

Could psychedelics relieve anxiety but skip the ‘trip’?

Cory A. Knox & Alex C. Kwan

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 weeks⁴. Despite the encouraging results in humans, the neural mechanisms underlying the therapeutic action remain unclear. Writing in *Science*, Muir and colleagues⁵ 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 psychedelic⁶.

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 tool⁷ 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 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

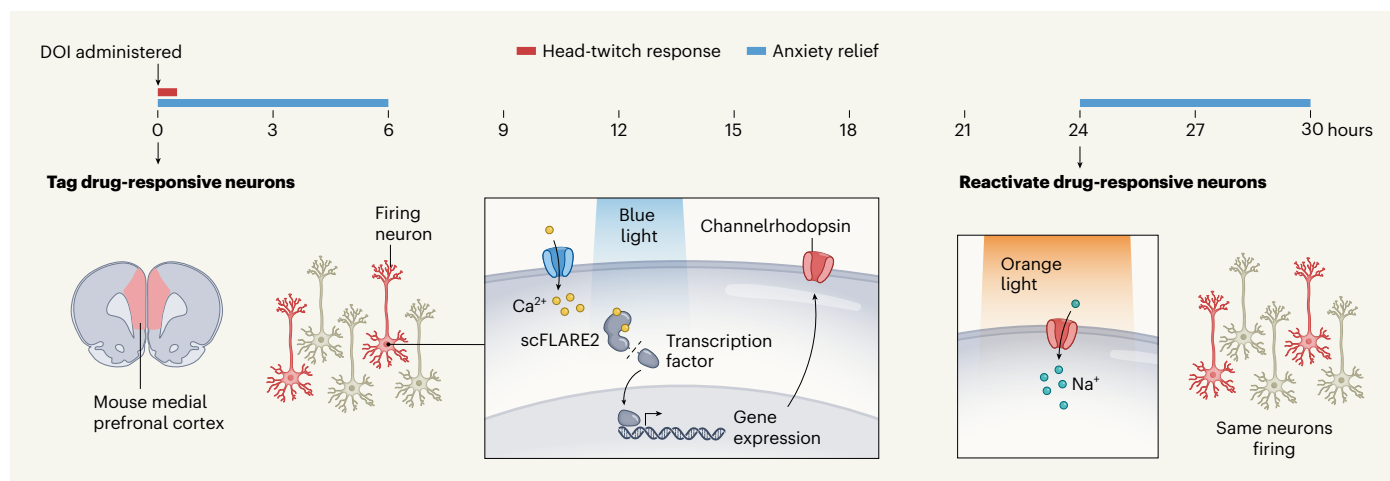


Figure 1 | Identifying the neurons that respond to an anxiety-relieving psychedelic drug. Muir *et al.*⁵ administered the psychedelic 2,5-dimethoxy-4-iodoamphetamine (DOI) to mice and observed a reduction in anxiety-related behaviours that lasted for 6 hours. Head-twitch responses, a measure of a psychedelic’s 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.

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 LSD⁴. 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 humans¹⁰.

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 hallucination¹¹. 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 neurons¹². 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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Ancient genomics

Origins of Eurasia's influential Yamna culture

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Ancient genomes from modern Ukraine and Russia reveal the origins of the Yamna people, pastoralists who migrated from the Eurasian steppe to Europe 5,000 years ago, spreading their ancestry, culture and, probably, language. **See p.124 & p.132**

Around 5,000 years ago, pastoralists of the Yamna, or Yamnaya, culture from the Pontic–Caspian steppe, which spans eastern Europe and central Asia north of the Black and Caspian seas, rode west into Europe and transformed the cultural and genetic landscape of the continent permanently¹. Previous studies^{1,2} have proposed that these people also brought with them Indo-European languages, now spoken in most of Europe. On page 132, Lazaridis *et al.*³ shed light on the demographic processes that shaped pre-Yamna populations in the Pontic–Caspian steppe and on page 124, Nikitin *et al.*⁴ reveal the genetic origins of the Yamna.

The Neolithic period (or New Stone Age, spanning roughly 10000–5000 BC) was a time of enormous cultural change and variation in the Pontic–Caspian steppe. Hunter-gatherer cultures persisted in the area while new cultures appeared, bringing along practices such as pastoralism, dairying and agriculture. The transition continued with the development of copper alloys¹ during the Eneolithic period (or Copper Age, spanning 5000–3000 BC), which preceded the Bronze Age.

The movement and coexistence of groups with distinct genetic backgrounds resulted in the groups genetically mixing (admixing) with each other. Evidence of this can be seen in Ukrainian Neolithic hunter-gatherers with ancestries related to populations from the

Caucasus (a mountainous region between the Black and Caspian seas)⁵ and in farmers of the Trypillia, Cernavodă and Usatove cultures, who had hunter-gatherer or steppe-related ancestries (or both)^{6–8}.

People of the Yamna culture were nomadic pastoralists who used horses and wheeled carts for herding and who buried their dead in large mounds called kurgans¹. In 2015, the first Yamna genomes were reported in two landmark publications^{9,10}. The studies demonstrated that, starting with a culture known as Corded Ware, which existed between the Late Neolithic period and the Bronze Age, almost all European populations carried a large proportion of Yamna-related ancestry. It has since been shown that the Yamna people had some ancestry from early farmers of Anatolia, a region south of the Black Sea¹¹ – but the specifics of the Yamna people's origin have remained elusive.

Lazaridis *et al.* and Nikitin *et al.* present genomic data for 367 individuals from the Pontic–Caspian steppe and surrounding areas, doubling the number of available genomes from the Eneolithic period and almost quadrupling those of Yamna people. The data set includes numerous previously unsampled cultural groups and locations. The studies challenge simplistic narratives of migration and replacement. They depict a dynamic