Past Performance Is Indicative of Future Returns

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Neuronal activity observed in response to trial outcome is hypothesized to drive learning and performance adjustment. The study by Histed et al. in this issue of *Neuron* observes persistent outcome-related neuronal activity lasting until the subsequent trial in both prefrontal cortex and the caudate nucleus which is correlated with behavioral adjustment.

Oscar Wilde once said, "Experience is the name everyone gives to their mistakes." Mistakes give us vital information that helps us perform future actions more cautiously and, ideally, more accurately. Imagine typing out an email and realizing that you had made several spelling errors. More than likely, you will slow down your rate of typing and pay greater attention in order to avoid mistakes. Numerous studies have shown that individuals monitor ongoing actions and behavioral outcomes to adjust behavioral performance (see Ridderinkhof et al., 2004, for review). For example, in tasks requiring fast reactions to external stimuli, subjects tend to slow down and respond more accurately after making an error. These changes in performance might arise from a neural system that represents the outcome of previous trials and uses such a representation to guide future responding.

Previous studies have established that rewards selectively activate neurons in the prefrontal cortex (e.g., Watanabe, 1996) and the basal ganglia (e.g., Apicella et al., 1991). More recently, it has become clear that some prefrontal neurons are sensitive to the outcomes of *previous* trials. For example, neurons in the dorsolateral prefrontal cortex encode past decisions and reward payoffs, as well as the conjunction between these variables and may provide signals that update the animal's expectation of reward (Barraclough et al., 2004; Seo and Lee, 2009). A recent study of the rat medial frontal cortex (Narayanan and Laubach, 2008) found neurons that fired at different rates after correct and error responses. Some of these neurons fired persistently throughout the intertrial interval until the start of next trial or even the next reward presentation. Outcome-related activity has also been found in the hippocampus (Wirth et al., 2009), where neurons fired at different rates after correct and error responses. In the striatum, there is evidence for separate groups of action- and outcome-related neurons that become active only after rewarded responses are made (Lau and Glimcher, 2007).

In this issue of *Neuron*, Histed et al. (2009) extend this body of work to examine outcome-related activity during a reversal learning task. They report the first evidence for the simultaneous processing of trial outcomes by neurons in two different brain areas, the prefrontal cortex and the caudate nucleus, a part of the basal ganglia. Monkeys were trained to associate a picture with either a leftward or rightward eye movement. Animals had to learn associations between two cues and two responses by trial and error. After correct responses, animals were rewarded with juice paired with a tone. After errors, a visual error stimulus was presented for 1 s before the start of the next trial. The interval between trials was 5.5 s. Once animals learned the stimulus-response mappings (by performing at 90% correct or better), the mappings were reversed without any overt signal given to the animal. Each recording session consisted of three to eight reversals, enabling the authors to dissociate learning-related effects from slow drifts of neuronal activity over the session (i.e., motivational changes).

Histed et al. (2009) used multielectrode methods to record simultaneously from neurons in dorsolateral prefrontal cortex (dlPFC) and the caudate nucleus. They found neurons in both brain areas that showed outcome-related activity (i.e., selective increases in firing rate following a correct or incorrect response) that was sustained throughout the intertrial interval. To quantify response- and outcome-related information in the neuronal activity, they devised a tuning index computed based on the receiver-operating characteristic (ROC), which is a simple and straightforward way to assess effects of categorical variables on neuronal activity (i.e., the presence or absence of reward, left or right movement). Histed et al. (2009) found that neurons in both brain areas contain information about the outcome of the preceding trial during the intertrial interval. They interpreted these signals as lasting traces of trial outcomes that could be used to combine reward signals over trials during learning and to enable performance adjustment, allowing the animal to change how it performs the task based on the reward that was earned on the last trial.

