Disrupted biochemical pathway in the brain linked to bipolar disorder

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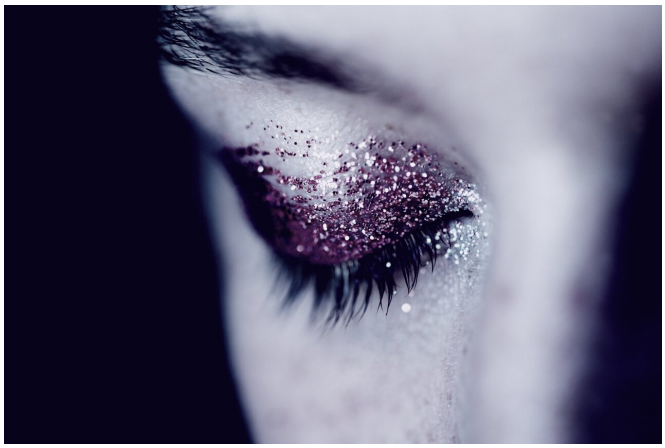

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Bipolar disorder affects millions of Americans, causing dramatic swings in mood and, in some people, additional effects such as memory problems.

While bipolar disorder is linked to many genes, each one making small contributions to the disease, scientists don't know just how those genes ultimately give rise to the disorder's effects.

However, in new research, scientists at the University of Wisconsin-Madison have found for the first time that disruptions to a particular protein called Akt can lead to the brain changes characteristic of bipolar disorder. The results offer a foundation for research into treating the often-overlooked cognitive impairments of bipolar disorder, such as memory loss, and add to a growing understanding of how the biochemistry of the brain affects health and disease.

The Cahill lab and their colleagues at Michigan State University published their findings March 24 in *Neuron*.

Akt is a kinase, a type of protein that adds tags of the molecule phosphate to other proteins. These phosphate tags can act as on or off switches, changing how other proteins work, ultimately influencing vital functions. In neurons, those functions can include how cells signal to one another, which can affect thinking and mood. When the Akt pathway is revved up, a lot of other proteins get phosphate tags. When it's quieter, those phosphate tags are absent.

The researchers discovered that men with bipolar disorder have reduced activity of this pathway, known at Akt-mTOR, in a brain region crucial for attention and memory. And when the researchers disrupted the pathway in mice, the rodents developed memory problems and crucial brain connections withered away, simulating changes in humans with bipolar disorder.

"This loss of Akt pathway function in people with bipolar disorder is probably contributing to cognitive impairment," says Michael Cahill, a professor of neuroscience in the UW-Madison School of Veterinary Medicine, who led the research. "The idea is that maybe we can target pathways like this one pharmacologically to help alleviate core symptoms of bipolar disorder."

To assess activity of the Akt pathway, the Cahill lab acquired brain tissue samples from deceased donors who had schizophrenia, bipolar disorder without psychosis, and bipolar disorder with psychosis, as well as healthy donors. The tissue samples came from the prefrontal cortex, known to control high-level functions, which is affected by bipolar disorder and the related disorder schizophrenia.

By measuring the number and variety of phosphate tags on proteins controlled by Akt in the tissue samples, the researchers could get a sense of the overall activity of the Akt-mTOR pathway.

Although they were originally expecting to see the biggest changes in patients with schizophrenia—which has the strongest genetic links to the Akt gene among the three related disorders—the researchers found that activity of the Akt-mTOR pathway was diminished in just one group of patients: men with bipolar disorder without psychosis.

"It was very different than we thought, which is kind of a good example of how in science you don't really know what you're going to get," says Cahill.

After seeing this correlation between bipolar disorder and a quieter Akt pathway, Cahill's group then asked what effect this diminished Akt pathway would have in the brain. To answer that question, they used viruses to deliver broken Akt proteins to the prefrontal cortexes of mice. The broken Akt proteins would override working ones, gumming up the Akt pathway.

In behavioral tests, the mice with gummed up Akt pathways demonstrated memory problems, no longer exploring changes to familiar environments.

Spending a lot of time investigating objects or other features that have changed their location is "their way of telling us that they recognize something is different," says Cahill. "That was impaired when we disrupted the Akt pathway."

But mice with less active Akt pathways still showed typical social behaviors, suggesting that the pathway wasn't responsible for other high-level brain functions.

When the scientists looked in the brains of mice with diminished Akt pathways, they found that the connections that neurons use to interact with other neurons, known as dendritic spines, had withered.

Dendritic spines are like intersections between the roads that information in the brain travels on. "With the number of intersections being reduced, it's harder to get where you want to go," Cahill says.

That disrupting the Akt pathway in mice seemed to replicate aspects of bipolar disorder that also occur in humans—memory problems, weaker neuron connections—provides the first clear link from this gene to the effects of bipolar disorder.

Yet, many questions remain. Women with bipolar disorder did not show the same changes in Akt-mTOR activity as men did. Nor did people with bipolar disorder with psychosis or those with schizophrenia, despite similar genetic links between the Akt pathway and these disorders.

Untangling these differences and fleshing out the path from genes to disease will require much more research. For instance, many other genes contribute to bipolar disorder, and those genes may play a larger role in these groups.

Going forward, Cahill's lab plans to follow individual circuits in the brain to discover just how the Akt pathway influences memory. That additional research should help unravel some of the enduring riddles surrounding bipolar disorder and how subtle genetic changes can lead to big differences in how people experience the world.

More information: Amanda M. Vanderplow et al. Akt-mTOR hypoactivity in bipolar disorder gives rise to cognitive impairments associated with altered neuronal structure and function, *Neuron* (2021). DOI: 10.1016/j.neuron.2021.03.008

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