People respond differently to psychedelic drugs—genetics could be the reason

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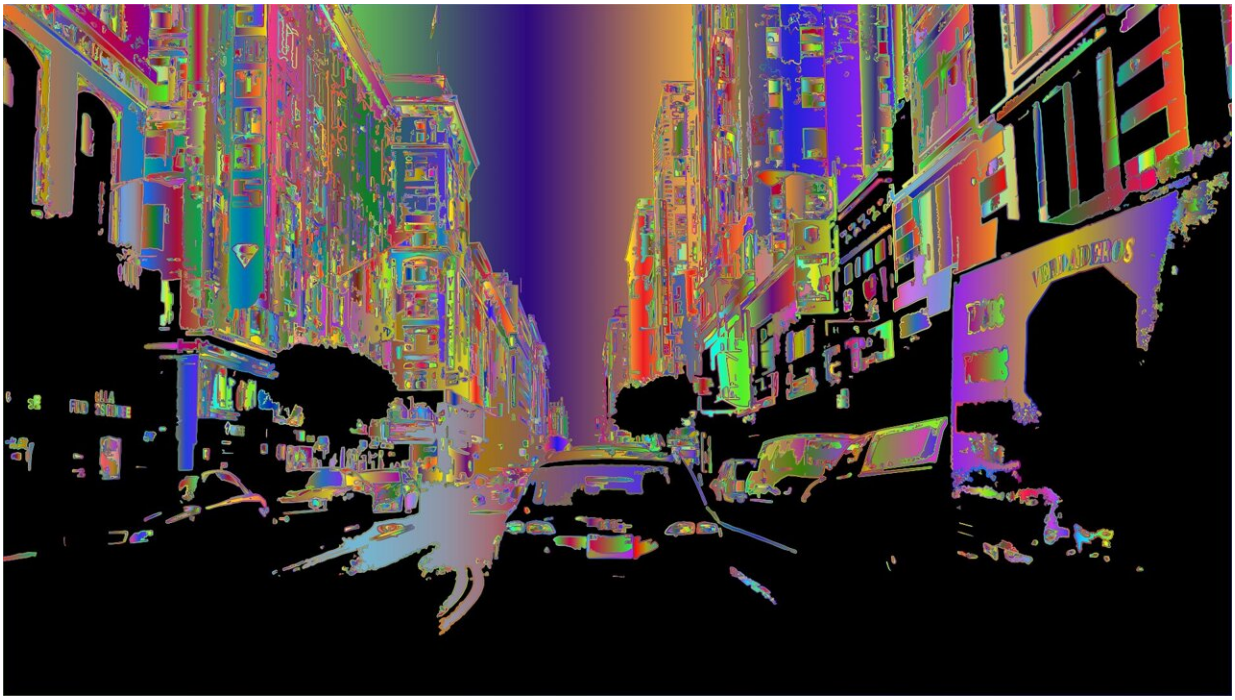

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Cluster headaches, anxiety and depression can be debilitating for people living with these conditions. Psychedelic drugs have shown benefits as treatments for these conditions in clinical studies, but not for everyone. Now, in *ACS Chemical Neuroscience*, researchers report that one reason could be common genetic variations in one serotonin receptor. They found that seven variants uniquely and differentially impacted the

receptor's in vitro response to four psychedelic drugs—psilocin, LSD, 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT) and mescaline.

Recently, there's been renewed interest and research in using psychedelic compounds that stimulate serotonin receptors in the brain because of several promising results from clinical trials. These receptors bind serotonin (5-hydroxytryptamine; 5-HT) and other similar amine-containing molecules, helping regulate people's mood, perceptions, cognition and emotions, as well as their appetite. In particular, the serotonin receptor known as 5-HT_{2A} is responsible for mediating the effects of psychedelic drugs. However, there are several naturally occurring, random genetic variations, known as single nucleotide polymorphisms, that can impact the 5-HT_{2A} receptor's structure and function. So, Bryan Roth and colleagues wanted to explore how variations in the serotonin 5-HT_{2A} receptor impact the in vitro activity of four psychedelic therapies.

The researchers used a series of assays to measure the effect that seven different SNPs had on in vitro binding and signaling of the 5-HT_{2A} serotonin receptor when in the presence of psilocin, LSD, 5-MeO-DMT or mescaline. Their results indicated that some gene variations, even ones at a distance from the binding site, alter the way the receptor interacts with the psychedelic drugs. For example, the single nucleotide polymorphism Ala230Th had both increased and reduced responses to the drugs tested compared to the original version of the gene, whereas the His452Th mutation showed only reduced effects. Based on their results, the researchers expect that patients with different genetic variations would react differently to psychedelic-assisted treatments. They suggest that physicians consider the genetics of a patient's serotonin receptors to identify which psychedelic compound is likely to be the most effective treatment.

More information: 5-HT2A SNPs Alter the Pharmacological

Signaling of Potentially Therapeutic Psychedelics, *ACS Chemical Neuroscience* (2022). DOI: 10.1021/acschemneuro.1c00815