input from each of these inputs is sufficient to support reward-related behaviors. An important caveat to note for nearly all optogenetic studies published to date is that the use of cylindrical optical fibers with blunt-cut tips creates a relatively narrow and small cone of light that may not capture all of the axon terminals expressing ChR2—particularly in large structures such as the NAc, which is organized spherically rather than cylindrically. Here, Britt et al. (2012) looked only at the medial shell of the NAc, but other recent studies in the NAc core or lateral shell could have different effects, as recently suggested (Lammel et al., 2012). Another possibility raised by Lammel and colleagues is that multiple distinct experiential qualities could support ICSS, including salience, alertness, motivation, and hedonic pleasure in addition to general reward and reinforcement (Lammel et al., 2011). It would also be interesting to characterize the ultrastructural organization across the NAc of axonal terminals arriving from the vHipp, PFC, and Amyg—how often do these axon terminals synapse onto the same cell, and how are these interactions assembled (axoaxonal synapses, on the same dendritic arbor, etc.)?

To conclude, even with the recent flood of insights toward causal relationships between the brain and behavior facilitated by optogenetic approaches (Tye and Deisseroth, 2012), there is still much to do. The paper from Britt et al. (2012) in this issue of *Neuron* makes an important contribution to the field by providing multiple new insights, raising provocative new questions, and opening the floodgates even wider than before to invite more research in this exciting new arena of systems neuroscience.

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Rules Got Rhythm

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Intelligent agents must select and apply rules to accomplish their goals. In this issue of *Neuron*, Buschman et al. (2012) demonstrate that oscillatory neuronal coupling is key to rule processing in monkey prefrontal cortex, notably when rules change during tasks.

Our lives are governed by rules. Whether we are engaged in sports, school, traffic, shopping, or work, it is necessary to know "the rules of the game." Knowledge of rules is indispensable in projecting the consequences of our actions and predicting which action may help us achieve a particular goal (Miller and Cohen, 2001; Bunge, 2004).

The concept of a "rule" refers to a learned association between a stimulus (e.g., a red traffic light) and a response (stopping the car) that can guide appropriate behaviors. A typical feature of rules is that the mapping between stimulus and action is context dependent—a yellow traffic light may suggest pressing the brakes or the gas, depending on other contextual signals (Miller and Cohen, 2001). Of critical importance in real-life environments is the ability to flexibly switch between rules. A change of rules can dictate that the same stimulus warrants a different course of action than it did a few minutes before (e.g., either filling or cleaning your favorite coffee mug).

For over a decade, neuroscientists have been unravelling the neural mechanisms underlying rules. Studies in monkeys investigating single-cell activity in tasks involving variable stimulus-response mappings demonstrate rule-specific firing rate changes of neurons in prefrontal cortex (PFC) (White and Wise, 1999; Wallis et al., 2001). Neurons encoding generalized, rule-like stimulus-response mappings have also been recorded in other brain structures, such as premotor areas, inferior temporal cortex, or basal ganglia (Muhammad et al., 2006). In humans, rule following and task switching are the subject of numerous fMRI studies, which demonstrate that rule processing involves not only PFC, but also a distributed network of brain regions (Bunge, 2004; Reverberi et al., 2012). The PFC interacts with temporal cortex and striatum during learning of novel rules, while maintenance and application requires frontoparietal networks and premotor and supplementary motor areas. Moreover, monitoring of rule use involves anterior cingulate cortex (ACC).

A model of cognitive control was first postulated more than a decade ago (Miller and Cohen, 2001). Neurons in PFC encode information about goals and appropriate actions leading to these goals. PFC exerts top-down control by sending signals to other areas that bias processing toward task-relevant information. These signals modulate numerous target areas, thus biasing the selection of sensory inputs, memory content, or behavioral responses. A key function of these signals is to enable neural pathways such that the proper mappings between stimuli and responses are established, leading to implementation of the appropriate rule (Miller and Cohen, 2001). This classical picture, however, leaves some questions unresolved. It is not clear how neurons encoding the same rule are dynamically linked. Coactivation of multiple rules in the same network is difficult to envisage, because the model does not specify how specific mappings between neurons related to one rule can be established in the presence of other signals that are part of competing rules. Furthermore, it is not clear how the appropriate rule can be selected from a larger repertoire of learned contingencies in a context-dependent and flexible manner. Moreover, a combinatorial code for rule-related information would be useful, allowing flexible reorganization of neural populations for implementation of novel rules. Finally, and most importantly, the application of rules for the control of goal-directed behavior requires the orchestration of activity between numerous brain regions, so flexible communication is required. These considerations suggest that rule processing presupposes a mechanism for dynamic linking of signals across neuronal populations.

