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A Timely Debate About the Brain

Neuroscientists have recently shown that multiple brain regions are used to judge short intervals, but fierce disagreement continues over how neurons in those regions measure time

YUDHIJIT BHATTACHARJEE

ANY DRIVER WILL AGREE THAT A YELLOW light at a traffic intersection presents a conundrum. Should one hit the brakes to stop or keep going—speeding, if necessary, to beat the red light? A number of factors could influence the choice, including the degree of recklessness of the driver, the urgency of the trip, and, not least, whether a police car is in sight. But the key element in the decision is the person's estimate of how much time it will take for the signal to turn red.

Time is integral to myriad other questions in everyday life: how long to grill one side of a burger before flipping it, how long to let a phone ring before hanging up, or how long to wait during a pause in conversation before treating it as a speaking cue. In both people and animals, the brain's ability to keep track of intervals is fundamental to innumerable behaviors. Some, such as walking and singing, rely on timing on the order of tens to hundreds of milliseconds. Others, such as foraging and making decisions, including the yellow-light problem, involve judgment of intervals on the scale of seconds to minutes and hours. As Warren Meck, a cognitive neuroscientist at Duke University in Durham, North Carolina, puts it: "Timing is everything."

For decades, researchers have sought to uncover the neural basis of time perception. They've been motivated in part by success at understanding the circadian clock: the biological timer that regulates the day-night cycle. In mammals, this 24-hour timepiece has a specific home: the brain's hypothalamus. Not surpris-

ingly, scientists have hoped to discover a localized structure somewhere in the brain dedicated to tracking shorter time intervals. But now, timing researchers are all but abandoning the search for such an interval timer in any single region of the brain. Instead, they are increasingly convinced that the brain judges intervals on short time scales—milliseconds to minutes and hours—with the help of a distributed network of neurons. This shift is being driven by a slew of findings from electrophysiological studies on animals, behavioral experiments involving patients with brain lesions, and neuroimaging studies of healthy people.

"We're finally getting some neural reality into the picture."

—Russell Church, Brown University

In addition to identifying the different brain regions that play a role in timing, these experiments are prompting scientists to reexamine the classic view of how neurons keep track of time. And even though that has not yet led to a mechanistic account that satisfies everybody, researchers say the effort is helping to take timing research beyond the speculative realm of psychology into the firmer territory of neuroscience. "We're finally getting some neural reality into the picture," says Russell Church, a psychologist at Brown University, who has studied timing for more than 30 years.

A distributed timekeeper

Inspired by the hypothalamic circadian clock, researchers began looking for a short-time-scale clock in the brain in the 1970s. Some focused on the hippocampus, assuming that time perception was related to memory. Others searched the cerebellum. By the mid-1990s, many were convinced that the clock was located in the basal ganglia.

Yet in recent years, neuroscientists have linked multiple areas throughout the cortex to time perception. Some evidence has come from neuronal recordings in animal brains. In 2003, for example, Michael Shadlen, a neuroscientist at the University of Washington, Seattle, and his graduate student Matthew Leon reported training monkeys to make eye movements based on duration judgments in the range of 0.3 to 1 second. The two found

that neurons in the animals' posterior parietal cortex increased their firing rate based on how much time had elapsed. The results suggested that these neurons track the flow of time relative to a remembered duration. Other teams of researchers, including one led by Yoshio Sakurai of Kyoto University in Japan, and a group led by Carlos Brody at Cold Spring Harbor Laboratory in New York, have observed similar patterns of neuronal activity in the prefrontal cortex of monkeys performing timing tasks.

Evidence for the involvement of different cortical areas in timing has also come from

studies of patients with brain lesions. In 2002, a team led by Giacomo Koch, then at Italy's University of Rome, reported on a patient with a prefrontal cortical lesion who underestimated durations of a few seconds—time to him seemed to pass more quickly than it actually did. The same year, a group led by Marc Wittmann of Ludwig Maximilians University in Munich, Germany, described patients with lesions in other cortical areas who also underestimated durations longer than 3.5 seconds. Then in 2003, Koch and his colleagues showed that they could induce healthy subjects to underestimate multisecond intervals by suppressing their prefrontal cortices with a focused magnetic field.

Some of the clearest evidence for a distributed picture of timing has come from neuroimaging studies. In one such study, researchers in France asked 12 subjects to compare the color and duration of two circles presented one after the other on a computer screen (*Science*, 5 March 2004, p. 1506). Each circle was colored one of three shades of purple and stayed on for one of three durations: 0.5, 1, or 1.6 seconds. In some trials, the subjects had to indicate if the second circle was bluer or redder than the first; in others they judged if the second circle appeared for a longer or shorter duration.

