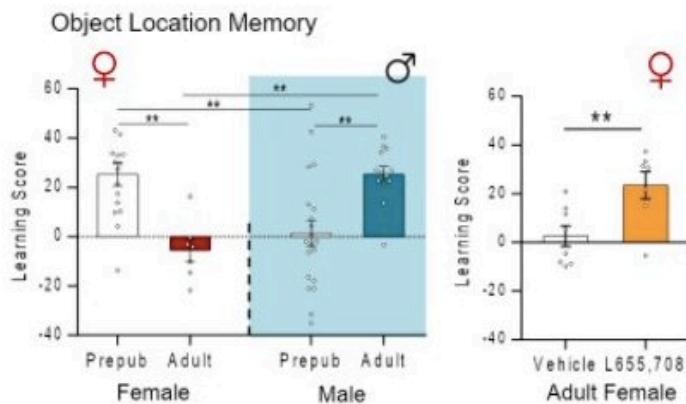


# Study finds that hippocampal learning worsens in female rodents and improves in males during puberty

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## Sex- and age-dependent differences in spatial learning.

Graphs show performance in an Object Location Memory task in which mice were tested for recognition of an object that was moved to a novel location. Left graph shows that, given 5 minutes of training, prepubescent females perform learn the object location whereas adult males do not. In males the opposite pattern is observed: prepubescent males fail to learn whereas learning is robust in adults. Right graph shows that treatment of adult females with a function blocker (L655,708) for the inhibitory synapse protein,  $\alpha 5$  GABA<sub>A</sub> receptor subunit restores learning in adult females to levels seen before puberty.

Credit: Christine M. Gall

Neuroscience research suggests that adult male rodents and humans perform better than females on spatial tasks. These are tasks that involve the ability to understand and remember the spatial relationships between different objects in space.

Past findings also suggest that males have a lower threshold for the long-term potentiation (LTP) of synapses in the CA3 and CA1 regions of hippocampus, which are known to be associated with learning and memory. While these findings agree with several past studies, knowledge of the cellular mechanisms of LTP and learning have come from studies of male rodents, instead of comparing mechanisms of males with those of [females](#) at different stages of development.

Researchers at University of California, Irvine have recently carried out a study investigating sex differences in LTP and memory that might emerge during adolescence. Interestingly, their findings, published in *Nature Neuroscience*, suggest that hippocampal spatial learning is in fact better in prepubescent female rodents, yet this trend is reversed in adulthood. The recent study was primarily conducted by Aliza A. Le, a graduate student at UC Irvine, under the supervision of Christine M. Gall and Gary Lynch.

"My colleague Gary Lynch and I have been studying mechanisms of LTP and hippocampus based learning, for some time now," Christine M. Gall, one of the researchers who carried out the study, told MedicalXpress. "In 2018, we published a paper reporting sex differences in the specific mechanisms of potentiation in hippocampal CA1, which is the area we study in this particular paper."

CA1 is one of the primary brain regions examined when investigating the neural mechanisms of learning. The first reason for this is that it is a simply organized structure, thus it is easy to image and study. The second is that it is known to be associated with spatial learning and

episodic memory (i.e., personal memories of everyday events).

"Gabrielle Rune in Germany was the first to report that LTP depended on estrogen in females and not in males," Gall explained. "Based on these findings, my research team and I worked out some of the chemical signaling pathways at the synapse that underlie this sex difference between males and females and also showed that in females they had a higher LTP threshold."

In their previous work, Gall, Lynch and their colleagues found that it was harder to induce LTP in female rodents than in males. As LTP is thought to be a primary cellular mechanism behind learning, their findings suggested that females learn spatial tasks at a different or slower pace than males.

"LTP is the change that occurs in your brain with at least some forms of learning," Gall said. "Our findings suggested there would be a different learning threshold in females and our findings showed that this was the case."

The researchers observed that when learning to complete spatial tasks, which are known to be associated with activity in the hippocampal CA1 region, females required a bit more training than males. Given that one of the key differences between the sexes is estrogen, a hormone that plays a key role in the reproductive development of females, Gall and her colleagues decided to take a closer look at LTP and hippocampal learning in females before and after puberty, which is when estrogen levels increase in females.

"Originally, we thought there would be no sex differences before puberty, but that was not the case," Gall explained. "We found that there was a very robust sex difference, but we were really surprised to find that females had a lower threshold for both LTP and learning than did

males. So, before puberty they learned more readily and with less training than males and it took less electrical stimulation to elicit LTP in the females than males."

The researchers then tried to block the major estrogen receptor that mediated synaptic plasticity in the female rodents' brain. They found that hippocampal learning was influenced by the same estrogen receptor both before and after puberty.

"In our recent study, we took a step back from what had observed in adult rodents, to see if the LTP threshold was different and found that this functional plasticity was more readily induced in females," Gall said. "First, we firmly documented this statistically and then we started testing hypotheses as to what the difference we observed might be."

When conducting their experiments, the researchers relied on the expertise of Lynch, who has been conducting electrophysiology-based experiments focusing on the CA1 and CA3 hippocampal regions for a long time. Based on the findings he gathered in his previous studies, Lynch hypothesized that changes in inhibition might be at the root of the changes in LTP and learning observed in females.

