Medical Xpress

Prioritizing the unexpected: New brain mechanism uncovered

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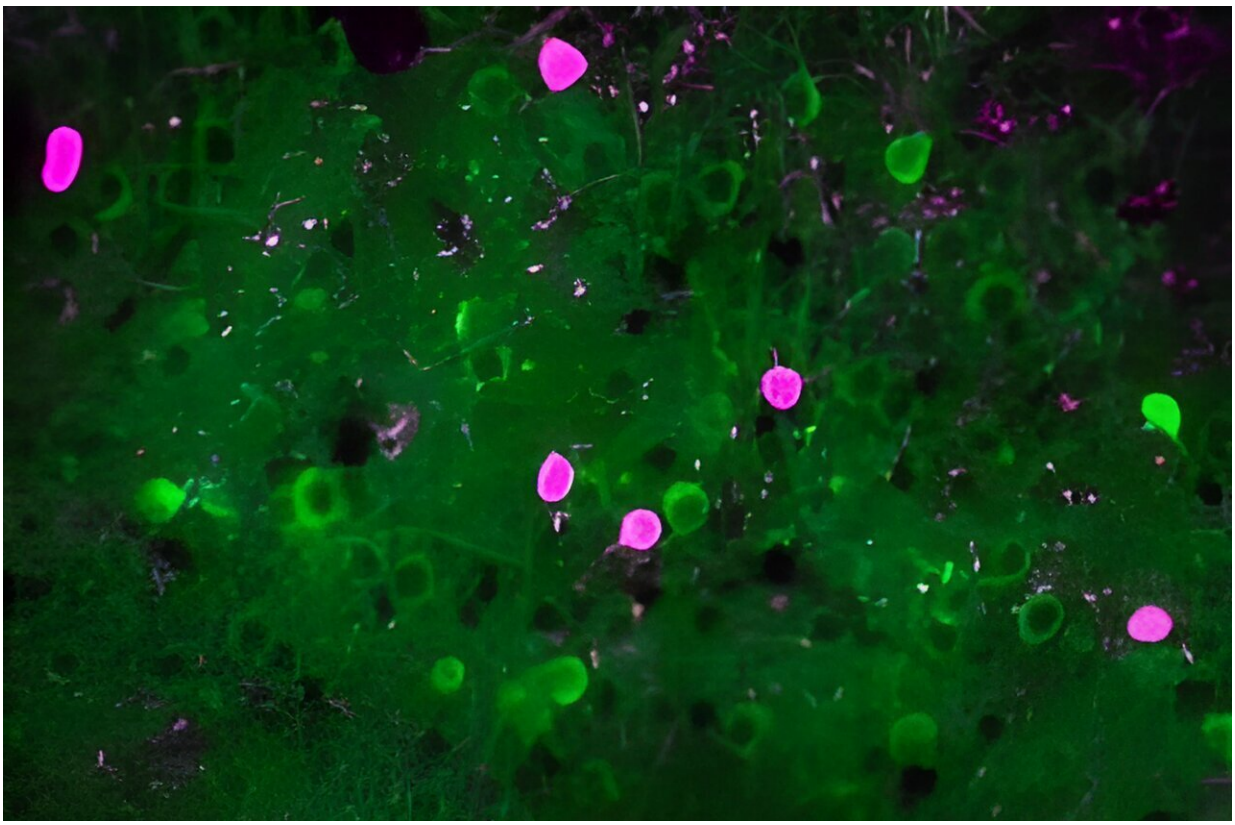


Neurons in the mouse visual cortex with VIP neurons in magenta. Credit: Sainsbury Wellcome Centre

Researchers have discovered how two brain areas, the neocortex and the thalamus, work together to detect discrepancies between what animals

expect from their environment and actual events. These prediction errors are implemented by selective boosting of unexpected sensory information. These findings enhance our understanding of predictive processing in the brain and could offer insights into how brain circuits are altered in autism spectrum disorders (ASDs) and schizophrenia spectrum disorders (SSDs).

The research, published in *Nature,* outlines how scientists at the Sainsbury Wellcome Centre at UCL studied mice in a virtual reality environment to take us a step closer to understanding both the nature of prediction error signals in the brain as well as the mechanisms by which they arise.

