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Neurophysiology of rule switching in the corticostriatal circuit

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Abstract

The ability to adjust behavioral responses to cues in a changing environment is crucial for survival. Activity in the medial Prefrontal Cortex (mPFC) is thought to both represent rules to guide behavior as well as detect and resolve conflicts between rules in changing contingencies. While lesion and pharmacological studies have supported a crucial role for mPFC in this type of set-shifting, an understanding of how mPFC represents current rules or detects and resolves conflict between different rules is still unclear. Meanwhile, medial dorsal striatum (mDS) receives major projections from mPFC and neural activity of mDS is closely linked to action selection, making the mDS a potential major player for enacting rule-guided action policies. However, exactly what is signaled by mPFC and how this impacts neural signals in mDS is not well known. In this review, we will summarize what is known about neural signals of rules and set shifting in both prefrontal cortex and dorsal striatum, as well as provide questions and directions for future experiments.

Keywords

Rule; set shift; prefrontal cortex; dorsal striatum; neurophysiology; corticostriatal circuit

Introduction

Our actions are governed by rules, allowing fast and efficient behavior without much cognitive effort. For example, while driving, walking or (sometimes) cycling, we stop at red lights and go at green lights without much thought to the actions needed to accomplish these tasks or the context in which we are acting. However, these learned general rules are not equally applicable in every situation, and we need to alter which rule we use depending on context (e.g., turning right on red or not driving on green if a pedestrian or vehicle is in front of you). In fact, rules guide most of our behaviors in everyday life, so much so that examples abound. For table settings, forks go to the left of the plate. When driving, we pass on the left. The selection of clothing for our day will vary with little effort depending on whether we are

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going to work, dinner with the boss or spending a day out on the range. While many experiences over the lifetime of an animal will remain consistent, environments and the interplay with conspecifics will require adaptability to changing situations.

Philosophically, this point may be best highlighted by the 5th century B.C.E. Greek philosopher Heraclitus, who posited a world constantly in flux and change with his famous ‘one cannot step in the same river twice’ quote (Plato and Reeve, 1998). This point highlights the fact that environmental and weather conditions change, along with the location and security of sources of food, water and mates. Perhaps having more foresight than he knew, Heraclitus touched on a hallmark behavioral trait common to most animals: the ability to modify learned responses when contingencies change. Importantly, we say ‘when’ contingencies change and not ‘if’, tacitly acknowledging the accuracy of Heraclitus’ insight, some 2500 years ago.

Over the past two decades, a wealth of research has indicated that the prefrontal cortex represents a crucial neural region for mediating flexible behavior (Bissonette and Powell, 2012, Bissonette et al., 2013, Hamilton and Brigman, 2015). Lesion (Dias et al., 1996b, a, Birrell and Brown, 2000, Colacicco et al., 2002, Bissonette et al., 2008, Roy et al., 2010), inactivation and pharmacological manipulations (Stefani et al., 2003, Floresco et al., 2006, Darrah et al., 2008, Floresco et al., 2008), genetic perturbations (Brigman et al., 2013, Bissonette et al., 2014, Marquardt et al., 2014) and recently optogenetic work (Cho et al., 2015) have all identified prefrontal cortical regions – specifically the medial PFC (mPFC) – as important for aspects of shifting between behavioral responses across many animal models, including mice, rats, non-human primates and humans. Together, this body of research suggests that prefrontal cortical regions are important for detecting when a previous response was not correct, and for initiating either a switch to another known response plan or for signaling the need to search for a new type of response. This system was considered important for mediating complex rule-based responding, and was possibly involved in actively directing action plans and responses to comply with whatever the current ‘rule’ is, however data which will be discussed below suggests this idea may be a bit too simplistic.

Once rules are identified, they need to be translated into actions to have any impact. Literature has shown a role for other brain areas in mediating rule shifts (Stelzel et al., 2010, Markett et al., 2011, Rodgers and DeWeese, 2014, Bissonette and Roesch, 2015c) in addition to PFC. Presumably, mPFC must convey rule signals to basal ganglia so that new action policies can go into effect thereby promoting efficient behavior. The mPFC has robust projections to medial dorsal striatum (mDS), constituting 15% of all mPFC efferent projections (Gabbott et al., 2005). The mDS is known to encode the relationships between stimuli and responses, the direction of impending movements, and the associations between response and outcomes (Ragozzino et al., 2002, Pasupathy and Miller, 2005, Balleine et al., 2007, Balleine et al., 2009, Kimchi and Laubach, 2009, Balleine and O’Doherty, 2010, van der Meer et al., 2010, Hilario et al., 2012, Bissonette and Roesch, 2015b). Recently, these mPFC projections to striatal striosomes has been manipulated optogenetically, demonstrating a causal role for cortical – especially mPFC – projections to striatum influencing cost-benefit decision making (Friedman et al., 2015). While mPFC function is thought to be more cognitive, medial dorsal striatum (mDS) is closely tied to the motor

system, and action selection in mDS is thought to occur under the guidance of mPFC. Experimental and modelling data suggest a role for mDS in maintaining a novel response pattern after a rule shift (Cools, 2011, Collins and Frank, 2013, Baker and Ragozzino, 2014). Nevertheless, it is unknown whether neural correlates in mDS are dependent on mPFC for maintenance of rule guided behavior, or even if communication between mPFC and mDS is required for shifting between rule-based response strategies.

