cline-inducible transgenic mouse that expresses a mutant form of CBP that lacks HAT activity (CBP{HAT$^-$}) in a spatially restricted and temporally inducible manner. Behavioral analyses of the CBP{HAT$^-$} mice revealed deficits in long-term but not short-term recognition memory, tested by a visual-paired comparison task, as well as deficits in spatial memory, assayed using the Morris water maze (notably, these deficits disappeared with intensive training). In contrast, long-term contextual fear conditioning was intact. Importantly, the defects in recognition memory and spatial memory were reversible upon termination of transgene expression, suggesting that pharmacological manipulation of the histone acetylation state might provide a potential therapeutic approach to ameliorate RTS symptoms. Korzus and colleagues also demonstrated that administration of another HDAC inhibitor, Trichostatin A (TSA), rescued the memory deficit in CBP{HAT$^-$} mice.

Recently accumulating evidence suggests that epigenetic mechanisms including DNA methylation and histone modifications are actively involved in neural plasticity, learning, and memory via regulation of critical gene transcription necessary for these biological processes (see Figure 1). These studies begin to uncover some of the mechanisms underlying the association between epigenetic diseases and mental retardation. Future challenges include identifying the signaling cascades leading to changes in histone acetylation and identifying the genes whose transcription is regulated via histone acetylation. Although additional studies will be necessary to reveal the gene-specific and coordinated regulation of the transcription network underlying normal neuronal function, the studies from Korzus et al. (2004) and Alarcón et al. (2004) shed light on the potential new "epigenetic therapeutic" approaches, i.e., developing drugs that can alter DNA methylation as well as histone modifications, to treat mental retardation and even other neurological diseases such as Huntington's disease.

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Posterior Parietal Cortex: Space…and Beyond

How do we decide how to react to a stimulus or event? To do so requires recognition of the stimulus itself as well as an appreciation of the context within which that stimulus is encountered. In this issue of *Neuron*, Stoet and Snyder report that neurons in the parietal cortex of monkeys can carry contextual information related to the rules that are relevant for solving a visual discrimination task.

In our interactions with the world, how do we select appropriate behavioral responses to the continuous stream of stimuli and events around us? Not only must we determine the identity of a stimulus, but we must also take into account the context in which that stimulus is encountered. For example, a ringing telephone would require different responses at home (answer the phone) than when dining in a restaurant (let the host or hostess get it). If we were unable to take such contextual cues into account when planning voluntary actions, every stimulus would lead to a highly predictable reflex-like response that could be highly inappropriate in certain situations. Fortunately, this is not the case for many species of animals, including humans and monkeys. Our actions are jointly determined by sensory stimuli, past experience with those stimuli, and the context in which they are encountered.

While much is known about how the brain processes and encodes visual stimuli, comparatively little is known about the neural representation of behavioral context (also known as rules or "cognitive set"). The representation of context or rules has long been known to involve the frontal lobes of the brain, particularly the prefrontal cortex (PFC). A classic test of PFC functioning is a card-sorting test called the Wisconsin card sorting task (WCST). In this task, subjects are asked to sort a deck of cards (each with shapes of various number, shape, and color) into several piles based on a rule (i.e., match the color of items on each card) that the subject has to figure out by trial and error. Once the subject has figured out the rule, the experimenter covertly changes the sorting rule (i.e., match the shape of items on each card) and leaves the subject to adjust to the new sorting strategy. Normal subjects are very good at performing this task. They quickly learn the currently relevant rule and can rapidly adapt their strategy when the rule is covertly

changed. In contrast, subjects with damage to the PFC are dramatically impaired. While they are able to learn the first rule, they seem to be unable to switch to a new strategy when the sorting rules are changed. Recent functional magnetic resonance imaging (fMRI) studies of normal subjects performing the WCST task have shown a higher degree of PFC activity than during control tasks (Konishi et al., 1999). In addition, several recent neurophysiological studies have shown that individual PFC neurons in monkeys can encode detailed information about the rule that is currently relevant for solving a complex behavioral task (White and Wise, 1999; Asaad et al., 2000; Wallis et al., 2001; Wallis and Miller, 2003). Hence, the PFC seems to play an important role in rule representation and rule learning.

