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What's Worth the Risk? A Neural Circuit for Trade-Offs

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Cost-benefit analysis in decision making takes place in everyday life for animals and humans alike. In this issue, a neural circuit specific for modulating these behaviors is identified in rats and reveals elusive functional distinctions between long-mysterious anatomical features of the brain.

Trade-off decisions are made frequently in the wild in order to ensure survival. For example, while foraging, should you brave the open fields, risking predators, or rather, keep safe and under cover at the expense of reduced access to resources? Of course there is no categorical answer. The degree of exposure and the exact value of its opportunities are among many important considerations. In short, animals and humans have constantly to seek an optimal balance between potential gains and costs.

In this issue of *Cell*, Friedman et al. (2015) have investigated the neural mechanisms mediating such cost-benefit trade-offs. They trained rats to choose between two arms in a T-maze—one associated with not only a high-value food (more concentrated chocolate milk), but also higher cost (aversion induced by light exposure). Friedman and colleagues were not interested in the aversive experience per se but in the mechanisms that trade off an aversive experience against desire for reward. For manipulations and recordings, the authors targeted the rat prelimbic cortex (PFC-PL), guided by prior observations from this group and others (see below). However, rather than solely focusing on one frontal brain region, Friedman and colleagues performed an ingenious and extraordinarily technically sophisticated series of experiments to understand how PFC-PL interacts with another brain region, the striatum, to bring about cost/benefit decision making.

For a long time, largely because of the Graybiel laboratory's work, we have known that the striatum is divided into two distinct but closely interdigitated anatomical components—the striosome and matrix—but it has been difficult to disentangle their behavioral roles. Friedman and colleagues now report neural activity in each of these compartments and relate it to simultaneously observed decision-making behavior.

Using viral injections targeting the PFC-PL or an adjacent control region called the anterior cingulate cortex (PFC-ACC), the authors could optogenetically manipulate activity in PFC-PL neurons predominantly projecting to the striosome compartment of dorsomedial striatum or PFC-ACC neurons predominantly projecting to the matrix compartment of dorsomedial striatum (Figure 1A). Inhibition of PL-PFC projections led to more approaches to high-reward/high-cost options, whereas excitation led to more avoidance (Figure 1B). While the PFC-PL projection effects appeared to be specific to aversion-reward cost-benefit trade-off decisions, inhibition of the PFC-ACC projections had more generalized effects on many kinds of decisions.

This linking of a very specific fronto-striatal circuit to a very specific behavior is already exciting in itself, but Friedman and colleagues went further and actually characterized PFC-PL and striosomal neural activity in relation to the cost-benefit decisions. What they uncovered was a highly specific pattern of activity that distinguished the striosomal-projecting PFC-PL neurons from other PFC-PL neurons and the PFC-PL recipient neurons in the striosome from neurons in the striatum matrix. PFC-PL neurons projecting to striosomes fired strongly at the decision point during cost-benefit trade-off decisions. Their peak firing was closely followed by high-frequency, putatively inhibitory, interneuron (HFN) activity, which in turn peaked just prior to a period of inhibition in the striosomal neurons that receive PFC-PL inputs. Further evidence for their suppressive effect on striosomal neurons comes from the fact that optogenetically inhibiting the PL-input-receiving neurons in the dorsomedial striatum, presumably some of which are HFNs, releases inhibition of the striosomal neurons during trade-off decisions. While striosomal neurons are normally suppressed during trade-offs, matrix neurons, on the other hand, are always active during a range of decisions, potentially explaining the generalized behavioral effects of PFC-ACC projection manipulation.

The results fit nicely with other recent findings pertaining to analogous brain regions in monkeys and humans (Figures 1C and 1D). For example, a recent Graybiel lab study suggested a role for the probable homolog of the rat PFC-PL in macaque monkeys, pgACC, in cost-benefit trade-off decisions (Amemori and Graybiel, 2012), and another study implicated it in representation of internal states that affect decision-making strategies (Wan et al., 2015). The emotional nature of the decisions is underscored by the fact that the anxiolytic diazepam reversed the increased rate of cost-avoiding decisions that are taken when the pgACC was stimulated in monkeys (Amemori and Graybiel, 2012).