In vivo recordings from animals performing tasks requiring flexible behavior provide the opportunity to view the individual contributions of neurons to the functions suggested above by lesion and inactivation studies. Well timed and controlled behavioral studies allow neural data to be effectively parsed and can identify common neural correlates of cognition across animal models. The best behavioral task should have the capability to fully counterbalance behavioral responses, such that one particular movement is not always associated with a single rule. The activity of an individual neuron should be analyzed for the nature of the response, working memory (depending on the particular task), learning and rule effects to eliminate potential confounds. Ideally a behavioral task should use an ABA format, forcing animals to switching back and forth between rules within one recording session, but this is often impractical due to satiety. One way deal with this issue is to embrace recent technological developments and ‘big data’, deploying large scale electrophysiological or optical Calcium imaging systems in conjunction with advanced statistical analyses. In this way, moment-to-moment fluctuations in single neuron activity reflecting other internal processes than the trial at hand, may be accounted for in statistical processing of large populations of simultaneously recorded neurons (Cunningham and Yu, 2014).

When examining activity related to rule shifting, it is important that we define what ‘rule encoding’ might look like from a neurophysiological perspective and how behavioral tasks may isolate such a complex phenomenon for electrophysiological analysis. If rules guiding behavior are known to the animal, prospective encoding should be observed since neurons should be ‘predicting’ or signaling the type or category of information that is likely to be presented while an animal engages with the task (Fuster and Bressler, 2015). Prospective encoding should develop as animals learn which rules, and therefore planned actions, are appropriate by rule block. Preceding prospective coding, however, should be retrospective coding, where feedback from immediately preceding decisions influences neural computation of sampled stimulus properties. These two forms of coding should work together, with retrospective coding providing the feedback signal that neurons can use to develop predictions and to develop prospective coding. Both signals may be critical for shifting between rules, where the recollection of previous stimulus properties and the success of a previous choice inform upcoming response options. Such signals have been observed in striatum (Kim et al., 2007, Goldstein et al., 2012, Kim et al., 2013) and prefrontal cortex (Genovesio et al., 2006 (Genovesio and Ferraina, 2014) (Bissonette and Roesch, 2015a) and will be discussed below.

Below, we provide a comprehensive review the neurophysiological data for animals performing rule shifting tasks in prefrontal and striatal systems, identifying common correlates, highlighting differences in interpretations and suggesting important future directions.

Neurophysiology of rule shifting in the Prefrontal Cortex

Groundbreaking electrophysiological work in the late 1990's had demonstrated that activity in single units in primate PFC reflected particular abstract rules(Asaad et al., 1998, White and Wise, 1999). Wallis, Anderson and Miller (2001) then demonstrated that neural correlates of rules were evident in dorsolateral prefrontal cortex (DLPFC) during cue sampling, but were also evident in Orbitofrontal Cortex (OFC) and ventrolateral PFC (VLPFC) during a delay epoch(Wallis et al., 2001). These landmark studies used visual stimuli with task rules which somewhat differed between experiments. Some tasks required switching between a spatial rule (i.e., always saccade to a particular direction) vs a cued or conditional rule (i.e. saccade towards the direction of a particular visual cue)(White and Wise, 1999). Other studies also used visual stimuli but required monkeys to either hold or release a lever, depending on whether a visual stimulus either matched or differed from a previous visual stimulus(Wallis et al., 2001, Wallis and Miller, 2003). While neural correlates of rules were observed in several PFC locations, the preponderance of rule signaling neurons was located within the DLPFC. This work was followed by further single unit studies in monkeys identifying clear correlations with rule-based decision-making and stimulus categorization(Wallis and Miller, 2003) and showing that activity of neurons in primate PFC anticipate upcoming rules and possibly use this information to guide choice selection(Yamada et al., 2010), which supported a role for prospective encoding. Additionally, experiments using visual stimuli that blended aspects of cats and dogs into two separate categories and asked monkeys to switch between rules (i.e., distinguish between cat 1 and cat 2, and dog 1 and dog 2, or distinguish whether the stimuli is more cat-like than dog-like, and vice versa) supported a role for multiple, separate neural ensembles simultaneously representing categorization of rules (Roy et al., 2010). These results were bolstered by experiments using both visual and auditory cues in different sequences to represent separate categories of response strategies for competing rules (Pan and Sakagami, 2012). Indeed, neurons in primate PFC are capable of representing multiple, independent categories (i.e., 'dog' vs 'cat' and 'cat 1' vs 'cat 2', as in the example above) and neurons which reflected both categories (for example, preference for 'cat' over dog, and 'cat 1' over 'cat 2') had the strongest neural signature of category or rule-based associations(Cromer et al., 2010).