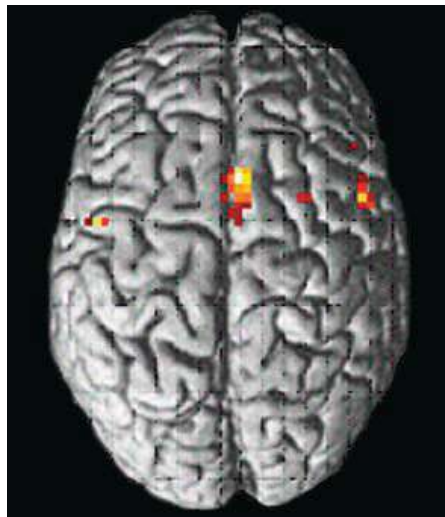
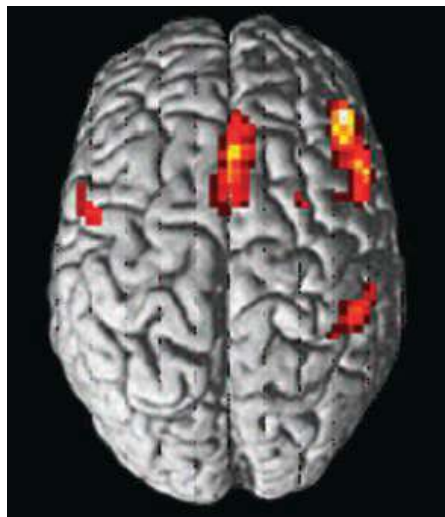
Functional magnetic resonance imaging scans of the volunteers showed activation of an extensive network of brain areas during the time estimation task; in contrast, only the V4 area of the visual cortex lit up during the color-judgment task. Also, the various areas that lit up during the timing task—including the prefrontal and parietal cortices and the basal ganglia—showed increases in activity as the subjects paid more attention to time.

“Although visual features such as color or motion or form can be linked to single-feature-specific processing areas, timing information appears to be coded in a distributed network of brain regions,” says Jennifer Coull, a cognitive neuroscientist at the Centre National de la Recherche Scientifique in Marseille, France, and lead author of the study. “Maybe we have to integrate several sources of information in order to estimate time because it is so much less tangible to our senses than visual features.”

In the August issue of *Human Brain Mapping*, a different French group led by Viviane Pouthas of the Salpêtrière Hospital in Paris reported activation in a similar set of brain regions when subjects timed intervals that were about 0.5 and 1.5 seconds long. The researchers also observed that a subset of these regions—including certain areas of the cortex and the striatum—showed higher activity when subjects estimated the longer duration. Pouthas says this subset could be playing a direct role in time estimation, distinct from other components of the task such as recalling and comparing intervals.

How it works: The old and the new

Although most researchers are now convinced that timing involves multiple regions of the brain, they disagree on how neurons actually keep track of time. Until recently, the prevailing theory had been that some neurons release pulses of one or more neurotransmitters at periodic intervals while other neurons accumulate them, in the same way that a cup placed under a steadily dripping faucet accumulates drops of water. As the receiving



Spread out. Multiple brain regions are activated in a time-estimation task (*top*); a few of these regions (*bottom*) show increased activation while estimating longer intervals.

neurons register more and more signals, the sense of time that has passed grows. Moreover, quantities of accumulated pulses corresponding to specific durations are recorded in long-term memory, allowing an individual to compare newly encountered time intervals to those previously experienced.

This account of time perception—known as the pacemaker-accumulator model—has held sway since it was proposed in the 1970s

by the late John Gibbon, a psychologist at Columbia University. Researchers have found the model to be a handy framework for explaining a fundamental feature of timing, seen in both animals and humans, called the scalar property—which is that the amount of error in estimating time intervals increases linearly with the duration being timed. The model has also provided psychologists with a good handle on a variety of other behavioral findings related to timing.

But now it is being challenged by some as too simplistic—and perhaps even fundamentally flawed. One challenger is Meck, a protégé of Gibbon and once a strong proponent of the pacemaker model. His group has recently put forth a new idea that has garnered support from many in the field but strong criticism from others.

