Chapter 11
Prefrontal Cortex and Basal Ganglia Attributes Underlying Behavioral Flexibility

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Introduction

The attribute model of memory was an early multiple memory systems conceptualization of how different brain areas encode and store specific types of memory (Kesner and DiMattia 1987). This neurobiologically based model proposes that the nature of memory can be explained by different attributes such as space, time, sensory-perception, response, and reward (affect), which are stored as memories in different forebrain areas. To test hypotheses based on the attribute idea, different behavioral paradigms have been developed for rats that emphasize the learning and memory of specific attribute information, for example, temporal order or egocentric response. After learning occurs, a specific brain area is lesioned, for example, hippocampus or striatum, and rats are tested on the retention of the originally learned information. Using this experimental procedure, several studies have demonstrated that lesioning a particular brain area produces a memory deficit for specific attribute information (Kesner 2009). Thus, the neurobiologically based attribute model of memory developed from evidence that certain brain areas store memories for particular attribute information.

Subsequent to this original formulation, the attribute model of memory was applied to investigate the structure of memory representation in the rodent prefrontal cortex (Kesner et al. 1996; Kesner 2000; Ragozzino and Kesner 1999, 2001; Ragozzino et al. 1998; Ragozzino et al. 2002). The prefrontal cortex is an interesting region of the brain to explore the attribute model as this area consists of several

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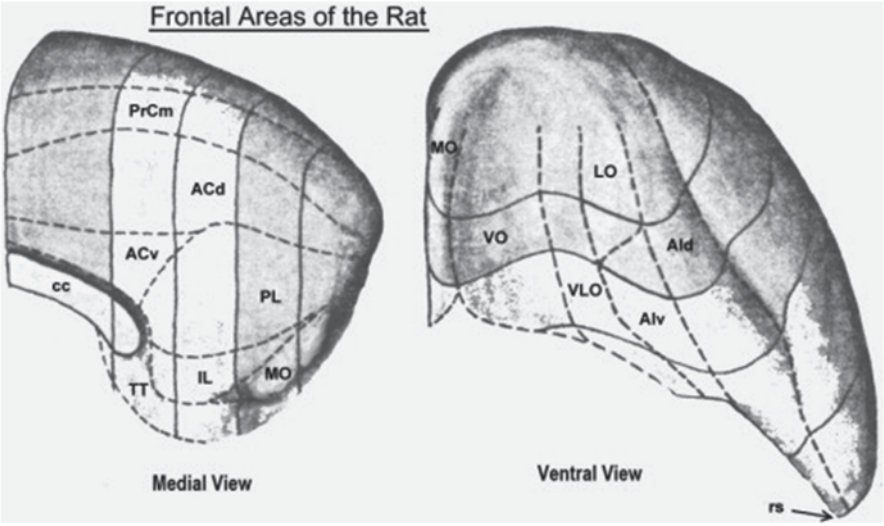

Fig. 11.1 Medial and ventral views of the rat frontal cortex. Abbreviations: *PrCm* precentral cortex, *AC* dorsal and ventral anterior cingulate, *PL–IL* prelimbic and infralimbic cortex, *MO* medial orbital cortex, *AI* dorsal and ventral agranular insular cortex, *LO* lateral orbital cortex, *VO* ventral orbital cortex, *VLO* ventrolateral orbital cortex. Reprinted with permission from Elsevier (Kesner and Churchwell 2011)

different subregions (see Fig. 11.1) that, to varying degrees, have distinct afferent and efferent connections (Uylings and van Eden 1990). The rodent prefrontal cortex can be subdivided based on structure and connectivity. One broad division of the prefrontal cortex is to separate it into a medial and a lateral sector. The medial area consists of the infralimbic cortex, the prelimbic cortex, the anterior cingulate cortex, and the medial precentral areas (Fig. 11.1). These delineations are based on the architectural makeup of the cortical layers as well as the thalamic projections that each area receives. Located centrally is the prelimbic area that is comparable to Brodmann's areas; area 24 and 32 (Uylings and van Eden 1990). The prelimbic area is densely interconnected with other areas of the prefrontal cortex (Eden et al. 1992; Heidbreder and Groenewegen 2003). It also sends projections to the dorsomedial striatum, as well as the subthalamic nucleus (Sesack et al. 1989; Gabbott et al. 2005). These areas represent the major inputs in the basal ganglia, a key area for motor actions. Additionally, the prelimbic area is one of the few areas of the brain that has reciprocal connections with the majority of the neuromodulatory neurotransmitter systems of the brain. Specifically, it has reciprocal projections with the ventral tegmental nucleus and substantia nigra pars compacta, the major dopaminergic neurons of the brain; the dorsal and median raphe nuclei, the serotonergic cells of the brain; the locus coeruleus, the primary source of noradrenergic innervation in the brain; and the nucleus basalis as well as the brainstem cholinergic nuclei, two major acetylcholine systems (Vertes 2004; Boix-Trelis et al. 2006; Hoover and

Vertes 2007). The connections of the prelimbic cortex with limbic and motor areas of the brain as well as its interconnections with the majority of the neuromodulatory systems of the brain suggest that it may play a critical role in the coordination of complex behavior such as those required for cognitive flexibility.

The lateral prefrontal cortex consists of the dorsal and ventral agranular insular along with the lateral orbital region. The primary afferent connections of these areas include the pyriform cortex and olfactory bulb, gustatory cortex and gustatory thalamus, parts of somatosensory I and II, visual association cortex, parietal cortex, perirhinal cortex, as well as the medial dorsal nucleus and central medial nucleus of the thalamus. The agranular region projects to the ventrolateral part of the striatum, whereas the lateral orbital region projects to the central part (Mailly et al. 2013). A ventral lateral region of the prefrontal cortex includes the ventral orbital and ventrolateral orbital cortices. These regions receive input from the parietal cortex, visual association cortex, medial dorsal nucleus, and central medial nucleus of the thalamus. These ventral orbital subregions project to dorsal and ventral striatum, posterior parietal cortex, secondary visual cortex, pyriform cortex, and olfactory bulb. Thus, several different prefrontal cortex subregions project to different areas of the basal ganglia, in particular the striatum, that suggests that the prefrontal cortex and basal ganglia may act in a cooperative manner to support various cognitive functions (Kesner and Churchwell 2011).

As the rat prefrontal cortex comprises various subregions, Kesner et al. investigated whether separate rat prefrontal cortex subregions facilitate working memory for specific attribute information (Kesner et al. 1996; Ragozzino and Kesner 1999; Ragozzino et al. 1998; 2002). For example, prelimbic and infralimbic cortex lesions impair working memory for spatial locations but not working memory for egocentric responses (Kesner et al. 1996; Ragozzino et al. 1998). In contrast, anterior cingulate and medial precentral lesions do not impair working memory for spatial locations, but do impair working memory for egocentric responses (Ragozzino and Kesner 2001; Ragozzino et al. 1998). Moreover, there is also evidence that the agranular insular cortex supports working memory for reward value (Ragozzino and Kesner 1999). Thus, at least for working memory, there is support for the idea that the rodent prefrontal cortex is organized such that separate subregions represent particular attribute information in memory.

