on the more specific sensory predictions, e.g., the taste properties of the outcome. The first incentive process is called General Pavlovian-Instrumental Transfer (G-PIT) and the second is called Outcome-Specific Pavlovian-Instrumental Transfer (S-PIT).

In experiments demonstrating G-PIT or S-PIT animals receive Pavlovian conditioning and instrumental conditioning in separate phases, and the motivational impact of the Pavlovian CSs on instrumental responding is then measured in extinction. G-PIT is usually demonstrated using a single response procedure, which is typically interpreted in terms of the general arousing properties of the CS; e.g., presentation of a Pavlovian CS associated with an appetitive reinforcer will tend to elevate performance above baseline, and above the level of responding elicited by a neutral CS or CSs associated with an aversive outcome, which tend to reduce performance below baseline. To demonstrate S-PIT, animals are usually given Pavlovian conditioning with two CSs each paired with different outcomes. In a separate phase, animals receive instrumental training with two different responses each paired with one of the outcomes used in Pavlovian training. During the critical transfer test, animals are presented with each of the Pavlovian stimuli in extinction, and their propensity to influence each instrumental response is measured. The typical outcome of such a test is that each CS elevates the performance of the response that predicts the same outcome; an integration of predictive information taken to indicate a form of cognitive control of action selection.

Traditionally, PIT procedures are only designed to examine one of these two types of instrumental transfer. However, Corbit and Balleine (2005) (see also Corbit, Janak & Balleine; 2007; Corbit & Balleine, 2011) have developed a three CS design able to demonstrate both the general arousing properties and the specific excitatory effects of a CS in the same experiment. In this design, rats first receive Pavlovian conditioning with three different stimuli paired with three different outcomes, followed by instrumental training in which two responses are paired with two of the three outcomes. Rats are then given the opportunity to perform the two responses in the presence of the three stimuli. Typically, a CS paired with a food reward not earned by either response elevates both responses (i.e. generates G-PIT) whereas the specific Pavlovian CSs only elevate performance of the action associated with the outcome predicted by the CS (S-PIT). Interestingly, Corbit et al. (2007) tested rats both food deprived and after a shift in their motivational state to satiety and found that, although they no longer exhibited G-PIT, the magnitude of S-PIT was unaffected. The results from this experiment provided further support for the well-established argument that S-PIT is resistant to outcome devaluation (Colwill & Rescorla, 1990; Rescorla, 1994; Holland, 2004). Furthermore, this study demonstrates that, in contrast to S-PIT, G-PIT is highly sensitive to motivational state, and provides a means of behaviorally dissociating sensory and affective influences of stimulus-outcome (S-O) associations on instrumental responding (Balleine, 1994).

Response-outcome learning in the ‘dorsal stream’

Beginning around 15 years ago (Balleine & Dickinson, 1998a), a growing body of evidence established that disrupting activity in a dorsal corticostriatal circuit, involving medial

Other studies have provided less ambiguous evidence. For example, rats with pre-training PL lesions failed to show sensitivity to outcome devaluation during an extinction test (Corbit & Balleine, 2003b; Killcross & Coutureau, 2003; Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009; Balleine & Dickinson, 1998a) and also failed to selectively reduce instrumental responding during contingency degradation (Balleine & Dickinson, 1998a; Corbit & Balleine, 2003b). These results collectively suggest that the PL is critical for the acquisition of R-O associations during instrumental learning. Importantly, it is now clear that the role of the PL in instrumental conditioning is time limited; cell body lesions of the PL made after instrumental training have no effect on subsequent sensitivity to outcome devaluation (Ostlund & Balleine, 2005; Tran-Tu-Yen et al., 2009; Gourley, Lee, Howell Pittenger & Taylor, 2010) suggesting that the PL is necessary for the formation of R-O associations, rather than their storage or expression. It also demonstrates that the PL is not involved in updating the value of the outcome after outcome devaluation, nor is it involved in incorporating the current value of O into the R-O association to make an instrumental choice (Ostlund & Balleine, 2005).

The robust projection from the medial PFC to the striatum has been previously described in a number of studies using anterograde and retrograde tract tracing (Sesack, Deutch, Roth & Bunney, 1989; Condé, Maire-Lepoivre, Audinat & Crepel, 1995; Gabbott, Warner, Jays, Salway, & Busby, 2005). Figure 2 focuses specifically on the projection from the PL to the posterior DMS (pDMS) in a male long-evans rat. We found that the PL projects directly to the DMS primarily from Layers V/VI, with a smaller projection arising from Layer II (Gabbott et al., 2005). Additionally, it can be seen that the basolateral amygdala (BLA) projects directly to the pDMS predominantly from the medial wall region of the anterior BLA, a projection that will be discussed in more detail later on.

It has now been determined that plasticity within this region of the pDMS is necessary during instrumental training to encode R-O associations. For example, Yin, Knowlton and Balleine (2005) trained rats to make two instrumental responses for a common outcome. Once both instrumental actions had been acquired, rats entered a critical instrumental training phase, during which each of these responses now provided two new outcomes (R1-O1, R2-O2). Immediately prior to this training, plasticity within the pDMS was disrupted in one group of rats via an infusion of the NMDA receptor antagonist DL-2-amino-5-phosphonopentanoic acid (APV). Control rats received an infusion of vehicle into the pDMS, or of APV into the lateral portion of the dorsal striatum (DLS). When tested the following day, drug-free, rats that had received vehicle or DLS infusions were sensitive to outcome devaluation, however rats that had received APV into the pDMS failed to show devaluation. Importantly, this effect was only observed when the APV was infused just prior to instrumental training; rats showed no impairment if the drug was infused shortly after the critical training phase, indicating that plasticity within the pDMS is necessary during R-O learning rather than during a consolidation window.

In contrast to the PL, we now know that the pDMS is not only critical for the formation of RO associations, it is also necessary for their expression. For example, both pre-training and post-training cell body lesions of the pDMS, but not the anterior DMS (aDMS), abolished sensitivity to outcome devaluation and contingency degradation (Yin, Ostlund, Knowlton, & Balleine, 2005). Yin et al. (2005) further demonstrated that the pDMS is specifically required at the time of choice in order to make instrumental decisions on the basis of outcome or response value. Rats that received an inactivation dose of the GABA-A receptor agonist, muscimol, into the pDMS after pre-feeding (devaluation), but prior to the extinction test, failed to show sensitivity to devaluation. Finally, the authors demonstrated that rats given contingency degradation training drug-free and tested in extinction failed to show response selectivity if the extinction test was conducted after a pDMS infusion of muscimol. Therefore, the pDMS is critically involved in both the acquisition and expression of R-O associations. The pDMS may, therefore, also be the site of long-term storage of the R-O association.