Neuroimaging studies that allow estimation of the activity across large areas of brain tissue have revealed that other prefrontal and anterior cingulate brain areas play roles in dynamic choices of different kinds. For example, the PFC-ACC area adjacent to PFC-PL is involved in other cost-benefit trade-offs where effort rather than aversion is the cost, and it is critical for behavioral flexibility

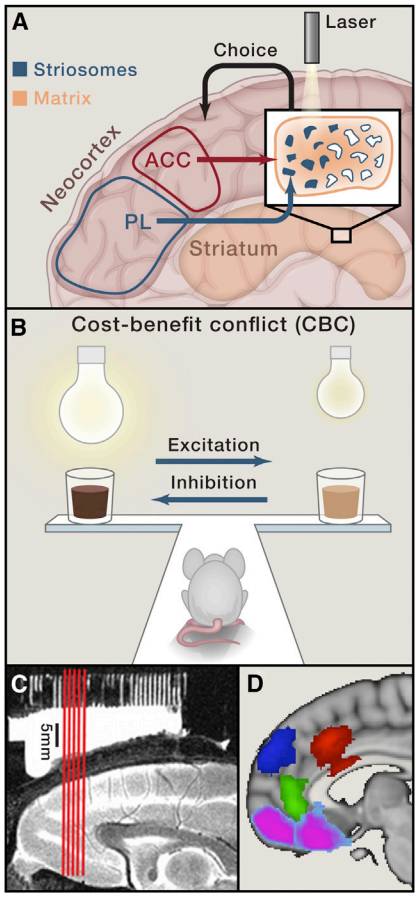

Figure 1. A Corticostriatal Circuit for Cost-Benefit Trade-Off Decisions

(A) Schematic of the rat PFC-PL and its projections to the striosomes in the dorsomedial striatum (blue) and the more posterior PFC-ACC projections, which are predominately to the matrix (orange).

(B) Rats ran T-mazes with different permutations of costs and benefits at each arm (e.g., more concentrated chocolate milk paired with brighter light). Optogenetically exciting or inhibiting the PFC-PL-to-striosome pathway yielded opposite effects specifically on the cost-benefit decisions.

(C) Recording site in macaque pgACC that was also linked to reward/fear cost/benefit decisions (panel from Amemori and Graybiel, 2012). This region resembles rodent PFC-PL because of its strong striosome projection.

(D) Some of the anatomically distinct human medial prefrontal regions identified in different type of decision tasks (blue, hypothetical/meta-representation/social value; red, foraging value; magenta, online or economic value; green, strategic value/trade-off decisions). Summary figure adapted from studies by Nicolle et al., 2012; Kolling et al., 2012; Wan et al., 2015; Neubert et al., 2015). The green area in the human brain resembles macaque pgACC and, therefore, the rat PFC-PL studied by Friedman et al., while the red area resembles the PFC-ACC studied by Friedman et al.

when the value of the environment changes (Rudebeck et al., 2006; Kolling et al., 2012). By contrast, a medial and lateral orbitofrontal network allows flexible online value computations and credit assignment (Rudebeck and Murray, 2014; Stalnaker et al., 2015), and dorsomedial prefrontal cortex is active in evaluations and decisions that involve hypothetical scenarios or social contexts (Nicolle et al., 2012). In many cases, we know that such evaluations and decisions are a result of activity not just in frontal cortex, but also in striatum. It will now be interesting to see how different types of decision making accord with, or deviate from, the pattern of cortical-striatal interaction described by Friedman and colleagues.

Neuroimaging, despite its limitations, has also emphasized network-based approaches to decision making. It has helped us to begin addressing the questions of whether and how different kinds of decision-making systems interact and compete to determine the framework in which a decision is cast (Kolling et al., 2014). The description of frontal cortical interactions offered by Friedman and colleagues not only accords with the increasing trend to attempt to understand decision making as the result of complex interactions between different brain regions, it also takes it to a new level in specifying the interactions of individual neurons. Although they focused on understanding the role of one very specific pathway in one type of decision, another possible use of their approach might be to explore how different ways of making a decision co-exist, interact, and compete when the appropriate decision framework is ambiguous. Friedman and colleagues' results also make it clear that we may have to look at interactions between very specific neural networks embedded within brain regions that have activity patterns that are distinct from, even opposite from, those in adjacent neurons in the very same areas. The armory of techniques wielded to such effect by Friedman and colleagues will hopefully be inspiring to the field, as it seems that proper dissection of decision-making mechanisms will require such sophisticated and ambitious efforts.

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