PERSPECTIVES: NEUROSCIENCE

# Will, Anterior Cingulate Cortex, and Addiction

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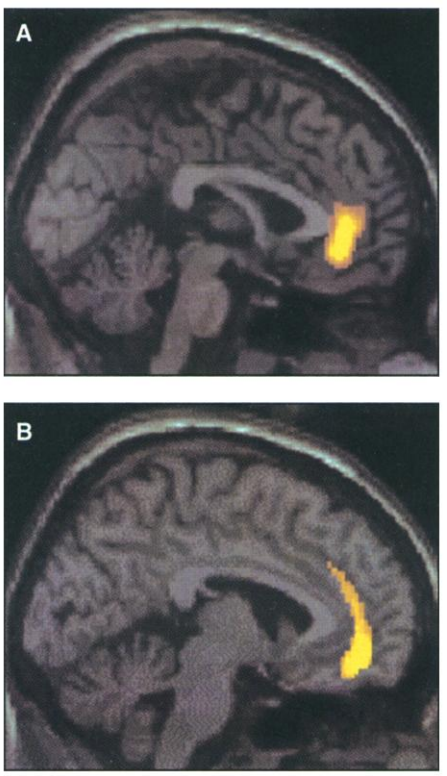
To survive, maximize benefit, and minimize harm, individuals need to select actions that optimize attainment of adaptive goals. Often, and particularly in cases where a long and possibly uncertain sequence of actions is required to attain a goal, it is necessary to exert "willed" control over selection of the appropriate behaviors (*1*). New clues about the neural mechanisms mediating this type of behavioral control are described by Shidara and colleagues on page 1709 of this issue (*2*). Using visually cued multitrial reward schedules in monkeys, they identify a group of neurons in the anterior cingulate cortex (ACC) of monkey brain that encode reward expectancy and may be crucial for boosting actions that will improve the odds of attaining the reward. Delineating such neural mechanisms will help us to understand the determinants of both normal and pathological patterns of action in humans.

The ACC is one of numerous interconnected brain structures that mediate willed control of actions. More specifically, the ACC contributes to the generation of emotional states (*3*) and to the executive control of the influence of those states on behavior selection (*3–7*). Consistent with these observations, electrophysiological studies of the ACC (primarily Brodmann area 24C) show that single neurons in this region respond to and differentiate between (i) primary appetitive and aversive events such as food and shock, (ii) rewards of varying magnitude, and (iii) stimuli and actions that differentially predict appetitive and aversive events (*8–11*). These data demonstrate that neural signals in the ACC encode motivational aspects of events along a good-bad (and perhaps a better-worse) continuum.

Although consistent with human studies of the ACC, electrophysiological recording from animal brains demonstrates that ACC activity may also encode the degree of reward expectancy. Shidara and colleagues have conducted a test of this hypothesis. In their study, monkeys received a reward contingent on completing a schedule of visual color discrimination trials. The schedule included a variable number of trials. At the onset of each trial, animals were presented with additional light cues. Increasing brightness of these cues signaled advancement through the schedule and hence an increasing likelihood that the animals would ultimately attain the reward. The light cues were the only information available about the schedule. The monkeys made progressively fewer errors as the rewarded trial approached, showing that the cue regulated the behavior of the animals. A subset of ACC neurons fired more rapidly in response to these predictive cues. Importantly, the neural responses were graded, such that the magnitude of the change in firing increased according to cues that signaled a progressively greater likelihood that reward would ultimately be attained. These changes in neural activity completely disappeared when the relation between the cue and the reward was randomized. The differential response of individual ACC neurons to identical cues presented during the predictive and randomized sessions suggested that graded changes in firing during the predictive sessions encode the degree of reward anticipation. Significantly, this neural encoding of anticipation occurred at a time when it could influence future actions and in conjunction with cues that did in fact modulate behavior.




**When rewards go awry.** The ACC (Brodmann areas 32 and 24) of cocaine-addicted patients has striking defects in both blood flow (perfusion) (**A**) and gray matter density (**B**) compared with controls (*23, 24*). Resting hypoperfusion was assessed was accessed by positron emission tomography with $^{15}O$ water as the blood-flow tracer; regions of reduced gray matter density were analyzed by voxel-based morphometry (*27*).

The degree of reward expectation can impact emotion and willed control of behavior. For example, and perhaps relevant to the Shidara *et al.* study, increases in reward expectancy can facilitate persistence in a course of action despite the interim failure to receive a reward. The cue-related firing patterns that Shidara *et al.* describe in the ACC (*12–14*) imply that the degree of reward expectancy is part of the reward-related information that determines the ACC's contribution to executive control of emotion and behavior. The degree of reward expectancy is influenced by multiple factors, including the probability and imminence of a reward (*12, 13, 15*). It will be instructive to determine whether the ACC is differentially influenced by one or more of these factors, or is instead sensitive to the overall level of reward anticipation (*16*). There is reason to suspect that the latter is true. The ACC is engaged during many types of tasks involving processing of stimulus information in relation to an array of motivational events and actions (*4–7*). These observations suggest a global and integrated contribution of the ACC to motivational influences on behavior.

Consistent with this role, abnormalities in the ACC (and other frontal regions such as the orbitofrontal cortex) have been implicated in a range of disorders involving disturbances in emotions and actions, including obsessive-compulsive disorder, post-traumatic stress disorder, depression, and mania (*4–7, 17–22*). Although not commonly cited in the literature, researchers including Shidara *et al.* have suggested that abnormalities in the ACC and interconnected regions contribute to drug addiction. Addicted individuals exhibit symptoms associated with insults to the ACC (and related regions), including anhedonia (absence of pleasure) and an inability to make adaptive decisions regarding future actions (*21, 22*). In fact, a hallmark of drug addiction is compulsive and uncontrollable drug use, despite knowledge of adverse conse-

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quences (*23*). Consistent with this symptom profile, neuroimaging studies show hypoactivity and low cell density in the ACC (see the figure) and associated structures of addicted individuals (*21*, *22*, *24*, *25*). It is thus possible that addicted individuals, like others who suffer from hypoactivity in these brain regions, are unable to experience normal affective responses to future events or to exert willed control (*1*) over actions that maximize benefit and minimize harm.