Plasticity in the pDMS depends not only on NMDA receptor activity but also changes in intracellular signaling involving particularly the Ras/Raf signaling pathway, which results in the phosphorylation of extracellular signal-related kinase (ERK). ERK signaling has an important role in both the acquisition and performance of goal-directed actions, with evidence suggesting instrumental training increases ERK phosphorylation in the pDMS

(Shiflett & Balleine, 2011a; 2011b; Shiflett, Brown & Balleine, 2010). Furthermore, inhibition of ERK activation by infusion of the MEK/ERK inhibitor U0126 into the pDMS prior to instrumental training, using similar procedures to those described above abolishes subsequent outcome devaluation, suggesting that blocking ERK activation in this region prevents the encoding of action–outcome associations. In addition to a role in learning, ERK is necessary for the performance of goal-directed actions; inhibition of ERK activity in the pDMS after training but prior to a devaluation choice extinction test was found to impair choice performance; during the test, rats showed no preference for the valued action compared to the devalued action (Shiflett et al., 2010). As found with muscimol and APV, these results were specific to the pDMS; ERK inhibition in the DLS did not affect action–outcome learning.

The vast majority (~95% in rodents) of neurons in the striatum are GABAergic medium spiny neurons (MSNs). These projection neurons form two major output pathways based on their projection targets in which information can be relayed back to the cortex via the thalamus. The neuropeptide substance P, dynorphin and the dopamine D1 receptor (D1R) is preferentially localized on MSNs that project to the SNr and the internal part of the globus pallidus (GPi) and is referred to as the ‘direct’ striatonigral pathway through its monosynaptic connection to nuclei that project outside the basal ganglia. On the other hand, enkephalin, the adenosine A_{2A} receptor and the dopamine D2 receptor (D2R) are preferentially localized on MSNs that project to the SNr and GPi through a multisynaptic pathway within the basal ganglia; these MSNs project to the external part of the globus pallidus (GPe), and the subthalamic nucleus (STN) before reaching the SNr/GPi. Segregation of the two pathways has been a matter of debate until recent development of bacterial artificial chromosome (BAC) transgenic mice expressing fluorescent proteins or Cre recombinase (see Bertran-Gonzalez, Hervé, Girault, & Valjent, 2010). These transgenic mice lines have allowed detailed experiments assessing the expression and distribution of the two populations of MSNs to reveal more clearly the characteristics of the two pathways. For example, in a careful analysis on the identification of the two populations of MSNs using the expression of enhanced green fluorescent protein (EGFP) under the control of D1R (*drd1α*-EGFP) and D2R (*drd2*-EGFP) promoters, it was estimated that 5% of MSNs in the dorsal striatum expressed both D1R and D2R (Bertran-Gonzalez, Bosch, Maroteaux, Matamalas, Hervé, Valjent, & Girault, 2008). On the other hand, Matamalas et al. (2009) demonstrated striatonigral neurons all express D1R and there were less than 1% of neurons retrogradely labeled from the SNr expressing EGFP in *drd2*-EGFP mice. Apart from this, these authors and others have also observed only a weak D1R MSN projection from the dorsal striatum to the GPe. (Gong, Zheng, Doughty, Losos, Didkovsky, Schambra, et al., 2003; Valjent, Bertran-Gonzalez, Hervé, Fisone & Girault, 2009; Ade, Wan, Chen, Gloss & Calakos, 2011). Together, these findings remain largely in agreement with the idea of segregation between the two pathways in the dorsal striatum. Figure 3 is a demonstration of striatonigral neurons in the DMS and NAc that project to the medial substantia nigra (SN) and VTA. Consistent with the topographic organization of corticostriatal and striatonigral projections (Tulloch, Arbuthnott & Wright, 1978; Berendse, Groenewegen & Lohman, 1992; Deniau, Menetrey & Charpier, 1996; Deniau, Mailly, Maurice & Charpier, 2007), labeling is most robust in the medial wall of the dorsal striatum and the NAc.

Ultimately, the direct and indirect pathways have opposing effects on activity within the output nuclei of the SNr and GPi. When stimulated by cortical input, the direct pathway has an overall disinhibitory effect, promoting action initiation, whereas the indirect pathway tends to promote action inhibition (Chevalier & Deniau, 1990; Mink, 1996). Although the classical model proposes an opposing interaction between the two pathways, it has been recently demonstrated that neurons from both pathways in the dorsal striatum are activated in coordination preceding contraversive movement (Cui, Jun, Jin, Pham, Vogel, Lovinger & Costa, 2013). Other optogenetic studies using the Cre-dependent viral strategy to express channelrhodopsin-2 in striatonigral and striatopallidal neurons have proposed distinct roles for each population during action selection (Kravitz, Tye & Kreitzer, 2012; Tai, Lee, Benavides, Bonci & Wilbretch, 2012) and may be consistent with the idea of coordinated activation of both pathways whereby activation of the direct pathway promotes action initiation and activation of the indirect pathway promotes inhibition of competing actions.

As well as controlling motor output, the SNr and GPi also control cortical feedback via projections to the mediodorsal thalamus (MD; Beckstead, Domesick, Nauta, 1979). Specifically, the MD feeds back to various regions of the prefrontal cortex (PFC), including the PL (Öngür & Price, 2000), providing a means of modulating activity in the PL-pDMS pathway. Research investigating the role of the MD in goal-directed instrumental learning has indicated a similar profile of involvement as the PL. Rats with pre-training lesions of the MD fail to show sensitivity to outcome devaluation or contingency degradation, despite intact response and outcome discrimination (Corbit, Muir, & Balleine, 2003). Post-training lesions of the MD also mirror PL lesions. Like post-training PL lesions, such lesions have little to no effect on outcome devaluation or outcome-induced reinstatement (Ostlund & Balleine, 2008).

In summary, R-O learning occurs in a specific corticostriatal 'dorsal stream' that includes the PL, pDMS and MD (see Figure 1). These structures have reasonably well established roles in the acquisition of instrumental R-O associations. Recently, primate and rodent studies have begun to present evidence implicating the medial portion of the OFC (mOFC) in goal-directed learning. For example, neuroimaging studies in humans have demonstrated decreases in activity in this region during the selection of a devalued relative to a valued action (Valentin, Dickinson & O'Doherty, 2007) or during performance of a high relative to a low instrumental contingency (Tanaka, Balleine & O'Doherty, 2008). Additionally, mice with bilateral mOFC lesions show greater instrumental perseveration during reversal learning (Gourley et al., 2010). Therefore, the limited research available suggests that this region of the cortex may also play an important role in some aspects of instrumental conditioning, however more research is needed to identify the specific involvement of the mOFC in goal-directed learning, and how it interacts with dorsal and ventral circuitry to modulate acquisition or performance.

The 'ventral stream' and the neural bases of goal-directed performance

Considerable evidence suggests that the influence of the ventral stream is restricted to goal-directed performance rather than learning, something that is particularly evident in the role of the nucleus accumbens (NAc) in goal-directed behavior. This region has often been

framed as the ‘limbic-motor interface’ because of its strong afferent connections with limbic structures and its efferents to motor output regions (Mogenson, Jones & Yim, 1980; Groenewegen, Wright, Beijer & Voorn, 1999). Studies assessing the role of the NAc in instrumental conditioning have revealed that rats with pre- or post- training lesions of the entire NAc or specific lesions of the core sub-region consistently show a reduction in the vigor of performance during the acquisition of instrumental responses relative to rats with sham lesions. Nevertheless, despite this general reduction in responding, rats with such lesions have been found to remain sensitive to changes in the instrumental contingency (Balleine & Killcross, 1994; Corbit et al., 2001). These findings suggest that, despite its involvement in response vigor or affective arousal, the NAc is not critical for the acquisition of instrumental actions.

