Just a little (lateral prefrontal) patience

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A new study finds causal evidence that the lateral prefrontal cortex, implicated in executive function, is critical for making decisions in which forgoing a small immediate reward can lead to a better future outcome. These results suggest that this area provides a neural signal that biases behavior in favor of delaying gratification.

From Charlie Sheen to Tiger Woods, there is a long list of people who might wish that some of their past decisions had been made with greater thought given to the future consequences. In addition to a fair number of tabloid-cover celebrities, this list would also include people who have run up large debts, failed to keep New Year's resolutions or struggled with addiction. Indeed, most of us have probably wondered at one time or another why we sometimes make myopic decisions and how in turn we might make more future-oriented ones.

In this issue of *Nature Neuroscience*, Figner and colleagues[1] provide an important new clue regarding the neural mechanisms involved in choosing delayed rewards over immediate ones. In their study, people were given a choice between receiving a larger amount of money at a later date and a smaller amount of money at a earlier time (**Fig. 1**). In some cases, most people agreed that the larger amount either was or was not worth the additional wait. For example, most people would pass up $20 today for $35 in a month, but would take the $20 today rather than wait for $20.10 a month from now. In other cases, however, the differences in amount and delay were balanced such that people were split. For example, would you rather have $25 in a month or $20 today?

An appealing hypothesis has been that, for difficult decisions such as these, the ability to choose patiently, to select the larger, delayed reward, depends on lateral prefrontal cortex. After all, the prefrontal cortex is the 'executive lobe'. It has been associated with planning behavior, complex decision-making and the inhibition of prepotent behavioral

Figure 1 Forward-thinking decisions? People were asked to choose between a small amount of money provided immediately or a larger amount for which they would have to wait.

responses. The prefrontal cortex is also one of the last regions to reach mature levels of myelination during human development[2]. And isn't the ability to consider delayed outcomes one of the hallmarks of adult behavior, especially in comparison with the desire for immediate gratification that is evident in children?

However, previous attempts to link lateral prefrontal cortex to choices between immediate and delayed rewards have been, on the whole, equivocal. Although some functional imaging studies have observed greater lateral prefrontal activity when people choose larger, delayed rewards over smaller, immediate ones[3,4], others have not replicated this finding[5,6]. Similarly, although some lateral prefrontal regions show increased activity in more patient individuals[6–9], other lateral prefrontal regions show the opposite effect[6,7]. Furthermore, although decreased gray matter volume in lateral prefrontal regions is associated with greater impatience[10], damage to dorsolateral prefrontal cortex does not seem to affect decision-making regarding delayed rewards[11].

In addition, these previous efforts are subject to important caveats in interpretation. Functional imaging can only determine an association between neural activity and choices, as both of these are observed, rather than manipulated, variables in a functional magnetic resonance imaging (fMRI) experiment. In contrast, lesion studies can determine that a neural region is necessary for certain choices, but a region's function could also be obscured in chronic patients if intact brain areas can compensate for ones that are damaged.

To overcome these limitations, Figner and colleagues[1] used transcranial magnetic stimulation (TMS) to non-invasively disrupt neural activity in lateral prefrontal cortex. Unlike fMRI, TMS can test claims of necessity. Unlike lesion studies, the disruption is reversible, with a time course that makes compensation from other brain regions less likely. When the authors applied TMS over left lateral prefrontal cortex, they found that people were more likely to choose the immediate reward, especially in those more difficult decisions in which the differences in amount and delay were balanced (for example, $25 in a month versus $20 today). This greater tendency toward impatient decisions disappeared after the effects of TMS had worn off and was not seen with sham stimulation. This effect was also specific in two interesting ways. First, it only occurred when an immediate reward was available; choices between delayed rewards were unaffected. Second, it only occurred when a choice had to be made; ratings of the attractiveness of each reward were unaffected.

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These results indicate that left lateral prefrontal cortex has a critical role in people's ability to choose larger, delayed rewards over smaller, immediate ones. They show that a brain mechanism exists that leads people to give greater weight to delayed outcomes and where this mechanism is instantiated neurally. The obvious next question is how. What exactly is left lateral prefrontal cortex doing?