Although the findings described above focus on the functional organization of the prefrontal cortex related to working memory, the prefrontal cortex is a brain area that has been proposed to support some of the most complex functions in mammals, including planning, temporal ordering, and behavioral flexibility (Kesner and Churchwell 2011). Many of these functions have been categorized into the singular, broader label of executive functioning (Kesner and Churchwell 2011). Thus, the prefrontal cortex offers an opportunity to examine whether the attribute model applies to the functional organization of the prefrontal cortex beyond learning and memory. My laboratory has been particularly interested in the neural basis of behavioral flexibility that developed during my postdoctoral training with Ray Kesner. We broadly define behavioral flexibility as the ability to adapt an indi-

vidual's behavior when a change in the internal or external environment signals that an ongoing choice pattern is no longer optimal. This chapter focuses on three main themes related to the neural basis of behavioral flexibility: (1) the role of different prefrontal cortex areas in behavioral flexibility. These studies developed from earlier experiments investigating whether different prefrontal cortex areas support working memory for specific attribute information; (2) the role of the dorsal striatum in behavioral flexibility. The dorsal striatum receives inputs from specific areas of the medial prefrontal cortex and lateral prefrontal cortex (Berendse et al. 1992; Mailly et al. 2013). Thus, there was interest in determining whether this striatal area plays a similar or distinct role in behavioral flexibility as prefrontal cortex areas that project to the dorsal striatum; and (3) the chapter will describe interactions between prefrontal cortex and basal ganglia circuitry in supporting behavioral flexibility using conditional discrimination tests. Most neurobiological studies of behavioral flexibility have used paradigms in which a change in outcomes, for example, a choice is no longer reinforced, signals that a switch in choice patterns should occur. However, many situations demand behavioral adaptations to external cues which proactively signal that a behavioral switch should occur. Less is known about the role of the prefrontal cortex and basal ganglia areas in behavioral flexibility under these conditions. Recent findings from our laboratory are presented, which indicate that distinct prefrontal cortex and basal ganglia circuitry interact to enable rapid adaptations under these conditions.

Prefrontal Cortex, Attributes and Rules

In studying the role of the prefrontal cortex in behavioral flexibility, the attribute model was influential in shaping the design of early experiments. In particular, the attribute model would predict that separate prefrontal cortex subregions contribute to behavioral flexibility based on the type of attribute information needed to flexibly adapt. Following this idea, various studies have been carried out in which a rat had to learn one type of discrimination for specific attribute information and then, by changing the reinforcement contingencies, had to learn using different attribute information (set-shifting) or learn a different choice using the same attribute information (reversal learning). In a set-shift test, a subject must learn to make a choice based on one attribute, while inhibiting a choice based on different attribute information. For example, in one study rats learned to choose between two different sand cups that were filled with distinct odors, that is, cinnamon and nutmeg, while each cup was also in a distinct spatial location in a maze (Ragozzino et al. 2003). The scented sand cups are randomly switched between spatial locations across trials. A subject first learns to choose a sand cup based on spatial location to receive a reinforcement independent of odor. After learning to choose based on spatial location, reinforcement is changed so that it is always associated with a particular odor, that is, sand cup scented with cinnamon. Thus, the rat must shift to always choose the sand cup scented with cinnamon independent of spatial location. In a reversal-

learning test, a subject must reverse what specific choice it employs to receive a reinforcement and learn to use a different choice based on the same attribute information. For example, a subject chooses between two different odors to receive a reinforcement. A cinnamon-scented sand cup is initially associated with reinforcement, while a nutmeg-scented cup is not associated with reinforcement. After initial learning, the contingencies are reversed such that the nutmeg-scented sand cup is associated with reinforcement. The prelimbic cortex and the orbitofrontal cortex are two prefrontal cortex subregions that have been most commonly studied to understand their contributions to behavioral flexibility.

Based on findings indicating that the prelimbic cortex supports working memory when spatial or visual object information must be used (Kesner et al. 1996; Ragozzino et al. 1998), one idea was that the prelimbic cortex would also support behavioral flexibility when conditions require the flexible use of spatial and/or visual object information. In set-shifting tests, prelimbic inactivation with a local anesthetic impaired performance when rats had to shift between using a spatial and visual object strategy (Ragozzino et al. 1999a). However, other studies indicated that lesions or targeted drug manipulations of the prelimbic cortex also impaired set-shifting performance even under conditions that did not involve the use of spatial and/or visual object information (Birrell and Brown 2000; Ragozzino 2002; Ragozzino et al. 2003; Ragozzino 2007; Stefani et al. 2003). Furthermore, prelimbic cortex inactivation or lesions did not impair visual object or place reversal learning or other types of reversal learning (Birrell and Brown 2000; Ragozzino et al. 1999b; Ragozzino et al. 2003). Important to note, these different discrimination tests do not have a salient working memory component although there is a delay between each trial. However, unlike the working memory tests used to examine the effects of prelimbic and infralimbic lesions where recently presented information had to be remembered and changes trial to trial, in these tests a subject must learn a particular rule that remains constant across a range of consecutive trials. Thus, the prelimbic cortex may contribute to different cognitive functions under some conditions that are dependent on specific attribute information and in other conditions independent of specific attribute information. Related to behavioral flexibility, the pattern of results suggests that the prelimbic area supports behavioral flexibility when conditions require a shift in strategies that can be determined by requiring rats to switch between different attribute information. In contrast, the prelimbic area is not involved in behavioral flexibility when conditions require a shift in choices using similar attribute information as is required in reversal learning.

Studies investigating the contribution of the orbitofrontal cortex to behavioral flexibility have yielded results that suggest that this prefrontal cortex subregion makes different contributions than the prelimbic cortex. Experiments involving orbitofrontal cortex inactivation or lesions found that these manipulations do not affect acquisition of different discrimination learning tests, for example, olfactory or visuospatial discrimination , but do impair reversal learning (Boulougouris et al. 2007; Churchwell et al. 2009; Ghods-Sharifi et al. 2008; Kim and Ragozzino 2005; McAlonan and Brown 2003; Riceberg and Shapiro 2012; Schoenbaum et al. 2002). This occurred in reversal-learning tests that involved the flexible use of odor, vi-

sual cue, tactile, or spatial information. In contrast, set-shifting is not impaired by lesions, local anesthetics, or gamma-aminobutyric acid (GABA) agonist infusions in the orbitofrontal cortex (Ghods-Sharifi et al. 2008; McAlonan and Brown 2003). Considered together, these findings from several investigations suggest that the orbitofrontal cortex does not support behavioral flexibility based on a particular type of attribute information, but more on the type of rule required for flexibly adapting an individual's behavior.

A comparison of results following prelimbic cortex versus orbitofrontal cortex manipulations on set-shifting and reversal-learning tests show a double dissociation in function between these areas. In particular, the prelimbic cortex supports behavioral flexibility when conditions require a set-shift, but not a reversal in choice patterns. Conversely, the orbitofrontal cortex supports behavioral flexibility when conditions require a reversal in choice patterns, but not a set-shift. Taken together, these results support a model proposed by Wise et al. (1996) to explain the functional organization of the primate frontal cortex in which different conditions require different types of rules to facilitate behavioral flexibility. These authors further proposed that these rules are mediated by separate primate prefrontal cortex areas. Specifically, the model proposes that there is a lower-order rule for the shifting of specific choices within a dimension. This rule allows the approach to and avoidance of a particular stimulus or scene as required in discrimination tasks that involve reversal learning. There is also a higher-order rule when conditions demand learning about stimulus attributes as opposed to within a stimulus. In these cases, learning must go beyond simply attaching a positive or negative valence to stimuli within a particular dimension and instead require attention to components of an object or scene or abstract rules about component objects or scenes. Thus, higher-order rules enable a subject to reconceptualize his or her approach to a task and attend to a new type of information. This model may be applicable to rodents such that the orbitofrontal cortex supports a lower-order rule to enable behavioral flexibility, while the prelimbic cortex supports a higher-order rule to facilitate behavioral flexibility.

