

Fool me once, shame on me—fool me twice, blame the ACC

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The anterior cingulate cortex (ACC) is thought to detect unfavorable outcomes and thus influence behavior. A new paper reports that ACC-lesioned monkeys respond normally to reduced rewards, but do not maintain their improved behavioral strategy. The ACC thus is not a simple error detector, but an integrator of past reward experience.

Consider the foraging habits of capuchin monkeys (*Cebus albifrons*) in the tropical rainforests of Peru¹. During the rainy season, these burly monkeys feed mainly on fruits ripening on a few trees within a restricted portion of the troop's range. During the dry season, few trees produce any fruit, and the monkeys primarily feed on less preferred but more widely available nuts on palm trees dispersed throughout the forest. The switch from fruit to palm nuts depends critically on the availability of fruit, but not palm nuts, as predicted by economic models of foraging decisions that emphasize the importance of profitability, in terms of energetic gain and handling costs, for guiding behavior².

These observations raise the question of how the monkeys (and by extension humans) determine when to switch from one behavioral strategy to another. One simple way to do this would be first to determine the profitability of the current strategy, by integrating rewards accumulated during recent foraging trips, and then to compare this value with the estimated profitability of the alternatives^{3,4}. Monitoring payoffs associated with past actions and using this information to adaptively alter future behavior is one of the most fundamental—yet least understood—of the problems the brain must solve. A new paper by Kennerley *et al.*⁵ in this issue demonstrates that the ACC is crucial for this process (Fig. 1a).

Although the precise function of ACC remains a subject of intense debate, it has long

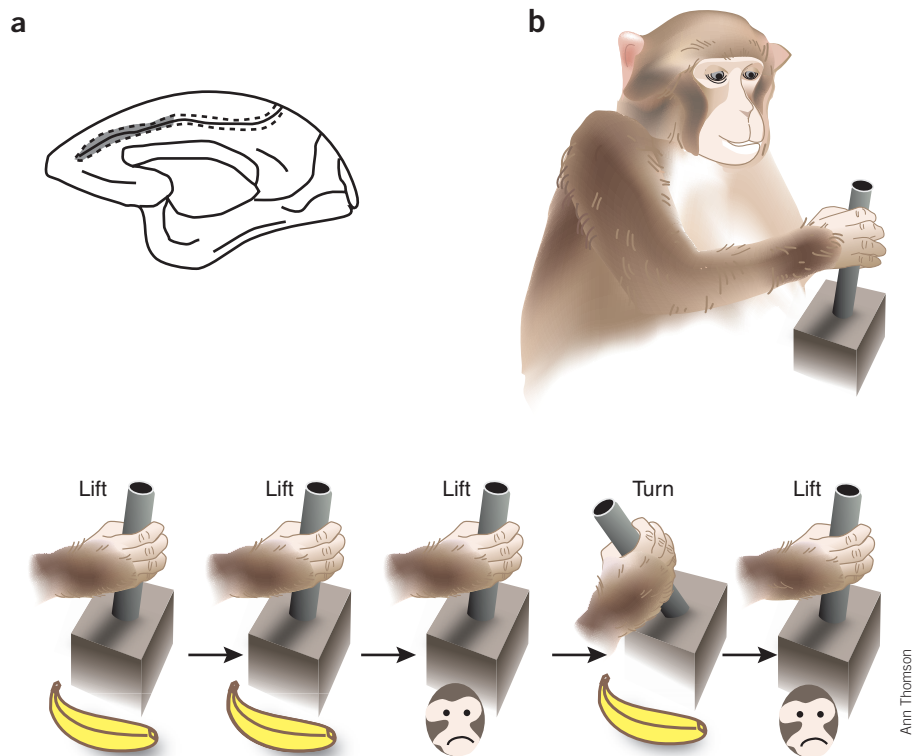


Figure 1 Monkeys with lesions in the anterior cingulate cortex (ACC) correct errors but fail to maintain the new rewarded behavior. (a) Medial view of the right hemisphere in the macaque. Shading, location of the lesion in the ACC (from ref. 5, fig. 1). (b) Behavioral responses of monkeys with ACC lesions in experiment 1. After one action—in this case, lift—was rewarded for 25 consecutive trials, the rewarded action was switched—in this case, to turn. Following an unrewarded lift response, lesioned monkeys switched to turning, but could not sustain this response on subsequent trials. Intact monkeys, however, had no difficulty with this task. Similar lesion-induced disruptions in behavioral performance were found in a reward probability matching task in a second experiment.