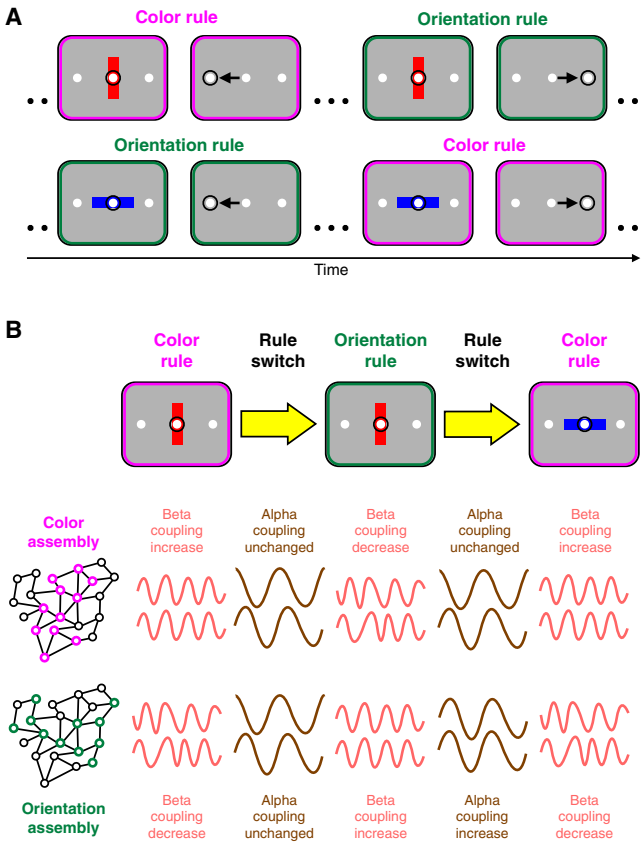

Figure 1. Rule-Specific Neural Synchrony in Monkey PFC
(A) Monkeys engaged in a visuomotor task, switching between different stimulus-response mappings. White dots indicate the fixation spot (middle) and two saccade targets. The circle represents the monkey's eye position. The rule was cued by the colored border of the visual display. In color rule trials, red stimuli were associated with leftward and blue stimuli with rightward saccades. In orientation rule trials, the monkey had to respond to horizontal stimuli with leftward, and to vertical stimuli with rightward, eye movements.
(B) Rule-dependent assembly dynamics. Based on the strength of beta-band LFP coherence, two partially overlapping assemblies were identified (left). Each assembly showed rule selectivity in beta-band coupling, which increased during application of its preferred rule but decreased when the non-preferred rule had to be used. In addition, the orientation assembly showed increased alpha-band coupling during switches away from its preferred rule. This was not observed for the color assembly.

Existing evidence strongly suggests that coupling of oscillatory signals can establish such dynamic and context-dependent links (Singer, 1999; Fries, 2005; Engel and Fries, 2010; Siegel et al., 2012). Oscillations provide an effective means to control the timing of neuronal firing and can mediate information transfer across brain regions if the oscillatory signals are synchronized (i.e., peaks and troughs are temporally aligned). With weak synchronization, functional coupling effectively shuts down and communication is blocked (Fries, 2005; Siegel et al., 2012).

In this issue of *Neuron*, Buschman et al. (2012) provide evidence that synchrony of neural oscillations is relevant for the encoding and maintenance of rules in monkey PFC. Macaque monkeys were trained to switch between two rules in a visuomotor task in which they obtained a juice reward (Figure 1). A visual stimulus was presented centrally; it was oriented either vertically or horizontally and was either red or blue. The animal responded by making a saccade to a target left or right of the fixation spot. Importantly, the mapping between the stimulus and the appropriate response (i.e., the current rule) varied across different trials (Figure 1A). In each

trial, the rule that the monkey needed to apply was signaled by a cue (the color of the border around the stimulus display). In one set of trials, the monkey had to judge the color of the stimulus and respond with a leftward saccade to a red stimulus but a rightward eye movement to a blue stimulus. In the other set of trials, the orientation of the stimulus was task relevant, and the color had to be ignored. A vertical stimulus was associated with an eye movement to the right and a horizontal stimulus with a saccade to the left. The key point is that the visual stimuli do not uniquely determine the response required to obtain the reward—the monkeys needed to understand and apply the rules to pick the correct response. While the monkeys were performing this task, neuronal spike activity and local field potentials (LFPs), which reflect rhythmic activity in small populations around the electrode tip, were recorded from dorsolateral PFC. To quantify neural synchrony, Buschman et al. (2012) computed coherence among pairs of LFP recordings. In addition, the degree of coupling between individual cells and the LFP was quantified by computing spike-field synchrony.

