Q&A

Gül Dölen: Opening the window

In 2019, neuroscientist Gül Dölen's laboratory at Johns Hopkins University in Baltimore, Maryland, found that the psychedelic drug MDMA resensitizes the brains of adult mice so they can learn from their social environment in a way that's normally reserved for adolescence. Dölen spoke to *Nature* about the potential power of using psychedelic compounds to harness such critical periods.

What is a critical period?
It's a window of time when environmental stimuli can induce lasting changes to the brain. Zoologist Konrad Lorenz first described the imprinting phenomenon with baby geese, which form lifelong attachments to whatever they find in their social environment in the first 48 hours after hatching. But there are many kinds of critical period. Psychologists who study children, for example, know there is a critical period for language development between two years of age and puberty.

Your lab identified the critical period for social reward learning. How does it work?
Social reward learning is the positive feelings we develop for places and things we associate with our friends and loved ones. Extrapolating from mouse data, we think that in people, the critical period is between 12 and 14 years of age. One obvious example is that teenagers are much more susceptible than adults to peer pressure, and also have an easier time adapting to different cultures. But demonstrating this robustly in humans is difficult because you need lots of participants and many developmental time points.

In mice, we used an assay in which they learn to associate one type of bedding with a preferred social environment, and another with an undesirable, isolated environment. We tested more than 1,000 mice, males and females, at 15 ages. Juvenile animals do it well but stop by adulthood (R. Nardou *et al*. *Nature* **569**, 116–120; 2019). The open state peaks around 40 days after birth, when they reach sexual maturity, and then declines, closing altogether by full adulthood, around day 90. But in mice, MDMA can reopen the critical period for social learning after it should have closed permanently.

MATTHEW RAKOLA FOR SPECTRUM

Gül Dölen sees the benefits of psychedelics.

What led you to try using MDMA to reopen this critical period?
We found that the molecule oxytocin induces plasticity in part of the brain called the nucleus accumbens in juvenile animals, allowing new connections to be formed. This capacity also declines with age, so we thought this oxytocin-related cellular mechanism might underlie the critical period for social reward learning.

We considered using oxytocin directly to try to induce plasticity and reopen the critical period, but oxytocin doesn't cross the blood–brain barrier. So we started looking for other ways to trigger the mechanism. We know that MDMA (commonly known as ecstasy) has prosocial properties — users say the drug makes them feel as if their heart has opened up. There are photographs of people at raves participating in 60-person 'cuddle puddles'.

There are also studies of MDMA's therapeutic effects for post-traumatic stress disorder (PTSD; see page S83). I suspect the key to the drug working against PTSD is that it enables patients to flexibly engage with their social memories, which are more malleable because the critical period has been reopened.

How did you test MDMA's ability to do that?
Most researchers who study MDMA look at its immediate effects, but we wanted to focus on the longer term, so we waited 48 hours after giving the drug before testing the animals. We found that in adult mice that were treated with MDMA, the social reward learning returned. Normally, young mice rapidly learn to associate a particular type of bedding with a more social situation and spend more time on that bedding. In adulthood, we know they no longer form these rapid associations because they spend the same amount of time on each bedding. But after taking MDMA, the adults once again rapidly learn an association between a type of bedding and their social condition. This is evidence that MDMA has reopened the critical period.

Can other psychedelic drugs have the same effect?
We are testing the hypothesis that other psychedelics reopen the critical period and restore the ability to induce oxytocin-mediated plasticity. In humans, these drugs work at different time scales, from ketamine, for which the subjective effects last 30 minutes to 2 hours, to ibogaine, for which they can last up to 3 days. We think that what feels like an altered state of consciousness, common to all psychedelics, is what it feels like to reopen critical periods. You can find this in the language people use to describe their experience with these drugs. They refer to returning to a state where they are living in the present moment, noticing everything and being really sensitive to the world.

How can clinicians and researchers make use of the power of psychedelic drugs to open many types of critical period?
Psychedelics could be powerful adjuncts to many therapies. For example, they could be paired with treatments for stroke, long after the normal period for function recovery has ended. This insight into critical periods could also broaden the types of mental-health condition that psychedelics can treat — not just the depression, anxiety, PTSD and addiction that are the current focus, but also anything that we haven't been able to treat because the relevant critical period has closed. Neuroscientists have been dreaming of having this master key for 50 years. If we have finally found it, the possibilities for using it therapeutically are enormous.

Interview by Alla Katsnelson.
This interview has been edited for length and clarity.