Recently, it has been shown using a task where primates either held or released a lever depending on whether a visual stimulus could be categorized as 'greater than' or 'less than' a sample stimulus of a quantity of dots that activation of different dopamine receptors in primate PFC can differentially modulate rule encoding, where D1 receptor activation increases signal to noise for neurons representing preferred rule activity, while D2 receptor activation decreases signal to noise for neurons representing a non-preferred or non-current rule(Ott et al., 2014). Taken together, this body of work has been able to identify neural correlates of rules in non-human primate PFC and has shown how these neural correlates pertain to a particular rule mostly when the rule represents a correct response option.

While identifying neural correlates of rules in PFC was important, it was necessary to identify how these rule representations are used to assist in shifting behavior. The aforementioned dopamine receptor study provides some information regarding how a shift in

rule-guided behavior may take place, however there are several questions which remain. Specifically, how are rules learned by the PFC, and how are they adjusted when contingencies change? By performing dual-location single neuron recordings, Antzoulatos and Miller (2011) demonstrated that learning of Stimulus-Response (SR) correlates occurs earlier in primate striatum than DLPFC (Antzoulatos and Miller, 2011). However, activity shifts within DLPFC better predicted behavior during rule shifts related to category learning, compared to than SR learning, which were better predicted by striatal activity. These data suggest that DLPFC is necessary for holding current and abstract rules online in order to better guide response selection, while the striatum may be more essential for directing behavior following SR associations. This idea of the striatal involvement is consistent with previous literature (Miller and Cohen, 2001, Bunge et al., 2003, Wallis and Miller, 2003, Histed et al., 2009, Cromer et al., 2010, Pan and Sakagami, 2012), though some recent work to be discussed below suggests the role of striatum in shifting rule-based strategies may be more complicated.

Much of the rodent literature has mirrored the primate work, focusing on prefrontal recordings during tasks requiring flexible behavior and the shifting between rule based response strategies. However, a primary difference between these experiments has been regarding the behavioral tasks. While primate work generally occurs in head fixed animals with an absolute minimum of movement artifacts, freely behaving animals are the method du jour when it comes to rat work. Multiple lines of evidence have highlighted the fact that, like in humans and non-human primates, rodent PFC is critical for shifting response strategies in rule-based tasks. A multitude of studies have demonstrated through lesions and pharmacological inactivations that rendering the mPFC inactive does not impair the initial learning of a response pattern or rule, but that shifting from the learned rule is impaired, as shown by perseverative responding towards the previous response direction in maze tasks, perseverative responding to odorants or digging material in digging tasks, or visual cues in touch-screen tasks (Dias et al., 1996b, a, Birrell and Brown, 2000, Colacicco et al., 2002, Stefani et al., 2003, Floresco et al., 2006, Block et al., 2007, Ragozzino, 2007, Bissonette et al., 2008, Darrah et al., 2008, Floresco et al., 2008, Roy et al., 2010, Brigman et al., 2013, Bissonette et al., 2014, Marquardt et al., 2014, Cho et al., 2015, Troudet et al., 2015). Together, these behavioral data support a role for rodent mPFC in detecting and shifting behavioral responses away from ineffective strategies towards new, more successful ones when contingencies change.

Neural activity in rat mPFC has been correlated with a variety of behaviors. Neurons in mPFC have been observed encoding expected value, action selection, stimulus-response associations, time estimation, maintaining information across delays, encoding correct and incorrect responses, signaling reward-related feedback and are known to be spatially selective (Nieder et al., 2002, Horst and Laubach, 2009, Narayanan and Laubach, 2009, Balleine and O'Doherty, 2010, Horst and Laubach, 2012, Laubach et al., 2015). Neural ensemble firing in mPFC reflects distinct active states during set-shifting, which is temporally related to behavioral performance (Durstewitz et al., 2010). Rule related activity in mPFC before auditory cues has been linked with improved auditory discrimination performance (Rodgers and DeWeese, 2014), again supporting a top-down control model, with PFC as the main executive. Meanwhile, separate subregions of mPFC, the prelimbic

cortex (plPFC) and infralimbic cortex (ilPFC) appear to perform different roles in rule learning. Lesions and *in vivo* neural recordings suggest that plPFC is important to initially encode the learning of the rule while rule activity of neurons in ilPFC develops slower than neurons in plPFC and ilPFC is more important for inhibiting previous response patterns (Rich and Shapiro, 2009, Oualian and Gisquet-Verrier, 2010).

Recently, Bissonette and Roesch (2015) used a behavioral task akin to those used in primate studies to address the question of how neurons in mPFC encode rules during rule switches and how these signals relate to feedback (Bissonette and Roesch, 2015a). In this case, rats were trained to nosepoke and hold their head in a central odor port for 500ms before receiving 500ms of cue information. Rats then responded to a left or right fluid well, and held their heads in the fluid well for 1000ms before receipt of reward. Animals switched daily from either an odor guided strategy to a light guided strategy, or vice versa and completed many switches over many days while activity of single neurons was recorded. Direction light and odor information were independently randomized. This meant that on 50% of trials animals received compatible information where both cues instructed the rat of the same response direction (right light and right odor, or left light and left odor) and 50% of trials the cues instructed the rat of incompatible directions, where rule information would be in conflict (right light, left odor, or left light, right odor). In this way, response direction, cue identity, rule identity, pre-cue anticipation, cue activity, reward anticipation and reward outcome activity could all be dissociated along precise timescales (Figure 1).