Experienced vs. predicted reward

The precise role of the NAc in instrumental conditioning has perhaps been most clearly revealed in tests of instrumental choice performance. Rats with pre-training lesions of the core are insensitive to selective outcome devaluation and exhibit a general reduction in all responses (Corbit et al., 2001). This insensitivity is unlikely to be due solely to a general motoric deficit as these rats also show a reduction in responding relative to the training baseline following devaluation. Furthermore, these same rats are able to express differential responding after selective degradation of the R-O contingency both during training and in a choice test. They are also able to show differential elevation in performance during a test of S-PIT, establishing that the NAc is not critical for action-outcome learning. On the other hand, rats with pre-training lesions of the shell sub-region do not show this effect and their performance remains sensitive to changes in experienced outcome value. These animals do, however, show a deficit in stimulus-guided action selection, and are unable to express S-PIT (Corbit et al., 2001). Subsequent studies have found that this dissociation between the NAc core and shell is at least partly dependent on the differential involvement of distinct opioid receptors subtypes; Laurent et al. (2012) found that μ -opioid receptors (MOR) and δ -opioid receptors (DOR) in the core and shell are involved in outcome-guided and cue-guided action selection, respectively. First, MOR knockout mice were found to have a deficit in reward-guided performance and were unable to show sensitivity to outcome devaluation although they showed intact S-PIT. In contrast, DOR knockout mice, although sensitive to outcome devaluation, failed to exhibit selective S-PIT. Subsequently it was found that these behavioral deficits differentially involved the core and shell. Similar to the effects found in the mice, infusions of the MOR antagonist CTAP into the core rendered rats insensitive to outcome devaluation, but had no effect on S-PIT whereas the infusion of naltrindole into the shell abolished S-PIT, but had no effect on outcome devaluation (notably, CTAP into the shell and naltrindole in the core were without effect).

General vs. specific transfer

Apart from this dissociation, the core and shell also differ with regard to their role in the influence of stimuli predicting the general affective and sensory-specific properties of the outcome on instrumental performance. Corbit and Balleine (2011) demonstrated that, using the three CS PIT design described above, inactivation of the core using muscimol infused prior to test reduced rats’ sensitivity to G-PIT without affecting S-PIT. In contrast,

inactivating the shell spared G-PIT but eliminated S-PIT. This is consistent with other studies showing that rats with lesions of the core, but not the shell, show a deficit in G-PIT (Hall, Parkinson, Connor, Dickinson & Everitt, 2001). In a study assessing levels of phosphorylated ERK (pERK) in a G-PIT design, it was found that both regions of the NAc had elevated levels of ERK phosphorylation compared to controls that received the instrumental test in the absence of CS presentations. Critically, however, there was a greater increase in pERK in the core than in the shell (Remus & Thiels, 2012).

There has been some evidence suggesting that the neural basis of this dissociation involves dopamine. Indeed, dopamine plays a major role in reward related processes including a role in mediating Pavlovian incentive motivation (Berridge & Robinson, 1998; Wassum, Ostlund, Balleine & Maidment, 2011; Ostlund & Maidment, 2012). Interestingly, Ostlund & Maidment (2012) found that systemic injections of the nonspecific dopamine antagonist flupenthixol altered the general invigorating effects of reward-related stimuli but had no effect on S-PIT. Consistent with this finding, systemic blockade of dopamine or reversible inactivation of the VTA, the origin of the mesoaccumbens dopamine signal, has been shown to attenuate G-PIT (Dickinson, Smith & Mirenowicz, 2000; Murschall & Hauber, 2006). Specific infusions of dopamine D1 or D2 receptor antagonists into the core or shell also attenuate G-PIT (Lex & Hauber, 2008) whereas infusions of amphetamine into the NAc to stimulate dopamine transmission enhance the G-PIT effect (Wyvell & Berridge, 2000). Corbit et al. (2007) assessed the role of the VTA in mediating the general and specific forms of PIT using the three CS PIT design. Inactivation of the VTA using a mixture of GABA-A and a GABA-B agonists affected both G- and S-PIT, although, whereas G-PIT was abolished, S-PIT was attenuated; in fact the relative percentage elevation over baseline was unaffected. The role of the VTA in the stimulus control of instrumental action remains, therefore, somewhat ambiguous, as most studies have only used a G-PIT paradigm. Nevertheless, these findings taken together suggest that the dopamine signal in the NAc could be important for the general incentive motivational effects of stimuli associated with reward although there is little evidence to suggest it plays any role in their ability to bias choice. As discussed, lesion and inactivation studies have indicated that the core is particularly critical for G-PIT (Hall et al., 2001; Corbit et al., 2001; Corbit & Balleine, 2011); therefore, it is possible that reciprocal connections between the core and VTA may be particularly important for driving the general motivating properties of reward-related stimuli.

In line with behavioral dissociations between the core and shell in the control of performance, studies assessing the neuroanatomy and connectivity of the two regions have also revealed differences in their neurochemical composition and distinct neural circuits. Neurochemical staining of acetylcholinesterase, substance P and calbindin can delineate the NAc into its two regions (Groenewegen et al., 1999). The NAc core and shell also differ in their afferent and efferent connections (Brog, Salyapongse, Deutch & Zahm, 1993; Zahm, 2000). Although the core has been viewed as more similar to the dorsal striatum in terms of its anatomy and output connections to the ventral pallidum (VP), STN and SN through ventral striatonigral and striatopallidal pathways, the shell has unique projections to the lateral hypothalamus and lateral pre-optic area (Humphries & Prescott, 2010). In addition, the region of the VP that receives the majority of the output from the shell also projects to

regions outside the basal ganglia, such as the MD, thus distinguishing the shell connectivity from the dorsal striatum and core (Humphries & Prescott, 2010). Like the dorsal striatum, the NAc is mainly composed of the two populations of MSNs distinguished by their selective expression of various neuropeptides and D1 and D2 receptors (Gerfen et al., 1990; Le Moine & Bloch, 1995). Also in similar fashion to the dorsal striatum, the ventral striatonigral pathway of the NAc is driven by D1R expressing MSNs. However, unlike the dorsal striatopallidal pathway, that is mainly composed of D2R containing MSNs with a very limited D1R containing MSN projection, the ventral striatopallidal pathway is composed almost equally of both populations of MSNs projecting to the VP (Lu, Ghasemzadeh & Kalivas, 1998; Zhou, Furuta, & Kaneko, 2003).