Histed et al. (2009) also investigated how the outcome of one trial impacts the amount of information neurons encoded on future trials. Interestingly, they found that correct responses increased the directional selectivity on neurons the next trial (i.e., the degree to which firing rate was modulated by movement in one direction compared to the other). For example, neuron might fire more during

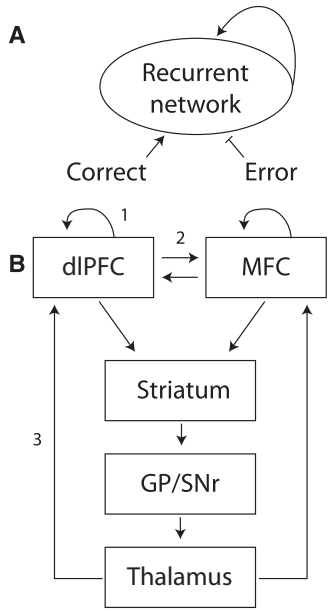

Figure 1. Potential Neural Circuits for Representing Trial Outcome over the Intertrial Interval

A major new finding from the paper by Histed et al. (2009) is that neurons in both dorsolateral PFC (dlPFC) and the caudate nucleus, a part of the striatum, fire persistently during the intertrial interval in a reversal learning task. Interestingly, the neurons fired in a reciprocal manner when the outcome of the trial (correct or error) was signaled to the animal (see Histed et al. Figure 2). Some neurons fire more after correct responses and fired less after errors. Other neurons showed the opposite pattern of activity. These activity patterns can be generated within recurrent networks that receives excitatory inputs following one outcome (correct response) and inhibitory inputs following the other outcome (error), as shown in (A). There are several potential anatomical routes that could link dmPFC and the striatum in a recurrent manner (shown in B). These include (1) recurrent connections within dlPFC, (2) reciprocal connections between dlPFC and other cortical areas such as the medial frontal cortex (MFC), and (3) connections from dlPFC through the basal ganglia and back to the cortex by way of the thalamus.

leftward movements compared to rightward movements if the preceding trial involved the animal correctly making a leftward movement to obtain a reward. Errors had the opposite effect, with reduced directional selectivity on the next trial. This effect was present over populations of neurons in both areas. They went on to show that behavioral accuracy improved after a correct response. This result supports the authors' interpretation that activity during the intertrial interval has a potential causal role in subsequent task performance.

One of the most interesting issues raised by Histed et al. (2009) is whether lasting traces of trial outcome arise from activity within a single brain region or are due to interactions among multiple brain areas. One brain region that should be examined with regard to this issue is the medial frontal cortex (MFC), which has a well established role in error processing (see Ridderinkhof et al., 2004, for review). Studies in human subjects have repeatedly shown error-related signals in EEG recordings such as the "error-related negativity" that occurs just after an errant response (e.g., Falkenstein et al., 1991). These error-related signals have been shown to be generated by MFC and have been suggested as triggers for updating task strategies (Holroyd and Coles, 2002; Frank et al., 2001). Neuroimaging studies have shown evidence for correlations between activity in MFC and dlPFC (Kerns et al., 2004). It thus seems reasonable that functional interactions between these areas could contribute to the lasting traces of trial outcome described by Histed et al. (2009). As a recent study has reported outcome-sensitive neural activity in MFC (Luk and Wallis, 2009), a promising future direction would be to make paired recordings in MFC and dlPFC using the task in the Histed study and to examine functional interactions between neurons in these cortical regions.

Many issues need to be addressed to understand exactly how performance adjustments are enabled by activity in prefrontal and striatal circuits. One major issue is how these signals emerge during the initial acquisition of the task. Are these signals found early in training, before animals show improved performance following correct responses, or are they only found in well-trained animals? The presence of outcome-related activity early in training would suggest that it more due to reward processing and not to performance adjustment. To date, there have been no neural recordings made during the initial acquisition of the kind of stimulus-response reversal task used by Histed and colleagues. There seems to be no clear technical reason for this.

