This Week in The Journal

Reward Strengthens Lingering Representations in Visual Cortex

Clayton Hickey and Marius Peelen

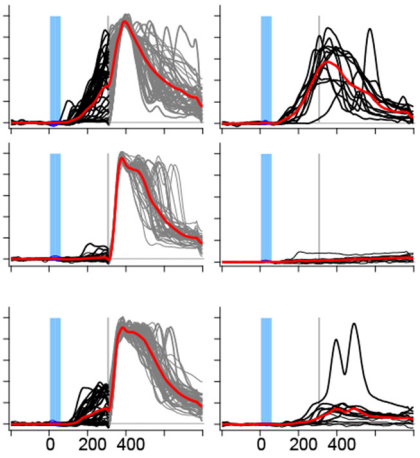
(see pages 7297–7304)

Animals quickly learn to identify cues that predict reward or danger, and they attend to such cues on subsequent encounters. Rewards are often obtained only after the predicting stimulus is gone, however. This raises a perplexing question: how can reward signaling influence the neural representation of a cue that is no longer present and increase its salience during future encounters? One possibility is that reward feedback potentiates lingering representations of previously viewed stimuli in visual cortex.

To test this hypothesis, Hickey and Peelen asked volunteers undergoing functional magnetic resonance imaging to view images of outdoor scenes and search for examples of two object categories, e.g., people or cars. After a delay, participants were asked to indicate which, if any, target category had been present in each scene. Correct trials were rewarded with a large or small number of points, with the magnitude assigned randomly on each trial. Because reward magnitudes were random, subjects were unlikely to expect a large or small reward on any trial, and thus the effects of such expectation on neural activity were minimized.

The authors used mulitvoxel pattern analysis to determine how much information about each object category was present in object-selective visual cortex during the reward period (when the scenes were no longer being viewed) and asked whether this was influenced by reward magnitude. They found that when the reward was small, residual activity in these cortical regions contained similar amounts of information about target and non-target objects that were present in the just-viewed scene. But when large rewards were received, the amount of information about the target category increased, while information about a nontarget object category decreased. This effect varied across participants, and in those that showed a large effect, performance on the next trial improved if the same target and nontarget objects were present on both trials.

These data support the hypothesis that reward magnitude influences the lingering neural representation of previously viewed objects, with large rewards strengthening the representation of attended stimuli. This prolonged activation may enable the neural representations of reward-associated stimuli to be strengthened, thus promoting their activation during subsequent encounters.



After trace conditioning, wild-type mice (top) began to blink after presentation of a light cue (blue bar), both before subsequent presentation of an air puff (gray bar, left) and when the air puff was omitted (right). Many FMRP-null mice (middle) didn't learn this conditioned response, and in those that did (bottom), the responses were more inconsistent and smaller in amplitude. Red trace shows average eyelid response for each mouse. See Siegel, Chitwood, et al. for details.

Re-Introduction of FMRP in PFC of Adult Mice Rescues Deficit

Jennifer J. Siegel, Raymond A. Chitwood, James M. Ding, Clayton Payne, William Taylor, et al.

(see pages 7305–7317)

Fragile X Syndrome (FXS) is the most common inherited form of intellectual disability and individuals with FXS often exhibit autism. FXS is caused by a trinucleotide expansion in the 5′ untranslated region of *FMR1*, which leads to methylation and transcriptional silencing of the gene and reduced expression of its product, Fragile X Mental Retardation Protein (FMRP). FMRP is an mRNA binding protein that regulates expression of numerous proteins, including proteins involved in neuronal development and synaptic transmission. It also binds to some voltage-sensitive ion channels, modulating their function.

Much has been learned about the function of FMRP by studying FMRP-null mice, and this has led to the development of several potential treatments. Most of these treatments have yielded disappointing or ambiguous results in clinical trials, however. One possible reason for this is that FMRP-null mice show mild, inconsistent cognitive phenotypes, complicating interpretation of preclinical trials. Furthermore, some FXS phenotypes likely result from developmental anomalies, which cannot be corrected in the adults that participate in clinical trials (Gross et al. 2015 Neurotherapeutics 12:584).

Siegel, Chitwood, et al. have developed trace eyeblink conditioning as an experimental procedure that might facilitate investigations of the effects of FMRP loss on cognitive performance in mice. Studies in rabbits have shown that a region of caudal prefrontal cortex is necessary for this type of conditioning, in which a tone is followed, after a delay, by a puff of air to the eye. Siegel, Chitwood, et al. report that FMRP-null mice were impaired on this task, and many never acquired the conditioned blink response. Mice in which FMRP was knocked out selectively in the mature PFC were also impaired, indicating that normal acquisition of the conditioned response requires ongoing expression of FMRP. Most notably, expressing FMRP selectively in the PFC of otherwise FMRP-null adult mice rescued most of the learning deficits.

These results offer promise for the future development of therapies to treat PFC dysfunction (impaired working memory, executive control, etc.) in FXS patients. First, the results show that at least one PFC-dependent function can be rescued in adult animals. Second, they provide a reliable test of PFC function in mice. Future work can use the trace eyeblink conditioning protocol to investigate how acute loss of FMRP leads to PFC dysfunction and to identify treatments to reverse this dysfunction.

This Week in The Journal was written by Teresa Esch, Ph.D.