Is the reward really worth it?

Steven W Kennerley

How does the brain evaluate whether the benefits of a decision outweigh the costs? A study now reveals that neurons in the anterior cingulate cortex encode costs and benefits, and altering brain activity here biases choices away from negative outcomes. These results link anterior cingulate cortex with the regulation of emotional states.

Humans and animals face a variety of decisions every day, many of which require experiencing some cost to obtain some benefit. Although you might fancy some fresh sushi for lunch, the downpour indicates your journey outside will be a wet one; perhaps grabbing a sandwich at the indoor canteen would be preferable. How does the brain evaluate whether the sushi will be rewarding enough to tolerate the cost of getting wet? Although we often make such choices with relative ease, decisions that have potentially negative consequences can evoke anxiety, and individuals who suffer from anxiety disorders and depression find cost-benefit decision-making particularly difficult[1]. In this issue of *Nature Neuroscience*, Amemori and Graybiel[2] demonstrate not only that neurons in the primate pregenual anterior cingulate cortex (pACC) encode the costs and benefits of a decision, but that pACC controls whether to choose alternatives associated with potentially negative outcomes, implying a link between pACC's valuation functions and the regulation of emotional states such as anxiety.

The anterior cingulate cortex has long been considered to be a critical structure in emotion. Papez (1937) argued that the cingulate gyrus may be the "receptive region for the experience of emotion"[3]. Indeed, the anterior cingulate cortex has widespread interconnections with limbic, cognitive and motor areas, making it a potential interface at which cognitive, emotional and motivational states can influence behavior[4]. As investigators began to examine pACC function in decision-making tasks, it became clear that pACC neurons encode many of the variables that influence a decision and that damage to pACC impairs cost-benefit decision-making[5–7]. However, a critical issue is how to link neural correlates of decision-making in the healthy brain to clinical disorders associated with impaired decision-making in the unhealthy brain, particularly in pACC. Abnormal pACC activity is associated with anxiety-related psychiatric disorders, including depression, obsessive-compulsive disorder, schizophrenia and addiction, and disrupting the region in and around pACC is a common treatment for these disorders[8,9]. On the basis of this evidence, Amemori and Graybiel[2] reasoned there might be a link between pACC's role in cost-benefit decision-making and the regulation of some forms of anxiety.

To explore this issue, the authors developed a cost-benefit decision task for macaque monkeys modeled after approach-avoidance (Ap-Av) protocols used in humans to quantify decision-related anxiety. On each trial, monkeys sat in front of a computer screen and made Ap-Av decisions between two options (**Fig. 1a**). The size of two colored stimuli indicated the negative (airpuff to the face) and positive (liquid reward) outcomes that would be experienced if the monkeys chose the approach option. Alternatively, the monkey could always choose the avoid option, which would provide a very small reward and had no negative outcome (airpuff). As a control task, monkeys were tested on an approach-approach (Ap-Ap) task that was identical to the Ap-Av task, except that both colored bars signaled potential reward and the monkey would not experience an airpuff. The authors reasoned that the anticipation of negative outcomes might evoke anxiety and that this should be specific to the Ap-Av task.

To test whether the Ap-Av task might evoke changes in anxiety levels, the authors administered the anti-anxiety drug diazepam to the monkeys and then tested their performance on the two different tasks. The results were clear: diazepam treatment significantly increased the number of approach choices in the Ap-Av task (**Fig. 1b**) in a dose-dependent manner, but it had no effect on the Ap-Ap task. In other words, anxiolytic drug treatment altered the decision boundary between the valuation of costs and benefits, causing subjects to be more willing to endure a negative outcome to obtain reward. This result indicates that the Ap-Av task provides an experimental context for exploring the neuronal representation of positive and negative emotional states.