Although there is considerable evidence that the prelimbic cortex and orbitofrontal cortex subregions support different rules to enable behavioral flexibility, these different prefrontal cortex subregions may support similar processes to enable various forms of behavioral flexibility. For example, a brain region may facilitate the ability to *initially* inhibit a previously relevant strategy and/or to generate a new strategy. In this case, inactivation of a prefrontal cortex subregion should produce a predominance of errors during the initial trials in a shift or reversal phase. These errors are commonly referred to as "perseverative errors." Another possibility is that a brain region supports a process that allows an individual to reliably execute or learn a new choice pattern once the new choice pattern is selected. This process would prevent or minimize regressions to the previously relevant choice pattern once the new, presently relevant choice pattern is selected. In this case, inactivation of a prefrontal cortex subregion should not produce a significant increase in errors during the initial trials of the shift or reversal phase, but rather should lead to a

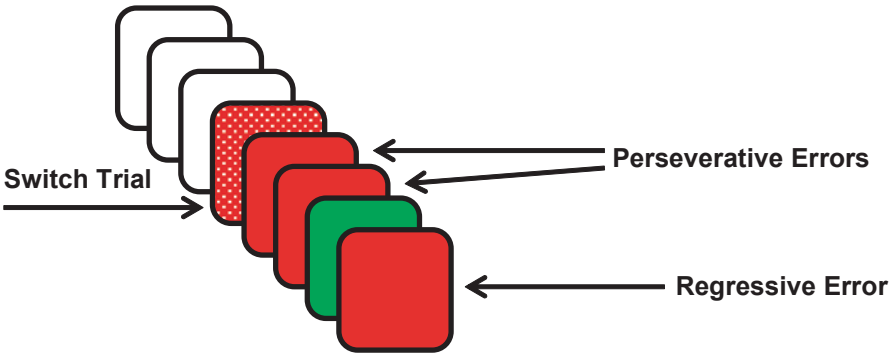

Fig. 11.2 Errors committed during set-shifting and reversal-learning tests. Errors are scored as either perseverative or regressive errors. *White blocks* represent trials from acquisition phase. *Patterned red block* represents the first switch trial from either a set-shifting or reversal-learning test. A *solid red block* represents an error trial. A *solid green block* represents a correct trial. Perseverative errors occur when errors immediately follow a switch trial error, until a correct response is made. Once a rat makes a correct response in a session, any errors following that correct response are considered regressive errors

greater number of errors once a rat has selected the new, presently relevant strategy. We have referred to these errors as "regressive errors" because a subject has chosen the new correct choice and has been reinforced for it, but regresses to the previous choice that is no longer reinforced (see Fig. 11.2). In multiple experiments where prelimbic cortex manipulations impaired set-shifting, a deficit resulted from an increase in perseverative errors but not regressive errors (Ghods-Sharifi et al. 2008; Ragozzino 2002 Ragozzino et al. 1999b, 2003).

Orbitofrontal cortex manipulations that have impaired reversal learning have also resulted from an increase in perseverative errors (Boulougouris et al. 2007; Kim and Ragozzino 2005). These findings suggest that despite the prelimbic cortex and orbitofrontal cortex supporting different forms of behavioral flexibility based on rules, both subregions facilitate the ability to *initially* inhibit a previously relevant choice pattern and/or to generate a new choice pattern.

Dorsomedial Striatum, Attributes and Rules

In view of the evidence that the prelimbic cortex and orbitofrontal cortex support behavioral flexibility related to the behavioral operation required to flexibly adapt, it is of interest that both regions project to the dorsomedial striatum (Berendse et al. 1992). Using a similar approach to investigate the contributions of the prefrontal cortex subregions to behavioral flexibility, a series of experiments have examined the effects of dorsomedial striatal inactivation on acquisition, reversal learning, and set-shifting tests.

Because the prelimbic cortex prominently projects to the dorsomedial striatum, one possibility is that the prelimbic cortex and dorsomedial striatum functionally interact to support behavioral flexibility. As the prelimbic cortex supports set-shifting, we first examined whether the dorsomedial striatum also contributed to set-shifting that required rats to switch between using a visual cue and egocentric spatial response strategy (Ragozzino et al. 2002b). Specifically, rats were tested in a cross-maze in which one arm was blocked leading to a T-maze shape. The stem arm was used as the start arm and the other two arms were used as choice arms. One choice arm contained a black visual cue and the other choice arm contained a white visual cue. The other two arms were used as start arms that were changed after every few trials. A rat could learn to make a choice based on a particular visual cue, for example, always enter the black arm, or due to an egocentric response, for example, always turn left. Dorsomedial striatal inactivation with a local anesthetic did not impair initial learning of a visual cue or egocentric response discrimination, but did impair set-shifting (Ragozzino et al. 2002b). More recent findings following neurotoxic lesions of the dorsomedial striatum also indicate that the dorsomedial striatum enables behavioral flexibility when a shift across attribute dimensions is required (Lindgren et al. 2013). However, dorsomedial striatal manipulations not only impair performance in set-shifting tests, but also produce deficits in reversal learning tests (Pisa and Cyr 1990; Ragozzino and Choi 2004). As N-methyl-D-aspartate (NMDA) receptors support synaptic plasticity (Spencer and Murphy 2000a; Boettiger and Doupe 2001; Akopian and Walsh 2002; Dang et al. 2006), the role of these receptors in the dorsomedial striatum related to behavioral flexibility has been examined. Comparable to dorsomedial striatal lesions or inactivation, infusion of the NMDA receptor antagonist (2R)-amino-5-phosphonovaleric acid (AP5) in this region impairs reversal learning but not acquisition (Palencia and Ragozzino 2004). Moreover, AP5 in the dorsolateral striatum does not impair reversal learning (Palencia and Ragozzino 2005). Thus, the dorsomedial striatum appears to play a broader role in behavioral flexibility then either the prelimbic cortex or orbitofrontal cortex alone.

While dorsomedial striatal manipulations lead to deficits in set-shifting or reversal learning, the behavioral flexibility deficit does not result from an increase in perseveration. Instead, dorsomedial striatal inactivation or NMDA receptor blockade in the dorsomedial striatum selectively increases regressive errors (Ragozzino et al. 2002b; Palencia and Ragozzino 2004; Ragozzino and Choi 2004). These results suggest that the dorsomedial striatum may dynamically interact with multiple prefrontal cortex subregions to facilitate behavioral flexibility in a distinct but complementary manner. More specifically, prefrontal cortex subregions may be critical for the generation of a new strategy or response pattern. This allows the initial inhibition of the previously relevant strategy. However, once a new strategy is generated, it must be executed into an appropriate response pattern. The striatum, in coordination with different prefrontal cortex areas, may facilitate the execution of an appropriate response pattern for a particular strategy that is generated. Thus, the striatum may link a particular response pattern with a specific strategy allowing for the reliable execution of a strategy once generated, as well as continual inhibition of previously relevant strategies.

Prefrontal Cortex—Basal Ganglia Interactions for Proactive Cue-Guided Behavioral Flexibility

The studies described above focused on understanding how distinct prefrontal cortex and striatal areas contribute to behavioral flexibility based on different discrimination tests in which a change in outcomes indicated that a behavioral switch should occur. However, these studies did not address more directly how different prefrontal cortex and basal ganglia regions may interact to facilitate behavioral flexibility. In addition, many of these investigations involved paradigms in which there was a single behavioral switch that had to occur over an extended time period, for example, a daily session as opposed to a few trials. Changes in environmental conditions often require rapid and repeated adaptations to achieve a goal. Moreover, previous paradigms to study behavioral flexibility have predominantly involved a change in outcomes to signal that a switch in a response pattern should occur. In many situations, cue information may be used proactively to switch actions to obtain a goal (Hikosaka and Isoda 2010).

