https://doi.org/10.1038/d41586-025-00454-z

News & views

Neuroscience

Could psychedelics relieve anxiety but skip the 'trip'?

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Interest in psychedelic substances as medicines is rising. Identifying the neural circuits that mediate the benefits of psychedelics could pave the way for long-lasting anxiety treatments without the short-term sensory disturbances.

Anxiety disorders are serious and debilitating, but undertreated. Psychedelics are a promising therapeutic option — in fact, the current renewed interest in psychedelics as medicines initially gained traction when pilot studies in the 2010s demonstrated that psilocybin (the psychoactive compound in 'magic mushrooms') could relieve illness-related anxiety[1–3]. These findings have continued to inspire clinical research, including a 2023 phase II trial showing that treatment with LSD (lysergic acid diethylamide) in combination with psychotherapy can reduce anxiety symptoms for up to 16 weeks[4]. Despite the encouraging results in humans, the neural mechanisms underlying the therapeutic action remain unclear. Writing in *Science*, Muir and colleagues[5] use neuron-tagging techniques in mice to uncover brain circuits that are essential for the anxiolytic (anxiety-relieving) effects of psychedelics.

The study focused on the drug 2,5-dimethoxy-4-iodoamphetamine (DOI), which is a 'classic' psychedelic. Like LSD and psilocybin, DOI can induce hallucinations and an altered mental state by acting on receptors for the neurotransmitter molecule serotonin. The authors used two behavioural tests to characterize anxiety in mice treated with either DOI or saline solution: anxious animals are more inclined to bury marbles and avoid exposed areas of their enclosures. Administering a single dose of DOI reduced anxiety-related behaviours, with the anxiolytic effect depending on the time that had elapsed since being exposed to the drug. For up to six hours after DOI administration, treated mice were less anxious than were control mice, but this was no longer the case a day later.

The mice were also tested using a head-twitch response assay, which assesses the hallucinogenic potential of a classic psychedelic[6]. Timing was also a key factor: head twitches were observed only 30 minutes after exposure to DOI, but the effect was absent by 6 hours. Together, these results indicate that DOI can induce both anxiolytic effects and head-twitch responses in mice, but that the changes follow distinct time courses.

To identify the brain circuits responsible for the drug's action, the authors used a molecular tool[7] called scFLARE2 to 'tag' drug-responsive neurons. When the animal receives a drug (such as DOI) that increases the firing activity of certain neurons, there is an influx of calcium ions into the neuronal cell body. The calcium signal, combined with light applied by the experimenter, activates scFLARE2. This induces expression of engineered genes specifically in the neurons that are activated immediately after DOI administration. Using this tool to drive the expression of a fluorescent protein, the authors found

