Stanford scientists uncover how brain regions keep each other on track

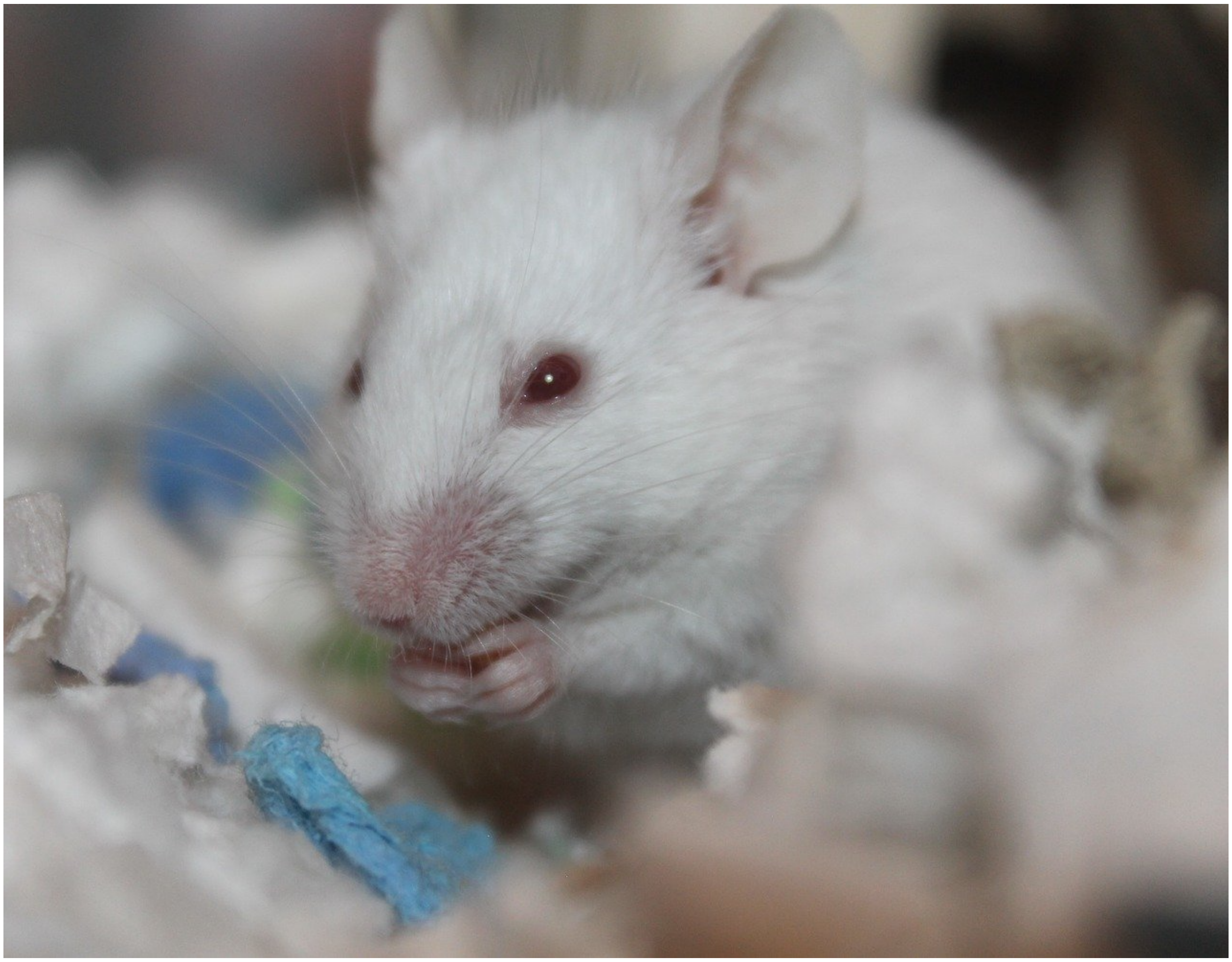


Image Credit: Pixabay

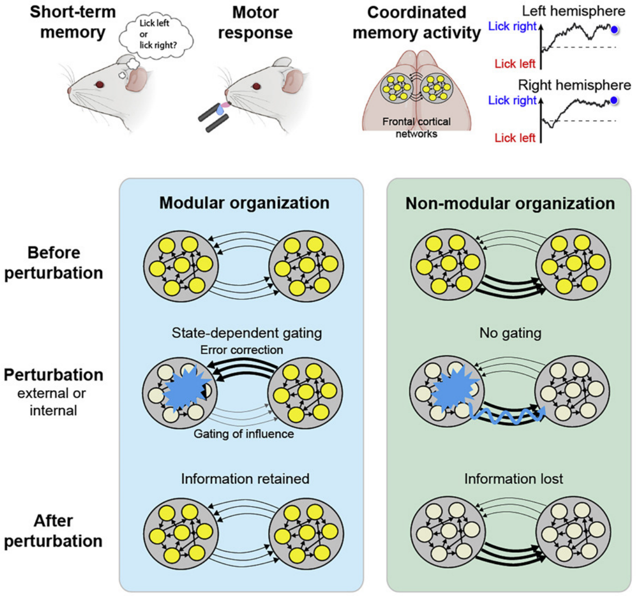
By Grace Huckins

Before smartphones, memorizing phone numbers for ten or twenty seconds—in the time it took to get from the phonebook to a landline, or from a helpful gas-station attendant to the payphone just outside—was a frequent requirement for functioning in the world. Fortunately, there's an easy, near-foolproof way to do it: just repeat the number to yourself in your head, over and over, until it finally comes time to punch it in.