To date, there has been significantly less examination of whether prefrontal cortex and basal ganglia areas support behavioral switching when cues can be used to proactively switch response patterns for an upcoming choice. Moreover, it is unknown whether the brain areas that support behavioral flexibility based on set-shifting and reversal learning support similar processes, for example, reduction in perseveration of a previously correct response pattern, under conditions that require cue-guided behavioral switching. Conditional discrimination tests offer a behavioral paradigm in which cues can be used to proactively switch behavior. In these paradigms, a cue, for example, 40 Hz tone, is associated with making a specific response, for example, press the right lever, to receive a reinforcement. On other trials a different cue is presented, for example, 200 Hz tone, that is associated with making a different response, for example, press the left lever, to receive a reinforcement. The cues are presented prior to making a response and are switched after a certain number of trials. Related to the prelimbic cortex, prelimbic lesions alone or prelimbic and infralimbic lesions do not impair acquisition of a conditional discrimination task (Chudasama et al. 2001; Delatour and Gisquet-Verrier 1999). More recently, a study trained rats on a conditional discrimination task in which one of the two different cue–response associations was presented for 5–10 consecutive trials before a switch to the other cue–response association (Leenaars et al. 2012). In this test, prelimbic inactivation selectively impairs performance for a switch trial. These findings suggest that the prelimbic cortex also supports behavioral flexibility when cue information must be used to proactively switch. However, it is unclear whether prelimbic inactivation also increases perseveration of the previous cue–response association and/or maintenance of the currently correct response pattern. Therefore, it is unknown whether the prelimbic cortex supports a similar process when a change in cues signals a switch, for example, inhibiting perseveration of a previously relevant response pattern, as when a change in outcomes can be used to switch a response pattern.

There is also limited understanding of how the prelimbic area may interact with other brain areas to support cue-guided behavioral switching. The prelimbic cortex has extensive projections to basal ganglia structures and together these areas may act in a cooperative manner to facilitate behavioral flexibility when a change in outcomes or a change in cues guides a behavioral switch (Afsharpour 1985; Chudasama and Robbins 2006; Jahfari et al. 2011; Kehagia et al. 2010; Mailly et al. 2013). The subthalamic nucleus and dorsomedial striatum are the two areas of basal ganglia that receive direct excitatory input from the prelimbic cortex that is mediated, at least in part, by NMDA receptors (Berendse et al. 1992; Conde et al. 1995; Gabbott et al. 2005; Magill et al. 2006; Maurice et al. 1998; Nambu et al. 2000; Sesack et al. 1989). Individual neurons in the nonhuman primate subthalamic nucleus show increased activity in response to a cue that signals when a switch from one response pattern to another will be rewarded suggesting that this area may be important for a proactive behavioral switch (Isoda and Hikosaka, 2008). In addition, dorsomedial striatal lesions or inactivation impair behavioral switching in conditional discrimination tests (Adams et al. 2001; Featherstone and McDonald 2005; Hallock et al. 2013). While the findings implicate the subthalamic nucleus and dorsomedial striatum in proactive behavioral switching, these paradigms typically involved cues for switching every 1 or 2 trials which may not be sufficient to establish a response set leading to switch costs as measured by switching errors or increased reaction time.

To begin addressing some of these issues, we recently completed a series of experiments to test conditional discrimination performance following a contralateral disconnection of the prelimbic cortex and subthalamic nucleus, as well as the prelimbic cortex and dorsomedial striatum. This involved infusions of the GABA agonists, baclofen and muscimol in the prelimbic cortex (Leenaars et al. 2012) and the NMDA receptor antagonist, AP-5 in the subthalamic nucleus (Baunez and Robbins 1999). The experiments further examined whether these pharmacological manipulations affected switch trial performance, initial perseveration of a previously relevant response pattern and/or maintenance of the currently relevant response pattern once selected.

To carry out these experiments, we developed a conditional discrimination test in a modified cross-maze (see Fig. 11.3). The stem arm served as the start arm and the other two arms served as choice arms. A white or black insert was placed in the start arm that covered the floor and side walls of the arm. Rats were trained to associate a start arm cue with choosing one particular choice arm, for example, a spatial location, to receive a food reward. Rats were tested for 57 trials per session. In the conditional cue–place association, the visual cue was changed in blocks of every 3–6 trials indicating that a behavioral switch should occur for the upcoming choice (see Baker and Ragozzino 2014a, b for details). The relatively short block length was chosen in order to emphasize the need to monitor task cues on every trial while also having a rat establish a response pattern prior to a switch. This is common in a proactive switch task in order to incur a switch cost such that performance is more difficult on a switch trial compared to that of non-switch trials (Hikosaka and Isoda 2010; Hyafil et al. 2009; Konishi et al. 2005). Consistent with the task

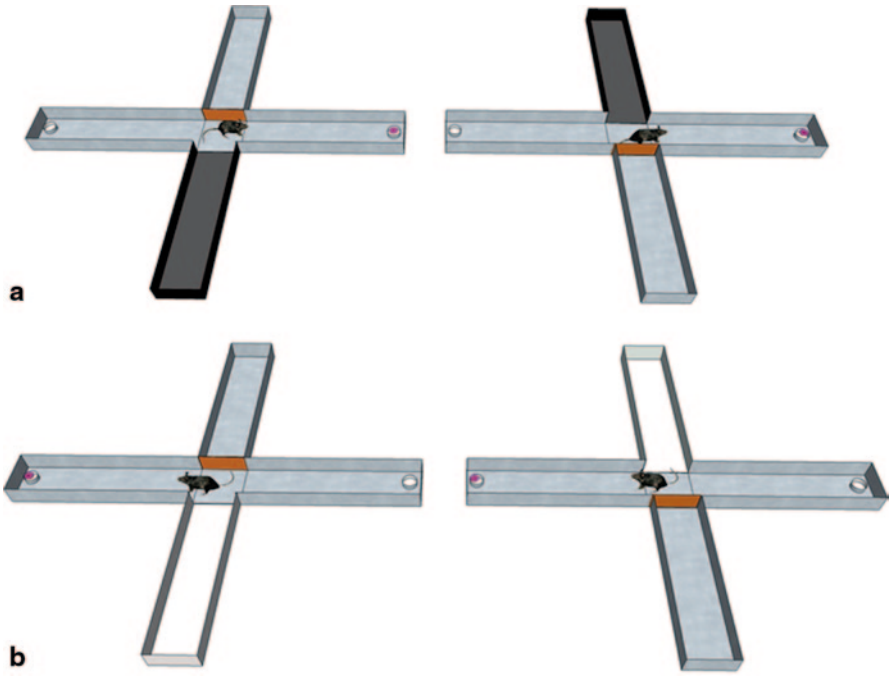

Fig. 11.3 Visual cue–place conditional discrimination. A visual cue was placed in the start arm. **a** In one condition, a *black* visual cue is placed in one of the two start arms and a rat must always enter the same maze arm to receive a cereal reinforcement. **b** In the other condition, a *white* visual cue is placed in one of the two start arms and a rat must enter the other maze arm to receive a cereal reinforcement. Rats learned to associate a start arm cue with entering a particular choice arm to receive a cereal reinforcement. Extra-maze visual cues surround the maze (not shown) that a rat can use to spatially guide their choice. The visual cues were randomly changed in blocks of every 3–6 trials within a 57 trial session. The *copper block* prevented entry into that arm on a trial. The *O-shaped* object in the foodwell represents a cereal piece reinforcement

having switch costs, we found that vehicle treated rats committed a significantly greater percentage of errors on switch trials compared to that of non-switch trials.

