News & views

Neuroscience

Timing is key for effects of psychedelics

Samuel C. Woodburn & Alex C. Kwan

Juvenile mice find social experiences more rewarding than do adults. The discovery that psychedelics can re-engage the social neural circuits for varying durations in adults points to a possible therapeutic mechanism for these drugs. **See p.790**

Psychedelics are drugs that alter perception and cognition. They include both 'classical' psychedelics, such as LSD and psilocybin, which target receptors for the neurotransmitter molecule serotonin, and related psychoactive substances, such as MDMA, ketamine and ibogaine. Clinical trials suggest that these drugs might be useful for treating mental illness[1–3], perhaps because of the changes they induce in neuronal growth and signalling, for example triggering the formation of synaptic connections between neurons[4–6]. But what distinguishes the neural plasticity elicited by the various psychoactive compounds? On page 790, Nardou *et al.*[7] report that various psychedelics can act on the same brain region — that involved in social learning — but for different lengths of time. The findings could explain why, despite their differences, the drugs confer related potential therapeutic benefits.

The study relied on a test known as the social reward conditioned place preference assay, which worked as follows. Nardou *et al.* first allowed adult mice to become familiar with a two-chambered arena in which each chamber contained a different type of bedding. They then conditioned the mice such that the animals associated one type of bedding with their cage mates and another type with isolation. They then placed the animals back in the first arena, and assessed their preference for the two bedding types. Reliably choosing the bedding associated with cage mates indicates a learnt preference for the social context (Fig. 1).

Members of the same research group had shown previously that juvenile mice are more likely to choose the cage-mate-associated bedding than are adults, reflecting a pro-social preference in young mice that decreases with age[8]. However, social learning could be re-established in adults if the animals were given MDMA two days before beginning the assay. This aspect of mouse behaviour might relate to increased emotional connectedness in humans — a notable effect of MDMA, which could underlie its therapeutic potential[9]. In the current study, Nardou *et al.* injected the mice with one of a range of psychedelic drugs (ketamine, psilocybin, LSD or ibogaine), or with saline solution as a control, and found that each of the drugs tested had the same effect as MDMA, enhancing the animals' pro-social preference.

The drugs tested by the authors differ widely in terms of the receptor proteins to which they bind, their psychological effects and their pharmacodynamics, with the duration for which people experience acute effects ranging from as little as 90 minutes for ketamine[10] to 16 hours or more for ibogaine and the products of its metabolism[11]. To investigate whether the drugs' effects were similarly varied in their ability to alter social learning, the authors repeated the animal experiment, varying the time between drug administration and the behavioural assay. Strikingly, they observed that, whereas ketamine became ineffective after one week, psilocybin remained active; LSD could work for up to three weeks; and ibogaine had the longest-lasting behavioural effect, working for up to four weeks.

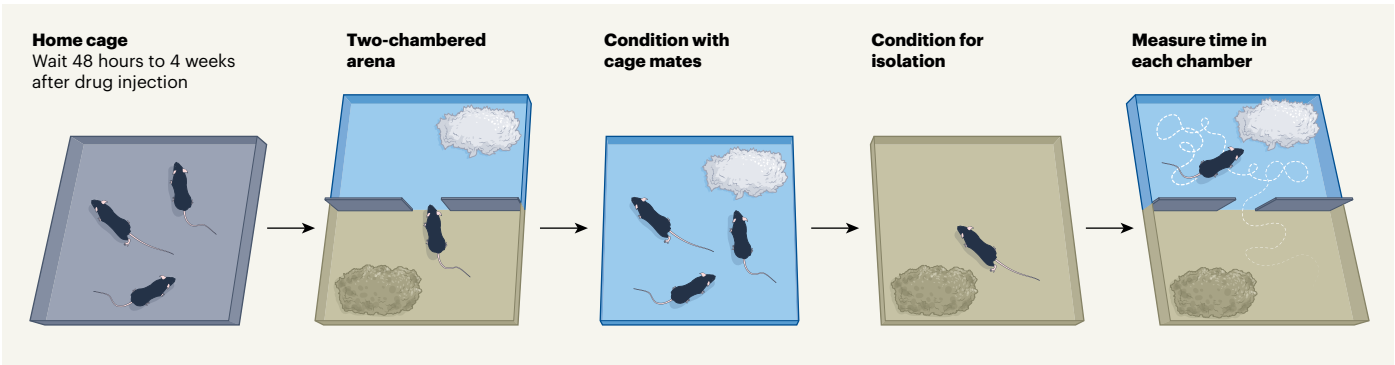

Figure 1 | A test for social-reward learning. Social-reward learning is the process by which mice learn to associate stimuli with rewarding social encounters. Nardou *et al.*[7] tested this ability in mice that had been injected with a psychedelic drug (MDMA, LSD, psilocybin, ibogaine or ketamine) and had been left in their home cages for between 48 hours and four weeks. After this time, the animals were placed in an arena in which each of two chambers contained a different type of bedding. After 30 minutes, the mice were placed in a cage containing their cage mates and one type of bedding, then in a cage on their own with the other type — this experience conditioned the animals to associate the bedding type with social interactions or with isolation, respectively. The mice were later placed back in the first arena, and the time they spent in each chamber was measured. Mice that had received a drug and were left in the home cage spent significantly more time in the chamber containing the 'social' bedding than did control animals that received a saline solution, indicating that social-reward learning had occurred. The duration for which the psychedelics were effective varied, and was in line with the amount of time for which the drugs have acute affects in humans. (Figure adapted from Extended Data Fig. 1 of ref. 7.)