The results replicate much of the non-human primate findings in rodent. Neuron correlates of particular rules were observed, similar to those observed in primates (Wallis et al., 2001, Muhammad et al., 2006) (Figure 2A). Of the 245 single neurons identified, 79 neurons, representing 73% of all task-modulated neurons, fired more for one 'preferred' rule over another. Activity in the pre-cue epoch for a preferred rule was observed, comparable to previous primate findings (Yamada et al., 2010). Additionally, the strength of rule activity increased as animals discerned what the appropriate rule block was and behavior improved but then decreased, suggesting a role for mPFC rule neurons in both maintaining a representation of a preferred rule but also in signaling a shift to other downstream areas. By looking at early (first two correct trials), middle (next eight correct trials) and late (last ten correct) trials for both the neuron's preferred and non-preferred rule blocks, two differences were observed. Over the course of the rule block, activity in the pre-cue epoch increased in the preferred rule by the middle trials, compared to early trials and remained elevated through the end of the block, demonstrating a development of prospective rule encoding for one rule over another. Additionally, neural activity for the preferred rule decreased by the late trials, compared to middle trials, suggesting that rule encoding neurons in mPFC are important for identifying the appropriate rule block, but that this rule information may be passed on to other neural areas who maintain this representation for longer times. Importantly, this activity seemed to be critical for accurate performance in that, when cue-related firing was weak, rats tended to make more mistakes.

It is clear from these results that signaling a rule *prior* to the decision is a critical feature of mPFC firing, however in the same cells; we also observed activity related to feedback *after* the response was made. These neurons significantly increased firing after correct responses

during reward delivery (Figure 2A) and significantly decreased firing after errant responses. Remarkably, the decrease in firing after errant decision was present not only at the time that reward would have been delivered if correct, but also immediately upon the first sign that it was a poor decision (houselights off). In addition to carrying information about whether the previous response was correct or incorrect, these neurons re-encoded the rule being followed at the time of reward delivery. Thus, at the time of feedback, these neurons encoded whether or not reward was delivered, and what rule was in effect. These signals are likely critical for assigning the correct rule context during set-shifting.

Interestingly, these ‘rule’ neurons, carried no information about the nature of the response (i.e., whether the animals was to move left or right). Instead, we found a separate population of neurons that were modulated by the impending response during cue sampling ($n = 29$, 27% of task-related neurons). However, on top of this ‘directional’ signal, we found higher firing on high conflict trials (Figure 2B) ($n = 28$, 10% of task-related neurons). High conflict trials are incompatible trials (red) during which the two rules are competing with each other. That is, one rule instructs go left, whereas the competing, irrelevant stimulus signals go right, or vice versa. In this subset of neurons, firing was significantly higher on incompatible (high conflict) trials compared to compatible (low conflict) trials. Thus it appears that these neurons are ‘detecting’ or ‘monitoring’ direction response conflict.

Like the rule neurons, mPFC direction neurons exhibited phasic changes in activity after the decision during the feedback phase, demonstrating significant increases in activity to rewarded outcomes and significant decreases after errors. In addition, these neurons also encoded how much conflict was present during the subsequent decision and what the decision was (i.e., left or right). Thus, these neurons not only informed the rest of the brain that there was conflict in the decision at hand, but how conflicted the animal was in the decision that was made (Figure 2B). This is interesting, because once reward was delivered, there was no conflict remaining. This feedback signal is likely important in signaling the nature of the previous decision, whether it was successful or not, and how difficult this decision was so that resources can be correctly allocated during future decisions.

It is unknown exactly how proposed brain areas monitor conflict between two competing responses. However, it has been suggested that monitoring conflict requires input from the competing sources, in this case, left and right output neurons. With this information the brain area can monitor simultaneous activation of upstream neurons (Cohen et al., 2000, Botvinick et al., 2001, Cole et al., 2009). The data described above suggest conflict encoding mPFC neurons can impact behavior in two ways. First, during the actual decision, elevated firing of conflict neurons might enhance activation of downstream areas to promote correct responding before the errant response occurs. Second, we found that these very same neurons encode the direction and the degree of conflict associated with the previous response during the feedback phase. Thus, these neurons can inform the circuit that the response just made was performed under conflict and led to reward. Such a signal might impact the strength of appropriate S-R associations directly in mDS or generally improve behavior by enhancing attention.

In conclusion, these data show the existence of two type of processing in mPFC during rule-shifting. One type signals rules during decision-making with activity that is correlated with behavioral performance and provides feedback information related to accuracy the rule currently being followed and a second population that signals the degree of conflict on challenging incompatible trial-types both during and after decisions. The former is likely involved in shifting rules when there are violations in contingences, whereas the later neural signals integrate the need for elevated attention during and after conflicted decisions.