Studies using this task led to a unique and interesting set of results across brain areas. More specifically, bilateral prelimbic inactivation impaired conditional discrimination performance by significantly increasing switch, perseverative, and maintenance errors (Baker and Ragozzino 2014a, b). This contrasts with past studies using set-shifting tests in which a change in outcomes signaled a shift to occur such that prelimbic cortex inactivation selectively increased perseveration of the previously relevant response (Dias and Aggleton 2000; Ragozzino 2007; Ragozzino et al. 1999b). In this test, one possibility in the cue-guided behavioral switch test is that prelimbic cortex inactivation simply impairs discrimination performance independent of behavioral switching. To test this, Baker and Ragozzino (2014a, b) trained rats in a conditional discrimination test as before, but in a control test required rats to execute a single visual cue–place discrimination without any switches to other

condition. Prelimbic cortex inactivation did not affect performance in a non-switch discrimination test. The increase in multiple types of errors following prelimbic inactivation likely reflects the inability to flexibly apply learned visual cue–place associations that leads to a more rigid and fixed response pattern. More specifically, bilateral prelimbic inactivation in the conditional discrimination test increased a turn bias that was independent of current cue information. Rats, even under saline treatment, exhibited a turn bias in the test, but this was significantly enhanced under the high dose of baclofen/muscimol injected in prelimbic cortex. However, the exaggerated turn bias is not a necessary consequence of prelimbic inactivation as this did not occur in a non-switch discrimination test. As described above, this conditional discrimination test is distinct from set-shifting and reversal-learning tests used in past studies because in a conditional discrimination test cues can be used on each trial to proactively determine when a behavioral switch must occur, while set-shifting and reversal-learning tests involve a change in outcome information, for example, change in reinforcement, to signal a behavioral switch should occur. Recent findings in a conditional discrimination test, suggest that the prelimbic cortex supports the use of cue information to allow the proactive selection of an alternative response pattern and maintenance of that response pattern when conditions require a behavioral switch. These results support the model of prefrontal cortex control of behavioral flexibility set forth by Wise et al. (1996). Specifically, although the conditional discrimination test requires a rat to reverse a response pattern based on a single attribute (spatial), as these reversals are determined by integrating visual cue and visuospatial information, a higher-order rule must be applied to successfully perform the task. As predicted by Wise et al. (1996) this higher-order rule processing requires the prelimbic cortex.

The role of the subthalamic nucleus in proactive behavioral switching was also examined using a conditional discrimination test. NMDA receptor blockade in the subthalamic nucleus also impaired performance in the proactive behavioral switch test (Baker and Ragozzino 2014a). However, in contrast to the effects of prelimbic cortex inactivation, NMDA receptor blockade in the subthalamic nucleus selectively increased switch and perseverative errors, but did not affect maintenance errors. Similarly, contralateral disconnection of the prelimbic cortex and subthalamic nucleus also increased switch errors in the conditional discrimination test. In addition, the contralateral disconnection increased perseverative errors leading a rat to repeatedly choose the previously relevant response pattern after the initial switch trial**.** In contrast, ipsilateral disconnection of the prelimbic cortex and subthalamic nucleus had no effect on performance. The findings following NMDA receptor blockade in the subthalamic nucleus are comparable to those in which subthalamic nucleus lesions impair inhibition of an initiated response in the stop-signal test (Eagle et al. 2008) and further suggest that the subthalamic nucleus is critical not only for inhibiting an initiated response, but also for inhibiting an ongoing response pattern when cues indicate an alternate response pattern should occur. Interestingly, this is true even after the initial switch as evidenced by the increase in perseveration if a switch error was committed.

To determine whether another basal ganglia region that receives prelimbic cortex input contributes to proactive behavioral switching, NMDA receptor blockade in the dorsomedial striatum, as well as contralateral disconnection of the prelimbic cortex and dorsomedial striatum was investigated (Baker and Ragozzino 2014b). Bilateral AP5 infusions in the dorsomedial striatum, as well as a contralateral disconnection of the prelimbic cortex and dorsomedial striatum impaired overall conditional discrimination performance. Similar to that observed with prelimbic cortex and subthalamic nucleus, ipsilateral disconnection of the prelimbic cortex and dorsomedial striatum did not impair performance. Besides increasing the number of switch errors, these manipulations significantly elevated the number of perseverative and maintenance errors. The significant increase in all error types following dorsomedial striatal NMDA receptor blockade emerged because this led a rat to commit errors across an entire block of trials 1–3 times in a session. This effect committing errors across an entire trial block was not due to the length of the previous block or the length of the block which was missed. Thus, the previous block of trials being short, for example, 3 trials or long, for example, 6 trials, nor the block in which errors were committed in all trials being short or long could explain the finding. One explanation for the failure to perform a given block is that the change in cue–reward contingencies fails to update the ongoing choice pattern resulting in the previous choice pattern being continually executed. In rats, the dorsomedial striatum has been implicated in relaying information about the expected value of an action based on recent task demands. In a recent study, rats were trained in a two-choice discrimination in which there were different probabilities for reward. The choices were reversed after 35 trials with multiple reversals in a session (Kim et al. 2013). Similar to the current experiments, rats were well-trained in the task in which multiple single units were recorded during the test. Although the activity of any single neuron only correlated weakly with a choice, there was an ensemble of activity in the dorsomedial striatum that preceded the actual choice and would change dynamically with a reversal in reward probabilities (Kim et al. 2013). This supports that the dorsomedial striatum is critical for the updating of expected value of an action or strategy.

Overall, while drug manipulations of all three brain areas impaired conditional discrimination performance, the pattern of errors that emerged were somewhat distinct and also differed from the same drug manipulations which also impaired performance on set-shifting and reversal learning tests. Moreover, the findings from these contralateral disconnection experiments suggest that the prelimbic cortex connections with specific basal ganglia areas dynamically interact to support proactive behavioral switching. The pattern of results raises the possibility that the prelimbic cortex is acting in a top–down fashion to control behavioral flexibility through two different basal ganglia pathways (see Fig. 11.4). Narayanan and Laubach (2006, 2009) have proposed that the dorsomedial frontal cortex encodes both prepotent responses and proactive inhibition such that when neurons encoding proactive inhibition predominate, a rat will be less likely to make a premature response. A similar top–down process may occur to allow proactive behavioral switching such that the prelimbic cortex encodes both inhibition of an ongoing strategy and