Interestingly, LFP coherence showed rule-specific effects in two different frequency ranges: the beta and the alpha band (Figure 1B). While beta-band effects (around 20–30 Hz) occurred immediately after stimulus onset, alpha-band coherence changes (around 10 Hz) were maximal after presentation of the cue signaling the current rule. This suggests that the observed coherence changes were associated with rule selection. For most electrode pairs, beta-band LFP coherence was rule specific (i.e., stronger for either the orientation or the color rule). Based on this, two assemblies could be identified: color and orientation (Figure 1B). For each assembly, beta-band synchrony increased in trials in which the rule preferred by the neurons was applied. Interestingly, these two assemblies were not completely disjunct; there were local populations that could couple, albeit with different strength, into either assembly. In agreement, analysis of spike-field synchrony showed that the strength of coupling of individual cells into these two assemblies depended on the rule that applied. Thus, beta-band coupling of orientation-preferring cells to the LFP of the orientation assembly was stronger in orientation rule trials compared to color rule trials.

Buschman et al. (2012) conclude that rule-specific beta-band coupling can dynamically link neurons involved in processing the same rule. Enhanced beta-band synchrony may then be relevant for dynamically selecting the assembly that is currently task relevant.

Interestingly, orientation-specific cells showed higher alpha coherence when a switch to the color rule occurred, but color rule-specific cells did not increase alpha coherence during switches to the orientation rule (Figure 1B). Based on reaction times, the orientation rule was easier to apply for the animals and they had greater difficulty switching away from it, indicating behavioral dominance of the stimulus orientation. Buschman et al. (2012) suggest that enhanced alpha-band synchrony may be required for suppressing the behaviorally dominant orientation assembly if it is not task relevant, in agreement with past work on the role of alpha-band oscillations for inhibition of task-irrelevant processes (Jensen and Mazaheri, 2010).

The results of Buschman et al. (2012) open up a new perspective on the mechanisms of rule use and task switching by positing that rules are implemented by dynamic functional coupling in the PFC network. This suggests several extensions to the cognitive control model proposed by Miller and Cohen (2001). Rule application may be enabled by a change in dynamic coupling across PFC neurons, leading to selection of task-relevant—and suppression of irrelevant—assemblies. Rule maintenance could be mediated by sustained coherence in the task-relevant assembly. Bias signals might primarily modulate the timing of activity, rather than changing average activity levels in their target neurons, and they would selectively enhance synchrony between relevant sensory, memory, and motor populations. Overall, this updated version of the model fits nicely with previously established roles of coupled oscillations for communication and selection (Singer, 1999; Fries, 2005; Engel and Fries, 2010; Siegel et al., 2012).

This study is one of few to date that relates research on oscillations and neural coherence to that of higher-level cognitive processes. The data may cast new light on how to implement compositionality (i.e., the ability to form more complex expressions from elementary symbols using syntactic rules) (Reverberi et al., 2012; Maye and Engel, 2012).

A question not addressed in the new study is whether rule processing also involves changes in theta-band (4–8 Hz) or gamma-band (>30 Hz) oscillations, which are both known to occur in PFC and are relevant for communication of PFC with other brain regions (Womelsdorf et al., 2010; Benchenane et al., 2011). In monkeys, theta-band oscillations in the ACC exhibit rule-specific changes (Womelsdorf et al., 2010). Studies in rodents indicate changes in theta-band coherence between hippocampus and PFC during rule acquisition (Benchenane et al., 2011). Future studies need to clarify the potential role of gamma-band activity for rule use, which in paradigms like binocular rivalry or attention tasks are important for selection of task-relevant assemblies (Singer, 1999; Fries, 2005; Siegel et al., 2012).

To establish a complete picture of the role of oscillatory rhythms in rule processing, many aspects of the updated model of cognitive control (Miller and Cohen, 2001) still need to be tested. This includes the exact nature of the bias signals arising from PFC during rule application, as well as the presumed large-scale changes in coherence in the pathways enabled by these bias signals. An important question is whether similar rule selectivity of neural coherence can be observed in other relevant brain structures such as the basal ganglia. Last but not least, it is currently unresolved how bias signals arise in PFC (i.e., how the PFC network "knows" which rule to activate in a given action context). There is no "homunculus" steering the wheel, so the answer will most likely involve the self-organizing dynamics of frontal networks.

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