Meck spent the 1980s and the early 1990s seeking to identify the neural pieces of the pacemaker-accumulator model. Although this system could in theory operate in a specific brain region, it could also involve multiple regions, as might be expected by the more recently embraced idea of a distributed neural network. Working with Chara Malapani, a clinical psychiatrist at the New York Psychiatric Institute in New York City, and others, Meck proposed in the mid-1990s that the brain's stopwatch was located in the basal ganglia, comprising dopamine-secreting “pacemaker” neurons in the substantia nigra and “accumulator” neurons in the striatum. Some of the evidence for this hypothesis came from studies of Parkinson's disease patients, whose poor performance on timing tasks was found to be linked to the loss of dopamine-producing neurons. Researchers found that medicating these patients with L-DOPA, a drug that increases dopamine levels, improved their timing.

Even though the dopamine work seemed to put flesh on the pacemaker theory, the model ran into trouble a few years later. At the time, Meck was already somewhat skeptical about the capacity of neurons to linearly sum up temporal pulses over the course of seconds to minutes. Then one of his doctoral students, Matthew Matell, marshaled evidence from the neurobiological literature that convinced Meck that dopamine could not drive neurons in the striatum to fire in the simplistic way proposed by the pacemaker model.

Meck and Matell have developed an alternative model in which the striatum reads out intervals from a snapshot of activity across a network of cortical neurons. The different neural populations in the cortex—all connected to neurons in the striatum—have firing rates that oscillate at different frequencies. At any given point, the pattern of activity across the cortical network—the synchronous firing by a certain ensemble of

neurons—represents the brain’s temporal signal, a distributed code that Matell calls the “clock input.”

When an event has to be timed, the cortical clock is reset through a synchronization of neuronal firing in the network. The neurons in the striatum track the evolving network’s

tum acts as a listener,” says Matell. “When the musical piece comes to a point where the violins and the flutes and the tympani all co-occur—that is, when a particular ensemble pattern of neurons is simultaneously active—the listener decides that a particular duration has elapsed. One could take this analogy further

and propose that attention or consciousness serves as the conductor of the symphony.”

The new model, which Meck and Matell have named the striatal beat frequency (SBF) model, represents a dramatic shift from the pacemaker model because it fundamentally rejects the intuitive

that comes as naturally to neurons as does coincidence detection.”

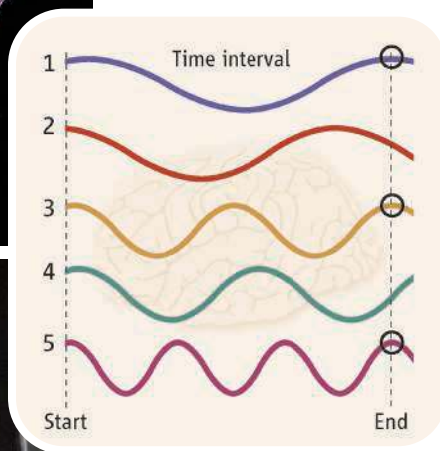
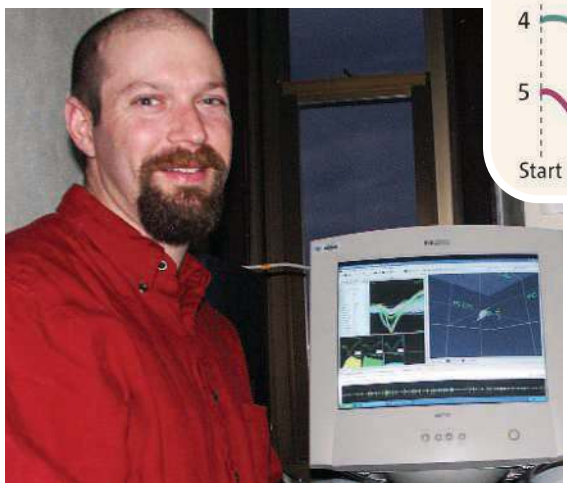
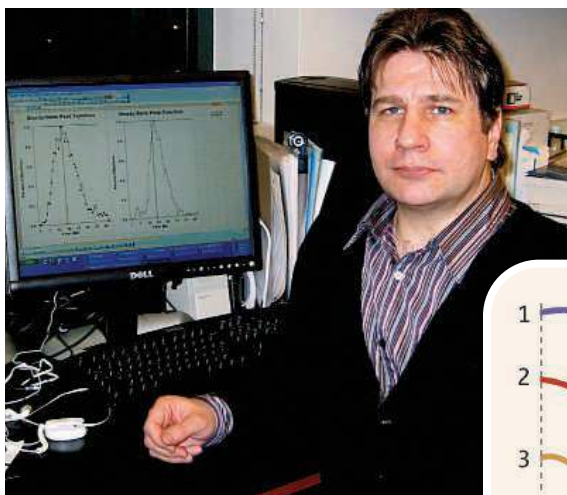
Not everybody has been as kind. “Pure fantasy” is how Shadlen describes the model. “Synchronous spikes are ubiquitous in the cortex; there are thousands of neurons firing simultaneously at any given time,” he says, arguing that it’s unrealistic to think that such widespread patterns might serve as distinct temporal codes. Shadlen contends that it’s more likely that “time is wrapped up inextricably with expectation” and is represented as part of an anticipatory buildup signal (in line with the pacemaker idea) in each of the cortical areas that might be involved in carrying out a task. As evidence, Shadlen points to work that he and a colleague reported in *Nature Neuroscience* last year in which they recorded such ramplike activity from neurons in the posterior parietal cortices of monkeys that performed eye movements based on time estimates.