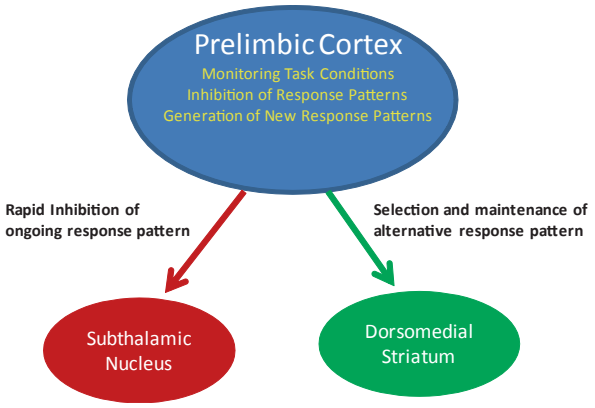

Fig. 11.4 Prelimbic cortex interactions with the dorsomedial striatum and subthalamic nucleus to facilitate proactive behavioral switching

generation of relevant strategies in response to specific cues. In this fashion, the prelimbic cortex would be critical for the monitoring of task cues to guide appropriate responses or rule applications on a trial-to-trial basis. When excitatory input from the prelimbic cortex to the subthalamic nucleus predominates, it allows an inhibition of the ongoing response pattern and selection of a different response pattern. In this manner, the prelimbic cortex and subthalamic nucleus together can rapidly terminate an ongoing or prepotent response when no longer relevant. Physiological evidence suggests that the prelimbic cortex–subthalamic nucleus circuit is ideally suited to this function. Prelimbic cortex stimulation is followed by a large burst of neuronal firing in the subthalamic nucleus after 4–8 ms (Maurice et al. 1998; Magill et al. 2006). Furthermore, recordings in the substantia nigra pars reticulata reveal that input from the subthalamic nucleus arrives before that from the direct pathway coming from the striatum (Fujimoto and Kita 1993; Ryan and Sanders 1994; Maurice et al. 1999). This is important for a proposed model of prelimbic cortex–subthalamic nucleus input in overriding a prepotent or ongoing behavior (Mathai and Smith 2011). The signal from this pathway arrives at basal ganglia output structures before that of the direct and indirect pathway allowing for modification of the output back to the motor cortex. In this way, the prelimbic cortex–subthalamic nucleus circuit represents an ideal mechanism for the top–down inhibition of an ongoing behavior or strategy when cues indicate the choice pattern should not be used.

Prelimbic cortex inactivation not only led to switch errors, but also increased maintenance errors. This would suggest that the prelimbic cortex interacts with other areas to support proactive switching. Results from prelimbic cortex–dorsomedial striatal areas suggest that these areas functionally interact differently than the prelimbic cortex and subthalamic nucleus to support behavioral switching. This is because contralateral disconnection of the prelimbic cortex and dorsomedial striatal areas selectively increased the likelihood of rats to miss an entire block of trials. One possibility is that the prelimbic cortex input to the dorsomedial striatum provides information about possible strategies or choice patterns in a context and the dorsomedial striatum facilitates the appropriate strategy selection (Kim et al. 2009; Tai

et al. 2012). In fact, neuronal signals in the dorsomedial striatum have been shown to encode information about the expected reward value of a given behavioral response based on previous reward feedback from making that choice (Stalnaker et al. 2012; Kim et al. 2013). One possibility is that cue information also can be used proactively by the dorsomedial striatum to select a strategy. If input from the prelimbic cortex to the dorsomedial striatum is disrupted, this may decrease information about possible strategies and limit the accuracy of selecting a strategy (Ragozzino 2007), which could lead on occasion to making errors for an entire block of trials. Thus, in the conditional discrimination test rats may have been unable to generate a different choice pattern appropriate to the cues on a given trial and the previous choice pattern is repeatedly selected. Thus, we propose that when cue information should be used to proactively switch choice patterns that a neural system that includes the prelimbic cortex and subthalamic nucleus supports the rapid inhibition of an ongoing choice pattern while concomitantly a neural system that includes the prelimbic cortex and dorsomedial striatum enables selection of an alternative choice pattern. This latter system also continues to be critical for maintaining the alternative choice pattern after being initially selected.

Conclusions

The neurobiologically based attribute model of memory asserts that the nature of memory can be explained by different attributes such as space, time, sensory-perception, response, and reward (affect), which are stored as memories in different forebrain areas**.** Tests of this model led to the development of several novel learning paradigms that emphasized the learning and memory of a specific type of attribute, for example, visuospatial information. Our investigations of prefrontal cortex and basal ganglia structures in behavioral flexibility employed the attribute model of memory approach by whether the prefrontal cortex contributed to behavioral flexibility based on separate subregions supporting the flexible use of specific attribute information. The findings from numerous studies suggest that different prefrontal cortex subregions support different forms of behavioral flexibility based on the level of the operation required to flexibly adapt (Kesner and Churchwell 2011; Ragozzino 2007; Wise et al. 1996). Although different prefrontal cortex subregions may support different forms of behavioral flexibility when a change in outcomes signals a behavioral switch should occur, these different subregions appear particularly important for initially inhibiting perseveration of a previously relevant strategy.

The dorsomedial striatum is an area that receives input from both the orbitofrontal cortex and prelimbic cortex. There is considerable support for the idea that this striatal region plays a role in various types of behavioral flexibility when a change in outcomes occurs. This is consistent with the diverse prefrontal cortex input it receives. In set-shifting and reversal-learning tests, the dorsomedial striatum supports behavioral flexibility by maintaining the new choice pattern after it has been initially selected. Thus, the dorsomedial striatum likely plays a distinct, but comple-

mentary role from different prefrontal cortex subregions in facilitating set-shifting and reversal learning.

There is recent evidence that the prelimbic cortex and different basal ganglia areas interact to enhance proactive behavioral switching. Under conditions in which cues signal that an upcoming response should be switched, these brain areas act in a cooperative manner to facilitate behavioral flexibility. During proactive behavioral switching conditions, the prelimbic cortex and subthalamic nucleus are part of a neural system that enables the rapid inhibition of an ongoing choice pattern while concomitantly a neural system that includes the prelimbic cortex and dorsomedial striatum enables selection of an alternative choice pattern and maintenance of that selection. These results demonstrate that specific prefrontal–basal ganglia circuitry not only supports behavioral flexibility when there is a change in outcomes but also when cues can be used to proactively switch response patterns. Further, the effect of a general increase in errors with prelimbic cortex inactivation in a conditional discrimination test suggests that under certain conditions, the prefrontal cortex may be required for more than just the initial abandonment of the previous choice pattern, but plays a critical role in monitoring task conditions to concomitantly inhibit one choice pattern and facilitate the use of a different choice pattern. This is particularly the case when cue information must be monitored on a trial-by-trial basis to switch ongoing behavioral responses. Overall, there is accumulating evidence that prefrontal cortex and basal ganglia structures are crucial to allow rapid and repeated adaptations across a variety of stimulus attributes in which changes in reward feedback or proactive cue information signal a behavioral switch should occur.

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References

Adams, S., Kesner, R. P., & Ragozzino, M. E. (2001). Role of the medial and lateral caudate-putamen in mediating an auditory conditional response association. *Neurobiology of Learning and Memory, 76,* 106–116.

Afsharpour, S. (1985). Topographical projections of the cerebral cortex to the subthalamic nucleus. *The Journal of Comparative Neurology, 236,* 14–28.

Akopian, G., & Walsh, J. P. (2002). Corticostriatal paired-pulse potentiation produced by voltage-dependent activation of NMDA receptors and L-type Ca(2+) channels. *Journal of Neurophysiology, 87,* 157–165.

Baker, P. M., & Ragozzino, M. E. (2014a). The prelimbic cortex and subthalamic nucleus contribute to cue-guided behavioral switching. *Neurobiology of Learning and Memory, 107,* 65–78.

Baker, P. M., & Ragozzino, M. E. (2014b). Contralateral disconnection of the rat prelimbic cortex and dorsomedial striatum impairs cue-guided behavioral switching. *Learning and Memory, 21,* 368–379.

Baunez, C., & Robbins, T. W. (1999). Effects of transient inactivation of the subthalamic nucleus by local muscimol and APV infusions on performance on the five-choice serial reaction time task in rats. *Psychopharmacology, 141*(1), 57–65.

Berendse, H. W., Galis-de Graaf, Y., & Groenewegen, H. J. (1992). Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. *The Journal of Comparative Neurology, 316,* 314–347.

Birrell, J. M., & Brown, V. J. (2000). Medial frontal cortex mediates perceptual attentional set shifting in the rat. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 20,* 4320–4324.