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been thought to monitor the consequences of voluntary actions^{6,7}. Supporting this idea, human subjects generate negative electrical potentials (error-related negativity, or

ERN) whenever they make errors in simple behavioral tasks⁸. The ERN is generated in the ACC and can be detected using functional magnetic resonance imaging (fMRI).

Ann Thomson

Cingulate activation does not occur only after errors, but also when people merely anticipate making an error or confront a problem, such as the Stroop task, evoking conflicting behavioral responses⁹.

It should come as no surprise that the nervous system supports a mechanism that monitors and even predicts probable errors. When errors are likely, the brain needs to marshal its resources to improve performance. Moreover, detection of errors is thought to be essential for learning^{3,10}. The role of the ACC in these processes, however, remains hotly debated, in part due to the different techniques typically used in humans and animals. Despite repeated demonstration of conflict-related and error-related activity in human ACC using fMRI, electrophysiological studies of ACC neurons in monkeys have failed to find reliable evidence for these effects¹¹.

From an evolutionary standpoint, the distinction between errors and correct responses seems highly artificial. Neither monkeys nor humans evolved to perform laboratory tasks. When capuchin monkeys forage for fruits and nuts, there are no real errors, only more and less rewarding outcomes. The work by Kennerley and colleagues suggests that the ACC serves principally to track the outcomes of choices made in the recent past. Rather than simply detecting predicted or experienced errors, the authors instead argue that the ACC integrates recent reward information to allow an animal, or human, to adaptively modify its behavior. This idea has the advantage of situating ACC function much more squarely within an evolutionary framework for understanding performance monitoring in the brain.

Evidence supporting this idea comes from a landmark study¹² in which monkeys were trained to push or turn a handle to receive rewards. The monkeys learned to perform one of the two actions consistently; when the reward associated with that action was reduced, the monkeys switched to the alternative action. Inactivation of the caudal portion of the ACC caused monkeys to either persist at the strategy that led to reduced rewards or to switch their strategy before the reward was reduced. These results suggested that the ACC monitors the reward consequences of actions but did not address exactly how it does so.

Building on this work, Kennerley and colleagues studied the behavior of three monkeys with lesions to the sulcal region of the ACC—precisely the same region associated with error and conflict signals in humans (Fig. 1a). The monkeys held a joystick that they could either lift or turn, and one of these actions was rewarded with a food pellet whereas the other was unrewarded. Every 25 trials, the scientists

switched which action—either lift or turn—was rewarded. The only way for the monkeys to detect the switch was to notice that the previously rewarded action was no longer rewarded. The optimal strategy in this task is known as ‘win, stay; lose, shift’. This is the same problem confronted by foraging capuchin monkeys when they decide whether to pursue fruit or nuts, and surely an adaptive behavioral function for many other species as well.

Control monkeys performed nearly flawlessly, but monkeys with ACC lesions did not. The pattern of errors made by lesioned monkeys, however, was very revealing. Consider the trial following 25 consecutive trials in which the monkey has lifted the joystick (Fig. 1b). If he continues with this behavior and lifts the joystick again, he receives no reward. Based on this feedback, the optimal strategy would be for the monkey to switch to turning the joystick. Surprisingly, both lesioned and control monkeys responded to the unrewarded outcome by switching to the other behavioral strategy—in this case, turning the joystick. Even more surprisingly, the lesioned monkeys soon went back to lifting the joystick. These observations suggest that monkeys with ACC lesions can detect ‘errors’ and adjust their behavior accordingly, but have difficulty consistently following a new strategy. To tease apart the mechanisms responsible for these deficits, the authors mathematically determined the influence of recent reward history on choice. They found that control monkeys had much longer time constants for the impact of reward on choice than did monkeys with ACC lesions. The lesioned monkeys only consistently used reward information from the previous trial. In this task, the ACC thus seemed to be critical in the integration of reward information over time to guide decisions.