Another important issue is how outcome-related information is represented within prefrontal and striatal circuits. Histed et al. (2009) show prefrontal and caudate neurons that fire in reciprocal manners when the outcome of the trial was signaled to the animals (see Figure 2 in the Histed paper). Some of these neurons fired more after correct responses and less after errors. Other neurons showed the opposite pattern of activity. These kinds of activity patterns could arise in a recurrent network in which some cells are excited after a correct response and others are inhibited. There are several anatomical routes that could mediate such recurrent activity, including recurrent connections within dlPFC, recurrent connections among dlPFC and other cortical areas involved in processing outcome (e.g., medial frontal cortex), and recurrent connections through the basal ganglia (see Figure 1). It is also possible that the persistent outcome signals are generated within individual neurons, as suggested by a recent study by Sidiropoulou et al. (2009). These authors showed that dopamine can modulate the intrinsic activity of prefrontal neurons independent of recurrent connections, by acting on metabotropic glutamate receptors.

We expect that the study by Histed and colleagues (2009) will create enthusiasm for research on these issues and hope that it leads to an improved understanding of how outcome-related brain activity develops during learning and how organisms can harness these signals to perform better after mistakes are made.

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Which Object Appeared Longer?

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In this issue of *Neuron*, Genovesio et al. report that neurons in the frontal cortex encode the relative duration of appearance of two sensory signals, together with the features of each signal. Such representations could provide a neural basis for episodic memory.

Time-interval detection is essential for the organization of behavior in the context of daily events (Buhusi and Meck, 2005). Both frontal and parietal cortex have been implicated in processing temporal information in the range of seconds (Onoe et al., 2001); in these areas, neuronal activity encoding elapsed time (Leon and Shadlen, 2003) or indicating internal time-generation (Mita et al., 2009) has been reported. These reports provide evidence that cortical structures participate along with subcortical structures in cognitively controlled (rather than automatic) time processing (Lewis and Miall, 2003). In order for an organism to determine which of multiple objects is present for longer or shorter times, information about time intervals needs to be combined with object information. Combining different types of information in this way constitutes an essential component of episodic memory. In this context, Genovesio et al. (2009) take up the issue of feature-based temporal encoding by cortical neurons in a study in this issue of *Neuron*.

The authors report the activity of neurons in the frontal cortex that represent feature- and order-based timing. In their study, monkeys were presented with two successive visual signals (S1 and S2, Figure 1) separated by an intervening time interval (Delay 1). Each signal, either red or green, could appear for either a long or short time. The order of the color and duration of presentation varied in such a way as to constitute four permutations, as illustrated in Figure 1. The duration of S1 and S2 were varied systematically to enable the analysis of responses to the relative duration of S1 and S2. After the second delay (Delay 2), the two signals were presented together, and the animal was required to report which signal (red or green) had lasted longer in the initial presentation by pressing an appropriate switch.

The investigators' main results are as follows. (1) Neuronal activity in the frontal cortex reflected signal duration, as well as its color and the order of presentation. (2) Neuronal activity also encoded relative duration, indicating which signal was longer and which was shorter. (3) Over time within a trial, the activity reflecting the temporal relationship of S1 to S2 was replaced with activity reporting whether the red or blue signal had lasted longer.

The prefrontal cortex has long been thought to play a central role in processing information in order to regulate the temporal structure of behavior. The report by Genovesio et al. reveals a number of new aspects of prefrontal participation in the representation of the temporal components of behavioral events. First, during the encoding of timing information, prefrontal neurons were found to integrate three characteristics of the sensory signals: duration, order, and color. This means that information about signal duration, stored in the prefrontal cortex, is labeled with temporal-order information (cf. Ninokura et al., 2003) and feature-characterizing information. Such multidimensional representation is necessary for the flexible and adaptive use of the prefrontal cortex (Duncan, 2001) in broad range of behavioral tasks, including feature-based timing detection. Second, the signal duration information was expressed as climbing or decrementing activity during the delay period, consistent with previous reports (Leon and Shadlen, 2003; Mita et al., 2009). The time course of this activity may be compatible with interval timing models, such as accumulators (Treisman, 1963), state-dependent networks (Karmarkar and Buonomano, 2007), or memory traces with multiple timescales. Third, a substantial population of neurons appeared to encode the relative duration of the two signals; i.e., whether the first or second was longer. Such a property of neuronal activity has been reported in the striatum (Chiba