To investigate the role of pACC in cost-benefit decision-making, Amemori and Graybiel[2] recorded the electrical activity of over 1,000 neurons in a large region of the pACC, including both banks of the anterior cingulate sulcus and the underlying cingulate gyrus. This is particularly noteworthy because most single-neuron studies of pACC have primarily focused on the dorsal bank of the cingulate sulcus[5]. Consequently, we know relatively little about the functional properties of neurons in these more ventral regions of pACC (but see ref. 10), despite pACC's aforementioned association with psychiatric illness. By varying the amount of experienced reward and airpuff across a wide range of values and observing choice behavior, the authors were able to determine which task variables modulated pACC neuronal activity during cost-benefit decision-making, with a particular focus on whether neurons were sensitive to decision costs, benefits or the overall subjective value, or utility, of the choice.

Several noteworthy features emerged in the neuronal data. Most of the neurons fell into one of two clusters (**Fig. 1c**). P-type

Steven W. Kennerley is at the Institute of Neurology, University College London, London, UK.
e-mail: s.kennerley@ucl.ac.uk

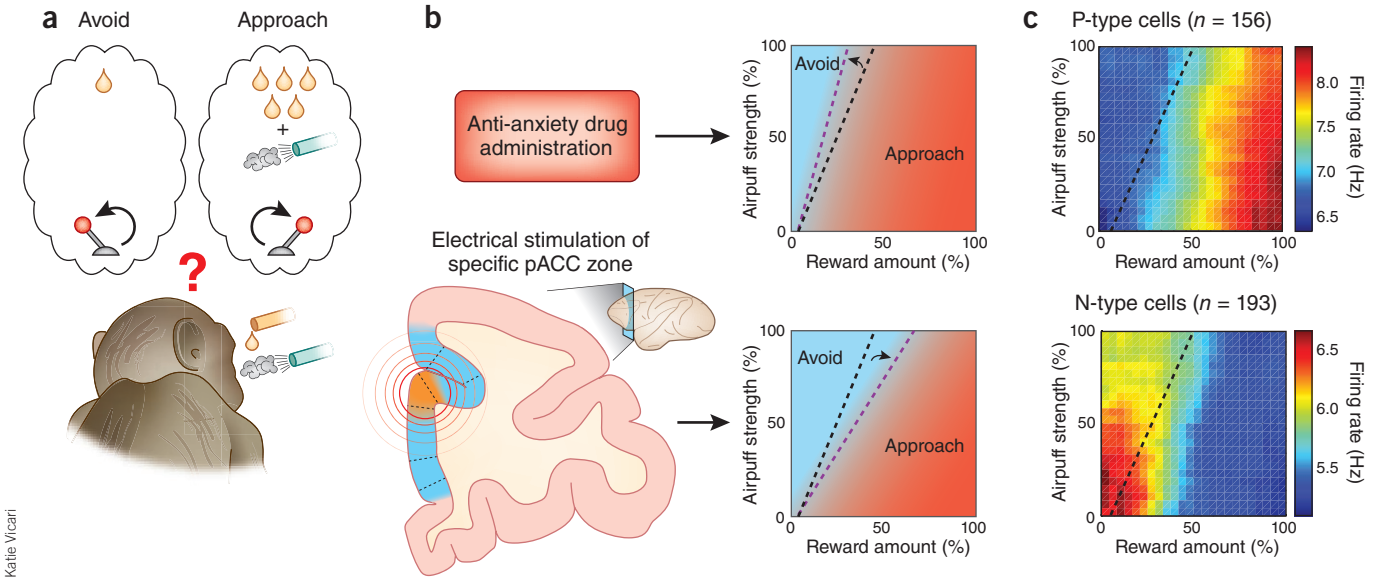

Figure 1 The role of the pACC during Ap-Av decision-making. (**a**) On each Ap-Av trial, the monkey chose between either an approach decision, which yields both a benefit (reward) and a cost (airpuff), or an avoid decision, which yields a small fixed reward without a cost. (**b**) P-type neurons were activated by the expectation of large reward or high utility approach choices, whereas N-type neurons were activated by the expectation of small reward or low utility approach choice, typically leading to avoidance choices. (**c**) Anti-anxiety drug administration (top) and microstimulation of the ventral bank of pACC (bottom) each altered the decision boundary between the valuation of costs and benefits, but in opposite ways, leading to an increase in approach and avoidance decisions, respectively. Black and purple dashed lines indicate decision boundary before and after experimental manipulations, respectively.