"When you stimulate brain regions over time, normally a few things happen," Gall explained. "If you apply four short pulses, normally there's an increase in response and then it declines. That's because the first response also activates inhibitory interneurons, which suppress later responses in a short train. That suppression was not evident prior to puberty."

Essentially, the researchers observed that before puberty, female rodents did not exhibit this inhibition (i.e., a period during which neuronal responses are suppressed). This observation inspired them to further examine specific responses that could be associated with the activity of

an excitatory receptor, known as the NMDA receptor.

"We were getting greater activation of the NMDA receptors in the females," Gall said.

"This would be consistent with changes in inhibition occurring in females during puberty."

In their experiments, the team also used a technique for looking at proteins at synapses, developed by their lab. While there are other existing methods for examining proteins at a high resolution, most of these are slow and do not evaluate large numbers of synapses.

On the other hand, the analytical technique created by Gall and her colleagues can be used to simply take images of tens of thousands of synapses within a shorter time frame and to measure proteins at those synapses using automated systems. This approach can be used to quantify GABA receptors and NMDA receptors, as well as inhibitory synapses, in a rodent's brain at different points in time.

"We found that there wasn't a change in the number of inhibitory synapses with age, but the protein composition of those synapses changed," Gall said. "We made a list of GABA receptor proteins that we wanted to look at, but prioritized some, because certain inhibitory synaptic receptors are known to be more prevalent in dendrites, as opposed to cell bodies. We focused on these, as well as on ones that past studies suggested were regulated by steroids." These studies identified a specific protein that changes at inhibitory synapses with age, and then using a drug that blocks the action of this protein, that learning in adult females could be enhanced to levels observed in prepubescent animals.

The findings gathered by this team of researchers could have numerous important implications. Firstly, they provide new insight about possible

sex differences in learning, showing that females might simply learn differently than males.

"Frequently, when exploring an environment, even if they're just looking at a picture, females tend to explore it more thoroughly compared to males, instead of only looking at the cues within that environment," Gall explained. "So, they really seem to be using a different learning strategy and in some tests that require participants to look at something and quickly get the answer, the female strategy is not going to be optimal."

Remarkably, when they compared the performance of female rodents to that of male rodents on a nonspatial task, namely a task that involved identifying objects, they found that they were matched, with neither sex outperforming the other. On the two [spatial tasks](#) they employed, on the other hand, females performed better than males before puberty and worse than males after puberty.

"One thought that we've had is that the higher threshold in females might have advantages in situations where people don't need to encode everything they encounter," Gall said. "Females may have a better filter for environmental noise and will be somewhat more specific about the things that they remember, whereas in the males the filter is set a little bit lower and there's going to be more encoding including non-salient cues."

In their future studies, Gall and her colleagues would like to test out their hypothesis, to determine whether the learning strategy used by females might be more advantageous when completing some tasks than others. To do this, however, they would first need to come up with new tasks that might favor the different learning strategies they hypothesized.

So far, most studies exploring learning mechanisms in the brain were conducted on male rodents, male primates, or other male animals. As a

result, neuroscientists have a good understanding of learning mechanisms, encoding and synaptic plasticity in the male brain, yet they are unsure about the extent to which they match those in the female brain.

"Our study highlights the fact that we've been walking right past a system that's got some fundamental mechanistic differences; even though we have a lot of neuropsychiatric disorders that are more prevalent in females, the vast majority of our studies focus on males," Gall said. "For example, more females have greater incidence of depression and anxiety, which often arise with the onset of puberty, so to better understand these disorders we need more studies on females."

The recent work by Gall and her colleagues outlines the possible reasons why the threshold for synaptic plasticity changes in females during puberty. However, it does not explain why hippocampal learning in males improves in males after puberty.

"It's not just the females that are changing, the males are also changing, but we don't really know why," Gall said. "As we did not see a change in inhibition in males over that age frame, which is a major phenomenon in the females, we're now looking at the signaling activities of neurotransmitter receptors in males, to try to understand why their encoding mechanism is also changing during adolescence."

Neuroscience studies have found that LTP learning is associated with a change in the shape of synapses in the brain. In the past, Gall's team and other neuroscientists have been trying to better understand the molecular mechanisms that underlie this shape change. In their next studies, the researchers at UC Irvine also plan to investigate the possible reasons why these molecular processes are more readily triggered in males as they enter adult life.

"Concurrently, we would also like to try to unveil the consequences of the [sex differences](#) we identified, to understand if there are instances where having a higher threshold for encoding is actually adaptive or beneficial," Gall said.

Previously, Gall and Lynch also conducted studies on male rodents evaluating the potential of spaced training. Spaced training essentially entails trying to teach rodents where objects are in a maze. The team found that intermittently removing them from the maze so that they could process what they learned led to more efficient learning.

These findings suggest that spaced training is very beneficial for training male rodents. In their future works, they would like to try to determine whether it is also advantageous for female rodents.

"Aliza Le, the graduate student who led the study, was thrilled to find that the females were doing better than the males before puberty and now plans to explore this finding further," Gall added. "I think we all want to see where this can go and understand the impact of these differences on learning, as well as on other domains, such as psychological disorders."

**More information:** Prepubescent female rodents have enhanced hippocampal LTP and learning relative to males, reversing in adulthood as inhibition increases. *Nature Neuroscience*(2022). [DOI: 10.1038/s41593-021-01001-5](https://doi.org/10.1038/s41593-021-01001-5).

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