5 QUESTIONS

5 Questions for Gul Dolen

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Gul Dolen has always been interested in the question of consciousness. As an undergraduate, she designed her own major, combining philosophy, linguistics, and art to explore questions of the mind. Where does consciousness come from, and what do we know about it?

In the following years, Dolen earned a MD and PhD in neuroscience at Brown University and MIT. Her graduate research focused primarily on mouse genetics, and during a postdoctoral fellowship at Stanford, she began studying social behavior and learning in animals. In 2014, she became an assistant professor of neuroscience at Johns Hopkins, and four years later, her work made headlines when she gave octopuses MDMA. *The Microdose* spoke with Dolen about her psychedelics research, and how it might reveal how psychedelics work in the body, as well as the question she's always been driven by: how does consciousness work?

How did you get the idea to study psychedelics in non-human animals?

When most people think about psychedelics, there's this laser focus on humans. There's this assumption that we're going to get the most information if we study them in humans, because the things that they trigger in humans are so unique to us. There's been a huge push to understand ourselves by comparing our brains to our nearest relatives; we look at monkeys and say, "Okay, well, we're smarter than monkeys, and we have extra layers of cortex in the brain, and so the smartness that we have must be in those extra layers of cortex."

But there's another way to approach this: you could try to understand how to build human consciousness not by studying the thing that is most similar to us, but by studying the thing that is most separated by evolutionary time or living on another planet. That's where something like the octopus comes into play: an octopus is separated from humans by hundreds of millions of years of evolution. Our last common ancestor with an octopus was 650 million years ago; to put that into perspective, the dinosaurs had come and gone in the interim.

Anatomically, an octopus's brain looks much more like a slug or any invertebrate brain than like ours. They don't have a cortex. But they are very intelligent, and similar to us in lots of ways: they can solve problems, and manipulate their environment with incredible locomotor dexterity. All of those rules that we thought we learned by comparing monkeys and humans are out the window. That's why I find the octopus fascinating; they are a being that solves the intelligence problem in a totally different way — and understanding their intelligence can tell us something fundamental about how we build complex functions like consciousness.

What happened when you gave octopuses MDMA?
MDMA is in the methamphetamine class of drugs, so I thought the octopuses were just going to be hyperactive, speeding around the tank. And in the higher doses of the drug, they *were* hyperactive, but as we got into the range of dosages more similar to what humans take, the octopuses started floating around and almost dancing. They showed playful behavior, like doing backflips and playing with the little airstone we had in their tank to aerate the water.

They also spent a lot more time on the social side of their tank, where another octopus was hanging out. Octopuses are not social, and none of them spent very much time on the social side of the tank before we gave them the drugs. As a neuroscientist, I'm always looking for simple behavior read-outs; behavior is complicated, and the more variables you have to control for, the more difficult the results are to interpret. But this was a super simple behavioral measure: how much time they spent in each chamber? And that showed an almost complete 180° in their behavior.

Did those results suggest anything to you about how MDMA works in the brain?

My lab has spent a lot of time figuring out what MDMA does, and we think in humans MDMA could be working in a part of the brain called the nucleus accumbens. Other people have implicated other parts of the brain: the amygdala, or the prefrontal cortex, or the default mode network. But the truth is, an octopus doesn't have an accumbens, an amygdala, a default mode network, or a prefrontal cortex, which means those mechanistic insights are probably not as telling as we think they are.

Octopuses may not have any of those brain regions but what they do have that is similar enough to what we have is the serotonin transporter. That's going to be familiar to anyone who's on a selective serotonin uptake inhibitor, orSSRI; the "SSR" of "SSRI" is that serotonin transporter, which selectively takes up excess serotonin in the cell's synapse, and brings it into the cell. What an SSRI does is sits in a binding pocket and blocks it, so that every time serotonin gets released, it doesn't get vacuumed up — then, there's more serotonin in the synapse. MDMA binds to that same spot, but instead of blocking it, it reverses the direction of the transporter, so serotonin is basically blasted into the synapse.

We went across the whole tree of life and looked at all the different branches, and the serotonin transporter is really old. What that tells us is that serotonin is also very old in its ability to induce social behavior. Octopuses have the brain circuitry required to engage in social behavior, but they normally don't express them except under mating conditions. It seems that MDMA, through the serotonin transporter, is able to override that suppression and make them more social.

In a 2019 *Nature* paper, you also found that MDMA makes mice more prosocial. Generally, young mice go through what's called a critical period for social behavior, after which they're less social — but MDMA appears to reopen that window. What might a psychedelic-induced open critical period look like in humans?

When you talk to people who are on psychedelics, it's like herding kittens. They're paying attention to everything: look at this leaf, my shoe won't fit and I put them on the wrong foot. People on psychedelics are in full on explorer mode, which is wonderful, but it's not very efficient. Habits get a bad rap, but you couldn't get out the door if you didn't have them.

Living in a world where you're trying to learn and pay attention to everything is emotionally and energetically costly. Neuroscientists call this the "explore/exploit trade-off." At some point, you do want a stable representation of the world that is not changing as much; that's why critical periods close. But reopening them could have potential therapeutic value with conditions like autism or strokes.

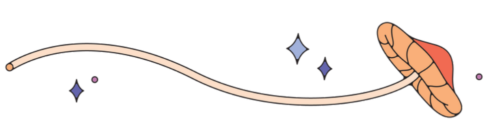
What do we know about other psychedelics' ability to reopen critical periods?

Honestly, when we did those experiments with mice, we thought that the reason we were able to reopen the social critical period in mice could just be because MDMA is an incredibly prosocial drug. So we were really surprised when we started to see evidence that it's not just MDMA that can reopen this critical period.

We're in year four of trying to figure out this mechanism, but so far, it seems like all psychedelics reopen this critical period, and they do it whether they are prosocial like MDMA, or primarily hallucinogenic like psilocybin or LSD, or dissociative like ketamine. It doesn't matter; they all do it. And what that tells us is that the pro-social character of the subjective effects of a drug is a red herring; instead, putting the brain in an open critical period state is the same as being in an altered state of consciousness. They're the same thing.

We also have evidence that the duration of the acute subjective effects is proportional to how long the drugs keep the critical period open. Ketamine lasts for about 30 minutes to two hours; the critical period closes one week after administration. MDMA and psilocybin last three to six hours; the critical period closes at three weeks. Ibogaine can last 36 to 72 hours, and so far we haven't found the upper limit of the critical period of it yet. How long the altered state of consciousness lasts is somehow mechanistically related to how long this critical period opens.

This interview has been edited and condensed for clarity and length.



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Wren Mar 2

Thanks so much for taking the time to reply, and for the link.

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Shay Writes Publication name TBD · Feb 26

So interesting! Thank you. Octopuses are amazing.

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