This study raises the exciting possibility that mimicking the effects of fractalkine may control microglia activation and provide neuroprotection in a variety of neurological diseases featuring neuroinflammation. Some success has already been achieved in preclinical models of neurodegenerative diseases by targeting neuroinflammation through the inhibition of microglial activation with agents like minocycline, dextromethorphan or vasoactive intestinal peptide, or by suppression of specific microglial toxic effectors using iNOS antagonists or nonsteroidal anti-inflammatory drugs[1]. Among these, several (for example, minocycline) are currently being tested in clinical trials for Parkinson disease and ALS. We may envision that fractalkine agonists that can permeate the blood-brain barrier, should they become available, would be prime candidates in neuroprotective clinical trials for these incurable neurodegenerative diseases. However, stimulation of the fractalkine pathway may be a double-edged sword if not finely tuned, as it may also aggravate atherosclerosis[15]. Thus, fractalkine-based human clinical trials will need to begin by determining how these drugs may affect susceptibility to cardio- and cerebrovascular accident.

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When is enough enough?

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How does the decision-making process stop? Lo and Wang propose that a large-scale interconnected network encompassing parietal cortex, basal ganglia and motor structures controls the balance between speed and accuracy.

A hallmark of higher brain function is the ability to contemplate the world rather than to respond reflexively to it. Indeed, the roots of cognition rest in the brain's ability to process information in a time frame that is not governed by immediate changes in the environment or the need to move. Of course, with freedom comes responsibility. Detachment from sensory and motor time implies that the brain must determine when its own contemplative processes should start and stop. As we gather information and weigh possible options in everyday decisions, eventually we must commit one way or another, or move on. It may be prudent to take time to reach a carefully reasoned position, but if time is at a premium, the benefits of speed may trump accuracy or at least permit commitment even when uncertainty remains.

Over the past decade, the neurobiology of decision making has begun to yield insights into how the brain integrates information and expected value to make simple choices. However, an important piece of the puzzle has been missing: how does the process stop? What controls the balance between speed and accuracy? In this issue, Lo and Wang[1] suggest that the basal ganglia may hold the key.

Decisions are proposed to be based on the accumulation of evidence to a subjective criterion level or 'threshold'[2]. When the collected evidence in favor of one choice reaches this threshold, the brain makes a commitment; decision making is terminated. A high threshold means more evidence is collected before a decision is made, thereby reducing the probability of mistakes but increasing the response time. This framework explains the speed-accuracy tradeoff and suggests that the brain might adjust this threshold to optimize its rate of reward[3]. Although there is considerable behavioral and electrophysiological support for the accumulation of evidence in some tasks[4], a neural substrate for the adjustable threshold remains elusive. Lo and Wang propose a biophysically plausible candidate: detection of threshold crossing and tuning of the threshold take place in a large-scale interconnected network encompassing parietal cortex, basal ganglia and motor structures. Their multimodule computational model simulates all steps of decision formation in a reaction-time task.

The model was developed to address a simple kind of perceptual decision (**Fig. 1a**)[4]. In one version of this task, subjects (humans and monkeys) indicate their judgment of the direction of a random dot motion stimulus by making an eye movement (saccade) as soon as they make a decision. On easy trials, there is overwhelming evidence for one direction, leading to accurate, fast decisions. On difficult trials, when the motion direction is ambiguous, the evidence trickles in over time and accrues slowly and inconsistently. The choices are less accurate and slower[4,5]. Some of the key neurons responsible for motion processing and evidence accumulation have been identified using neural recording and stimulation in the monkey (see ref. 6 for citations).