Additionally, the NAc shell differs from the rest of the striatum in that the proportion of the population of MSNs expressing both D1R and D2R is higher in the shell (17%) than the core (6%) and dorsal striatum (5%; Bertran-Gonzales et al., 2008). Gangarossa et al. (2013) have also recently demonstrated that, whereas the organization of MSNs expressing D1 or D2 receptors in the core remains similar to the dorsal striatum and appears to be randomly distributed, the shell has a heterogeneous distribution of the two populations of MSNs. Indeed, there have been reports of functional differences between quadrants of the NAc shell (Peciña & Berridge, 2005; Britt & McGehee, 2008; Mahler & Aston-Jones, 2012). For example, Peciña and Berridge (2005) reported what they refer to, on the basis of licking data, as a μ -opioid hedonic “hotspot” in the rostradorsal quadrant of the medial NAc shell and, in contrast, a “coldspot” in its caudodorsal quadrant. Infusions of the MOR agonist, D-al²-N-Me-Phe⁴-Gly¹-col⁵-enkephalin (DAMGO) into the “hotspot” increased the expression of specific licking-related fixed action patterns (which the authors referred to as “liking” responses), whereas infusions into the “coldspot” suppressed these responses. It has been suggested that the functional specificity observed in the shell may be explained by the differences in the connectivity of these quadrants or by quadrants being transitional regions (Thompson & Swanson, 2010; Zahm, Parsley, Schwartz, & Cheng, 2013). However, each of these regions also differs in their distribution of D1 and D2 receptor expressing neurons, which as previously mentioned, also exclusively co-express other neuropeptides such as endogenous opioids. Hence, the functional differences between these regions may also find an explanation along these lines. More studies will be needed to examine whether different distributions of populations of neurons within the NAc shell can drive different behavioral effects, and whether there are other rostral-caudal and dorsal-ventral functional differences in the performance of goal directed behavior.

In summary, in the context of instrumental performance, it appears that there are two distinct neural circuits mediating the effects of changes in the reward value, and the effects of reward-related stimuli within the ventral stream. The core mediates the control of the selectivity of actions based on information about the value of an outcome, as well as general response-energizing effects of reward-related stimuli. On the other hand, a separate neural circuit involving the shell controls the response-biasing effects of reward-related stimuli. These distinct circuits reflect different motivational processes contributing to instrumental choice performance. Whereas outcome value-driven response selection within the core requires information about the R-O association, stimulus-driven response selection within the shell requires information about the Pavlovian S-O association, as well as perhaps an O-

R association, incorporating the stimulus properties of the outcome with a representation of the instrumental response (Balleine & Ostlund, 2007).

The ventral stream originating from the PFC

A number of regions in the PFC provide input to the NAc, particularly the mPFC, including the PL and more ventral infralimbic (IL) regions (Ding, Gabbott & Totterdell, 2001) as well as the OFC (Hoover & Vertes, 2011). While the PL has strong direct projections to the NAc core via large numbers of Layer II and Layer V/VI pyramidal neurons, its projections to the shell arise predominantly from Layer V/VI (Ding et al., 2001). Similarly, the OFC has direct projections to the NAc core and shell (Hoover & Vertes, 2011). Fluorogold labeling of regions within the PFC projecting to the NAc, specifically the PL and lateral OFC (lOFC), are shown in Figure 4.

Although both the PL and OFC project to the entire accumbens, each of these regions are thought to contribute to different types of associative process. As discussed, the PL is largely involved in the formation of R-O associations during early instrumental learning. However, the ventral OFC (vOFC) and lateral OFC (lOFC) are not involved in the acquisition of R-O associations; neither pre- nor post-training lesions of these regions in the OFC have an effect on instrumental responding during acquisition or outcome devaluation (Ostlund & Balleine, 2007). Instead, rats with lesions of the lateral OFC (lOFC) are unable to show effects of Pavlovian reinforcer devaluation (Gallagher, McMahan & Schoenbaum, 1999). In this task, in a similar fashion to instrumental outcome devaluation, a particular reinforcer that has been paired with a Pavlovian CS is devalued after training. As with instrumental devaluation, sham lesioned controls showed reduced conditioned Pavlovian responding (i.e. magazine entries) during presentations of the devalued CS. In contrast, rats with lOFC lesions failed to show any such reduction. Therefore, rats with lOFC lesions are specifically impaired at value-driven responding in Pavlovian tasks, but not instrumental tasks, suggesting that the lOFC is necessary for encoding information about the expected outcome of Pavlovian stimuli. In support of this, rats with pre- and post-training lesions encompassing both the vOFC and lOFC are also unable to use S-O associations to guide instrumental choice during S-PIT (Balleine, Leung, & Ostlund, 2011; Ostlund & Balleine, 2007). In a recent electrophysiological study in rhesus monkeys, Luk and Wallis (2013) recorded neurons in the OFC during two choice tasks. In one task, monkeys had to make a choice between two actions based on stimuli that predicted different outcomes (S-O), and in another task, choices had to be made based on the knowledge of the outcome associated with an action (R-O). The authors found that more OFC neurons fired during the execution of Pavlovian actions made in response to stimulus presentations than during responding driven by instrumental outcome knowledge.

It is worth discussing here a recent report that is apparently at odds with this analysis. Gremel and Costa (Gremel & Costa, 2013) recently found, using very different behavioral procedures, evidence of a loss of goal-directed action after lesions and chemogenetic inactivation of a region in frontal cortex including the ventral and lateral OFC in mice. Although their lesion and genetic manipulations certainly included these regions of OFC, they may also have included other regions of frontal cortex outside the OFC. Their infusions

of neurotoxin were very large for mice (i.e., 0.3 μ l of ibotenic acid in a single infusion) and induced damage that their histology shows extended around 2 mm mediolaterally centered on the vOFC (their infusions of virus produced a similarly large area of infection). It is very likely that these infusions would have produced similar damage antero-caudally (fluid spread being spherical in homogeneous tissue), and, hence, that they would have damaged or inactivated much of the frontal cortex anterior to the genu of the corpus callosum. Given the consistent evidence described above and the widespread changes in the frontal region likely produced in this study, the effects reported by Gremmel and Costa appear more consistent with damage to regions outside the OFC.

The dramatic functional differences between PL and OFC afferents to the ventral striatum described in prior research provides, therefore, consistent support for the view that the ventral striatum is differentially utilizing R-O and S-O associations to guide instrumental performance. We have discussed above that this dissociation is maintained at the level of the striatum; whereas the core is critically involved in instrumental action selection on the basis of outcome value, the shell is necessary for action selection driven by Pavlovian stimuli and it appears likely that the PL and ventral and lateral regions of the OFC are contributing information pertaining to the R-O and S-O association to the NAc core and shell, respectively, to guide outcome value-based and stimulus-based instrumental choice. One obvious problem with the hypothesis described here is that, at the time of choice, the PL is not necessary for animals to use outcome value to guide instrumental performance; rats with post-training lesions of the PL continue to show outcome devaluation (Ostlund & Balleine, 2005). Therefore, if the PL is providing information regarding the R-O association to the NAc core, then this information must be transferred during initial instrumental training and there is little evidence to support this possibility. There is also limited evidence to support the hypothesis that regions in the OFC and NAc shell are working in concert during stimulus-guided behavior. Although neurons from the vOFC and lOFC projecting to the shell are c-Fos activated during S-PIT (Balleine et al., 2011) further research is needed to determine the necessity of the connection between the OFC and the NAc shell in this effect.

