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Psychedelics and the social brain

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In the MIND Bioblog series, we present personalities who have influenced the development of psychedelic therapy, research, and the culture surrounding the psychedelic experience. Dr. Katrin Preller is a Junior Group Leader at University of Zürich, and Visiting Assistant Professor at Yale University. Her research revolves around the neuropharmacology of social cognition. The following conversation covers her interest in how using psychedelics and cognitive neuroscience can help improve our understanding of self and sociality in health, psychopathology, and psychotherapy. Moreover, we take a deep dive into the question of what mechanism(s) may underlie psychedelic therapy.

Lucca Jaeckel: You did your PhD work on the neurobiological effects of psychoactive drugs like cocaine, MDMA and heroin. What interested you in studying these drugs, and what then drew you toward psychedelics after this?

Katrin Preller, PhD: When I started my PhD, I was interested in understanding what the brain does to make us feel what we feel and think how we think. I wanted to understand the neuropharmacology behind the processes that influence our everyday life. And one way to do that was to look at the neurobiological long-term consequences of perturbing the brain by regularly doing psychoactive substances. That's how I ended up working with cocaine, MDMA, and heroin users.

I think this work has important implications for the therapy of addiction disorders. However, it did not quite satisfy my interest in really understanding the causal influence of psychopharmacology on our thinking and emotional processing. It's very rare that people only use cocaine or only use MDMA. That makes it really hard to establish any causal link in these types of studies.

While working on that, I then learned about psychedelic research, which I wasn't even aware of when I started. So, I got interested in psychedelic science and thought that this might help me to solve some of the

questions that I had. Specifically, with psychedelics, we can perturb the system in a causal way. And, given the relative specificity of these substances' effects on the serotonin system, we can make causal inferences about how receptor-level changes affect thinking and emotional processing. So that really got me into psychedelic research and is the reason I started doing a postdoc together with Franz Vollenweider.

Of course, that was already a few years ago. My interest in psychedelic substances and their effects has, since then, broadened to also include their therapeutic potential, but I'm still very much interested in these basic neuropharmacological questions.

Considering this "causal mechanism question," of course the administration of a psychedelic drug and its pharmacological consequences specifically stand out as a causal factor in determining the neurocognitive, social, behavioral, and emotional effects. But there's also this big elephant in the room, that alongside the direct pharmacological effects there's contextual and placebo effects, such as the way expectancy and social setting influence outcomes. What do you think about this?

I mean, this is obviously very relevant, especially for therapeutic work. But I think it's less important for the basic neuroscientific work because we're mainly using objective tests there — to the extent we can, of course.

When we're looking at, for example, brain imaging, it's unlikely that people can consciously change their brain activity or the connectivity in their brain. So, for these basic neuropharmacological questions, I think it's less of an issue.

However, it becomes terribly relevant when we're talking about therapeutic effects where we're not necessarily just looking at the acute effects of the substance, but are interested in what happens days, weeks, or months after the experience. And this could of course, be very much shaped by expectation because we're then looking at symptoms and hopefully symptom relief. This continues to be a somewhat unresolved issue, because it is terribly hard to blind these studies. This means that it's also very hard to get rid of expectancy effects and also disappointment effects if people realize they did not receive the active substance.

Moving forward, I think we really need to address this by having better control conditions. That is, of course, hard. Even if we administer another psychoactive substance as a control condition, it remains hard to blind people. We don't really have a good solution for this right now.

I guess a way in which one could argue that you are already studying context-dependent effects, is that you are studying the social cognitive effects of psychedelics. So, by looking at how social context is processed differently, this may give us insight into how our context is affecting the outcomes. How exactly do you study the social cognitive effects of psychedelics? And how do you think this contributes to our understanding of the clinical effects of psychedelics?

So, the first reason why I study social cognition with psychedelics is that we don't really understand social cognition and social interaction very well, especially not their pharmacological basis. And on the other hand, we know that basically all psychiatric disorders are characterized by a disconnection from the social environment. And this is very hard to treat with the methods that are currently available. I think the way that psychedelics are influencing how we perceive our social environment is a key mechanism when it comes to therapeutic work.

So, what we've done so far is we've mainly looked at how psychedelics influence social processing in an acute state. We did that mainly with computerized tests trying to simulate social interactions while people are lying in an fMRI scanner. This way we are trying to objectively measure how the brain reacts to the social environment under the acute influence of a substance.

In our therapy studies, which are being conducted right now, we don't look at such acute effects as much. Instead, we want to find out if there are long-term consequences on social processing in these patients, and whether these potential changes in social processing also relate to symptom improvement in our patients. To do that, we perform some of these tests for which we already found psychedelic-induced changes acutely, and we do them post-acutely, a few weeks after administration. Then we test if there is a relation to treatment effects, meaning symptom improvement.

Now, these are lab-based tests, right? I think that moving forward, it would be important to collect objective real-world data on social interaction and social ability, to really see if this effect that we think could contribute to symptom improvement is actually something that also happens in the everyday life of our patients.

