MIND FOUNDATION

Beyond the therapeutic alliance

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> "Rather than having the mdma-assisted psychotherapy and then sending them home with a journal and some happy thoughts, what we really ought to be saying is that the therapeutic window is actually for weeks, if not months after the acute psychedelic effects have worn off."

At the Johns Hopkins University School of Medicine, Department of Neuroscience, neurobiologist and MIND's scientific advisory board member Gül Dölen, MD-PhD, studies the mechanisms by which psychedelic drugs work to treat diseases of the social brain like PTSD, addiction, and severe forms of autism. Dölen spoke to me about her 2019 Nature paper,1 which showed that MDMA re-opens a "social critical period" in the mouse brain when it is sensitive to learning the reward value of social behaviors – but only if the mouse is in a social setting. Based on this research, Dölen and her colleagues believe two things are required for MDMA, and potentially all psychedelics, to be therapeutic in the context of social brain diseases: 1) the re-opening of the critical period and 2) the right social context for the memory to be reshaped. Not only does this view challenge current psychedelic therapy models; it also suggests a way forward for psychiatric treatments more generally.

Priming the brain for psychedelics

Saga Briggs (SB): Based on your animal studies, how do you think psychedelic drugs might work in humans to treat social brain diseases like PTSD?

Gül Dölen (GD): When we think about what happens when someone has PTSD, what we're dealing with is that during their childhood or youth [during this maximum sensitivity to the social environment, or "social critical period"], they were in a social environment and something bad happened to them, and in that moment, their

response was very adaptive. They were protecting themselves by putting up walls, by guarding themselves from whatever was causing that injury.

But then the critical period closes, and over time, that adaptive response starts to become less and less adaptive until they reach adulthood and they're unable to form intimate relationships. They're unable to keep a job. They have a very negative view of themselves in terms of self-esteem, that they're not deserving of love and being in the world. The memory becomes an extremely well-ingrained worldview, and it's hard to dislodge it. And so the idea is that what we're doing with MDMA is going back and allowing them to rewrite that memory in a way that's adaptive, now that the traumatic event has been removed from their environment.

And so I think that in the end of the Nature paper1, we kind of ended with, "Oh, well, [psychedelic drugs] might be just making the therapeutic alliance stronger," but based on other more recent data and thinking about it longer, I think that it's more than just the therapeutic alliance. It's about making available those memories to modification.

SB: How does this memory modification work exactly?

GD: The way I'm talking about it now is I call it "open state engram modification." So you put the brain on MDMA in an open state where you're going to be sensitive to your social environment again, and then –either through therapy or through processing your own memories or looking at photographs or journaling—what you're doing is bringing back the memory engram that is relevant to the trauma in this state where you are available to manipulate it and make those memories malleable and rewrite them to respond to the realities of your current world.

SB: And do you think that has to happen in a social setting, per se? I think in your Nature paper you mention this phenomenon only happened when mice were with other mice. But of course, many people have transformational experiences taking psychedelics on their own.

GD: I actually think probably one of the most surprising and profound findings of the paper is the setting dependence, because every other explanation that has been made of how these psychedelic drugs work from literally everybody else has always overlooked the fact that these experiences are very much modified by the set and setting, that they're context dependent. You know, it's not like people who have PTSD are taking MDMA and going to raves and coming back cured. Yes, you can have profound experiences that are important in a therapeutic way outside of a doctor's office. But you're not going to have it if you spent the whole time just partying. In that case you're not engaging those [traumatic] memories.

Going beyond the acute effects

SB: Is this the same mechanism you believe could work to treat severe forms of autism?

GD: Before we can dive in on the human trials for autism, we kind of want to get a little bit more information about autism. One of the things that happened when I was a graduate student is that, my graduate advisor Mark Bear and I, we put forward this theory that if you turn down the signaling of a specific glutamate receptor [mGluR5], it balances out the exaggerated protein synthesis observed in autism.2 This theory had a lot of enthusiasm and excitement and seemed to be validated by animal research that was replicated by twenty-eight other labs. After those preclinical animal studies got so much press, the big pharmaceutical companies jumped on board and they thought they were going to cure autism with this mGluR modification. And then the clinical trials failed, and it was a big disappointment for the whole field of translational neuroscience. It was devastating because we all thought it was going to work, and then it didn't. So in trying

to think about why it didn't work, there were a lot of different possible explanations. But I think it's that every single one of the animal studies was carried out either from genesis [doing the manipulation genetically so they were born with the modified gene] or they were given [the modification] very early in development and just given it chronically for their whole lives. Whereas, in the human trials, the youngest recruited patients were sixteen years old, but most of them were adults—well past the age when their social critical period would be closed.