Finally, parallel to the dorsal stream, information from the NAc can be relayed back to the PFC via midbrain or pallidal projections to the MD. The MD, as previously discussed, is involved in the acquisition of response-outcome learning, presumably through its connections with the PL and, indirectly, the DMS. However, after acquisition, the MD is no longer necessary for actions based on either outcome value or the discriminative properties of the outcome, as shown by normal performance in both outcome devaluation and outcome reinstatement tests (Ostlund & Balleine, 2008). In contrast, the MD remains important for the expression of cue-directed behavior, and rats with post-training lesions of the MD are unable to express S-PIT. In addition, rats with MD lesions fail to selectively reduce conditioned responding during Pavlovian contingency degradation; instead showing a general reduction in responding to both the degraded and non-degraded stimulus (Ostlund & Balleine, 2008). Interestingly, whereas the effects of pre-training lesions of the MD produce deficits that mirror those produced by pre-training lesions of the PL, the effects of post-training lesions of the MD are remarkably similar to lesions of the ventral and lateral regions of the OFC, where rats with lesions to either structure indiscriminately increase performance of both responses in S-PIT and indiscriminately reduce conditioned approach to both stimuli

when only one has been degraded (Ostlund & Balleine, 2007, 2008). These findings thus provide behavioral support for the anatomical role of the MD as the major feedback center from the striatum to the cortex.

In this context it is interesting to compare the indirect and direct inputs to the prefrontal cortex from the midbrain (SNr and VTA) and the MD. Figure 5 shows a PFC hemisphere containing anterograde and retrograde labeling arising from, and targeting, respectively, the MD and retrograde labeling showing PFC neurons projecting to the VTA/SN. Similar to past tracing studies looking at connections between these structures (Groenewegen, 1988; Cornwall & Phillipson, 1988; Carr & Sesack, 2000; Gabbott et al., 2005), injections of the two tracers produced labeling in different cortical layers. Projections from the MD to the PFC, as revealed by anterograde labeling produced by CTb, were located primarily in Layer III, with some weak projections in Layer I. This is anatomically separate from the cortical projections from the MD, which were primarily in Layer VI, and, therefore, also anatomically separated from the major layer V projections from the PL to the VTA/SN (Vazquez-Borsetti *et al.*, 2009). This pattern was generally consistent across the PL and OFC, however there was much more labeling overall within the PL. Evidence that the thalamus may play a key role in regulating feedback between the cortex and striatum has already been advanced by some work looking at the reciprocal and nonreciprocal connections between the cortical layers and the thalamus and the potential for relaying information between the parallel corticostriatal loops (see Haber & Calzavara, 2009; Sherman & Guillery, 2011; Sherman, 2012). The significance of the clear anatomical segregation of projection neurons within the PFC, as well as the anatomical separation of input pathways, has not yet been fully understood and future research into these systems is likely to provide a far greater insight into the complex cortical-cortical interactions that drive top-down processing.

The sections above have described a set of structures involved in what appears to be a distinct corticostriatal loop important for the performance of goal-directed behavior. This involves a stream of information from the ventral and lateral regions of the OFC to the NAc shell and finally to the MD that is important for the influence of predictive learning on choice between goal-directed actions. It should be noted, however, that both the MD and the ventral and lateral OFC are involved in learning S-O associations and it appears that without normal acquisition of S-O associations animals are, unsurprisingly, unable to use that information to modulate instrumental performance. In addition, whereas the PL and MD are not required for the expression of outcome-guided instrumental decisions, the NAc may use the information encoded within the PL during acquisition to guide instrumental choice. This argument presents a novel prediction that the connection between the NAc and the PL is necessary during instrumental acquisition for animals to express value-guided choice during performance, perhaps in combination with other cortical inputs to the NAc such as the gustatory insular cortex (GC; Parkes & Balleine, 2013). To our knowledge, this hypothesis has yet to be tested. Finally, as has been briefly mentioned, both the dorsal and ventral streams require input as to both the emotional and sensory properties of the outcome for the successful acquisition and performance of instrumental actions. There is a substantial body of evidence that this information is contributed by a distinct neural system centered on the

basolateral amygdala (BLA), and that this ‘limbic stream’ ultimately modulates output from the dorsal and ventral streams to control instrumental behavior.

Finally, it is worth noting that the functional separation of the dorsal and ventral streams described should not be taken to infer complete anatomical separation. In fact, the PFC projects broadly and topographically to the entire striatum and as revealed in a recent 3D reconstruction, these projections are also likely to affect a number of different parallel streams of information concurrently (Mailly, Aliane, Groenewegen, Haber & Deniau, 2013). For example, along with the discussed projections from the OFC to the ventral striatum, these regions of the OFC also project to the BLA and dorsal striatum (Pan, Mao & Dudman, 2010; Schilman, Uylings, Galis-deGraaf & Groenewegen, 2008), indeed, very recent research has demonstrated that input to the dorsal striatum from the IOFC can restore behavioral inhibition in a mouse model of obsessive-compulsive disorder (Burguiere, Monteiro, Feng & Graybiel, 2013). Hence dorsal and ventral striatal activity is modulated by multiple cortical inputs and the challenge for researchers is to identify how these inputs interact or compete to modulate behavioral output.

Integrating dorsal and ventral streams: Incentive processing within the BLA and efferent structures

Although, at present, while it is not known precisely how, mechanically speaking, information in the dorsal and ventral streams is integrated to effect action control, there are some obvious points of convergence. Although efferents from dorsal and ventral striatum converge onto similar regions of the substantia nigra reticulata and thalamus their terminal fields do not appear to overlap. Perhaps the more likely point of convergence, therefore, is in the cortical areas that modulate primary motor cortex and that receive input from circuits to which both the dorsomedial and ventral striatum contribute. It has long been recognized that the thalamo-cortical pathway diverges onto multiple cortical targets allowing the basal ganglia to influence multiple functions and it is reasonable to suppose that this divergence could provide the opportunity for multiple basal ganglia regions to converge on modulatory regions such as premotor and supplementary motor regions (e.g. Hoover & Strick, 1993; Schell & Strick, 1984).

