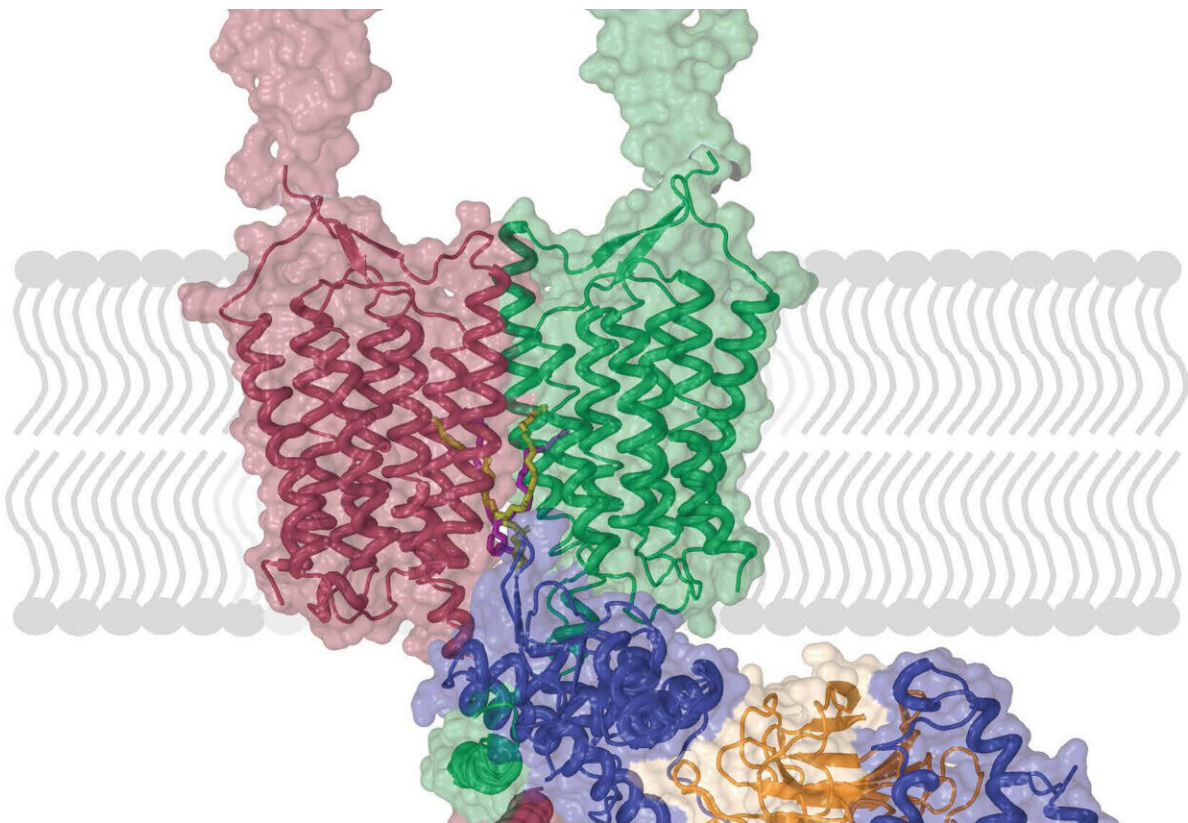


Chronic stress and depression boost this brain receptor; a new study maps out how to block it

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Cryo-EM cartoon rendition of the structure of a brain receptor linked to depression, shown with its signaling complex. The assembly is called GPR158-RGS7-G5. The GPR158 protomers are shown in green and raspberry colors, RGS7 in blue and G5 in orange. The lipid bilayer is gray. Image courtesy of Martemyanov lab, Scripps Research Florida. Credit: Martemyanov lab, Scripps Research Florida

Scientists at Scripps Research, Florida have determined the near-atomic-scale structure of an unusual brain-cell receptor called GPR158, which has been linked to depression and anxiety.

The structural study reveals both the receptor and its regulating complex, advancing understanding of basic cell receptor biology. It also enables work on potential therapeutics designed to block GPR158 as a strategy for treating depression, anxiety and possibly other [mood disorders](#).

