MIND FOUNDATION

Ascension, peak, return

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To learn more about the serotonin system and serotonin receptors, take a look at: The Psychedelic Compendium – Serotonin Receptors.

Lukas Basedow: For the study that we are discussing, you performed PET brain scans before administering psilocybin to healthy participants. I would like to know what your primary goal was for this study – what was your driving question?

Dr. Dea Siggaard Stenbæk: In a previous study, we saw a strong correlation between occupancy at the serotonin 2a [5-HT2a] receptor [a measure of how many of the receptors are currently bound with a molecule, such as psilocin or serotonin] and the intensity of the experience induced by psilocybin when we let participants rate the drug intensity every 20 minutes.

For this study, my initial approach was to think about '*how can we do some psychological evaluation of the psychedelic experience that goes well with neuroscience.'* Studying these experiences combined with a lot of scanning during the session is very difficult and may affect the experience. My main interest in this was trying to see if I could use a very simple measure to track how the experience unfolds.

We first asked ourselves, how can we model the intensity of a psychedelic experience? Once we started with this, we saw that subjective drug intensity really fit very nicely into three phases.

This insight is useful when you accompany people during a psilocybin experience because it is a long process — it takes six to eight hours. Breaking the whole session down into minor pieces would be clinically helpful, for instance, when you want to set up music or when you want to train therapists. And these phases have been spoken about before, but not a lot of empirical evidence has been gathered to model them.

People tend to focus on the findings related to the 5-HT2a receptor in this paper because that's the really new part. But actually, my approach was more to model how the intensity of the experience temporally unfolds.

L: And could you explain how you actually did the study? What kind of methods were you using to answer your question?

D: What we did was that we had people come in and prepared them for their psychedelic experience and during the preparation they also had a PET scan. Then we had them come in on a separate day, and we gave them the psilocybin, and during this psilocybin experience we asked them every 20 minutes: 'How intense is the experience for you right now?' We did this throughout the whole experience and in the end the participants completed this mystical type experience questionnaire.

Afterward, we had them come in the next day to talk about their experience, debrief them, and evaluate whether there was any need for further conversation with them.

L: Could you shortly explain to our readers what the PET scan is that you mentioned just now?

D: When you scan the brain, there are at least two categories of scans you can do. You can scan the structure and brain function with MRI, or scan the brain chemistry with PET. When you have a receptor that sits on a neuron, like the 5-HT2a receptor, you can inject a radioactive ligand [a substance that binds to that receptor] into the body that has affinity for this receptor. When you then do a PET scan, it's actually that radioactive ligand that you see in the scan. More specifically, you can see how much of it sticks to the 5-HT2a receptor so we can have an idea of how much of this receptor is available in the brain.

L: That's a great explanation, thank you. So, could you summarize the main findings of this study?

D: Basically, we found that the psilocybin experience can be divided into three phases, the onset, the peak, and the return, which is kind of intuitive, but it has not been shown empirically before in this way. Also, we saw that the time participants stayed in these three phases was related to the 5-HT2a receptor availability. Specifically, participants with lower availability of the 5-HT2a receptor before ingesting psilocybin were in the peak phase for longer and in the return phase for less time. This also correlated with the profoundness of the mystical-type experience, meaning that the lower availability of the 5-HT2a receptor, the longer time in the peak, and the shorter time in the return phase were all related to a more profound mystical-type experience.

L: I have two follow-up questions. First, you mentioned that a shorter time in the return phase is related to the strength of the mystical experience. Do you have some hypothesis on how these things could be related? What might connect the strength of the mystical experience with the time spent in the return phase?

D: The length of the peak is inversely correlated with the length of the return to normal waking consciousness. So, what I think is going on is that you have some set number of hours of drug effect, because at some point it will leave your body again, right? And you can divide this time in different ways, so if you spend a lot of your time in the peak, you have less time to return. This is what we see this correlation reflecting. I think that it is actually the length of the peak that is important, but that will have a bearing on how long you have left to return.