Over and above cortical modulation by the dorsal and ventral streams, it has long been argued that the orchestration of this integration between striatal regions is mediated by limbic modulation, most notably by the basolateral amygdala (BLA; (Mogenson *et al.*, 1980). The BLA is often referred to as the ‘emotional brain’ (LeDoux, 1996) largely due to the extensive literature implicating the amygdala in Pavlovian fear conditioning (e.g. LeDoux, 2003). Research into Pavlovian and instrumental reward-related learning suggests, however, that the BLA may be more generally involved in processing emotional events of both a positive or negative nature. Recently, it has been suggested that the BLA’s cortical and striatal efferents are involved in conveying outcome value, imbedded within the sensory-specific properties of the outcome, to the dorsal and ventral streams during acquisition and performance of instrumental and Pavlovian conditioning (Balleine & Killcross, 2006). As has been emphasized in previous sections, both the dorsal ‘learning’ stream and the ventral ‘performance’ stream use information regarding the specific sensory

and emotional features of the outcome to modulate the acquisition and expression, respectively, of R-O associations. The BLA is extremely well placed anatomically to modulate and indeed integrate information processed in each of these streams.

A diagrammatic representation of the BLA inputs to the dorsal and ventral streams in the rat brain is shown in Figure 6. The BLA shares strong reciprocal connections with various regions of the prefrontal cortex, including the PL and OFC, so it is in a position to modulate top-down processing in both the dorsal and ventral streams from their respective cortical inputs. In addition to this, the BLA has direct projections to the DMS within the dorsal stream, and the NAc core and shell within the ventral stream, meaning it can directly modulate striatal output during reward learning and performance. Perhaps most critically, the BLA has direct connections with the gustatory cortex (GC; Sripanidkulchai, Sripanidkulchai & Wyss, 1984; Yamamoto, Azuma & Kawamura, 1984) that, when lesioned or inactivated, produces a specific set of deficits that suggest a role in encoding the sensory properties of the appetitive outcome during learning (Braun, Lasiter & Kiefer, 1982; Braun, 1989; Balleine & Dickinson, 2000; Parkes & Balleine, 2013). Importantly, the GC also maintains strong connections with the NAc core.

Limbic control of value-guided response selection

Pre-training lesions of the BLA produce a general and vast array of impairments in outcome-driven response selection, including impairments in outcome devaluation and contingency degradation (Balleine, Killcross, & Dickinson, 2003; Johnson, Gallagher, & Holland, 2009), and deficits in the ability to respond according to the current value of the outcome in a rewarded test following outcome devaluation (Balleine et al., 2003; Corbit & Balleine, 2005). One explanation for these findings is that rats with BLA lesions are unable to use the sensory features of the outcome to update or encode its incentive value (Balleine & Killcross, 2006), hence rats fail to respond on the basis of outcome value during either the extinction test or when the reward is presented. Additionally, because the sensory features of the outcome aren't incorporated into any outcome representation, rats with BLA lesions should be unable to use sensory information to guide instrumental performance. Balleine et al. (2003) also provided evidence for this. Rats were trained to make two responses for two different outcomes. Following instrumental acquisition, rats entered a training phase in which both responses were available, but only one outcome was delivered in each session. That is to say, when R1 provided O1 then R2 would not provide anything. In this task, rats had to use the identity of the outcome being delivered as a discriminative stimulus to tell them which response to make. Sham lesioned rats readily did this, however, BLA lesioned rats failed to show response selectivity consistent with the outcome being delivered. Likewise, rats with BLA lesions fail to show outcome-induced augmentation of instrumental responding on the response that had produced that outcome (Blundell, Hall, & Killcross, 2001).

As shown in Figure 2, the medial wall of the BLA has strong projections to the pDMS. The existing evidence described above indicates that the BLA is critical for the formation of an outcome representation that includes both the sensory (i.e. taste) features of the outcome as well as the motivational or value-based features. It follows, therefore, that the formation of

an R-O association within the dorsal stream requires amygdala input to contribute information regarding 'O'. As mentioned this amygdala input could be via its bidirectional cortical projections, particularly to the PL, or the input could be via direct projections to the pDMS. Although it is still entirely possible that either, or even both of these connections are necessary for incorporating outcome properties into the R-O association, the limited existing evidence suggests that the BLA-PL connection is not necessary for goal-directed responding. Coutureau, Marchand & Di Scala (2009) demonstrated that rats with bilateral pre-training lesions of either the PL or the BLA failed to show sensitivity to outcome devaluation at test, confirming previous reports (Balleine et al., 2003; Corbit & Balleine, 2003b). In contrast, rats with a unilateral lesion of the PL in one hemisphere, and a unilateral lesion of the BLA in the opposite (contralateral) hemisphere showed normal outcome devaluation. Critically, this contralateral disconnection means that although the two structures are independently functioning in each hemisphere, the communication between them has been (largely) severed. Under these circumstances, Coutureau et al. (2009) found that rats are still able to acquire and express goal-directed behavior. Therefore, the evidence suggests that the BLA input to the pDMS, rather than the PL mediates R-O learning. In support of this argument we have very recently found direct evidence for the involvement of the BLA in pDMS-related goal-directed learning using a similar disconnection procedure (Corbit *et al.*, in press). We confirmed the direct projection from the BLA to pDMS and found that a unilateral lesion of the BLA and inactivation of the contralateral pDMS during a critical session in which rats acquired goal-directed action was sufficient to block that learning (Corbit et al., in press).

We now know that the BLA is necessary during both the acquisition and the expression of outcome-guided instrumental responding. As is the case with pre-training lesions, rats with post-training lesions of the BLA are also insensitive to outcome devaluation (Ostlund & Balleine, 2008), providing further support for the role of the BLA in updating outcome values during devaluation. As shown in Figure 4, the BLA has strong projections to the NAc core and shell. As discussed previously, pre-training lesions of the NAc core impair sensitivity to outcome devaluation (Corbit et al., 2001). Additionally, pre-training NAc core lesions have no effect on contingency degradation (Corbit et al., 2001), suggesting that the disruption in devaluation is not due to a general inability to encode R-O associations but, rather, because the NAc core plays a role in bringing the influence of outcome value to bear on instrumental performance. It is possible, therefore, that during outcome devaluation, the value of the instrumental outcome is updated through incentive learning within the BLA, and that this information is then used by the BLA to inform NAc core output, controlling behavior during instrumental choice.

There is now evidence that projections between the BLA and the NAc core are necessary for successful outcome devaluation. Shiflett and Balleine (2010) performed a disconnection procedure that involved a pre-training excitotoxic lesion of the BLA in one hemisphere, and of the NAc core in the same or the opposite hemisphere. As predicted, rats with contralateral disconnection of the BLA from the NAc core failed to show outcome devaluation on the extinction test, whereas those with ipsilateral lesions were normal. Despite this impairment,

these rats showed normal instrumental acquisition during training, and were perfectly capable of selecting an action based on Pavlovian stimuli, maintaining intact S-PIT.