In the study, published Nov. 18 in the journal *Science*, the researchers used ultracold, single-particle electron microscopy, or cryo-EM, to map, at a resolution of about a third of a billionth of a meter, the atomic structure of GPR158, both on its own and when bound to a group of proteins that mediate its activity.

"We've been studying this receptor for more than 10 years, and have done a lot of biology on it, so it's really gratifying to see for the first time how it's organized," says lead author Kirill Martemyanov, Ph.D., Professor and Chair of the Department of Neuroscience at the Scripps Research.

Clinical depression, also called major depressive disorder, is estimated to affect roughly 20 million people in the United States in any given year. Current treatments work on other known [receptors](#), including monoamine, but don't always work well for all people and alternative options are needed.

Martemyanov and his team found in a 2018 study that GPR158 is present at unusually high levels in the prefrontal cortex of people diagnosed with [major depressive disorder](#) at the time of their death. They also found that exposing mice to chronic stress increased levels of

this receptor in the mouse prefrontal cortex, leading to depression-like behavior—whereas eliminating GPR158 activity in chronically stressed mice made them resistant to depression and the effects of stress. Additionally, the activity of GPR158 receptor has been also linked to prostate cancer.

Historically, GPR158 hasn't been easy to study. It is called an "orphan receptor" because scientists haven't yet identified the molecule responsible for turning its signaling function "on" in a manner similar to flipping a switch. The receptor is also considered unusual because, in the brain, unlike most receptors in its family, it exists in close association with a [protein complex](#) called the RGS signaling complex. RGS is short for "regulator of G protein signaling" and it acts as a powerful brake on cellular signaling. However, it has been unclear why GPR158 engages it.

In the new study, solving the receptor's structure offered many insights into how GPR158 works. First, scientists found that it binds RGS complex in the same way that many receptors typically engage their conventional transducers, leading to the idea that it employs RGS proteins as means of transducing its signal. Second, the structure revealed that the receptor exists as two interconnected copies of the GPR158 proteins stabilized by phospholipids.

"These are fat-related molecules that effectively staple the two halves of the receptor together" Martemyanov explains.

Finally, on the other side of the receptor that faces outside of the cell, an unusual module called the cache domain was revealed. The authors believe the cache domain serves as a trap for the molecules that activate GPR158. Cache domains have never been observed in these types of receptors before, demonstrating the unique biology of this orphan receptor.

First author Dipak Patil, Ph.D., a staff scientist in the Martemyanov laboratory, says solving the structure provides many new insights.

"I am thrilled to see the structure of this unique GPCR. It is first of its kind, showing many new features and offering a path for [drug development](#)," Patil says.

The challenge is now to use the information gleaned from the structure to inform the design of small molecule therapeutics to combat depression, Martemyanov adds.

He is now exploring several possible approaches, including disrupting the two-part arrangement, interfering with engagement of RGS complex, or by specifically targeting the cache domain with small, drug-like molecular binders. Regardless of the road taken, availability of structural information should greatly facilitate drug development efforts to treat depression, Martemyanov says.

This study was made possible by the latest technological advances in microscopy, including freezing proteins at ultra-cold temperatures and examining their organization through the lens of powerful microscopes, a technique called cryogenic electron microscopy, or Cryo-EM.

"The microscope uses a beam of electrons instead of light to image protein assemblies. The shorter wavelength of electrons compared to light allowed us to visualize our sample at near-atomic resolution," says structural biologist Professor Tina Izard, Ph.D.

Patrick Griffin, Ph.D., Scripps Research, Florida scientific director, co-authored the study, applying a structural proteomic platform technology.

"The promise of Cryo-EM for achieving significant breakthroughs in solving structures of biomolecules is enormous. Our Institute is firmly

committed to expanding Cryo-EM microscopy, which is made possible through the recent acquisition and installation of a new microscope on campus."

The study was a collaboration including researchers from Columbia University and Appu Singh, Ph.D., a structural biologist at the Indian Institute of Technology in Kanpur.

More information: Dipak Patil et al, Cryo-EM structure of human GPR158 receptor coupled to RGS7-G β 5 signaling complex, *Science* (2021). [DOI: 10.1126/science.abl4732](https://doi.org/10.1126/science.abl4732).
www.science.org/doi/10.1126/science.abl4732

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