neurons were activated by task variables related to the expectation of large reward or high utility when the monkeys chose the approach option. In other words, these neurons appeared to be sensitive to positive motivational states. Conversely, N-type neurons were activated by task variables related to the expectation of small reward or low utility when the monkeys chose the avoidance option. Thus, N-type neurons seemed to be sensitive to negative motivational states. Furthermore, when the authors examined the spatial distribution of the P- and N-type neurons, they found that both types of neuron were present and intermixed across the region of pACC that was sampled, but, in a specific region of the ventral bank of the cingulate sulcus, the N-type neurons were significantly more prevalent than the P-type neurons.

Although previous studies have shown that neurons in frontal cortex, including pACC, often exhibit positive and negative coding relationships in decision-making tasks[11,12], the current results imply that P-type and N-type neurons might make unique functional contributions to cost-benefit decision-making. To test whether there is a causal link between N-type neurons and negative motivational states that might promote avoidance decisions, the authors applied electrical microstimulation to different pACC sites at the time when monkeys evaluated the cost-benefit alternatives. If pACC has a critical role in decision-making, disrupting normal pACC activity with microstimulation should induce a change in choice behavior. Although stimulation had little effect in the Ap-Ap task when neither decision had an associated cost, microstimulation of pACC in the Ap-Av task produced a significant increase in avoidance decisions (**Fig. 1b**), but only when applied in the ventral bank of the cingulate sulcus, precisely where N-type neurons predominate. Subsequent administration of the anti-anxiety drug diazepam fully reversed the microstimulation effect in this subregion of pACC. Taken together, these findings provide convergent evidence from several techniques that suggests that pACC not only is critical for cost-benefit decision-making but also may be critical for regulating negative emotional states such as anxiety.

As impressive as these results are, they also raise several important questions for future research. First, other brain areas in the frontal cortex, including the orbitofrontal cortex[13] and lateral prefrontal cortex[14], contain neurons that are sensitive to positive and negative outcomes; thus, it remains an open question whether the P- and N- type neurons in pACC are performing functionally unique computations in comparison with positive and negative coding neurons in these other frontal areas. Second, although N-type neurons were preferentially located in the ventral bank of the cingulate sulcus, where microstimulation induced avoidance decisions, many of these N-type neurons encoded motivationally positive variables related to the reward, rather than motivationally negative variables related to the cost of the airpuff. This raises an important question about the mechanism of the microstimulation effect: does pACC microstimulation disrupt and decrease the influence of reward-related representations, or does pACC microstimulation activate and increase the influence of cost-related representations? Both of these mechanisms might produce an increase in avoidance decisions.

Finally, it would interesting to know whether pACC influences cost-benefit decision-making for other types of decision cost, such as physical effort. Several studies have shown that damage to anterior cingulate cortex biases choice toward actions that are associated with less effort even when a more rewarding option is available[6,15]. If pACC neurons also regulate whether particular rewarding outcomes are worth investing physical effort, this might provide new insight into why patients with clinical depression often exhibit a lack of physical activity; indeed, altered pACC activity is associated with clinical depression[8].

The results of Amemori and Graybiel[2] add to a growing literature linking pACC with cost-benefit decision-making[5–7], but also suggest that these functions may be linked to the regulation of emotional states. A better understanding of the neuronal mechanisms that

support cost-benefit decision-making may provide new insight into the pathophysiology of psychiatric disorders, including anxiety-related disorders, in addition to informing the potential efficacy and side effects of disrupting pACC function as a therapy for psychiatric disorders[9].

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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Astrocytes join the plasticity party

David J Rossi

In the developing cortex, spike timing–dependent long-term depression requires cannabinoid-induced glutamate release from astrocytes. Astrocytes may be integral to the coincidence detection that guides plasticity and map formation.