In a second experiment, Kennerley and colleagues tested the ability of both sets of monkeys to perform another type of foraging task. The physical set-up was the same as the first one, but the payoff structure was modeled on reinforcement parameters used in classic studies of behavioral choice¹³ and later modified for use in electrophysiological studies of decision making¹⁴. Two actions—lift and turn—were each rewarded probabilistically at different rates. When a particular action was rewarded, it remained so until the monkey chose that action. The optimal strategy is to sample both options with probabilities matching the probabilities of reinforcement¹³. Control monkeys quickly adapted to any ratio of reinforcement probabilities, but monkeys with ACC lesions were much slower to develop matching. This experiment confirms the results from the first that the ACC is essen-

tial for making good decisions based on the history of reward outcomes.

The most fascinating result from the present study is that monkeys with ACC lesions were able to use reward information to adaptively modify their strategy on a single trial, but could not sustain this new behavioral response on subsequent trials. This dissociation suggests that the process of adaptively modifying behavior in response to changing reward conditions may be a separate process from consolidating this behavior into a new strategy. It seems that the ACC is selectively involved in the second process but not the first. This conclusion leaves several important questions unanswered: chief among them, what is the mechanism that detects diminished payoffs and immediately alters behavior, and how does this process interact with the temporal integration processes occurring within ACC?

One possibility is suggested by recent work on the role of the locus coeruleus (LC), a subcortical nucleus with widespread noradrenergic projections, in behavioral control. Afferent projections from the ACC and the orbitofrontal cortex (OFC) are proposed to shift the LC into either phasic or tonic modes of signaling¹⁵. Phasic noradrenaline is hypothesized to induce exploitation of a currently profitable behavioral strategy, whereas tonic noradrenaline signaling is hypothesized to induce exploration of new strategies. Destruction of the ACC could disrupt transitions between phasic and tonic LC signaling, thus potentially accounting for the decision-making anomalies found in the study by Kennerley and colleagues.

This research has many applications to neurological disorders. The ACC is implicated in depression, anxiety disorder, obsessive-compulsive disorder and many forms of addiction. One trait that these mental disorders share is a failure to use recent information about actions and their consequences to make good decisions. An understanding of how such processes work is thus essential for developing reliable treatments for these disorders, and may also explain the strategic behavior of monkeys choosing between foraging on fruit or nuts. The work by Kennerley and colleagues represents a fruitful step in this direction.

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Fractalkine: moving from chemotaxis to neuroprotection

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Microglia are thought to contribute to neurodegeneration. Now ablating the receptor for the chemokine fractalkine is shown to increase microglial inflammatory response and neuronal death *in vivo* in several models of CNS insult.

Chronic neurodegenerative disorders, including Alzheimer disease, Parkinson disease and amyotrophic lateral sclerosis (ALS, also called Lou Gehrig's disease), involve neuron death and inflammation in specific brain regions. Areas of degeneration are populated by resident inflammatory cells of the CNS, such as microglia and astrocytes, and, to a much lesser extent, by infiltrating T-cells. Inflammation, which is traditionally thought to eliminate cellular debris, was considered until recently to be a trivial secondary response to neuronal death. However, *in vitro* evidence indicates that, upon activation, microglia themselves promote neurodegeneration by producing a barrage of cytotoxic molecules, including proteases, reactive oxygen species, nitric oxide, prostaglandins and cytokines¹.