To date, there has been very limited use of mice for the study of rule encoding, as most research has used some form of disruption of tissue and circuit to test hypotheses (Birrell and Brown, 2000, Bissonette et al., 2008, Brigman et al., 2013, Bissonette et al., 2014). *in vivo* neural recording activity in tasks requiring mice to learn rules and shift are somewhat limited (Bissonette et al., 2015, Cho et al., 2015) and available behavioral tasks might be better suited for EEG or LFP experiments. Continuing to develop mouse task homologs comparable to non-human primate in the context of behavioral neurophysiology will be necessary to determine the impact which genetic manipulations have on neural mechanisms related to rule shifting and how it might be disrupted in animal models of psychiatric dysfunction.

Neurophysiology of rule shifting in the Striatum

While rule signals in the PFC are clearly important for the shifting of behavior, other downstream areas must be using this information to make behavioral adjustments. The dorsal striatum receives major projections from the PFC, and has been identified as critical for assisting in flexible behavior, goal-directed behaviors and associations between actions and outcomes. Here we summarize what is known about the functional neurophysiology of the striatum for encoding rules and shifting behavior when contingencies change.

Work has shown that PFC also encodes the specific identity of cues, while recordings in the striatum have shown some evidence of rule encoding, but limited activity reflecting specific identity of cues (Muhammad et al., 2006). Indeed, recording data from the striatum suggests that the onset of learning new associations in striatum precedes PFC in some instances (Pasupathy and Miller, 2005) and that this striatal activity may be critical to sustaining associations between previously correct decisions, overtime culminating in successful learning (Histed et al., 2009). Interestingly, neural signals related to associative learning took place quicker in the striatum than PFC, suggesting that signals of rewarded actions may first originate in striatum, before being identified and encoded by PFC (Pasupathy and Miller, 2005). These data suggest that striatal signaling of correct responses and outcomes is important for PFC to 'learn' to associate and group sets of responses under a particular rule. If this is true, then the role of striatum remains that of a more simplistic associative structure, under the direction of executive cortical areas. Some recent data, however, has complicated this interpretation.

A large body of work has identified a critical role for the medial dorsal striatum (mDS) in mediating flexible behavior (Ragozzino, 2002, Ragozzino et al., 2002, Stefani and Moghaddam, 2006, Ragozzino, 2007, McDonald et al., 2008, Castane et al., 2010, Baker

and Ragozzino, 2014) and in reward and decision-making (Yin et al., 2005, Balleine et al., 2007, Balleine et al., 2009) while also highlighting how similar the functions of this corticostriatal circuit are between humans and rodents (Balleine and O'Doherty, 2010). Specifically, several studies have investigated shifting between rule based strategies rather than other forms of flexible behavior (Stefani and Moghaddam, 2006, Block et al., 2007, Lindgren et al., 2013, Baker and Ragozzino, 2014). Lesions and pharmacological inactivation of mDS led to set shifting impairments, though the impairment was different than those observed with mPFC inactivations. Without a functioning mDS, rats demonstrated impairment in the formation of sets and the maintenance of new sets when shifts in responses were required (Lindgren et al., 2013, Bissonette and Roesch, 2015c). Recent work has even uncovered a critical role for cholinergic interneurons of the medial and ventral striatum in shifting between rule based responses in the rat (Aoki et al., 2015) and ventral striatal neurons showing outcome representations while animals learn new tasks (Atallah et al., 2014). However, our understanding of how dorsal striatum presumably uses and interprets signals from PFC about how and when to shift between rule based response strategies is very limited. This represents an unfortunate gap in our knowledge, as the dorsal striatum has recently been identified as a source of impairment in shifting between rule based responding in patients with Autism Spectrum Disorder (Miller et al., 2014), schizophrenia (Waltz et al., 2007, Morris et al., 2015) and in patients and animal models of Parkinson's disease (Gauntlett-Gilbert et al., 1999, Monchi et al., 2004, Floresco et al., 2006, Floresco et al., 2008, Price et al., 2009, Aarts et al., 2010, Cools, 2011, Dirnberger and Jahanshahi, 2013, Florio et al., 2013, Robbins and Cools, 2014).

As a first step to addressing this question, Bissonette and Roesch (2015) recorded from individual neurons in dorsal medial striatum of rats performing the rule-shifting task described above, to determine what is being encoded in mDS (Bissonette and Roesch, 2015c). Is mDS simply an associative structure that just carries information about the direction of the response and the stimuli that preceded it or is activity in mDS modulated by the rules that are governing behavior?