The precise pattern of coincident activity in the cortex changes over time and could thus serve as a duration code, responds Matell. “Using the symphony analogy, there are many musicians playing pretty much throughout a piece of music. And yet, the piece of music is distinguishable at one point in the piece from another point in the piece.” Matell adds that the neurons recorded in Shadlen’s monkey experiments could be firing in response to a temporal readout provided by the striatum rather than representing time themselves.

John Wearden, a psychologist at Keele University in the U.K., levels another charge against the SBF model and similar ideas sometimes grouped as nonclock models. Because different times in the SBF model are represented as different patterns of neuronal activity, he says, there’s no way to tell if one interval is longer than another, even though that’s something people naturally judge all the time.

The SBF model permits such comparisons, counters Matell: “If you provided me with two durations, I could time the first duration—let’s say that’s the longer one—learn its cortical snapshot, and then evaluate whether the second cue finished before my ‘time’s up’ for the first or vice versa,” he says.

Trying to address some of the field’s skepticism, Meck and Matell are looking to refine and test their model by recording neurons from multiple sites in rat brains, and by electrophysiological and neuroimaging studies of Parkinson’s disease patients. Regardless of whether the SBF model survives, they and many others feel there’s little chance of returning to the classic view of a discrete hourglass in a single brain region. As Buonomano puts it, “The notion that timing relies on a centralized single pacemaker-accumulator is on its deathbed.”



The right moment. Warren Meck (*top*) and Matthew Matell (*bottom*) propose that striatal neurons recognize a learned interval from detecting the pattern of coincident activity across different neural populations. The input from populations that are active at that instant (1, 3, and 5) cause the striatal neurons to step up their firing rate, marking an interval’s end.

activity, until some kind of reinforcement arrives, marking the end of the timed interval: a pellet of food for a rat in a timing experiment, or the change of light for a driver at a traffic intersection. Each reinforcement triggers the substantia nigra to release a wave of dopamine onto striatal neurons, helping to establish a link between their firing and the pattern of activity in the network at that moment. After a number of experiences with a given duration, the striatal neurons start to recognize the snapshot of coincident activity at the moment of reinforcement and are driven to intensify their firing at that moment, indicating that the timed interval is up. This snapshot is filed away in memory for future reference, although Meck and Matell’s model doesn’t fully explain how this is done.

“You could imagine the cortical network as a symphony playing a concerto, while the stri-

atum acts as a listener,” says Matell. “When the musical piece comes to a point where the violins and the flutes and the tympani all co-occur—that is, when a particular ensemble pattern of neurons is simultaneously active—the listener decides that a particular duration has elapsed. One could take this analogy further and propose that attention or consciousness serves as the conductor of the symphony.”

The new model, which Meck and Matell have named the striatal beat frequency (SBF) model, represents a dramatic shift from the pacemaker model because it fundamentally rejects the intuitive

notion of time flowing like sand in an hourglass, collecting in a heap as the moments pass. Not only does the new model predict the scalar property of timing, say the two researchers, it is supported by neurophysiological findings. In experiments in which rats were trained to estimate a 40-second duration, Meck, Matell, and a colleague found that the firing rate of striatal neurons peaked at the end of the trained interval, as predicted by the SBF model. Meck and Matell say the recent studies pointing to a distributed picture of timing buttress their theory.

The SBF model “elegantly allows for the timing of multiple intervals and higher-order temporal structure,” says Dean Buonomano, a cognitive neuroscientist at the University of California, Los Angeles. “But more importantly, it eliminates the need of an accumulator: Counting is not a computation