Collectively, these data show that the durability of a drug's effect on social-reward learning can vary significantly, approximately in line with the duration of the drug's acute effects in people. This provocative piece of evidence suggests that the duration of acute effects, and not the drugs' receptor targets, might be what matters for their effect on social behaviour.

To dig into the neural mechanism underlying their observations, Nardou *et al.* focused on the hypothesis that the drugs might not change synaptic wiring directly, but instead increase the likelihood that the strength of signalling between neurons is altered if the synapses are stimulated by other neurotransmitters — a phenomenon known as metaplasticity. The social reward conditioned place preference assay has previously been shown[12] to rely on a type of metaplasticity in which signalling by the hormone oxytocin depresses activity across synapses (known as long-term depression) in a brain region called the nucleus accumbens. Nardou and colleagues recorded synaptic activity from medium spiny neurons in slices of nucleus accumbens obtained from mice treated with ketamine, MDMA, LSD or ibogaine. The drugs produced telltale signs of oxytocin-dependent metaplasticity. Importantly, LSD's metaplastic effects were longer lasting than were those of ketamine, corroborating the behavioural findings.

Finally, RNA sequencing of neurons in the nucleus accumbens revealed that the various psychedelics increase the expression of genes associated with the extracellular matrix (a network of proteins and molecules that surround and support neurons, including those at synapses). Restructuring of the matrix can permit neural plasticity[13], so the authors propose that matrix remodelling might be a key cellular process that underlies the actions of psychedelics.

Together, Nardou and colleagues' work indicates that the timing of a drug's action and the metaplasticity it induces are key elements of psychedelic-induced neural plasticity. But many aspects of the process remain to be defined. For instance, given that the drugs target distinct receptors, it is unclear how their effects can converge to induce metaplasticity in the nucleus accumbens. Despite the authors' findings, there is debate as to whether oxytocin receptors in the nucleus accumbens are needed for MDMA to mediate pro-social preference[14]. It also remains to be seen whether psychedelics' effects on non-social behaviours are linked to their pharmacokinetics, and whether metaplasticity is the mechanism that governs the action of psychedelics in other brain regions. This might be difficult to test *in vivo* because of the many neurotransmitter systems that are active concurrently in live animals.

The study has implications for the clinical use of psychedelics. An attractive feature of psychedelic-assisted therapy is the durability of the potential benefit — for instance, one or two doses of psilocybin is reported to reduce depression symptoms for months[2,3]. Nardou and colleagues' work shows that different psychedelics could yield behavioural effects that last for varying times related to the length of their acute actions. The work raises the interesting question of whether a psychedelic's subjective effects in humans are crucial for its efficacy in treating mental-health problems. If so, newly synthesized non-hallucinogenic analogues of these drugs might not yield therapeutic benefits, contrary to previous proposals[15]. However, further testing will be required to confirm this.

Clearly, not all types of neural plasticity are good for the brain — for example, plasticity caused by drugs of misuse, such as cocaine, nicotine and amphetamines, can result in addiction[16,17]. Moreover, some aspects of drug-induced plasticity observed *in vitro* might not reflect a drug's effects *in vivo* (although they might still be valuable as a measurement for drug screening). By appreciating and embracing the varieties of drug-induced plasticity, we can begin to unpack the nuanced mechanisms by which each drug acts. This, in turn, could lead to improved clinical protocols and accelerate drug discovery, to realize psychedelics' therapeutic potential.

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A.C.K. declares competing interests. See go.nature.com/43wu56j for details.
This article was published online on 14 June 2023.

Evolution

The long infancy of sterol biosynthesis

Fabien Kenig

A newly discovered fossil record of steroid molecules, spanning 1.64 billion years, points to ancient organisms in the eukaryotic domain being capable of only early steps in the synthesis of sterol molecules. **See p.767**

The biosynthetic pathways that give rise to molecules called sterols are well established in the scientific literature. These pathways include the modifications (oxidation and cyclization) of a molecule called squalene to form lanosterol and cycloartenol, which are protosterols — precursors of other sterols. Numerous other steps are then needed to make cholesterol and other related sterols (known as crown sterols) that are found in organisms with cells that have a nucleus (eukaryotes); organisms called crown eukaryotes are either living eukaryotic species or extinct eukaryotic species that are descended from the last common ancestor of all living eukaryotes. Under favourable conditions, the carbon backbones of sterols can be preserved in ancient sedimentary rocks as molecular fossils, which are versions of the molecules that arise as a consequence of geological processes. Brocks *et al.*[1] report on page 767 that their exploration of molecular fossils has uncovered an approximately 640-million-year-long period of Earth's history when sterol biosynthesis had not yet evolved the complex pathways that exist today.

Brocks *et al.* show that sedimentary rocks dated to between 1,640 million years and approximately 1,000 million years ago (a time frame corresponding to the mid-Proterozoic