Scientists link bipolar disorder to unexpected brain region

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Bipolar disorder is characterized by transitions between depression and mania. Credit: Wikipedia

While bipolar disorder is one of the most-studied neurological

disorders—the Greeks noticed symptoms of the disease as early as the first century—it's possible that scientists have overlooked an important part of the brain for its source.

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have shown for the first time that ensembles of genes within the striatum—a part of the brain that coordinates many primary aspects of our behavior, such as motor and action planning, motivation and reward perception—could be deeply involved in the disorder. Most modern studies of bipolar disorder have concentrated on the brain's cortex, the largest part of the brain in humans, associated with higher-level thought and action.

"This is the first real study of gene expression in the striatum for bipolar disorder," said Ron Davis, chair of the Department of Neuroscience at TSRI, who directed the study. "We now have a snapshot of the genes and proteins expressed in that region."

The study, published recently online ahead of print in the journal *Molecular Psychiatry*, also points to several pathways as potential targets for treatment.

Bipolar disorder is a mental illness that affects about 2.6 percent of the U.S. adult population—some 5.7 million Americans—with a sizable majority of these cases classified as severe. The disease runs in families, and more than two-thirds of people with bipolar disorder have at least one close relative with the illness or with unipolar major depression, according to the National Institute of Mental Health.

In the new research, tissue samples from 35 bipolar and non-bipolar control subjects were analyzed. The number of genes differentially expressed in tissue samples from the two groups turned out to be surprisingly small—just 14 in all. However, co-expression network

analysis also revealed two modules of interconnected genes that were particularly rich in genetic variations associated with bipolar disorder, suggestive of a causal role in the disorder. One of these two modules was particularly striking, as it seemed to be highly specific to the striatum.

"Our finding of a link between bipolar disorder and the striatum at the molecular level complements studies that implicate the same brain region in bipolar disorder at the anatomical level, including functional imaging studies that show altered activity in the striatum of bipolar subjects during tasks that involve balancing reward and risk," said TRSI Research Associate Rodrigo Pacifico, who was first author of the new study. Analyzing reactions to risk was important because bipolar patients may act impulsively and engage in high-risk activities during periods of mania.

Pathway analysis also found changes in genes linked to the immune system, the body's inflammatory response, and cells' energy metabolism. Davis noted, "We don't know if these changes are a cause of the disease or the result of it. But they provide additional gene markers in bipolar disorder that could potentially lead to the future development of diagnostics or treatments."

The study, "Transcriptome Sequencing Implicates Dorsal Striatum-Specific Gene Network, Immune Response and Energy Metabolism Pathways in Bipolar Disorder," was supported by funding from the State of Florida.

More information: R Pacifico et al, Transcriptome sequencing implicates dorsal striatum-specific gene network, immune response and energy metabolism pathways in bipolar disorder, *Molecular Psychiatry* (2016). DOI: 10.1038/mp.2016.94

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