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Listening to the Crowd: Neuronal Ensembles Rule

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In this issue of *Neuron*, Durstewitz and colleagues show that neuronal populations in the medial prefrontal cortex (mPFC) of rats reflect abrupt changes in behavioral strategy as animals learn to act according to new rules in a rule-switching task.

In animal learning experiments, changes in performance are often seen as a gradual process, where new associations or rules are learned progressively over time by trial and error. However, humans often report specific moments of sudden insight, “a-ha!” moments, something that has long fascinated psychologists and others. Indeed, on closer examination, animal studies also reveal abrupt changes in performance, where learning appears to occur over one or just a few trials (Gallistel et al., 2004). It has been suggested that this phenomenon is actually quite common; the reason slow changes are often reported may be simply that performance is being estimated by averaging across trials and animals. This averaging inevitably smoothes out the true learning curves of individual animals. By applying appropriate statistical measures that provide a more sensitive measure of changes in a time series, abrupt changes in performance can sometimes be revealed (Gallistel et al., 2004; Suzuki and Brown, 2005).

While the fact of abrupt learning has gained acceptance as a behavioral phenomenon, the neural substrates un-

derlying such changes remain quite mysterious. Although some forms of synaptic plasticity can be induced in just a short period of high frequency stimulation, most theoretical models, such as reinforcement learning, usually rely on slow and gradual changes in synaptic connections to implement learning (Dayan and Abbott, 2001), suggesting that insight learning depends on features of neural circuits that are not accounted for in conventional models. A key step toward unraveling this conundrum would be to monitor the changes in circuit activity as abrupt learning takes place.

In the current issue of *Neuron*, Durstewitz and coworkers (2010) take a step in this direction, using state-of-the-art statistical analysis along with multielectrode recordings in rats performing a rule-learning task to show a correlation between rapid switches in behavioral performance and rapid switches in medial prefrontal cortex (mPFC) ensemble activity.

Durstewitz and colleagues (2010) trained rats on a “rule-switching” task (Figure 1A). In this task, first the subject must follow a “visual” rule in which the

light above a left or right lever signals where reward is available. Once good performance is achieved, the rule is switched to a “spatial” rule: now reward is delivered at one side only, independent of which light is on. In rats, this task is known to depend on an intact mPFC (Floresco et al., 2009) and is considered to be an analog of the Wisconsin card-sorting test, a task used to study response flexibility in humans. Rats acquired the new rule rapidly, with performance increasing abruptly in a few trials, as shown using change point analysis, consistent with the idea that animals go through an “a-ha!” moment when evidence is sufficient to change response rules.

To investigate the neural mechanisms that underlie abrupt rule switches, the authors recorded the activity of up to 16 mPFC neurons simultaneously during the performance of the rule-switching task. The neuronal correlates of associative learning have been studied previously at the single neuron level in several tasks and brain areas, particularly in nonhuman primates (Suzuki, 2008). In these studies, the firing of single neurons (e.g., Chen and Wise, 1996; Zach et al., 2008) or

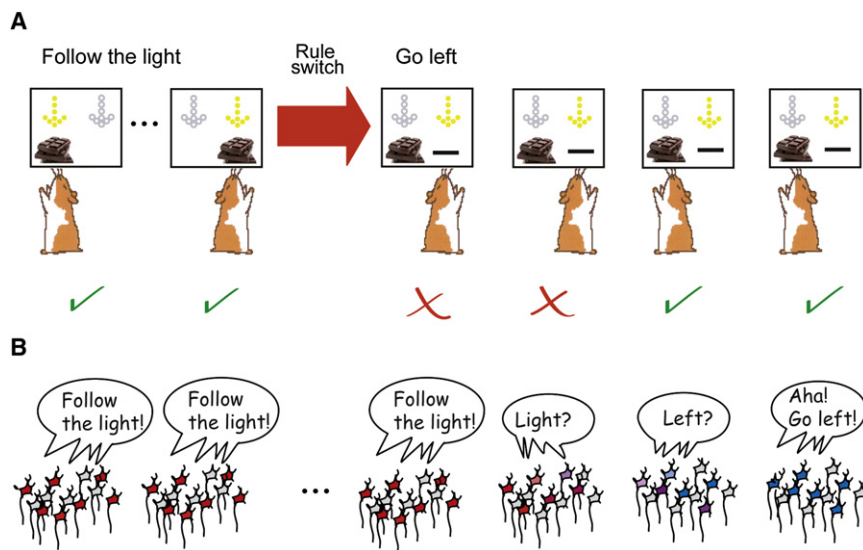


Figure 1. Neuronal Ensembles Differentiate between Rules during a Rule-Switching Task
 (A) Rule-switching task. At the beginning of the session, rats collect reward by pressing the lever signaled by the light. When the rule is switched, rats learn by trial and error that reward is available at one location only.
 (B) Neuronal ensembles show distinct patterns when rats are performing the visual and spatial rules (leftmost and rightmost panels). During learning, ensemble activity goes through intermediate states, though the switch between steady-states is usually very rapid.

correlations between pairs of neurons (Komiyama et al., 2010) reveal changes wrought by learning.

