

Researchers find surprising relationships in brain signaling

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If the violins were taken away from the musicians performing Beethoven's 9th symphony, the resulting composition would sound very different. If the violins were left on stage but the violinists were removed, the same mutant version of the symphony would be heard.

But what if it ended up sounding like "Hey Jude" instead?

This sort of surprise is what scientists from the Virginia Tech Carilion Research Institute had during what they assumed to be a routine experiment in neurodevelopment. Previous studies had shown that the glycoprotein Reelin is crucial to developing healthy [neural networks](#). Logically, taking away the two receptors that Reelin is known to act on early in the brain's development should create the same malformations as taking away Reelin itself.

It didn't.

"We conducted the experiment thinking we'd see the same defects for both cases – Reelin deficiency and its receptors' deletion – but we didn't," said Michael Fox, an associate professor at the research institute and the lead author of the study. "If you take away the receptors instead of the targeting molecule, you get an entirely separate set of abnormalities. The results raise the question of the identity of other [molecules](#) with which Reelin and the two receptors are interacting."

The [study](#), first published online in June in *Neural Development*, could

prove useful for the development of therapies and diagnostics to combat [brain disease](#).

In the early stages of [neural development](#), neurons grow from the [retina](#) to a small portion of the brain called the [thalamus](#). All sensory information coming into the brain gets routed through this region, before being transmitted to the [cerebral cortex](#) for further processing. Because these retinal neurons carry specific types of information, they must connect to specific places in the thalamus, which Reelin helps them find.

In the experiment, the scientists bred mice lacking both Reelin receptors known to be critical for neurons to navigate their targets during development. The scientists expected the neurons in the mutants to become lost and unable to find their targets, which is what happens in Reelin-deficient mice. Instead, the neurons were able to locate their targets, but those targets had wandered off.

While these results were surprising, they weren't the most interesting of the experiment. Although most neurons look the same to people without advanced training in neuroscience, many different types are intermixed in distinct regions with strict borders. How these borders are formed, however, is still an open question.

"Many of us have questioned how you can have such a crisp boundary between two regions of the brain," said Jianmin Su, a research assistant professor at the research institute and first author of the study. "I always thought it was a large number of cells creating some kind of cue or environment, but that isn't what this experiment indicates."

In the mice without the Reelin [receptors](#), neurons from one part of the thalamus migrated to an area where they weren't supposed to be. Even though only a handful of neurons were misplaced, they did not mingle with their new neighbors. They stayed separate.

"The result is a baffling curiosity that nobody in the lab expected – just how distinct these little regions can be," Fox said. "How do just a few cells create such a barrier? How many cells does it take? Maybe these little islands can teach us something about how you create boundaries between larger regions of functionally similar cells."

This experiment isn't the only example Fox has had recently of neurons invading regions in which they weren't supposed to be. In a second experiment, researchers examined how neurons from the cortex connect to the thalamus during the initial stages of development.

And neurons seem to be polite.

The results showed that neurons from the cortex grow to the edge of the part of the thalamus dedicated to visual signals, called the dorsal lateral geniculate nucleus, but then stop. In fact, they stay on standby for nearly two weeks before making their way into the region. It seems as though they're waiting for the [retinal neurons](#) to make their connections before beginning to make their own. If researchers surgically removed the eyes or genetically removed the retinal cells connecting the eyes to the thalamus, neurons from the cortex invaded more than a week earlier than they were supposed to.

"It turns out that the cortical [neurons](#) are waiting for the retinal axons to mature and find the most appropriate spots to connect before they're allowed to come in," said Fox. "There's some form of instructional role that retinal axons play in the timing of the cortical axons entering."

Provided by Virginia Tech

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