Microglia in the brain can behave differently from microglia in a dish, and it has remained unclear how microglia could promote neurotoxicity *in vivo*. In this issue, Cardona and collaborators² take a major step in this direction by making a compelling case that chemokines are critical for regulating the function of microglia and for mediating microglia-dependent neurotoxicity *in vivo*. The authors use three different *in vivo* models of CNS insult to show that without the receptor for a chemokine called fractalkine, excessive microglial activation occurs in response to both inflammatory and neurotoxic stimuli. The authors also show that ablation of the fractalkine receptor exacerbates neuronal loss in mouse models of Parkinson disease and ALS.

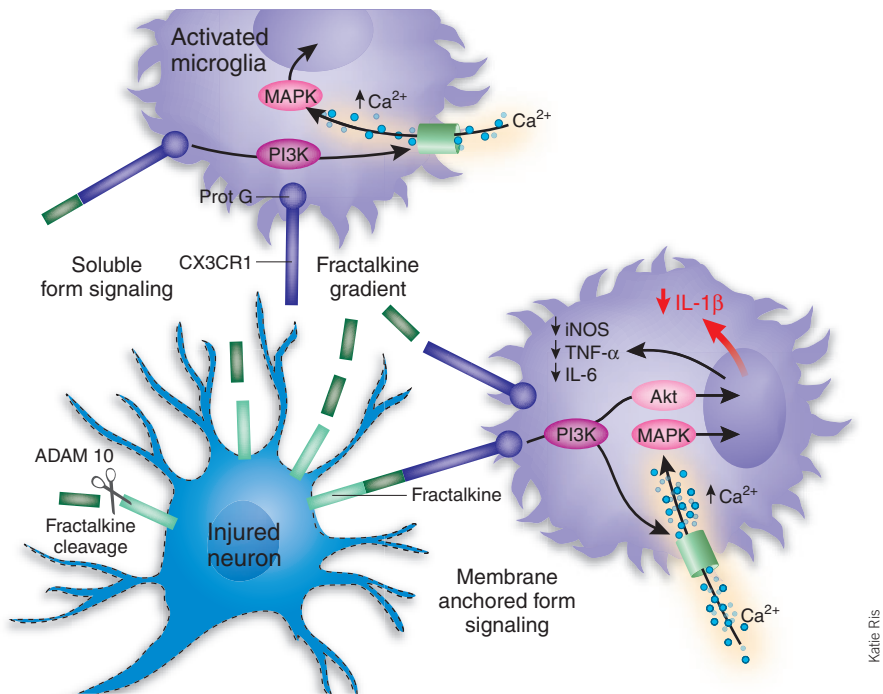


Figure 1 Fractalkine is primarily expressed by neurons, whereas its G protein–coupled receptor (CX₃CR1) is mainly expressed by microglia. Fractalkine is either membrane bound or soluble; the latter results from the cleavage of membrane-bound fractalkine by the metalloproteinase ADAM10. CX₃CR1 ligation triggers phosphatidylinositol-3 kinase (PI3K)-dependent Ca²⁺ influx, which is greater with membrane-bound than soluble fractalkine. Downstream to PI3K, CX₃CR1 signaling activates the mitogen-activated protein kinase (MAPK, important for chemotaxis) and Akt pathways (important for cell survival). Both fractalkine forms mediate chemotaxis, whereas the membrane-bound form also captures microglia. Fractalkine acts as an anti-inflammatory molecule *in vitro* by attenuating the secretion of interleukin-6 and tumor necrosis factor-α (TNF-α) and the upregulation of inducible nitric oxide synthase (iNOS) in LPS-activated microglia. The new data from Cardona *et al.* indicate that fractalkine controls the degree of microglia activation and ensuing neurotoxicity by attenuating the production of interleukin-1β (IL-1β).

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Chemokines (short for ‘chemotactic cytokines’) induce chemotaxis of neighboring cells. They are produced by a wide variety of cell types. So far, we know of ~50 distinct human chemokines that, despite a relatively low sequence homology, share common

tertiary structures. They also have conserved cysteine residues near the N terminus whose relative positions define four chemokine subfamilies. The biological effects of all chemokines are mediated by specific receptors that belong to the large family of