Normal functionality of the mammalian neocortex is critically dependent on the proper development of the underlying cellular architecture and synaptic connectivity. Thus, characterizing the mechanisms of neocortical development is fundamental to understanding normal neocortical function and neurodevelopmental disorders and is important for guiding regenerative therapies for neurodegenerative diseases. At the most basic level, the development of the neocortex results in functional subdivisions, such as the primary somatosensory and visual cortices, and there is a further topographic organization within such functional subdivisions, whereby neighboring neurons communicate with neighboring sensory or motor locations in the periphery. Early in development, such neocortical topography is initiated by genetic and molecular guidance cues, but fine sculpting of topographic maps is dependent on neural activity and consequent synaptic plasticity[1,2]. In particular, it is thought that differential induction of long-term potentiation (LTP) and long-term depression (LTD) of synaptic strength in neighboring synapses determines the size and shape of functional topographic units, such as ocular dominance columns in the primary visual cortex and whisker barrels in the primary somatosensory cortex[2,3]. However, the mechanisms that determine whether a given pattern of neural activity will trigger LTP or LTD at individual synapses are not well understood. In this issue, Min and Nevian[4] present an elegant set of experiments that elucidate the central role of astrocyte cannabinoid and glutamate signaling in translating specific patterns of pre- and postsynaptic activity into LTD in the developing primary somatosensory cortex.

David J. Rossi is in the Department of Behavioral Neuroscience at Oregon Health & Science University, Portland, Oregon, USA.
e-mail: rossid@ohsu.edu

Experimental support for the role of LTP and LTD in sculpting neocortical topography is particularly well established at excitatory synapses between layer 4 spiny stellate cells (L4 cells) and layer 2/3 pyramidal cells (L2/3 cells) in the rodent primary somatosensory cortex (barrel cortex). These cells are organized in a topographic representation of the whiskers of the snout, with barrel-shaped clusters of cells responding preferentially to individual whisker stimulation. Although the topographical map maintains a degree of plasticity in adult rodents, there is a critical period of development, during which clipping individual whiskers powerfully alters map topography, with barrels representing lost and spared whiskers shrinking and expanding, respectively[5]. The exact network interactions are not fully understood, but it is thought that, in part, the induction of LTP and LTD at synapses between L4 cells and L2/3 cells shapes the barrels during development, with LTP and LTD functionally adding L2/3 cells to or removing them from the barrel, respectively[1,3,5]. Accordingly, much effort has been focused on discovering signaling rules and mechanisms that determine whether LTP and LTD occur at this synapse[6–12]. These studies have identified spike timing–dependent plasticity as a rule governing whether L4-to-L2/3 transmission undergoes LTP or LTD. Specifically, when a postsynaptic action potential follows a presynaptic action potential in a time window of tens of milliseconds, it induces LTP, whereas the reverse order of action potentials induces LTD[9,12].

Mechanistic studies of spike timing–dependent plasticity at the L4-to-L2/3 synapse have determined that timing-dependent LTP is triggered by Ca^{2+} influx through postsynaptic NMDA receptors similarly to LTP in the hippocampus and other synapses[9]. In contrast, timing-dependent LTD (tLTD) is more complex, requiring the activation of postsynaptic metabotropic glutamate receptors (mGluRs), postsynaptic voltage-gated Ca^{2+} channels, presynaptic NMDA receptors and, notably, cannabinoid receptors, which are activated by endocannabinoids that are generated in the postsynaptic cell (consequent to coincident activation of postsynaptic mGluRs and voltage-gated Ca^{2+} channels)[6,9,10,12]. Given the prominent presence of cannabinoid receptors on presynaptic glutamatergic terminals, combined with tLTD being expressed presynaptically (through reduced vesicle release probability), it has been proposed that coincident activation of presynaptic NMDA and cannabinoid receptors triggers tLTD[9,10,12]. However, there is no direct evidence that the cannabinoid receptors that trigger tLTD are actually located on presynaptic terminals, and nothing is known about the source of glutamate that activates presynaptic NMDA receptors.

To directly assess the mechanisms mediating tLTD, Min and Nevian[4] used patch-clamp recording and Ca^{2+} imaging in slices of rodent barrel cortex, monitoring astrocyte Ca^{2+} during the induction of tLTD at L4-to-L2/3 synapses. They found that, contrary to current hypotheses, the tLTD-inducing