Astrocytes derived from patients with bipolar disorder malfunction

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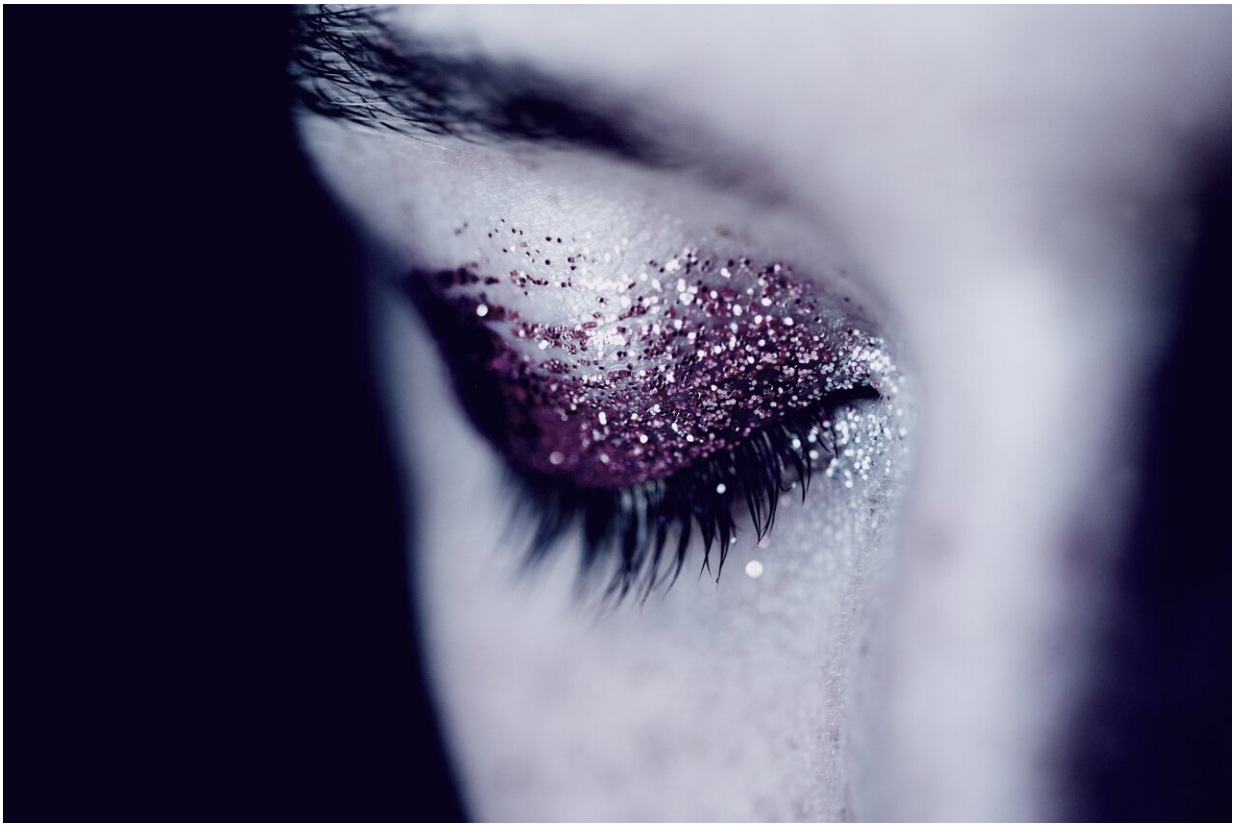

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Brain cells called astrocytes derived from the induced pluripotent stem cells of patients with bipolar disorder offer suboptimal support for neuronal activity. In a paper appearing March 4th in the journal *Stem*

Cell Reports, researchers show that this malfunction can be traced to an inflammation-promoting molecule called interleukin-6 (IL-6), which is secreted by astrocytes. The results highlight the potential role of astrocyte-mediated inflammatory signaling in the psychiatric disease, although further investigation is needed.

"Our findings suggest that IL-6 may contribute to defects associated with bipolar disorder, opening new avenues for clinical intervention," says co-senior study author Fred Gage of the Salk Institute for Biological Studies.

Approximately 1-3% of individuals suffer from bipolar disorder, which is characterized by recurrent mood states ranging from high energy and elation, known as mania, to low energy and depressive episodes. Several lines of evidence suggest a link between imbalanced inflammatory signaling and bipolar disorder. For example, these patients show signs of chronic inflammation and have a higher prevalence of inflammation-related conditions such as cardiovascular disease, diabetes, and metabolic syndrome. Moreover, they have higher concentrations of circulating pro-inflammatory cytokines such as IL-1β and IL-6, particularly during manic episodes.

"While mild inflammation can be beneficial for many neural processes, the overproduction of IL-6 may worsen the symptoms of bipolar disorder and may be an important therapeutic target," says co-senior study author Maria Carolina Marchetto of the Salk Institute for Biological Studies and the University of California, San Diego and the University of California San Diego's Department of Anthropology.

Astrocytes are known to participate in the inflammatory cascade within the brain. These cells are activated by IL-1β and other pro-inflammatory cytokines and in turn secrete cytokines that participate in the process of neuroinflammation. "Due to a growing understanding of the role of

neuroinflammation in psychiatric disorders, we wondered whether altered inflammation-driven signaling in astrocytes was associated with bipolar disorder," says co-senior study author Renata Santos of Salk and the Institute of Psychiatry and Neuroscience of Paris.

The researchers previously developed a method for rapidly generating inflammation-responsive astrocytes from human induced pluripotent stem cells (iPSCs). In the new study, they compared the inflammation signatures in iPSC-derived astrocytes generated from six patients with bipolar disorder and four healthy individuals.

The response of astrocytes from patients to pro-inflammatory cytokines revealed a unique transcriptional pattern, which was characterized by higher expression of the IL-6 gene. As a result, these cells secreted more IL-6, which negatively impacted the activity of co-cultured neurons. Exposure to the culture medium of the astrocytes was sufficient to decrease neuronal activity, and this effect was partially blocked by IL-6-inactivating antibody. Moreover, blood levels of IL-6 were higher in patients compared to healthy individuals.

"These results suggest that secreted factors from astrocytes play a role in regulating neuronal activity and that, in the case of bipolar disorder, IL-6 at least in part mediated the effects of inflammation-primed astrocytes on neuronal activity," says first author Krishna Vadodaria of the Salk Institute for Biological Studies.

Moving forward, the researchers plan to further investigate the effect of IL-6 on neuronal activity. In the meantime, the findings should be interpreted with caution. The experiments may not mimic conditions of chronic inflammation associated with bipolar disorder, and the culture system did not include many cell types involved in potentially relevant immune responses. In addition, iPSC-derived astrocytes are relatively immature compared to those in the brains of bipolar patients, and there

is a lack of reliable biomarkers for pinpointing exact developmental age.

"At this moment, direct extrapolation of the results to patients remains challenging," Gage says. "Despite these limitations, our findings elucidate aspects of the understudied role of astrocytes in neuroinflammation in psychiatric disorders."

More information: *Stem Cell Reports*, Vadodaria et al.: "Altered Neuronal Support and Inflammatory Response in Bipolar Disorder Patient-Derived Astrocytes" www.cell.com/stem-cell-reports … 2213-6711(21)00084-9 , DOI: 10.1016/j.stemcr.2021.02.004

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