It is already well known that dorsal striatum plays an important role in signaling response directions for impending movements. Indeed, we found a population of neurons ($n = 29$, 16% of all task-related neurons) that was modulated by response direction (i.e., fired more strongly in for one response direction). In addition, and like we observed in mPFC, we found that activity of these neurons was also modulated by the degree of conflict during cue sampling. However, these neurons were not detecting or monitoring conflict as in mPFC, but exhibited reduced directional signals as a result of the response conflict. For example, if a neuron that signaled 'right' fired strongly when the two cues were in agreement (i.e., odor and light signal right), firing was reduced when the two cues were in disagreement (e.g., odor signals right and light signals left). This conflicted directional signal did not change over time or by rule block, and remained invariant throughout the task (Bissonette and Roesch, 2015c). These neurons are likely to be tightly linked to motor output, which is impacted by presence of conflict throughout the recording session.

Surprisingly, and much like mPFC, the firing of many mDS neurons ($n = 126$, 69% of all task-related neurons) was selective for the rule independent of other factors. As with mPFC,

the rule signal in these neurons even preceded the onset of the cue presentation (Fig. 2C), reflecting activity in a similar pattern to previous primate PFC work (Yamada et al., 2010) and even fMRI work in humans (Boettiger and D'Esposito, 2005) but also in human fMRI work regarding the role of striatum in rule-based learning and performance (Cools et al., 2004, Seger and Cincotta, 2006). mDS rule neurons robustly signaling one rule over another, significantly increasing firing for one rule block but not increasing activity for the other. Rule neurons also showed a dynamic firing pattern, increasing in activity from early to late within the preferred rule block as described for mPFC (Figure 2c). This increase in firing significantly preceded when rats behaviorally reached criterion by many trials, suggesting that as rule signals in the dorsal striatum grow in strength, animals begin to shift their selection of responses reflecting the new rule context.

Interestingly, a separate population of 'directional' neurons ($n = 29$, 15% of task-related neurons) showed a similar conflict directional signal, but only early in learning in one particular rule block (Figure 2D). The firing of these neurons was correlated with improved behavioral performance, demonstrating that when activity more accurately reflected the current rule in mDS, rats were better at resolving conflict and abiding by relevant rule. It is possible that the resolution of directional conflict in later trials (Fig. 2E) represented a neural mechanism by which rule signals influence direction selection in the context of a changing rule, and thus mediates improved action selection leading to flexible behavior. Notably, this type of neuron was not present in mPFC, thus the integration of rule and response direction at the single unit level might be a critical function of mDS. Indeed, inactivation of mDS in our task disrupted performance (Bissonette and Roesch, 2015c).

What, then, is the relationship between 'rule' neurons and 'response' neurons? In PFC, it appears that the role of rule neurons may be to detect changes in rules and broadcast this change. These neurons exhibited a change in firing rate very early in a rule block which increased activity for one rule over another, before settling back to baseline firing rates. By contrast, rule neurons in mDS more gradually ramp up activity for their preferred rule, maintaining this firing rate throughout the remainder of the block. These neurophysiological signals match predictions from lesion and inactivation literature, demonstrating the need for an intact mPFC in shifting rules and for intact mDS in maintaining shifted rule strategies. As the mDS rule neurons maintain the current rule policy, a separate population of neurons which integrate both rule and direction are impacted, resolving the direction conflict (Figure 2D,E) and leading to improved behavioral performance. As such, rule neurons appear to maintain the current rule policy, while the rule and direction neurons integrate current rule policies with preferred response directions, thus modify behavioral responding.

This data firmly suggests that the dorsal striatum may be the seat of maintenance of rules used to guide action selection, while PFC areas may be more critical in assisting the shift between strategies. This work is different from the rule shifting and rule learning work mentioned earlier where neural signals related to new rewarded associations developed first in striatum and later in PFC (Pasupathy and Miller, 2005). In this task, rats knew all particular associations well, but were required to shift between the learned rules. Still, it was surprising that a plurality of the task-related activity in rat striatum was related to either rules or integrated rule and direction information. The rule signal in mDS suggests that rule

information is stored here as a cache, supported by previous lesion data(Yin et al., 2005) and that mDS is not solely part of a tree system, searching for appropriate response strategies, as has been suggested(Daw et al., 2005). This is not to suggest that mDS is *solely* acting as a cache for rule signals and not functioning as part of a search tree, but to suggest that when animals switch between learned rule-guided actions, signals in mDS might represent the development of appropriate cache of updated rule information. Together this strongly supports a critical role for dorsal striatum in mediating action selection in rule-based tasks and these electrophysiological data support previous lesion and pharmacological work(Ragozzino et al., 2002, Block et al., 2007, Lindgren et al., 2013, Baker and Ragozzino, 2014, Aoki et al., 2015).