Strangely enough, that's pretty much how the subconscious brain solves the problem of short-term memory, too. Say you're in a job interview, and you have to keep in mind your interviewer's question while crafting an answer. Or even simpler: You're participating in a psychological experiment where you have to remember the position of a red dot on the screen after it disappears. Much like someone repeating a phone number to themselves, a population of your neurons will remain active after the dot blinks off, persistently recording its location so you can access that information once you need it. It's because some neurons have the ability to stay active for short periods so that we can keep track of what we are doing, follow conversations, and, yes, remember phone numbers for a minute or two.

But maintaining patterns of neuronal activity isn't trivial. Just like being interrupted by someone while walking from phonebook to landline might completely erase a phone number from your mind, so too can neuronal interruptions cause failures of short-term memory. Scientists theorize that distributed networks of neurons support each other in maintaining that persistent activity—if one node in the network fails to maintain the right activity pattern, another node can help restore that pattern. But that approach also opens the brain to risk: if the information in one part of the network gets corrupted, that corruption might conceivably spread to the rest of the network, like a child spreading a misheard word in a game of telephone. Somehow, brain regions have to figure out how to let good information in and keep bad information out.

To figure out how the brain solves this problem, a group of scientists led by Prof. Shaul Druckmann at Stanford University and Prof. Nuo Li at Baylor College of Medicine investigated a small short-term memory network in mice. In order to engage the animals' short-term memory, the researchers trained them to do a task in which their whiskers were stimulated either toward the front or the back, and they had to—after a delay—report the position of the stimulation by licking to the left or the right. It's this delay that was crucial; persistent activity in a brain region called the anterior lateral motor cortex (ALM) allowed the mouse to recall the necessary information while waiting to make its choice. There are, in fact, two ALMs in the brain—one in the left hemisphere, and another in the right—and they are connected to each other via the corpus collosum, the bundle of nerve fibers that bridges the brain's two halves. Previous research has shown that the ALMs support each other in storing that information. But how exactly does this support work?



Answering this question took some dedicated experimental work. Typically, neuroscientists only record from a single brain region at once. For this study, though, the team had to look at both ALMs at once, which required two recordings, and then perturb one of the ALMs, which required a third tool. But meeting these experimental challenges allowed the team to get more insight into this brain network, and these sorts of patterns of brain activity in general, than had ever before been possible.

“What was cool about this particular paper is that we were able to take simultaneous population activity measured in more than one area, and then infer something about how these areas interact, and have this inference predict something completely different,” Druckmann says.

To make those inferences, the team disrupted the activity in either the left or right ALM and observed whether the opposite region could maintain its own activity. In some mice, when one ALM was effectively shut off, that disruption crossed over into the other and effectively abolished the memory. But in other mice, the unaffected ALM retained its persistent activity, in a display of the robustness such network structures are thought to facilitate. And in those mice where the non-disrupted ALM maintained its activity, the other ALM was able to effectively recover and return to that same pattern of activity when it was no longer disrupted. Crucially, the extent to which the disrupted ALM recovered was indeed able to predict “something completely different”—namely, the mouse’s performance on the task—which suggests that these differences were relevant to behavior and not merely an interesting, but inconsequential, observation.

In the more successful mice, one ALM stepped in to remind its partner of the necessary information when the other got distracted, like a pair of friends trying to remember a phone number together. The downside of this strategy is that the distracted friend could instead interrupt their partner. The team hypothesized that, to avoid this risk, each ALM might switch between two states—one where it received information from its partner, and another where it blocked that information. They fit a model where ALMs that strongly encoded the mouse’s choice were in one state, and ALMs without strong encoding were in another state, to their data. In the strongly encoded state, they found, ALMs received very little information from their counterparts; in the weakly encoded state, they received a lot of information. In other words, when the ALM knew what it was doing, it worked to ignore all distractions, including its partner; but when lost, it asked for help.

Druckmann thinks that this state-switching mechanism isn’t just unique to the ALM, since other brain regions show sometimes-perplexing patterns of dynamics. Perturbations that should in principle affect brain activity in a given region, for example, may not end up having any impact at all, perhaps because another brain region is supporting the original pattern of activity. Better understanding these unexpected phenomena, Druckmann says, could improve not only our understanding of the brain but also how we treat its illnesses. In the past several years, brain stimulation has become a far more common treatment for conditions like depression, but it can be difficult to figure out just how to stimulate the brain to elicit the desired effect. “Soon it won’t be a technological limitation of how many electrodes you can put in and how much current,” Druckmann says. “It will be, How do we actually plan a perturbation to make the condition better?” He hopes that neuroscientists, by probing the complexities of brain network dynamics, can eventually help clinicians design and target more effective treatments.

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