Although these results suggest that BLA input to the NAc core is necessary for value-based response selection in the performance of goal-directed actions, disconnection studies only confirm the functional relation between two structures and do not provide any evidence regarding the nature of any connection, direct or otherwise. In fact, recent evidence suggests that the functional interaction between the BLA and NAc core may be due to indirect connections involving the GC. Parkes and Balleine (2013) found that, whereas inactivation of the BLA abolished instrumental outcome devaluation, it only did so if the inactivation was made prior to devaluation; when made after devaluation it had no effect, suggesting that the BLA is involved in encoding incentive value but not in retrieving that value. In contrast, inactivating the GC had effects consistent with a role in retrieval; inactivation prior to test abolished sensitivity to outcome devaluation. Finally, to test whether the BLA and GC form a network in encoding and retrieving changes in incentive value to guide instrumental performance, Parkes and Balleine (2013) used a novel temporal disconnection procedure. Capitalizing on the fact that the BLA-to-GC connections are lateralized, they inactivated the BLA on one side prior to devaluation and the GC contralaterally prior to test. By blocking the GC on the BLA inactivated side from acquiring incentive-based information and the GC contralaterally prior to test, it was hoped to block sensitivity to devaluation. This is exactly what was found. In contrast, when BLA and GC inactivation was induced in the opposite temporal order (i.e. GC → BLA), devaluation was not affected. Generally, therefore, it can be hypothesized that, at the very least, the control of instrumental performance by the NAc core depends not only on inputs from the BLA but also from the GC.

Limbic control of stimulus-guided response selection

It is likely that during Pavlovian conditioning, the BLA is responsible for encoding the association between the Pavlovian stimulus and the sensory features (e.g. taste, odor, texture) of motivationally significant outcomes (Balleine & Killcross, 2006). Lesions of the BLA produce vast deficits in tasks that require the encoding and maintenance of outcome representations; although rats with BLA lesions show normal conditioned responding during acquisition of Pavlovian associations between neutral stimuli and rewards (Hatfield, Han, Conley, Gallagher, & Holland 1996; Blundell et al., 2001; Setlow, Holland & Gallagher, 2002), they are unable to use outcome representations to mediate conditioning (Dwyer & Killcross, 2006), and are unable to use the reinforcing properties of a Pavlovian CS to acquire secondorder conditioning (Hatfield et al., 1996). Likewise, rats with BLA lesions are insensitive to Pavlovian devaluation (Hatfield et al., 1996; Blundell, Hall & Killcross, 2003; Johnson, Gallagher & Holland, 2009), indicating that the BLA plays a fundamental role in using the sensory-specific aspects of rewards to form and update outcome-specific associations (Balleine & Killcross, 2006). From this perspective, the BLA would be involved in encoding the sensory properties of the reward and this information used to provide value information such as palatability (Balleine, 2005; Berridge, 2001). Hence, the BLA may be critical for assigning and updating the values of outcomes incorporated into S-O associations. Consistent with this view, rats with BLA lesions are unable to use Pavlovian conditioned stimuli to guide instrumental responding during S-PIT (Blundell et al., 2001)

and, as with the NAc shell, BLA lesions abolish S-PIT without affecting G-PIT (Corbit & Balleine, 2005).

There is evidence that the BLA interacts with the NAc to incorporate the appetitive affective properties of the outcome with S-O associations that guide behavior. For example, contralateral disconnection of the BLA from the NAc will prevent the development of conditioned appetitive responding to stimuli associated with reward (Cador, Robbins & Everitt, 1989; Everitt, Cador & Robbins, 1989; Everitt, Morris, O'Brien & Robbins, 1991; Robbins, Cador, Taylor & Everitt, 1989; Setlow et al., 2002; Di Ciano & Everitt, 2004; Ambroggi, Ishikawa, Fields & Nicola, 2008). Likewise, it has been demonstrated that BLA input to the NAc is necessary for appetitive stimulus-evoked firing of NAc neurons (Ambroggi et al., 2008; Popescu, Popa & Paré, 2009). Finally, there is now evidence that specific Pavlovian control over instrumental performance requires connections between the BLA and NAc shell (Shiflett & Balleine, 2010). As previously discussed, the functions of NAc shell and core can be dissociated on a number of levels; whereas the core is necessary for outcome devaluation, the shell is critical for S-PIT (Corbit et al., 2001). Shiflett and Balleine (2010) demonstrated that rats with pre-training contralateral lesions of the BLA and NAc shell showed normal Pavlovian and instrumental acquisition, as well as normal outcome devaluation, but were unable to modulate instrumental performance on the basis of the specific Pavlovian associations formed during conditioning (S-PIT). Once again, this finding is consistent with the output model of the ventral striatum proposed. In this experiment, rats were able to encode the specific S-O associations during Pavlovian conditioning; however, the contralateral disconnection meant that this information could not be transferred to the NAc shell to inform instrumental choice.

Conclusions

In an attempt to understand the parallel corticostriatal circuits implicated in goal-directed instrumental conditioning, this review has presented evidence suggesting that information originating from cortical structures may indeed be largely segregated into a dorsal stream that is involved in learning and a ventral stream that is involved in guiding instrumental performance. During instrumental training, the contingency between the response and outcome is encoded within the PL-DMS pathway. This information is integrated with information from the BLA regarding the sensory-specific and value-based properties of the instrumental outcome. We have hypothesized here that this integration occurs within the pDMS.

There is evidence that the expression of instrumental learning in performance relies predominantly on the ventral striatum. We have proposed here that during instrumental choice, information regarding the sensory-specific and rewarding properties of instrumental and Pavlovian outcomes are encoded within the BLA, and transferred to the NAc core and shell, respectively, to inform value-guided and stimulus-guided instrumental actions. There are several lines of evidence consistent with this: 1) the shell and core sub-regions of the ventral striatum are critically necessary for stimulus-guided and value-guided instrumental choice, respectively; 2) the BLA is necessary for both stimulus-guided and value-guided instrumental choice; and 3) input from the BLA to each of these sub-regions is also

necessary for each of these forms of instrumental choice. Despite this evidence, there are alternative mechanisms via which information may be translated into performance during instrumental choice. It is clear, for example, that the pDMS is also necessary for the expression of goal-directed instrumental performance since, as discussed, rats with pre- or post-training lesions of the pDMS also fail to show outcome devaluation (Yin et al., 2005). Of course, any performance should respect the encoded R-O association and it may, therefore, be necessary for such information to join with incentive factors to control performance suggesting that a deficit in either R-O retrieval or in incentive learning is sufficient to produce a deficit in that performance.

In fact, one of the largest unanswered questions is how and when R-O information encoded within the dorsal stream is incorporated into the ventral output stream. The current review has proposed that the temporal involvement of the striatal streams necessarily implies that the flow of information is in the direction of dorsal striatum-to-ventral striatum. Such a directional flow almost certainly requires transmission of information through cortical regions. Although there is substantial and clear evidence that cortical input is important for both the dorsal and ventral streams, there is also a growing body of evidence suggesting that some regions, such as the PL, are not involved in instrumental responding beyond the initial acquisition. This therefore leads to the surprising hypothesis that the information formed within the PL in particular, is transferred to the ventral striatum during training or shortly afterwards, and this information is then stored and subsequently used to guide instrumental choice. There are, however, several ways in which information may be transmitted from the dorsal stream through the PFC to the ventral striatum. The corticostriatal loops discussed in the present review offer a clear pathway. In this case, information within the pDMS is fed back to the PFC through the MD.