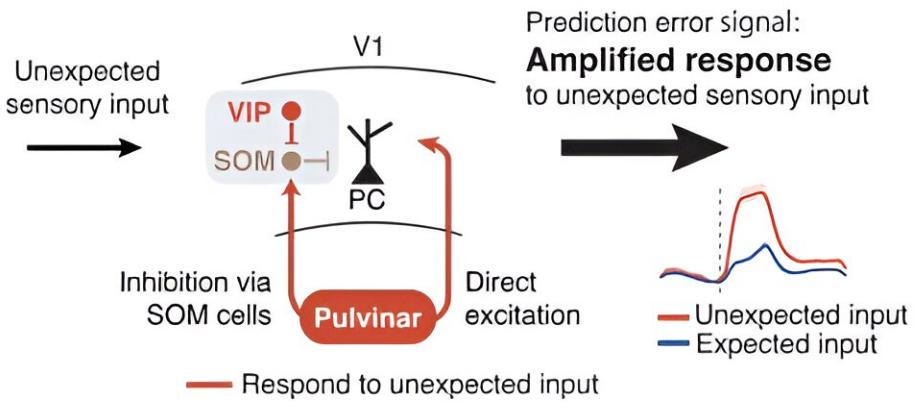
"Our brains constantly predict what to expect in the world around us and the consequences of our actions. When these predictions turn out wrong, this causes strong activation of different brain areas, and such prediction error signals are important for helping us learn from our mistakes and update our predictions. But despite their importance, surprisingly little is known about the neural circuit mechanisms responsible for their implementation in the brain," explained Professor Sonja Hofer, Group Leader at SWC and corresponding author on the paper.

To study how the brain processes expected and unexpected events, the researchers placed mice in a virtual reality environment where they could navigate along a familiar corridor to get to a reward. The virtual environment enabled the team to precisely control visual input and introduce unexpected images on the walls. By using a technique called two-photon calcium imaging, the researchers were able to record the neural activity of many individual neurons in the primary visual cortex, the first area in our neocortex to receive visual information from the eyes.

"Previous theories proposed that prediction error signals encode how the

actual visual input is different from expectations, but surprisingly we found no experimental evidence for this. Instead, we discovered that the brain boosts the responses of neurons that have the strongest preference for the unexpected visual input," explained Dr. Shohei Furutachi, Senior Research Fellow in the Hofer and Mrsic-Flogel labs at SWC and first author on the study.

"The error signal we observe is a consequence of this selective amplification of visual information. This implies that our brain detects discrepancies between predictions and actual inputs to make unexpected events more salient."



VIP and pulvinar interactions. Credit: Sainsbury Wellcome Centre

To understand how the brain generates this amplification of the

unexpected sensory input in the visual cortex, the team used a technique called optogenetics to inactivate or activate different groups of neurons. They found two groups of neurons that were important for causing the prediction error signal in the visual cortex: vasoactive intestinal polypeptide (VIP)-expressing inhibitory interneurons in V1 and a thalamic brain region called the pulvinar, which integrates information from many neocortical and subcortical areas and is strongly connected to V1.

But the researchers found that these two groups of neurons interact in a surprising way.

"Often in neuroscience, we focus on studying one brain region or pathway at a time. But coming from a molecular biology background, I was fascinated by how different molecular pathways synergistically interact to enable flexible and contextual regulation. I decided to test the possibility that cooperation could be occurring at the level of neural circuits, between VIP neurons and the pulvinar," explained Dr. Furutachi.

And indeed, Dr. Furutachi's work revealed that VIP neurons and pulvinar act synergistically together. VIP neurons act like a switchboard: When they are off, the pulvinar suppresses activity in the neocortex, but when VIP neurons are on, the pulvinar can strongly and selectively boost sensory responses in the neocortex. The cooperative interaction of these two pathways thus mediates the sensory prediction error signals in the visual cortex.

The next steps for the team are to explore how and where in the brain the animals' predictions are compared with the actual sensory input to compute sensory prediction errors and how prediction error signals drive learning. They are also exploring how their findings could help contribute to understanding ASDs and SSDs.

"It has been proposed that ASDs and SSDs can both be explained by an imbalance in the prediction error system. We are now trying to apply our discovery to ASDs and SSDs model animals to study the mechanistic neural circuit underpinnings of these disorders," explained Dr. Furutachi.

More information: Sonja Hofer, Cooperative thalamocortical circuit mechanism for sensory prediction errors, *Nature* (2024). DOI: 10.1038/s41586-024-07851-w.
www.nature.com/articles/s41586-024-07851-w

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