Boettiger, C. A., & Doupe, A. J. (2001). Developmentally restricted synaptic plasticity in a songbird nucleus required for song learning. *Neuron, 31,* 809–818.

Boix-Trelis, N., Vale-Martinez, A., Guillazo-Blanch, G., Costa-Miserachs, D., & Marti-Nicolovius, M. (2006). Effects of nucleus basalis magnocellularis stimulation on a socially transmitted food preference and c-Fos expression. *Learning & Memory* (*Cold Spring Harbor, N. Y.*)*, 13,* 783–793.

Boulougouris, V., Dalley, J. W., & Robbins, T. W. (2007). Effects of orbitofrontal, infralimbic and prelimbic cortical lesions on serial spatial reversal learning in the rat. *Behavioural Brain Research, 179,* 219–228.

Chudasama, Y., & Robbins, T. W. (2006). Functions of frontostriatal systems in cognition: Comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biological Psychology, 73*(1), 19–38.

Chudasama, Y., Bussey, T. J., & Muir, J. L. (2001). Effects of selective thalamic and prelimbic cortex lesions on two types of visual discrimination and reversal learning. *The European Journal of Neuroscience 0953-816X* (*P*)*, 14,* 1009–1020.

Churchwell, J. C., Morris, A. M., Heurtelou, N. M., & Kesner, R. P. (2009). Interactions between the prefrontal cortex and amygdala during delay discounting and reversal. *Behavioral Neuroscience, 123,* 1185–1196.

Conde, F., Maire-Lepoivre, E., Audinat, E., & Crepel, F. (1995). Afferent connections of the medial frontal cortex of the rat. II. Cortical and subcortical afferents. *The Journal of Comparative Neurology, 352,* 567–593.

Dang, M. T., Yokoi, F., Yin, H. H., Lovinger, D. M., Wang, Y., & Li, Y. (2006). Disrupted motor learning and long-term synaptic plasticity in mice lacking NMDAR1 in the striatum. *Proceedings of the National Academy of Sciences of the United States of America, 103,* 15254–15259.

Delatour, B., & Gisquet-Verrier, P. (1999). Lesions of the prelimbic-infralimbic cortices in rats do not disrupt response selection processes but induce delay-dependent deficits: Evidence for a role in working memory? *Behavioral Neuroscience, 113,* 941–955.

Dias, R., & Aggleton, J. P. (2000). Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: Differential involvement of the prelimbic-infralimbic and anterior cingulate cortices in providing behavioural flexibility. *The European Journal of Neuroscience 0953-816X* (*P*)*, 12,* 4457–4466.

Eagle, D. M., Baunez, C., Hutcheson, D. M., Lehmann, O., Shah, A. P., & Robbins, T. W. (2008). Stop-signal reaction-time task performance: Role of prefrontal cortex and subthalamic nucleus. *Cerebral Cortex* (*New York, N. Y.: 1991*)*, 18*(1), 178–188.

Eden, C. G., Lamme, V., & Uylings, H. (1992). Heterotopic cortical afferents to the medial prefrontal cortex in the rat. A combined retrograde and anterograde tracer study. *European Journal of Neuroscience, 4,* 77–97.

Featherstone, R., McDonald, R. (2005). Lesions of the dorsolateral striatum impair the acquisition of a simplified stimulus-response dependent conditional discrimination task. *Neuroscience, 136,* 387–395.

Fujimoto, K., & Kita, H. (1993). Response characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. *Brain Research, 609,* 185–192.

Gabbott, P. L., Warner, T. A., Jays, P. R., Salway, P., & Busby, S. J. (2005). Prefrontal cortex in the rat: Projections to subcortical autonomic, motor, and limbic centers. *The Journal of Comparative Neurology, 492,* 145–177.

Ghods-Sharifi, S., Haluk, D. M., & Floresco, S. B. (2008). Differential effects of inactivation of the orbitofrontal cortex on strategy set-shifting and reversal learning. *Neurobiology of Learning and Memory, 89,* 567–573.

Hallock, H. L., Arreola, A. C., Shaw, C. L., & Griffin, A. L. (2013). Dissociable roles of the dorsal striatum and dorsal hippocampus in conditional discrimination and spatial alternation T-maze tasks. *Neurobiology of Learning and Memory, 100,* 108–116.

Heidbreder, C. A., & Groenewegen, H. J. (2003). The medial prefrontal cortex in the rat: Evidence for a dorso-ventral distinction based upon functional and anatomical characteristics. *Neuroscience & Biobehavioral Reviews, 27,* 555-579.

Hikosaka O., Isoda M. (2010). Switching from automatic to controlled behavior: Cortico-basal ganglia mechanisms. *Trends in Cognitive Sciences, 14,* 154–161.

Hoover, W. B., & Vertes, R. P. (2007). Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Structure and Function, 212,* 149-179.

Hyafil, A., Summerfield, C., & Koechlin, E. (2009). Two mechanisms for task switching in the prefrontal cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 29*(16), 5135–5142.

Isoda, M., & Hikosaka, O. (2008). Role for subthalamic nucleus neurons in switching from automatic to controlled eye movement. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 28,* 7209–7218.

Jahfari, S., Waldorp, L., van den Wildenberg, W. P. M., Scholte, H. S., Ridderinkhof, K. R., & Forstmann, B. U. (2011). Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. *Journal of Neuroscience, 31*(18), 6891–6899.

Kehagia, A. A., Murray, G. K., & Robbins, T. W. (2010). Learning and cognitive flexibility: Frontostriatal function and monoaminergic modulation. *Current Opinion in Neurobiology, 20*(2), 199–204.

Kesner, R. P. (2000). Subregional analysis of mnemonic functions of the prefrontal cortex in the rat. *Psychobiology, 28,* 219–222.

Kesner, R. P. (2009). Tapestry of memory. *Behavioral Neuroscience, 123,* 1–13.

Kesner, R. P., & Churchwell, J. C. (2011). An analysis of rat prefrontal cortex in mediating executive function. *Neurobiology of Learning and Memory, 96,* 417–431.

Kesner, R. P., & DiMattia, B. V. (1987). Neurobiology of an attribute model of memory. In A. R. Morrison & A. N. Epstein (Eds.), *Progress in psychobiology and physiological psychology* (pp. 207–277). New York: Academic.

Kesner, R. P., Hunt, M. E., Williams, J. M., & Long, J. M. (1996). Prefrontal cortex and working memory for spatial response, spatial location and visual object information in the rat. *Cerebral Cortex, 6,* 311–318.

Kim, J., & Ragozzino, M. E. (2005). The involvement of the orbitofrontal cortex in learning under changing task contingencies. *Neurobiology of Learning and Memory, 83,* 125–133.

Kim, H., Sul, J. H., Huh, N., Lee, D., & Jung, M. W. (2009). Role of striatum in updating values of chosen actions. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 29,* 14701–14712.

Kim, H., Lee, D., & Jung, M. W. (2013). Signals for previous goal choice persist in the dorsomedial, but not dorsolateral striatum of rats. *The Journal of Neuroscience, 33,* 52–63.

Konishi, S., Chikazoe, J., Jimura, K., Asari, T., & Miyashita, Y. (2005). Neural mechanism in anterior prefrontal cortex for inhibition of prolonged set interference. *Proceedings of the National Academy of Sciences of the United States of America, 102*(35), 12584–12588.

Leenaars, C. H., Joosten, R. N., Zwart, A., Sandberg, H., Ruimschotel, E., Hanegraaf, M. A., Dematteis, M., Feenstra, M. G., & van Someren E. J. (2012). Switch-task performance in rats is disturbed by 12 h of sleep deprivation but not by 12 h of sleep fragmentation. *Sleep, 35,* 211.