Medial DS is not the only striatal area critical for set-sifting. Both the lateral striatum and the ventral striatum are thought to be involved, but are underexplored regions in terms of the electrophysiological underpinnings of rule-based behaviors. Though dorsolateral striatum (IDS) is well known for its role in stimulus-response encoding, is directionally selective and important for motor and skill learning (Graybiel, 1997, 2008, Yin et al., 2009, Thorn et al., 2010, Yin, 2010, Santos et al., 2015), understanding how rule signals from mDS or PFC impact neural correlates in IDS remains unknown. Using a different task (visual touch screen reversal task), *in vivo* recordings in mice have demonstrated that neurons in IDS do modulate firing as animal performance improves. Indeed, both the neurophysiological activity and cell counts of c-fos positive neurons identify populations of IDS neurons which increase activity with learning(Brigman et al., 2013, DePoy et al., 2013). While not tested in the same set shifting context as previous studies, these data do support a possible role for IDS in maintaining new response strategies. Likewise, the role of VS in shifting rule based behavior is also understudied. While a role for dopamine in mediating shifting of affective sets is well documented(Stefani and Moghaddam, 2006, Floresco, 2007, Haluk and Floresco, 2009), how neural correlates in VS are impacted during rule shifting and how changes in dopaminergic signaling impact these correlates remains unknown. As mentioned above, extremely little is known about the role of mouse striatum encoding rules and mediating shifts between different rule based strategies. Given the developing trend of computational models implicating striatum in many aspects of cognition(Cools, 2011, Collins and Frank, 2013) and recent research of behavior from humans with psychiatric disorders such as Autism, Schizophrenia and Parkinson's disease(Miller et al., 2014) (Waltz et al., 2007, Robbins and Cools, 2014, Morris et al., 2015), developing appropriate behavioral tasks suitable for single unit recording in mice is critical to furthering our understanding of aberrant functional circuitry.

Neurophysiology of rule switching in the corticostriatal circuit

Formalizing these data into a more simplified model (Figure 3), we present a theoretical model based on these physiological data and aforementioned behavioral data. It portrays activation of mPFC (blue), mDS (green), and motor output neurons (black) on incompatible trials, during the first couple trials (A), several trials into (B) and late (C) into a set shift from the light rule to the odor rule. In this figure, the thickness of lines reflects the theoretical strength of activation of neurons. The trial type portrayed in this example is the condition where the odor signals left, but the light signals right. During the first couple trials

into the shift from light to odor rules (Fig. 3A), light rule encoding mDS neurons are still robustly active (i) and rule-direction light mDS encoding neurons (green box) still strongly encode for right movements (ii), thus animals tend to respond incorrectly (errant response to the right). Not receiving reward on error trials produces negative feedback to mPFC neurons (iii), which would subsequently weaken the influence that light rule neurons have on this circuit. During the next several trials (Fig 3B), rats begin to correctly respond by making a response in the leftward direction (i.e., following odor rule). During these trials, both light and odor rule and rule-direction neurons are activated (i-iv) simultaneously, resulted in both left and right output commands (v). This ‘response conflict’ is detected by ‘conflict’ neurons that compute both the degree of conflict and the direction of the response to strengthen leftward responding in downstream mDS neurons (vi). Meanwhile, odor-rule neurons in mPFC start to come online (vii), signaling the need for attention and the updated relevant rule. Combined, these two signals might directly impact mDS in order to immediately impact ongoing behavior, while downstream representations of rules in mDS are being updated (vii). Note, both mPFC rule and conflict neurons provide positive feedback when the trials is correct and, in addition, re-activate the rule and conflict information present during the decision period. These signals might modify weights to promote accurate rule representation and correct responding on future trials. After animals have shifted (i.e., late in the trial block; Fig. 3C), light-rule neurons are no longer activated in mDS, whereas mDS odor rule and odor rule-direction neurons are activated according to the new rule, thus leading to the correct leftward responses (Fig. 3Ci-iii).

The model above is based on the physiological data at hand, but clearly these are not the only brain areas involved. For example, correct dissociation of stimulus information is an important first step towards making any deliberative choice for action. Different regions of the thalamus: the mediodorsal nuclei of the thalamus (MD), the ventral midline thalamus and the anterior thalamus, have been shown to mediate some aspects of shifting attention to task relevant stimuli, which is a critical step in selecting the necessary rule to guide responding (Block et al., 2007, Cholvin et al., 2013, Wright et al., 2015). Indeed, the MD to ventral striatal pathway has been shown to be necessary for inhibiting inappropriate choices or strategies (Block et al., 2007) while both dopamine and glutamate mediated activation of NDMA receptors in ventral striatum has also been identified as playing a key role in shifting rules guiding behavioral response strategies (Haluk and Floresco, 2009, Ding et al., 2014). *in vivo* electrophysiological experiments dissecting out this circuit during set shifting tasks are needed to provide a better picture of how this complex circuit works. Good tasks controlling for many movement and behavioral aspects in rodents still need to be developed, to allow us to harness the untapped potential of mouse genetic models. Judicious use of optogenetic experiments will also play an important role in future experiments, investigating the precise timing and role of particular cell types within the cortico-striatal circuit.