The convergence of addiction research and clinical and functional studies of brain regions such as the ACC has implications for the treatment of addicts and for related public health policies (*26*). The merging of these research areas also illuminates new lines of investigation that may enhance our understanding of both adaptive and pathological regulation of actions. For example, in light of the Shidara *et al.* data, it will be important to test whether addicted individuals suffer from multiple deficits in emotion and executive control of actions.


**References and Notes**

1. Willed control of behavioral selection involves dynamic emotional and cognitive analyses of past and expected events and the influence of these analyses on decisions about future actions. These influences may contribute to the initiation of actions, persistence of adaptive actions, and inhibition of impulses to engage in alternative but less beneficial behaviors.
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12. E. Procyk, J. P. Joseph, *Eur. J. Neurosci.* **14**, 1041 (2001).
13. Y. Kubota *et al.*, *Brain Res.* **721**, 22 (1996).
14. Shidara *et al.* (*2*) reported task-related firing patterns that are consistent with this conclusion.
15. Probability of a reward is the likelihood that a reward will occur if a given action is completed. Imminence is the time that must elapse or the number of events that must take place before a reward is received.
16. For example, if one extended the Shidara *et al.* protocol (*2*), one could compare the following: (i) responses to cues that signal different within-trial probabilities of reward but are randomized temporally and sequentially with respect to reward delivery; and (ii) responses to cues that signal different within-trial temporal reward delays but are identical or randomized with respect to within-trial probabilities of reward.
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27. Both displays used statistical parametric maps of *t* values, generated in SPM 99 (Wellcome Department of Neurology, UK), overlaid on an MNI (Montreal Neurological Institute) template, to show the regions of significant difference between cocaine patients and controls for (A), maximum *t* value = 4.11 at voxel level threshold $P < 0.01$; $P < 0.001$ corrected, with small volume correction sphere of 10 mm at $x = 0$, $y = 44$, $z = 0$; for (B), maximum *t* value = 6.58; $P < 0.01$ corrected).


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# A Bite to Remember

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Simple learning in animals can be induced by four types of experimental protocol—habituation, sensitization, classical conditioning, and instrumental conditioning (see the figure). In classical conditioning, an animal learns about stimuli that predict important events such as food or danger. An example is Pavlov's dog who learned that the sound of a bell predicts the delivery of food. In instrumental conditioning, an animal learns that a particular behavior has a specific consequence—for example, a rat learns to push a lever in order to get food.

A critical issue concerns whether each form of learning is truly unique or whether they represent artificial categories imposed by researchers. Dissecting this problem is complicated by the fact that most experimental protocols induce two or more forms of learning (*1*, *2*). For example, classical conditioning contains an instrumental component because the response (salivation at the sound of the bell) is rewarded by the important event (food). Similarly, during instrumental conditioning, the setting and cues associated with training lead to a form of classical conditioning called context conditioning, which tells the animal what to expect in that environment (pressing the lever leads to food delivery) (*3*). But behavioral experiments alone cannot tell us conclusively about the relationships among the different forms of learning; we also need to understand the cellular mechanisms underlying each of them. On page 1706 of this issue, Brembs *et al.* (*4*) take a step in this direction with their analysis of the behavior of the sea slug *Aplysia californica* during instrumental conditioning. By investigating the behavior of the animal and correlating it with the activity of single neurons, these authors were able to unravel a dopamine reward pathway resembling that in mammals.

What we know about the cellular mechanisms of learning is primarily based on work using sensitization (*5*) and classical conditioning protocols (*5*–*7*). In contrast, the cellular mechanisms underlying habituation and instrumental conditioning are poorly understood. Instrumental conditioning presents a particularly tricky problem to understand at a mechanistic level. Modern theorists (*3*) see the contingencies constituting instrumental conditioning as S(R-O), which means that in the presence of a specific stimulus (S), a response (R) leads to an expected outcome or reward (O). To determine the changes in neural activity (plasticity) that accompany instrumental learning, researchers need to understand the neural pathways underlying each of the elements of the contingency (S, R, and O).

Byrne and his colleagues (*8*, *9*) have developed a way to study instrumental conditioning in *Aplysia* both in vitro and in vivo. Their protocol examines the biting phase of the feeding response in *Aplysia*, which can occur spontaneously. The esophageal nerve normally carries sensory feedback during food ingestion. By stimulating the esophageal nerve directly, spontaneous biting behavior can be reinforced even in the absence of food (*4*). An examination of the nervous system of trained animals shows that training alters the biophysical properties of the B51 neuron. The B51 sensory neuron is important for determining the output of the buccal motor system that regulates biting (*8*, *9*). This neuron seems to be the point of convergence between the biting response and reinforcement. Using an in vitro system, Brembs *et al.* (*4*) applied the neurotransmitter dopamine to cultured B51 neurons each time they fired in a pattern that mimicked ingestion. As a result of this reinforcement, the biophysical properties of the B51 neuron changed, rendering it more excitable and more likely to fire. This led to an increase in the frequency of ingestion-like firing patterns of B51.

In mammals, dopamine is known to be crucial for instrumental conditioning [reviewed in (*10*)]. More specifically, dopamine is the key neurotransmitter mediating the re-

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