As we have briefly mentioned above, the MD may be a key structure in which information can be integrated across parallel loops, either through direct projections to other regions in the PFC or through the thalamocortical projections to Layer III of the cortex, which is particularly necessary for intra-cortical and corticocortical projections (Figure 5; Ferino, Thierry, Saffroy & Glowinski, 1987). This suggests that input from the MD can be also readily transmitted to other regions and layers within the PFC prior to feeding back down to the striatum from Layers II and V/VI. In addition to corticostriatal loops, there are also feedback circuits within the midbrain that may be critical for integration of information. For example, the PFC also sends dense projections to the VTA/SN (Figure 5) and it has been shown that this projection targets specific cell populations in the midbrain where terminals synapse selectively onto GABA neurons projecting to the NAc and dopamine neurons projecting back to the PFC (Carr & Sesack, 2000). Midbrain-striatal feedback loops have also been found to connect neighboring structures through the VTA and SNc in a spiraling architecture that links NAc to the DMS (Haber, Fudge & McFarland, 2000). These spiraling connections have been advanced as one means of linking ventral and dorsal streams (Belin et al, 2009), however how this architecture accounts for the divergent (e.g. goal-directed actions vs. habits) functions within these streams has not been made clear.

Finally, there is now emerging evidence that circuits such as the thalamostriatal and nigrostriatal pathways have divergent effects on goal-directed actions. In a recent study by

Bradfield, Bertran-Gonzalez, Chieng & Balleine (2013) the excitatory connection from the parafascicular thalamus to the cholinergic interneurons in the pDMS, although not important for initial acquisition of action outcome associations, is critical for updating new action outcome contingencies. On the other hand, optical stimulation of dopamine neurons in the SNc have been reported to influence instrumental learning, providing possible evidence of a role for dopamine in the acquisition and updating of these contingencies through the corticostriatal loops (Rossi et al, 2013).

Whatever the mechanism of dorsal and ventral information integration, what is clear is that the BLA provides distinct information to both the dorsal and ventral striatal streams. The BLA is required for all stages of goal-directed behavior (acquisition, retrieval, action selection) and lesions of the BLA impair acquisition of R-O and S-O associations as well as performance of outcome-guided and cue-guided action selection. A number of recent studies have begun to use cell-specific manipulations within distinct circuits to understand the precise roles of various inputs (Britt, Benaliouad, McDevitt, Stuber, Wise & Bonci, 2012; Stuber et al., 2011; Van Zessen, Phillips, Budygin, & Stuber, 2012). For example, Stuber et al., (2011) demonstrated that mice increase instrumental responding for optical stimulation of the glutamatergic input from the BLA to the NAc but not for glutamatergic input from the PFC to the NAc. Additionally, brief optical inhibition of the BLA input to the NAc reduced cue-evoked intake of sucrose. Generally, therefore, we hypothesize that the BLA may play the role of orchestrating the integration of dorsal and ventral streams not only through direct inputs but also indirectly through inputs to other critical cortical regions, particularly the OFC and GC, that themselves make strong connections within the ventral stream.

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Figure 1.

Simplified sagittal representation (adapted from Paxinos & Watson, 2007) of the corticostriatal loops that constitutes the dorsal 'learning' stream (blue) and ventral 'performance' stream (green), within the rat brain. Abbreviations: PFC: prefrontal cortex; PL: prelimbic cortex; IL: infralimbic cortex; OFC: orbitofrontal cortex; DMS: dorsomedial striatum; NAc: nucleus accumbens; MD: mediodorsal thalamus; VTA/SN: ventral tegmental area/ substantia nigra.

Figure 2.

Coronal sections of a rat brain showing projection neurons within the prefrontal cortex and basolateral amygdala (BLA) projecting to the posterior dorsomedial striatum (pDMS). Top left: Rats were injected into the pDMS with the retrograde tracer, Fluoro-gold (FG – 0.15 μ L) at (from bregma) (AP): -0.45 ; (ML): -2.2 ; (DV): -3.5 . For this and subsequent images, rats were left for at least 2 weeks before being transcardially perfused with 4% paraformaldehyde (PFA) and post-fixed for at least 1 hour, before being sliced coronally at 30 μ m thickness. The bottom panel shows half brain maps of a coronal section of the prefrontal cortex (left) and a posterior section containing the BLA (right). Insets show retrograde tracing within the prelimbic cortex (top: middle) and the BLA (top: right).

Figure 3.

Coronal sections of a rat brain showing projection neurons within the dorsal and ventral striatum projecting to the ventral tegmental area (VTA) and substantia nigra (SN). Inset top left: Top left: Rats were injected into the medial VTA/SN with Fluoro-gold (FG– 50 nL) at the coordinates AP: –5.3; ML: –0.8; DV: –8.3. The main left panel shows a half brain map of a coronal section containing the dorsal and ventral striatum. Insets show retrograde tracing within the dorsomedial striatum (DMS; top right) and the nucleus accumbens (NAc; bottom right).

Figure 4.

Coronal sections of a rat brain showing projection neurons within the prelimbic cortex (PL), lateral orbitofrontal cortex (IOFC) and basolateral amygdala (BLA) projecting to the nucleus accumbens (NAc). Top left: Rats were injected into the NAc with 50 nL of Fluoro-gold (FG) at the coordinates; AP: +1.7; ML: -0.7; DV: -7.6. The bottom panels show half brain maps of a coronal section of the prefrontal cortex (left) and a posterior section containing the BLA (right). Insets show retrograde tracing within the PL (top: left centre), the IOFC (top: right centre) and the BLA (top: right).

Figure 5.

Coronal sections of a rat brain showing projection neurons within the prefrontal cortex (PFC; centre). Rats received an injection of the anterograde and retrograde tracer, cholera toxin b subunit (CTb – 50 nL), into the mediodorsal thalamus (MD; top left), at the coordinates; AP: –2.5; ML: –0.7; DV: –5.3, and an injection of Fluoro-gold (FG – 50 nL) into the ventral tegmental area and substantia nigra (VTA/SN; bottom left) at the coordinates; AP: –5.3; ML: –0.8; DV: –8.3. Anterograde tracing indicated that MD input to the prelimbic cortex (PL; top right) was localized to Layer I and Layer III, with the majority of anterograde labeling in Layer III, whereas output from the PL to VTA/SN and MD were from Layers V and VI, respectively. A similar pattern of labeling was present in the lateral orbitofrontal cortex (IOFC; bottom right).

Figure 6.

Simplified sagittal representation (adapted from Paxinos & Watson, 2007) of the inputs from the limbic stream centered on the basolateral nuclei of the amygdala (BLA), to the cortical and striatal components of the dorsal and ventral streams. Abbreviations: PFC: prefrontal cortex; PL: prelimbic cortex; IL: infralimbic cortex; OFC: orbitofrontal cortex; DMS: dorsomedial striatum; NAc: nucleus accumbens; MD: mediodorsal thalamus; VTA/SN: ventral tegmental area/ substantia nigra; BLA: basolateral amygdala.