So, the idea that I would love to pursue is, well, maybe the reason that the clinical trials failed is because the mGluR therapy was right, but the critical period was closed. What we really needed to do is give a mGluR modulator, plus a psychedelic, to reopen the critical period. So that under the conditions of an open social critical period, the biochemical imbalance would be corrected and then you would get therapeutic efficacy.

SB: Would open state engram modification be a lasting treatment for these diseases? How long did the effect last for the mice in your study?

GD: Yeah, actually, I think that's the second most important thing that we found in this study: Every other study trying to figure out the mechanisms of this has really focused on the acute effects of the drugs. And what we found is that after MDMA, the critical period starts to open about six hours after the acute dose. And then it kind of peaks out at 40 hours and stays up for at least two weeks, and then by a month it comes back down. So just to kind of put that into perspective, two weeks in a mouse is probably more like two months in a human.

I think that also informs how we might want to be doing these clinical trials. Rather than having the MDMA-assisted psychotherapy and then sending them home with a journal and some happy thoughts, what we really ought to be saying is that the therapeutic window here is actually for weeks, if not months after the acute psychedelic effects have worn off. We need to treat that period of time as precious and really make there be a lot of intensive focus and therapeutic activity happening during that window rather than just kind of setting them off and letting them be on their own.

Where therapy meets big pharma

SB: In what other ways could these findings influence treatment models?

GD: This speaks to a debate that's going on right now in psychedelic therapy. The pharmaceutical companies are really wedded to this idea that if we can understand the mechanisms of these drugs, on a pharmacological level, then eventually we can design a drug that activates whatever mechanism is curing depression or PTSD or whatever it is, and then we can design out all of those nasty psychedelic side effects. The psychedelic journey can be gone, right? Like, that's their dream.

And then you have on the other side the psychologists, who say, "No, that can't be right because we know that we can achieve these psychedelic therapeutic effects even without the drug, as long as we can get them to this mystical place. We can do it with meditation, we can do it with a little bit of breath work, etc. And furthermore, the strength of that mystical experience correlates with the strength of the therapeutic effects."

So these are the two sides of the debate. And I think our finding about the setting dependence of psychedelics in opening the critical period kind of offers a middle ground between these two worldviews. What it says is that the binding of the drug to the receptor opens a critical period—that's the pharmacological effect that the drug companies have been so furiously searching for. Our hypothesis is that that is the mechanism. Any drug or any manipulation that can reopen the critical period has the potential for that therapeutic effect. But then on top of that, the setting dependence of it means to me that what the psychedelic journey is doing and the setting

is doing is priming the brain so that the right memory and the right circuit is being brought into reactivation or made available for modification in this open state.

It's a middle ground between these two different views of how the [drug] is working. And I think it really says, mechanistically when we are evaluating a potential hypothesis or a new compound or a new way of doing these clinical trials, we need to address this issue of "are we opening the critical period and are we effectively triggering the relevant engram?" Because if we're not doing either of those things, it's not going to work.

Future directions

It remains to be seen whether critical period reopening will become a deliberate aim of psychedelic therapies, especially as other labs begin to claim therapeutic efficacy with trip-less synthetic versions3 of psychedelic drugs. Regardless, there appears to be significant, untapped therapeutic potential to be explored in the months following standard psychedelic treatment. In the case of PTSD, this window could prove invaluable. In the case of autism, which is not universally considered a disease, the conversation is more complex. While the notion of "curing" autism has been and should be challenged, for example by questioning the ethics of fundamentally changing core aspects of an individual's personality, Dölen's work stands as a pivotal contribution to the field for those who might seek treatment.

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