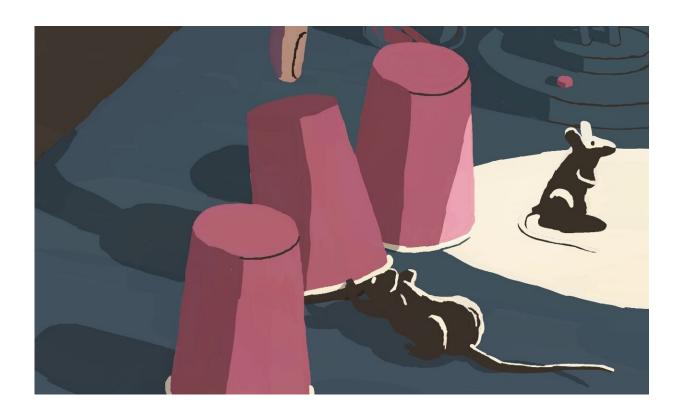# Mice 'detectives' hint at how humans read between the lines

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Where's the prize? Thanks to their inference skills, mice are just as likely to find it as humans. Credit: Diogo Matias

Some people are annoyingly good at "reading between the lines." They seem to know, well before anyone else, who is the killer in a movie, or the meaning of an abstract poem. What these people are endowed with is a strong inference capability—using indirect evidence to figure out

hidden information.

But inference is not a skill possessed by the lucky few. On the contrary—everyone uses inference regularly, often without realizing it because it comes so naturally. It has been crucial for human survival, used it to figure out when and where to search for food by genetic ancestors. For instance, humans used indirect evidence, such as faint rustling sounds in the vegetation or the presence of half-eaten leaves to infer that a rabbit must be near.

Even though inference plays such an important role, neuroscientists have long struggled to understand how it is actually generated in the brain. One approach has been to design experiments that tap into this cognitive skill in rodents, who are much more like us than most people realize.

However, designing experimental tasks to probe inference in rodents has proven to be a challenge. While some tasks turned out to be too difficult, others gave ambiguous results, as they could also be solved with less sophisticated strategies.

Now, scientists at the Champalimaud Centre for the Unknown in Lisbon, Portugal, found a way out of the dilemma. In their study, published today (February 11th) in the scientific journal *Neuron*, the team presents their elegant experimental design, along with an identification of key brain regions involved, and a matching video-game version for humans.

A puzzle worthy of a mouse detective

Zachary Mainen, the principal investigator who headed the study, believes the new test is more compatible with the nature of mice. "Instead of imposing conditions where the mice would have to behave like 'little humans,' we decided to create a task that would feel more natural to the mouse, relying on its innate foraging skills—the same

skills it relies on when searching for food or water."

In the experiment, mice had to use inference to discover the location of a water reward. "The water reward could, at any given moment, be available at one of two water spouts. If the mice were successful in piecing together the evidence, they would optimize their behavior, switching between spouts to receive a reward with minimal delay," Mainen explains.

The location of the reward was controlled by two independent variables, both of which were unknown to the mice. "The mice had to infer what those variables were by trial and error, gradually deciphering the rules of the game," says Pietro Vertechi, an author of the study.

The first variable was the probability of receiving water at the active water spout. "Even when a spout was active, it didn't always give water. The mice had to realize that the lack of water on any given try didn't necessarily mean that the spout wasn't active," Vertechi explains.

The second variable added more complexity to the task: the probability that the spouts would switch between the active and the inactive state (which effectively means switching the location of the reward) was set at a certain value, which the mice also had to figure out.

This design enabled the researchers to control precisely how challenging the experiment would be. For instance, a relatively easy scenario would have high probabilities of both receiving a water reward and of a location switch. In that case, lack of a water reward would likely mean that the mouse was at the wrong spout.

On the other hand, it would be much more difficult for the mice to decide what to do if both probabilities were low. In that case, lack of water on a given try wasn't a very strong indication that switching had

happened.

Sniffing out the rules of the game

Surprisingly, the mice were able to figure out quite quickly what was going on. "They optimized their behavior within few sessions," says Vertechi, "adjusting the number of attempts at a spout according to the rules of the game. As a result, they tolerated many more failures in the hard, uninformative condition than in the easy one."

The scientists considered it impressive that mice could master this complex task. But how did they show that these results were compatible with inference and not another problem-solving strategy?

According to Eran Lottem, an author of the study, the standard strategy rodents are thought to apply would have resulted in a completely different outcome. "Researchers generally believe that mice are driven by the direct rate of reward. If that was the case, they would just stay at the spout that gave them more reward on average, and keep trying for much longer at that spout, even after it had become inactive. Instead, our mice switched as soon as they were certain that their spout was no longer active, no matter how rewarding it had been in the past. This strongly supports that what the mice were doing was inference."

Mouse versus human

To directly compare performance across species, the team developed a version of the task for humans. "This is also a kind of a 'foraging' task, but this time, instead of searching for water, the subjects were searching for prey," says Dario Sarra, another author of the study.

In the human version, subjects played a video game in which the hidden

information was the location of a monster that was hiding behind a castle. The goal was to hit the monster by throwing rocks. Just like the mice, the subjects had to figure out two sets of variables: the probability of being able to hit the monster when in the right location, and the probability of a location switch.

Their results demonstrated that mice and humans solve the task in a remarkably similar manner. "Not only was the strategy practically exactly the same, we found that both species are sensitive to the same challenges," says Sarra. "Specifically, the inference process took longer, in both species, when the probabilities of reward and state-switch were low, creating overall higher uncertainty. However, regardless of difficulty, humans figured out what was going on much faster than the mice, reaching optimal performance already in the first session."

According to Mainen, their results imply that "video games make mice out of us. Some video games, like the one we developed, tap into fundamental behaviors, in this case foraging. We were surprised to find that both species behaved so similarly. But then again, it just goes to show how much these two species have in common."

Next steps

The team intends to use the human and the mouse versions of the task as a tool to study the neural mechanisms underlying this cognitive process. "In this study, we started exploring some of these questions. Particularly, we observed that a brain area called the orbitofrontal cortex played a key role in the inference process. In trials where the orbitofrontal cortex was inactivated, mice reverted to a simpler, more naive strategy. This is an exciting finding, that will help us move forward with deeper investigation into how inference happens in the brain," says Mainen.

In addition, the team is curious to see whether the video game version of

the task could be used to characterize specific psychological profiles. "For instance," Vertechi explains, "Do people that suffer from impulse control disorders, or depression, tend to adopt specific strategies? If we find that the answer to this question is yes, then we could take advantage of the analogous rodent task to assess neural mechanisms underlying these specific profiles," he concludes.

More information: *Neuron* (2020). DOI: 10.1016/j.neuron.2020.01.017

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