Lindgren, H. S., Wickens, R., Tait, D. S., Brown, V. J., & Dunnett, S. B. (2013). Lesions of the dorsomedial striatum impair formation of attentional set in rats. *Neuropharmacology, 71,* 148–153.

Magill, P. J., Sharott, A., Bolam, J. P., & Brown, P. (2006). Delayed synchronization of activity in cortex and subthalamic nucleus following cortical stimulation in the rat. *The Journal of Physiology, 574*(3), 929–946.

Mailly, P., Aliane, V., Groenewegen, H. J., Haber, S. N., & Deniau, J. M. (2013). The rat prefronto-striatal system analyzed in 3D: Evidence for multiple interacting functional units. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience, 33,* 5718–5727.

Mathai, A., & Smith, Y. (2011). The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? Frontiers in Systems Neuroscience 5.

Maurice, N., Deniau, J. M., Glowinski, J., & Thierry, A. M. (1998). Relationships between the prefrontal cortex and the basal ganglia in the rat: Physiology of the corticosubthalamic circuits. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 18*(22), 9539–9546.

Maurice, N., Deniau, J. M., Glowinski, J., & Thierry, A. M. (1999). Relationships between the prefrontal cortex and the basal ganglia in the rat: Physiology of the cortico-nigral circuits. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 19,* 4674–4681.

McAlonan, K., & Brown, V. J. (2003). Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. *Behavioural Brain Research, 146,* 97–103.

Nambu, A., Tokuno, H., Hamada, I., Kita, H., Imanishi, M., Akazawa, T., & Hasegawa, N. (2000). Excitatory cortical inputs to pallidal neurons via the subthalamic nucleus in the monkey. *Journal of Neurophysiology, 84*(1), 289–300.

Narayanan, N. S., & Laubach, M. (2006). Top-down control of motor cortex ensembles by dorsomedial prefrontal cortex. *Neuron, 52*(5), 921–931.

Narayanan, N. S., & Laubach, M. (2009). Delay activity in rodent frontal cortex during a simple reaction time task. *Journal of Neurophysiology, 101*(6), 2859–2871.

Palencia, C. A., & Ragozzino, M. E. (2004). The influence of NMDA receptors in the dorsomedial striatum on response reversal learning. *Neurobiology of Learning and Memory, 82,* 81–89.

Palencia, C. A., & Ragozzino, M. E. (2005). The contribution of NMDA receptors in the dorsolateral striatum to egocentric response learning. *Behavioral Neuroscience, 119,* 953–960.

Pisa, M., & Cyr, J. (1990). Regionally selective roles of the rat's striatum in modality-specific discrimination learning and forelimb reaching. *Behavioural Brain Research, 37,* 281–292.

Ragozzino, M. E. (2002). The effects of dopamine D(1) receptor blockade in the prelimbic-infralimbic areas on behavioral flexibility. *Learning & Memory* (*Cold Spring Harbor, N. Y.*)*, 9,* 18–28.

Ragozzino, M. E. (2007). The contribution of the medial prefrontal cortex, orbitofrontal cortex, and dorsomedial striatum to behavioral flexibility. *Annals of the New York Academy of Sciences, 1121,* 355–375.

Ragozzino, M. E., & Choi, D. (2004). Dynamic changes in acetylcholine output in the medial striatum during place reversal learning. *Learning & Memory* (*Cold Spring Harbor, N. Y.*)*, 11,* 70–77.

Ragozzino, M. E., & Kesner, R. P. (1999). The role of the agranular insular cortex in working memory for food reward value and allocentric space in rats. *Behavioural Brain Research, 1,* 103–112.

Ragozzino, M. E., & Kesner, R. P. (2001). The role of rat dorsomedial prefrontal cortex in working memory for egocentric responses. *Neuroscience Letters, 308,* 145–148.

Ragozzino, M. E., Adams, S., & Kesner, R. P. (1998). Differential involvement of the dorsal anterior cingulate and prelimbic/infralimbic areas of the rodent prefrontal cortex in spatial working memory. *Behavioral Neuroscience, 112,* 293–303.

Ragozzino, M. E., Wilcox, C., Raso, M., & Kesner, R. P. (1999a). Involvement of rodent prefrontal cortex subregions in strategy switching. *Behavioral Neuroscience, 113,* 32–41.

Ragozzino, M. E., Detrick, S., & Kesner, R. P. (1999b). Involvement of the prelimbic-infralimbic areas of the rodent prefrontal cortex in behavioral flexibility for place and response learning. *The Journal of Neuroscience, 19,* 4585–4594.

Ragozzino, M. E., Detrick, S., & Kesner, R. P. (2002). The effects of prelimbic and infralimbic lesions on working memory for visual objects in rats. *Neurobiology of Learning and Memory, 77,* 29–43.

Ragozzino, M. E., Ragozzino, K. E., Mizumori, S. J., & Kesner, R. P. (2002b). Role of the dorsomedial striatum in behavioral flexibility for response and visual cue discrimination learning. *Behavioral Neuroscience, 116,* 105–115.

Ragozzino, M. E., Kim, J., Hassert, D., Minniti, N., & Kiang, C. (2003). The contribution of the rat prelimbic-infralimbic areas to different forms of task switching. *Behavioral Neuroscience, 117,* 1054–1065.

Riceberg, J. S., & Shapiro, M. L. (2012). Reward stability determines the contribution of orbitofrontal cortex to adaptive behavior. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 32,* 16402–16409.

Ryan, L. J., & Sanders, D. J. (1994). Subthalamic nucleus and globus pallidus lesions alter activity in nigrothalamic neurons in rats. *Brain Research Bulletin, 34,* 19–26.

Schoenbaum, G., Nugent, S. L., Saddoris, M. P., & Setlow, B. (2002). Orbitofrontal lesions in rats impair reversal but not acquisition of go, no-go odor discriminations. *Neuroreport, 13,* 885–890.

Sesack, S. R., Deutch, A. Y., Roth, R. H., & Bunney, B. S. (1989). Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: An anterograde tract-tracing study with *Phaseolus vulgaris* leucoagglutinin. *The Journal of Comparative Neurology, 290,* 213–242.

Spencer, J. P., & Murphy, K. P. (2000a). Bi-directional changes in synaptic plasticity induced at corticostriatal synapses in vitro. *Experimental Brain Research. Experimentelle Hirnforschung. Experimentation Cerebrale, 135,* 497–503.

Stalnaker, T. A., Calhoon, G. G., Ogawa, M., Roesch, M. R., & Schoenbaum, G. (2012). Reward prediction error signaling in posterior dorsomedial striatum is action specific. *The Journal of Neuroscience, 32,* 10296–10305.

Stefani, M. R., Groth, K., & Moghaddam, B. (2003). Glutamate receptors in the rat medial prefrontal cortex regulate set-shifting ability. *Behavioral Neuroscience, 117,* 728–737.

Tai, L. H., Lee, A. M., Benavidez, N., Bonci, A., & Wilbrecht, L. (2012). Transient stimulation of distinct subpopulations of striatal neurons mimics changes in action value. *Nature Neuroscience, 15,* 1281–1289.

Uylings, H. B., & van Eden C. G. (1990). Qualitative and quantitative comparison of the prefrontal cortex in rat and in primates, including humans. *Progress in Brain Research, 85,* 31–62.

Vertes, R. P. (2004). Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse, 51,* 32–58.

Wise, S. P., Murray, E. A., & Gerfen, C. R. (1996). The frontal cortex-basal ganglia system in primates. *Critical Reviews in Neurobiology, 10,* 317–356.