Then, what we're also interested in, in our therapeutic studies, is the interaction with the therapist – of course this is also a social interaction and a quite important one when it comes to therapy. We're assessing how the quality of interaction between the therapist and the patient changes or not after the administration of a psychedelic. The data are basically being analyzed as we speak; hopefully, we'll be able to show you some results within the next few months.

Like these real-world interactions, a lot of the things that are affected by psychedelics seem to be on a high level of complexity or abstraction. Things like consciousness, the self, and the beliefs people have about the reality of the world seem to be affected by psychedelic drugs. This makes it kind of difficult, but also interesting, to study these substances. One similarly complex issue, relevant to your work, is how self and sociality are related: how tight is the link between the two and what does it mean that humans have a social brain?

From the studies that we have, it's quite obvious that self-processing and social processing are linked. Still, it's pretty hard to characterize the exact nature of that, because we have limited ability to influence social interaction, and we have limited ability to influence self-processing. Psychedelics really provide a unique window into doing that.

It's very clear that, in psychiatric patients, there is this disconnect between the self and the social environment. The pandemic that happened over the last two years really showed us this link very clearly—the link between how well and how much we can interact with others, and mental health issues.

Psychedelics really give us the opportunity to study this relationship in a causal way. Hopefully they can also help us improve self-processing and social cognition, because they really are key to mental health.

Would you say there's something that psychiatry can learn from psychedelics about treating mental health conditions or for understanding mental health conditions, in terms of what they tell us about self and social processing?

There's a lot that psychiatry can learn from psychedelics, not only related to social processing. But we have a major knowledge gap here, and that is about the exact mechanism of action: Why do these substances help people? Social and self-processing are just two hypotheses among many others. What we're starting to see now is that whatever it is psychedelics do to help patients seems to be something that is transdiagnostic. Probably, there are certain things that are more important for one indication than for others. But we see something that seems to be beneficial for a wide range of psychiatric illnesses. I think figuring out what exactly it is that psychedelics do to help patients can have a huge impact on psychiatry.

The other thing where I think that psychedelics are making a large contribution to psychiatry is the idea of pharmacologically-assisted psychotherapy. That's a model that may have not been getting enough attention

so far. It seems like a lot of psychiatry is currently just about giving a drug and expecting that patients get better. But we know from a lot of studies, not only with psychedelics but also with regular antidepressants, that there is a synergy between therapy and pharmacological treatment. So, the drug is really augmenting the therapeutic process. And I think psychedelics very prominently bring this back to our attention. It shows that we need to consider pharmacotherapy in the context of psychotherapy.

If we consider psychoactive drugs in general, also illegal drugs or illicit recreational drug use, do you think there's something that is special about psychedelics or that there is something that we can learn about how we deal with drugs more generally from this substance-assisted psychotherapy scheme?

I mean, I'm not a politician or sociologist who could really talk about issues of legalization and things like that. But what we do see is that, first of all, all psychoactive substances in a way induce some kind of altered state. The quantity and quality of this altered state may differ, of course. Along with this, the risk potential of different substances is different. Some substances are more addictive and others less, for example. And some drugs, like psychedelics, induce this altered state of consciousness, which we know is easier to navigate in a professional setting where people can help guide you through the process.

There are similarities and there are differences. Of course, there are differences in the mechanism of action. And they have different implications for how they should be used.

Especially when we're thinking about medical purposes again, it is most important to understand the mechanisms of action. For this it could be really interesting to do cross-pharmacological studies. So, to compare different pharmacological agents in the same individuals. It's difficult to compare whether ketamine actually does one thing and psilocybin something different, because we're still lacking these studies. I think for those psychoactive agents which are currently being developed or tested as medication we should really move forward and do these cross-pharmacological studies.

Maybe that was already one of your answers to my next question, but if you look at the field of psychedelic research at the moment, what do you think is the most important thing to focus on right now? What are the questions that haven't been addressed before?

We need to understand the mechanisms of action. Why do people get better? Because this will have huge implications on how the therapy should be conducted. And right now, the field is moving forward with testing psychedelic therapy for a lot of different indications and looking at clinical efficacy in small studies. This is important; I'm not questioning that. But I think it is at least as important to understand why the substances are helping people, because this will have an influence on how you conduct the therapy.

If you are leveraging, let's say, a neuroplastic effect, you can enhance that with certain types of trainings, for example. But if you're thinking about these substances as inducing some spiritual or mystical effect, this will have consequences on how you conduct therapy, how you use the substance, and things like that. As long as we don't really understand why they help, it is really hard to optimize the therapy.

Also, as there are more and more studies and they're growing larger and larger, we will also see that these substances will not help everyone in the current therapeutic model. There will be patients who don't get better. By understanding the mechanisms of action and optimizing the therapeutic approach, we may eventually be able to tailor the approach to the person. I think this will be highly beneficial for patients and will really allow this line of work to make the best of the effects that these substances have.