The model of Lo and Wang begins by mimicking the responses of neurons in the lateral intraparietal area (LIP), which represent the accumulating evidence for one of the direction choices[6]. During decision making, LIP neurons respond with ramp-like changes in their firing rates. The activity rises when the monkey chooses the target in the cell's response field (**Fig. 1b**), and it declines for the opposite choice. Furthermore, the slope of this ramping activity is steeper for stronger motion, consistent with the accumulation of sensory information about direction of motion. Finally, for all strengths of motion, the buildup in the neuron's activity reaches a fixed level just before the saccade, in accordance with a threshold-crossing termination process[7] (**Fig. 1c**). Lo and Wang implement this cortical module using a neural network with fast and slow reverberatory dynamics (mediated by AMPA and NMDA conductances). Wang showed previously that this implementation

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could mimic the continuous accumulation of sensory evidence in LIP (ref. 8). However, the earlier model lacked a mechanism to detect when the activity of cortical neurons reaches a threshold to initiate the eye movement.

A natural candidate for this function is the superior colliculus (SC), an oculomotor structure in the midbrain that is involved in commanding eye movements. The SC receives inputs from the retina and visual cortex, as well as a strong input from cortical areas involved in planning eye movements, including area LIP. In fact, some SC neurons respond similarly to the very LIP neurons that are implicated in the motion decision task[9]. However, another class of neurons, known as burst cells, discharge immediately before the initiation of a saccade. They seem to act as a trigger for the movement itself. The all-or-none activity in these cells makes them suitable for detecting when the input from LIP (and perhaps other sources) exceeds a threshold. However, there is another important element in the circuit.

If burst neurons were set off every time the SC received information from the cortex about a possible eye movement, the eyes would be flitting about at the drop of a hat—or the beginning of a thought. Fortunately, the SC receives a tonic inhibitory input from the basal ganglia (the substantia nigra pars reticulata, SNr) that is thought to check the SC, thereby allowing the brain to make preliminary calculations before committing the motor system to action[10]. This tonic inhibition from SNr can be removed when cortical activity drives the caudate nucleus, which in turn inhibits SNr (**Fig. 1b**). This circuit seems to contain the key elements for establishing a threshold and sensing when the activity in cortical neurons—representing the mounting evidence for a decision—reaches a criterion.

Lo and Wang applied sophisticated theoretical tools to analyze this complex circuit. They began by developing a quasi-realistic neural network that successfully simulates the main elements: LIP neurons, as described above, that integrate evidence from the visual cortex and SC neurons that burst before saccades. We say "quasi-realistic" because the neurons in the model have synaptic conductances and action potentials, yet are simple enough to permit large-scale modeling of the kind usually carried out in unrealistic network simulations. The level of detail is just enough to allow Lo and Wang to gain a very useful insight. They asked where in this network the threshold could be set.

There are two possibilities: the strength of the LIP-to-SC connection and the strength of the tonic inhibition from SNr. Using a phase plane analysis borrowed from dynamical systems theory, Lo and Wang demonstrate that changing the strength of cortico-collicular synapses could modulate the decision threshold, but only over a very limited range of settings. It turns out that the circuitry that gives rise to the all-or-none bursting cannot achieve the desired flexibility over speed and accuracy seen in behavioral experiments[5]. On the other hand, the tonic inhibitory control from SNr permits greater flexibility, consistent with the general principle that the basal ganglia allows circuitry to behave as if it were going to produce an action although no body parts move (the seeds of thought, perhaps). As a result, cortico-caudal synapses have a dominant role in controlling the decision threshold.

This finding is especially interesting because the caudate receives projections from midbrain dopamine neurons. These neurons