I was curious about what makes people stay in the peak phase for longer, since this seems to be clinically relevant because that it is the foundation for experiences that can have lasting positive effects. One possibility is that people kind of rehearse their peak experience. In a sense, they are good at staying there and reinforcing the peak, building these experiences. Another possibility was that there are biological differences between people that can help us explain why some tend to stay there longer. So, having these unique data about the 5-HT2a receptor, it was obvious to look at that and see: 'Does this play a role in determining how long someone stays in the peak?'

L: My second follow-up question is: Do you have a hypothesis for why this 5-HT2a receptor availability is related to the strength of the mystical experience and the length of the peak effect?

D: It might seem counterintuitive since people tend to think that you would have a wilder experience when you have more receptors. But what we saw before, when looking at the 5-HT2a receptor, is that people with high levels of mindfulness actually downregulate this receptor [they have a reduced number of it on the available on the cell surfaces of their neurons]. Other research has also shown that people with lower levels of 5-HT2a receptor availability had lower levels of neuroticism. With this in mind, our findings do not seem so strange anymore.

One hypothesis we have right now is that lower levels of the 5-HT2a receptor actually reflect a higher concentration of serotonin in the brain. The brain tends to downregulate receptors as it finds it necessary to have proper signaling. We also know that when you give certain types of antidepressants, the 5-HT2a receptor is downregulated, and we hypothesize that this is because the concentration of serotonin has increased in the brain. If that is true —and we do not know exactly if that is true —it would mean that people with lower levels of the 5-HT2a receptor probably also have a higher concentration of serotonin in the brain. And it is serotonin combined with psilocybin that stimulates the receptors when you go into the psychedelic experience; there may be a synergy there. I do not think anybody really knows at this point, as most times in science, we need to do more research.

L: Okay, this means that a reduced level of 5-HT2a receptor availability might reflect higher serotonin levels in the brain, which might lead to a stronger psychedelic experience. You also mentioned that if people take antidepressants it will increase serotonin levels and downregulate the 5-HT2a receptor density, correct?

D: Yes.

L: Could you relate this finding to reports of people taking antidepressants having less intense psychedelic experiences?

D: There is really no research answering this question. There is anecdotal evidence that people that take SSRIs have this numbing effect when they take psychedelics. It remains to be seen if that is the case. But this brings up another problem, which is that there are actually two questions: There is the question of what happens when you stimulate the 5-HT2a receptor and there is the question of what baseline levels of this receptor actually reflect.

I am not sure whether having a lower 5-HT2a receptor at baseline is reflecting the same as when you give an antidepressant, and the receptor is downregulated. Because the second one is a drug-induced down-regulated state and the other is just a natural state of the system. Since we cannot be sure that these two situations can be equated, we still have to conduct some research. I know of studies going on right now where they want to randomize to placebo and SSRI and then give a psychedelic experience on top of that to test these kinds of ideas. The next step would be to see if that downregulated state of 5-HT2a corresponds

to what we see when we just do a baseline PET scan. [For more information on SSRIs and psychedelics feel free to read Camile Bahi's post on the potential risks of this drug combination]

L: One last question, not related to your study – Could you give us some insight into the history of psychedelic research in Denmark?

D: I think what happened in Denmark probably reflects what had gone on in most countries. There was a lot of enthusiasm in the 60s, mostly about LSD, and there were studies done particularly in one hospital. Unfortunately, some studies had negative consequences for the participants, and we had legal trials going on afterward. After that, all psychedelic studies were closed down, and they were considered very dangerous drugs. With these studies that we have done here, our group is actually the first in Denmark doing psychedelic research in modern times. And so far, we have only had good experiences giving these substances to people.

L: Thank you for that insight and congratulations on this great study and your successful research program!

REFERENCES

1. Stenbæk, D. S., Madsen, M. K., Ozenne, B., Kristiansen, S., Burmester, D., Erritzoe, D., Knudsen, G. M., & Fisher, P. M. (2020). Brain serotonin 2A receptor binding predicts subjective temporal and mystical effects of psilocybin in healthy humans. *Journal of Psychopharmacology-*. https://doi.org/10.1177/0269881120959609