In this issue of *Neuron*, Stoet and Snyder (2004) show that another brain region, the posterior parietal cortex (PPC), is likely involved in the representation of rules or cognitive set. While the parietal cortex is best known for its role in visuospatial representations and spatial attention and/or planned eye movements, this study adds to a growing body of work suggesting that areas within the parietal cortex also play a role in the representation of nonspatial information (Sereno and Maunsell, 1998; Sawamura et al., 2002; Nieder and Miller, 2004), particularly if that information is relevant for solving the task at hand (Toth and Assad, 2002). In this study by Stoet and Snyder (current issue), monkeys were trained to perform two button-pressing tasks: an orientation discrimination task and a color discrimination task (Stoet and Snyder, 2003a, 2003b). In the orientation task, monkeys had to press the left button if an oriented bar was close to vertical and the right button if the bar was close to horizontal. In the color task, monkeys pressed the left button for redish bars and the right button for blueish bars. The same set of 104 stimuli (rectangular bars of varying color and orientation) was used for each task. Once the monkeys were expert at performing each task independently, they were trained to switch between the two task rules. Orientation rule and color rule trials were randomly interleaved, and, at the beginning of each trial, the currently relevant rule was indicated with a visual "task cue." A yellow screen or upright triangle as task cue indicated that the color rule was in effect for that trial. If the task cue was a blue screen or inverted triangle, the orientation rule was in effect on that trial. Recordings from parietal cortex revealed a population of neurons whose spiking activity (action potentials) reflected the rule that monkey was instructed (by the task cue) to use on the upcoming trial. The majority of rule-selective neurons in this study were found in the lateral bank of the intraparietal sulcus, within the PPC. Interestingly, rule selectivity was strongest during the delay period, approximately 400–600 ms after the onset of the task cue but before the upcoming, to-be-discriminated, sample stimulus. Because an identical set of stimuli were used in the two tasks and the positions of stimuli on the screen were randomized from trial to trial, these results cannot be explained by differences in visual stimulation, spatial attention, or planned eye movements between the two rules. Rather, this signal may reflect the monkey's preparation for attending to the relevant feature dimension (color or orientation) in the upcoming stimulus. This signal could provide *context* to the upcoming sample stimulus and could instruct the monkey about how to deal with future events in the task.

This fits in well with recent neurophysiological studies in the frontal lobe, such as those by Jonathan Wallis in Earl Miller's laboratory at MIT (Wallis et al., 2001; Miller et al., 2003). In their studies, monkeys were trained to perform a picture-matching task in which they switched between two "abstract rules": matching and nonmatching. When the match rule was in effect, monkeys had to indicate (with a lever release) whether two sequentially presented stimuli were identical matches. If the nonmatch rule was in effect, monkeys instead had to release a lever if the two stimuli were not the same as one another. Matching and nonmatching are abstract rules because they can be applied to any stimulus and are not directly dependent on the physical features of the stimuli. Wallis et al. found that, with training, monkeys were able to master the concepts of visual matching and nonmatching; monkeys could even apply these rules to stimuli that they had never seen before. Recordings from PFC and premotor cortex (PMC) revealed that, like the monkeys' behavior, neuronal activity encoded detailed and robust activity about the rule (match or nonmatch) that the monkeys were cued to use on each trial. Similar to the Stoet and Snyder results in PPC (described above), neurons in frontal lobe areas like PFC and PMC conveyed information about the currently relevant abstract rule that could provide *context* for future events in a trial.

As Stoet and Snyder point out in their discussion, the relationship between rule signals in frontal and parietal areas is unclear. One possibility is that rule signals are primarily generated and/or represented in frontal cortex and are reflected in more posterior areas such as PPC via feedback connections. This could be best addressed by conducting simultaneous recordings from both the frontal and posterior parietal areas during a rule-switching task. A detailed analysis of the time course of rule signals might reveal that, after the task cue (which instructs the monkey about the rule to use for that trial), rules are evident first in the PFC and later in the PPC. This would suggest a "top-down" flow of rule-related information from PFC to PPC. Suggestive evidence for such a scheme is evident by comparing results from Wallis et al. and Stoet and Snyder. From these studies, it appears that rule information in PFC and PMC first appears approximately 175–250 ms after the task cue is presented, while PPC rule selectivity appears later, after approximately 300 ms (Figure 3 in Stoet and Snyder [this issue]). However it should be stressed that this is only suggestive evidence at best, since these two studies were conducted using different behavioral tasks, monkeys, and analysis techniques.

It is also unclear whether abstract rules (i.e., matching and nonmatching in the Wallis and Miller studies) and less abstract feature-based rules (i.e., orientation and color rules in the Stoet and Snyder study) share common neuronal representations or whether they engage distinct brain areas and/or networks. In the Stoet and Snyder study, the task cue instructed the monkey that it should prepare to focus its attention toward either the color or the orientation of the upcoming sample stimulus. In the Wallis et al. study, the task cue does not signal differences in relevant features of the upcoming

stimuli but, rather, instructs the monkey about the appropriate motor responses for matching and nonmatching stimuli. It is conceivable, if not likely, that diverse rules such as these are served by largely distinct neural systems. One possibility, supported by the behavioral deficits on Wisconsin card sorting tasks by prefrontal patients, is that the prefrontal cortex is more involved in the "executive control" aspects of behavioral tasks. These might include error monitoring, actively switching from one strategy to another once a rule has changed, and inhibition of inappropriate responses. The rules themselves might be stored via long-term memory in sensory and/or motor association areas and actively selected or suppressed by the PFC during behavior.

The results of this study are an important contribution to an emerging body of evidence that the PPC represents more than just relevant (or attended) spatial information. Instead, the parietal cortex also has access to information about the behavioral relevance of nonspatial cues that may serve to provide a useful context for upcoming stimuli or events. But whether this information is, in part, generated by neurons in the parietal cortex and plays a critical role in rule-based behaviors remains to be investigated through future experiments.

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