Here, Durstewitz et al. (2010) first compared the activity of neurons during steady-state performance of both visual and spatial rules (i.e., before and after the rule switch) and found that single mPFC neurons, despite their relatively low firing rates, could sometimes differentiate between the two steady states. This type of selectivity can be interpreted as a representation of the ongoing rule, a finding that reinforces results from studies of rule-encoding in primate mPFC (Mansouri et al., 2006; Wallis et al., 2001). Interestingly, these rule-selective mPFC neurons showed differential activity throughout the trial rather than locked to a particular event. This might suggest that the network switched to a different state, with a different overall activity, according to the ongoing strategy. Although the activity observed is consistent with rule representation, to further support this idea, it would be important to know what happens if the rules are switched back and forth.

Such single neuron analyses required averaging over trials during each of the two rules or, more generally, before and

after learning. Trial averaging gives statistical power, but does not allow one to address the precise origin of the neuronal changes that give rise to rapid jumps in behavioral performance. Although more sophisticated analysis techniques such as state-space generalized linear models (Czanner et al., 2008; Suzuki and Brown, 2005) have been proposed as methods for estimating neuronal changes in a finer time scale, these techniques have not yet been widely applied to the analysis of neuronal processes during learning.

To analyze the neural activity in the mPFC in a way that could give them estimates of the network state on a trial-by-trial basis, Durstewitz et al. (2010) took advantage of the fact that they had recorded from multiple neurons simultaneously. Simple averaging across neurons, which are likely to show a variety of different behavioral correlates, would not be sufficient. Therefore, it was necessary to apply more sophisticated statistical approaches. The authors first constructed population vectors for describing the activity of neural ensembles. Using a dimensionality-reduction technique, they then visualized the activity of the ensembles in two dimensions. This revealed that the neuronal

ensemble took on different states during the two rules (Figure 1B, leftmost and rightmost panels). Decoded in this way, the population could provide more information about the ongoing rule than was possible by reading single neurons.

Having established that neural populations switch between two states that reflect the current rule, it was then possible to investigate the dynamics of the transition from one state to the other as the rats learned the new strategy over a period of around 100 trials. The authors found that during the learning phase the activity of neural ensembles evolved through intermediate states, in such a manner that the distance to either of the steady states associated with the rules was directly correlated with the ability to predict the rat's choice—that is, when the neuronal ensemble activity was closer to that observed for the spatial rule in steady state, the animal was more likely to behave according to this rule, and vice versa. Thus, the activity of the population of neurons contained accurate information about the rule the rat was using to guide its behavior.

A few studies have previously explored the dynamics of neuronal responses as associative learning progresses at the single neuron level. Among those, Wirth et al. (2003) and Paton et al. (2006) are noteworthy, as they show that changes in single neuron firing rates occur around the same time as changes in behavioral performance, suggesting a causal relationship. Durstewitz et al. (2010), using analyses based on simultaneously recorded ensembles rather than single neurons, were able to take this approach one step further and examine how the mPFC encoding of rules changes on a trial-by-trial basis. Using two different approaches—hidden Markov models and change point analysis—they could show that, in about half of the recorded ensembles, transitions from one rule to the other occurred abruptly (less than ten trials), a time scale very similar to that observed for behavioral changes.

Thus, Durstewitz et al. (2010) reveal state transitions in neuronal ensembles that are sufficiently rapid to potentially account for the rapid rule-switching behavior observed in the same animals. Moreover, the abrupt nature of the neural transitions suggest that, at least in mPFC

and during this learning paradigm, the learning process does not correspond to a gradual process of accumulation of evidence.

The results reported in this issue by Durstewitz et al. (2010) suggest that ensembles of mPFC neurons represent the ongoing rule, possibly contributing in this way to maintaining a memory of the relevant strategy or a reference frame to allow for detecting changes or violations, consistent with the proposed role of PFC in monitoring behavior (Ridderinkhof et al., 2004).

A final important question that remains elusive is to establish the causal relationship between the observed neuronal ensemble activity and the behavior. Are the observed changes in neuronal ensemble state responsible for the change in behavioral strategy or are they too reflections of a third underlying cause? To begin to address this, the authors took advantage of the fact that the abrupt transitions in behavioral strategy took place at highly variable times during the learning process depending on which animal was being tested. Remarkably, there was a very good match between the trials on which

the neural state and performance transitions occurred across animals. However, the changes in behavior preceded in some cases the switches in neural states, suggesting that even though changes in neural activity occur in parallel to the acquisition of the new rule, it may not be those changes that drive the behavior.

Ultimately, answering the causality question will require manipulating the activity in populations of neurons that are defined not necessarily by a common cell type, but which may join forces as the result of the unique set of experiences which has shaped the structure of the brain. While technically challenging, the recent explosion of optogenetic technology suggests that such an experiment may become reality in the not-too-distant future.

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