Future directions

Little is known about the role that prediction errors may play in updating rule encoding. Typical experiments do not have the necessary temporal resolution paired with *in vivo* electrophysiology to discern the role that dopamine and prediction error signals may play in rule shifting. Human work shows a critical role for dopamine in functional connectivity

between frontal and striatal systems(Nagano-Saito et al., 2008). Powerful future approaches may involve *in vivo* Ca++ imaging of large populations of cortical neurons. Further, identifying the respective roles of more precise cortical regions like the anterior cingulate cortex, prelimbic and infralimbic cortices will be important to identify what regions are responsible for what aspects of shifting rule-guided behavior. There exists some tantalizing evidence supporting a potential dissociable role for prelimbic and infralimbic cortices in mediating different aspects of flexible behavior(Rich and Shapiro, 2007, Oualian and Gisquet-Verrier, 2010), but *in vivo* neurophysiological experiments in conjunction with optogenetic approaches will provide more conclusive evidence. Dopamine in VS is known to be critical for flexible behavior(Haluk and Floresco, 2009).

Recent theoretical work has suggested that all of these functions in mPFC and ACC -error detection, reward prediction errors and conflict monitoring - may reflect the same underlying process(Alexander and Brown, 2011). This work considers these signals to be part of a generalized surprise/attention system. In each of these cases, activity in mPFC and ACC might reflect unexpected non-occurrence of an expected outcome. The activity caused by unexpected outcomes could explain why several studies have suggested that mPFC and ACC activity is high when there are violations in expectations(MacDonald et al., 2000, Paus, 2001, Brown and Braver, 2005, Totah et al., 2009). As identified above, very little animal physiological work has been conducted, addressing questions of neural signatures of rule-based behavior and switching.

Finally, determining exactly which of these neurophysiological signals are critical to shift and to maintain a shifted response pattern is important. Optogenetic experiments targeting cell types in either prefrontal cortical or striatal regions will help tease apart the respective roles within this circuit. Thus, after decades of clever behavioral tests and experimental manipulations, we are at a technological point where we may be able to conclusively identify the origins of rules guiding behavior, and identify how these rules are signaled through the brain, ultimately being translated into movement and changed behavioral responding. Identifying these sorts of signals is important not only for basic knowledge and for interpreting how altered neurophysiology in various psychiatric or neurological situations leads to impaired adaptability, but also for fields such as neuroprosthetics and robotics. Heraclitus had the philosophical foresight to recognize that the world is in a state of constant change and modern neuroscience finally has the tools to determine exactly how we navigate this changing world.

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Highlights

- Prefrontal cortical neurons encode rules and signal rule changes
- Prefrontal cortical neurons monitor direction and conflict
- Dorsal striatal neurons signal rule policies
- Dorsal striatal rule policies resolve conflict and improve behavioral performance

Figure 1. Behavior timing schematic and breakdown of trial-types (A) Schematic of odor port, fluid wells and directional cues as well as flow chart with timing of a successful trial. (B) Examples of trial-types and response types, demonstrating compatible and incompatible trials with directional information presented by both cues and demonstrating the controlled, counterbalanced nature of the task timing and rule presentation.

Figure 2.

Circuit diagram, suggesting how neural signals of rules and conflict mPFC and mDS may lead to flexible behavior, using real neural data from previous research. (A) mPFC rule neurons detect the necessary rule and signals this (green vs gray lines) to mDS which develops and maintains the appropriate rule signal (difference between green dashed and green solid line) as mPFC decreases signaling of this rule. Meanwhile, mPFC neurons detect directional conflict (difference between red and blue lines) (B) and signal this to both mPFC rule neurons and mDS. Both sets of mPFC neurons use trial feedback to either bolster or weaken neural support for previous actions. Once mDS rule neurons (C) have encoded the new rule policy, local rule policy signals combined with attention signals from mPFC on conflict trials are used to resolve directional conflict as observed in mDS direction neurons (directional conflict illustrated by the difference between thick blue and thick red lines in D, and no difference in E) (D,E). As this conflicted directional signal is resolved, behavioral performance improves in the new rule contingency, demonstrating a neural mechanism for flexible behavior. Neural data shown is from populations of single neurons identified through a multiple linear regression modelling of firing rates during the cue epoch. Data is aligned to cue onset to show firing rates during pre-cue and cue epochs. While not aligned to reward delivery, feedback for correct responses is still visible ~2.5s out from cue-onset (for precise alignment and analysis, please see (Bissonette and Roesch, 2015c, Bissonette and Roesch, 2015a)).

Figure 3.

Theoretical model of how this corticostriatal circuit performs during a shift in rules. (A) In the first few trials after a rule shift, striatal rule neurons (i) and rule-direction neurons (ii) still signal the previous rule, leading to behavioral errors which provide error feedback (iii) onto mPFC conflict and rule neurons. (B) After several trials, rule neurons in striatum increase firing for the new rule (i) and begin to decrease firing for the old rule (ii), leading to improved action selection (iii-v). Correct responses provide positive feedback to mPFC conflict (vi) and rule (vii) neurons, which more strongly signal the new rule and conflict. (C) Later in the new rule block, the system stabilizes where striatal odor rule neurons (i), not light rule neurons, provide appropriate signals to rule-direction neurons (ii) which signal the correct response (iii) even on challenging conflict trials, leading to positive feedback and a continuation of this response pattern.