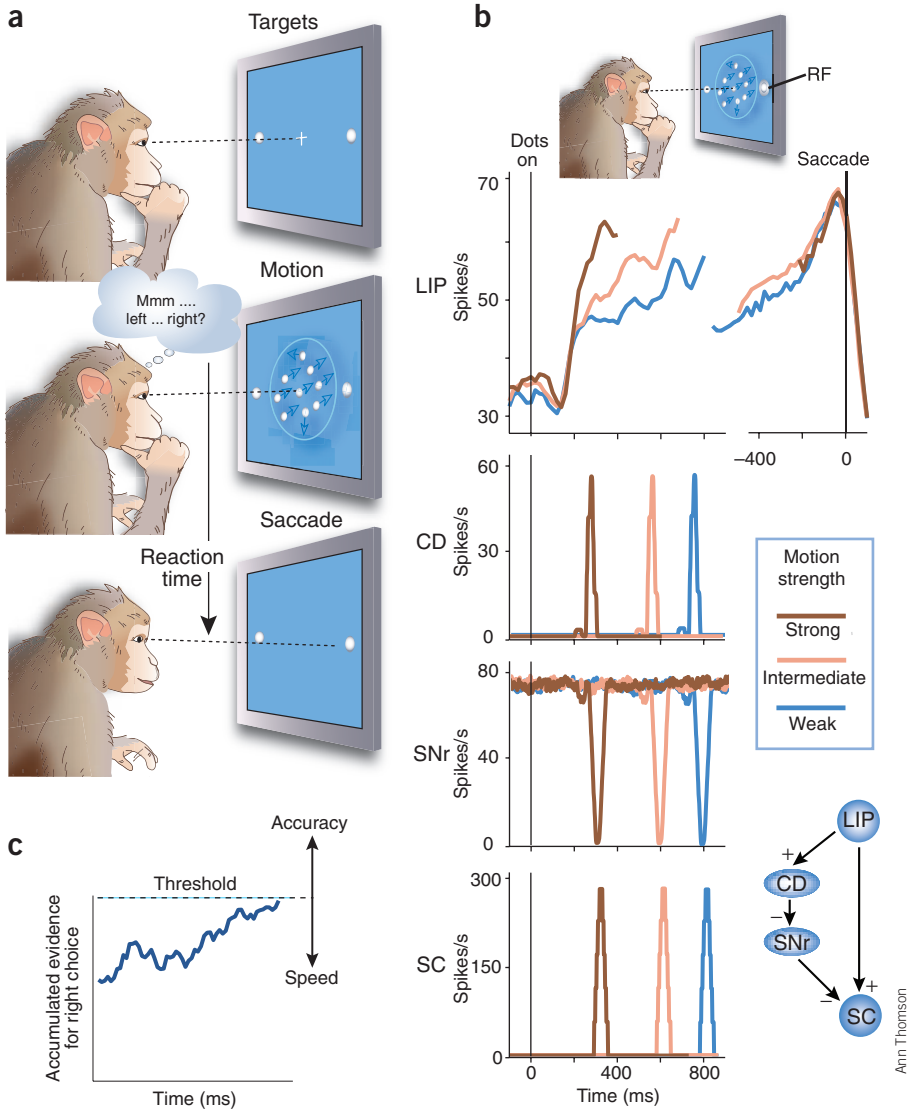

Figure 1 Model for decision making proposed by Lo and Wang. (**a**) Reaction time version of the direction discrimination task. The dynamic random dots persist until subjects indicate the perceived direction of motion by making an eye movement to one of the targets. (**b**) Neural responses from the key structures in the brain circuit (inset) proposed by Lo and Wang. Neurons in lateral intraparietal cortex (LIP) reflect accumulation of evidence in favor of the target located in their response field (RF). The threshold crossing in LIP is detected by neurons in the superior colliculus (SC), which trigger the motor response. The basal ganglia inhibit SC and adjust the threshold. A pause in this inhibition also contributes to the threshold detection in SC. The illustrated LIP activity comes from neural recordings[4]; the activity of basal ganglia and SC are generated by the model. CD, caudate; SNr, substantia nigra pars reticulata. (**c**) Sequential sampling model for decision making. The traces represent the accumulated evidence for the right direction choice. A decision is formed when the accumulated evidence for one of the choices reaches a criterion level or 'threshold'. This threshold is adjustable and governs the speed and accuracy of decision. Models of this type explain the speed and accuracy of decisions in the task shown in **a**.

convey reward-related signals[11], and their activity can strongly modulate cortico-striatal connections[12]. It has been hypothesized that monkeys might change their threshold to optimize reward rate in the motion discrimination task[3]. Reward-dependent plasticity in these connections could be responsible for altering the decision threshold to perform this optimization. It remains to be seen whether the mechanism hypothesized by Lo and Wang is actually responsible for flexible and optimal decision thresholds.