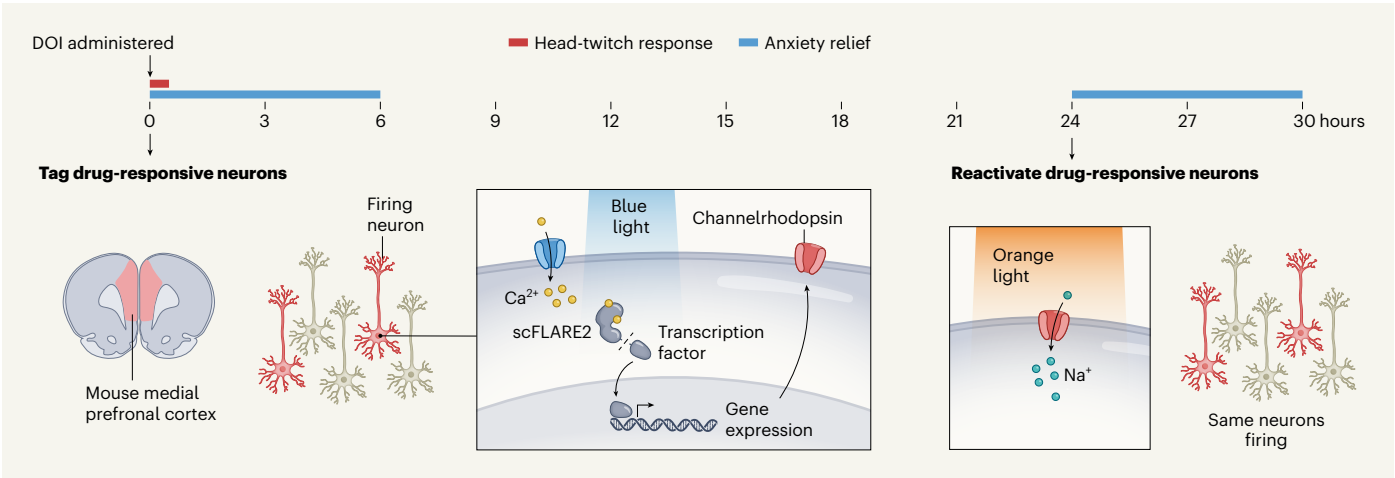

Figure 1 | Identifying the neurons that respond to an anxiety-relieving psychedelic drug. Muir *et al.*[5] administered the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) to mice and observed a reduction in anxiety-related behaviours that lasted for 6 hours. Head-twitch responses, a measure of a psychedelic's hallucinogenic potential, lasted only 30 minutes, indicating that the beneficial effects of DOI and its hallucinogenic effects follow different time courses and therefore might be mediated by distinct neuronal circuits. The researchers tagged drug-responsive neurons in the medial prefrontal cortex, a region of the brain involved in emotion and cognition, using a molecular tool called scFLARE2. When calcium ions (Ca^{2+}) that enter activated neurons and blue light were applied by the experimenter, a transcription factor derived from the scFLARE2 construct induced transcription of an engineered ion channel called channelrhodopsin. After 24 hours, the researchers applied orange light to stimulate channelrhodopsin, causing an influx of ions (including sodium ions, Na^+) and activating the same population of drug-responsive neurons. This evoked long-lasting anxiety relief but not head-twitch responses.

that DOI activates about 40% of the neurons in the medial prefrontal cortex, a brain region involved in cognition and emotional regulation. By comparison, only 5% of these neurons were activated in control mice.

Next, the authors used the same tool to reactivate the identified drug-responsive neurons using an experimental approach known as optogenetics. On the first day, DOI was administered and scFLARE2 was used to tag responsive neurons and drive expression of a protein called channelrhodopsin, a light-activated ion channel. On the second day, the experimenters used LEDs to activate channelrhodopsin, causing the tagged neurons to fire. Strikingly, with no drug in the brain at that point, reactivating only drug-responsive neurons in the medial prefrontal cortex was sufficient to reduce anxiety in mice without evoking any head-twitch responses. The take-home message is that the longer-term (anxiolytic) effects of the psychedelic DOI are mediated by a distinct set of neurons in the medial prefrontal cortex, but the acute (hallucinogenic-like) effects are not (Fig. 1).

Although classic psychedelics such as psilocybin and LSD might be promising therapeutics for anxiety disorders, they also elicit intense subjective experiences in humans. Muir and colleagues' findings suggest that the different psychedelic-mediated behavioural effects are dissociable at the level of neural circuits in mice. An exciting possibility is that the behavioural effects could also be dissociated in humans, such that the long-term therapeutic benefits could be gained without the acute perceptual and emotional effects. This could perhaps be achieved using designer compounds that preferentially target specific brain circuits.

The study has caveats, however. Anxiety symptoms involve several brain regions such as the amygdala and ventral hippocampus (both involved in regulating emotion states and response to stress), which also contribute to the effect of psychedelics on anxiety-related behaviours[8,9]. These regions were not examined by Muir and colleagues. Moreover, the anxiolytic effect shown in this study was relatively short-lived, which does not reflect the enduring, weeks-long changes observed in humans treated with LSD[4]. Future studies could use a different experimental paradigm, such as fear extinction (a test of whether a treatment decreases an animal's conditioned fear of a stimulus), which might provide a better model for translation to humans[10].

Another limitation is that, although the head-twitch response assay is widely used for animal studies, it mainly indicates the engagement of serotonin receptors rather than hallucinations per se. This model also lacks face validity (that is, the observed behaviour in the animal does not resemble a human behaviour) and has false positives when used as a read-out of hallucination[11]. Therefore, although the acute and anxiolytic effects of psychedelics can be dissociated in rodents, the extent to which these behavioural changes can be disentangled in humans remains to be tested.

An important question raised by this study relates to the identity of the tagged neurons that underpin the behavioural effects. The authors' examination of gene expression suggests that several cell types could be involved. Because scFLARE2 relies on calcium influx, only neurons with increased firing are tagged, so the tool would miss neurons in which firing is suppressed by a psychedelic. Identifying inhibited neurons might be necessary to gain a full picture of the action of psychedelic drugs on cortical neurons[12]. Nevertheless, Muir and colleagues illustrate the power of using modern systems-neuroscience tools to dissect the neural mechanisms of psychedelics. The results hint at a future in which scientists can fine-tune and shape the behavioural effects of psychedelics.

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The authors declare competing interests (see go.nature.com/3eqs3tw).