Although they do not draw firm conclusions on this question, Figner and colleagues[1] seem to favor a 'classical self-control' mechanism. This proposal builds on previous work demonstrating that medial prefrontal cortex, and possibly other regions, compute the subjective value of different options during decision-making[5,12,13]. This proposal adds a second self-control mechanism, whereby lateral prefrontal cortex can interrupt or override the reward valuations computed elsewhere in the brain, such that delayed rewards that would otherwise be valued lower than immediate ones are still ultimately selected. In this case, lateral prefrontal cortex would have a direct effect on choices and there would be a disjunction between valuation and choice that would explain the differential effects of TMS on attractiveness judgments and choices.

Other models are consistent with these data, however. For example, lateral prefrontal cortex might act to modulate or provide input to, rather than override, valuations computed elsewhere in the brain. A similar proposal was made recently in an fMRI study of dieters resisting good-tasting, but unhealthy, foods[12]. In this case, the effects of lateral prefrontal cortex on choice would be indirect and would be completely mediated by changes in value signals in other brain regions. This model could account for the dissociations in the TMS data if the lateral prefrontal cortex only comes online during choices involving immediate rewards. Furthermore, the modulatory role proposed for prefrontal activity in this model is similar in form to that proposed for other domains of cognition[14].

In either case, an important goal for future work is to understand the specific computations being performed in lateral prefrontal cortex. What causes lateral prefrontal cortex to be engaged during decision-making, why might it be engaged more in some decisions than in others and how does this computation affect processing in other brain regions? Previous work suggests several possibilities to be explored, including whether prefrontal cortex encodes behavioral goals, task contexts or decision rules. One speculation along these lines is that prefrontal cortex computes social costs. Being impatient and choosing the immediate reward might implicitly be regarded as a negative social signal, in the same way that accepting inequitable outcomes proposed by social partners, being taken advantage of, is a negative cue[15].

One reason a computational explanation is so important is that this level of understanding is most likely to inform translational efforts. From clinics to financial advice centers, there are ongoing efforts to promote more patient decisions, future-oriented choices that give greater weight to long-term, delayed outcomes. Public health campaigns try to persuade people to eat better, exercise and avoid smoking or using drugs. Financial advisors encourage people to save more for retirement and to avoid loans that are beyond their means. These practical efforts would be informed by an understanding of the computational mechanisms that are involved when people choose delayed rewards over immediate ones. On this front, the study of Figner and colleagues[1] provides an important step forward. By understanding the influence of lateral prefrontal cortex, perhaps we could all get a little more patience.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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Anxious interactions

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The molecular mechanisms responsible for anxiety remain largely unresolved. A study in this issue finds that an interaction between receptors for a hormone and a neurotransmitter regulates anxiety.

Fear is an important evolutionary force. Animals need to distinguish between different environmental factors and respond to aversive situations in a way that maximizes their chance of survival and that of their offspring. Normally, a fearful state protects us from potential danger or threat. In humans, however, certain environmental cues, such as being asked to give a speech in front of others, are able to trigger lasting behavioral changes that can be converted into maladaptive, pathological fear and anxiety. Giving a speech in front of an audience typically generates states of fear and normal anxiety, but those disappear once the talk has been completed. People with anxiety disorder[1], on the contrary, find it almost impossible to accomplish this task and have pathological anxiety states in response to even the suggestion of being invited to give an oral presentation. Unfortunately, we don't have a clear understanding of why this happens. The absence of clear pathological alterations in the brain of individuals with psychiatric disorders, such as anxiety and depression, is currently one of the most challenging aspects of neuroscience research. The quest to uncover these changes has led to the development of a multitude of hypotheses, many of which are focused on a single hormone or neurotransmitter. In this issue, Magalhaes *et al.*[2] connect two signaling systems that have been separately implicated in anxiety behaviors, finding that the two interact to induce anxiety.

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