Although it is clear that a decision threshold is pivotal in a reaction-time setting, this basic mechanism need not be limited to situations where an explicit time pressure exists. Even when the environment establishes a definite epoch for decision making, people often reach decisions based on a limited amount of information. This is why the first five minutes of a job interview are so important. If you do not make a good first impression, you may not be deemed worthy of further consideration. It might seem like a poor strategy not to use all the available evidence for making a decision in these types of situations. However, there are costs associated with further deliberation, including the inability to consider other decisions during that time. Therefore, applying a decision threshold could be important even when there is no explicit time pressure.

This raises the intriguing possibility that the use of a decision threshold is ubiquitous in higher brain function. Threshold mechanisms are involved in target selection and saccade initiation[13]. A less obvious role for these mechanisms might be for use in memory retrieval. The idea of using bounded accumulation to understand memory retrieval receives support from psychological measurements of memory retrieval time[14], suggesting that similar mechanisms may operate in memory and perceptual decisions[15]. A decision threshold might also be useful for the perception of temporal intervals, which are essential for learning relationships between observations, inferring causes and consequences, and anticipating events. Indeed a 'done now' signal may be useful for flexible sequencing of behavior. This signal is what the brain needs to operate on a time frame that transcends reflexivity. It requires neurons that can detect the threshold crossing without being strongly tied to a motor response, such as the caudate neurons in the model.

Is there enough realism in Lo and Wang's model to lend credibility to their insights? Therein lies the art of computational neuroscience. In our view, the computational modeling of Lo and Wang should be viewed as an important step in the march from principle to circuits and cells. It is a critical part of the translational pathway from principles of systems neuroscience to a biological level of understanding that will produce treatments for disorders of higher function. The path in this case travels from mathematical formulations of the decision process to its neural correlates in the brain and the uncovering of computational mechanisms like integration and threshold crossings. The next step is to understand how these operations are achieved by real neural circuits. This is an exciting area that will require experiments motivated in part by the type of quasi-realistic modeling of simplified neural circuits exemplified by the new paper. This balance between simplification and mechanistic insight may be of the very same nature as the balance between speed and accuracy in simple decisions. As Lo and Wang conclude, there is wisdom in preserving flexibility in this balance.

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The ebb and flow of attention in the human brain

Trey Hedden & John D E Gabrieli

Lapses in attention can impair performance independent of the task. A new imaging study reports that reduced activity in prefrontal attentional control regions at the beginning of a trial predicts longer reaction times.

In 1988, world champion speed skater Dan Jansen entered the Winter Olympics as a heavy favorite, but—perhaps preoccupied by the recent death of his sister—he slipped and fell in both the 500- and 1,000-meter events. In the next Winter Olympics, a small stumble left Jansen in fourth place, a third of a second behind the gold medal winner. Making a final attempt for an Olympic medal in 1994, Jansen lost his balance and managed only eighth place in the 500 meters, an event in which he was the world record holder. Yet in the 1,000 meters, Jansen not only won the gold medal, but also broke the world record in the process.

Although the stakes are rarely so high, performance in everyday tasks can vary tremendously within the same individual. One moment we are efficient; the next moment we have a lapse of attention and make an error. One source of variability is the occasional lapses of attention that can be caused by multitasking, daydreaming or an inability to block out distracting thoughts or environmental stimuli. Using functional magnetic resonance imaging (fMRI), in this issue, Weissman and colleagues have begun to illuminate the neural correlates of such lapses in attention on a moment-to-moment time scale[1].

The authors used a straightforward, yet sophisticated, technique. They measured localized blood flow with event-related fMRI during individual trials, and then correlated it with how long participants took to respond to each trial ('reaction time'). Participants identified the letters H or S in the global/local task[2], in which a large (global) letter is made up of smaller (local) letters, and pressed one button for S and another button for H. Sometimes they had to identify the global letter, and other times the local letters. The global

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