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Is (Re)connection a Basic Principle Of Action Behind Psychedelics? | MIND Blog

DATE PUBLISHED

28 August 2020



> *The paper discussed in this interview is:*
> *Mertens, L. J., Wall, M. B., Roseman, L., Demetriou, L., Nutt, D. J., & Carhart-harris, R. L. (2020). (Https://journals.sagepub.com/doi/10.1177/0269881119895520)*

Lukas: Could you tell us a bit about your academic journey? What were the stations that brought you to your current position?

Lea: I did my bachelor's degree in psychology and I always knew that I wanted to work clinically and help patients. But then throughout my studies, I got really interested in scientific research, though I always knew that if I want to go into research, then it must be clinically relevant. So I developed an interest in psychopharmacology because the psychological effects of different kinds of drugs and medications kind of blew my mind. I then decided to do a research master's1 and through my master's program, I got in contact with psychedelic research. The deeper you dig and the more you get involved in this topic the more fascinating it gets!

Through my supervisors at Maastricht University, I got involved at Imperial College2 for my master's thesis which, to be honest, was just a bit of luck. Then I worked in this amazing research group and I got in contact with Prof. Dr. Gründer3 who is a professor in Mannheim at the Central Institute of Mental Health. He had some vacancies and open PhD positions and we decided that we would like to pursue psychedelic research together in Germany which is a very, very difficult task to do! Now we are on this path together and that is how I ended up where I am. Also, I recently started my psychotherapy training, so I am doing research and clinical work at the moment.

Lukas: Great, let us take a look at the paper. What did you want to find out with this specific project?

Lea: I am particularly interested in how psychedelics work on different levels. This means I am interested in the biological level, for example in what psychedelics are doing to our receptors, but definitely also the psychological level. So during my master's program, I wanted to do some brain imaging work and I was very happy when Robin [Carhart-Harris4] offered to let me conduct an additional analysis of the imaging data they had from the big clinical trial for treatment-resistant depression.5 What we wanted to do was to unravel changes in brain function that might underlie the beneficial treatment effects of psilocybin. They had some publications already6 on these changes and based on this I did two follow-up analyses to take a closer look.

Lukas: Could you briefly summarize what it was that you found?

Lea: As I said, the data were already there and Roseman et al.6 had shown that one day after the psilocybin treatment there was increased reactivity to emotional faces in a brain region called amygdala, which is thought to be involved in emotional processing. Also, this increased activity correlated with treatment responses one week later.

However, finding that increased amygdala reactivity is related to antidepressant effects is super counter-intuitive. When looking at findings from antidepressant research, that just is not what you would assume. Nevertheless, this was the main finding they had, and we wanted to look a bit further and see whether the changes in amygdala reactivity were potentially linked to changes in functional connectivity that could underlie this increased reactivity. That is why we conducted a psychophysiological interaction analysis [this method allows scientists to investigate task-dependent changes in functional connectivity between brain regions] on the same functional MRI (fMRI) data to see whether there are differences in amygdala functional connectivity to prefrontal control regions like the ventromedial prefrontal cortex (vmPFC) during emotional processing.

What we found is that there was decreased functional connectivity between the vmPFC and the amygdala one day after treatment compared to baseline. This finding is definitely interesting because we can hypothesize that there might be decreased inhibitory input from prefrontal regions to the amygdala after psilocybin treatment. Again, that is very hypothetical, because directionality cannot be assumed, but it is something that should be looked into in subsequent trials and analyses.

Lukas: Is there a way you could describe the kind of psychological correlates of the neuroscientific changes you found? So, what would it feel like to have these changes in amygdala reactivity and functional connectivity between the vmPFC and the amygdala?

Lea: It is always difficult to link neurobiological findings directly to behavioral consequences. So in my analysis, we found an association between decreased functional connectivity of the amygdala and the vmPFC and levels of rumination one week after treatment. One theory is that this increased reactivity of the amygdala together with this decreased functional connectivity can be interpreted as a revival of emotional responsiveness and emotionality. So to feel reconnected to your feelings would be a psychological correlate. But again, that is hypothetical and should be researched more.

Nevertheless, this theory is quite interesting because there are a lot of depressed patients that report feelings of numbness and feelings of emotional disconnection. Maybe one therapeutic mechanism of psilocybin could be this reconnection with emotionality.

Lukas: You mentioned already that the findings of Roseman et al.6 and your findings are kind of counter-intuitive given what we assume about the relationship between amygdala reactivity and depressive symptoms. Previous research mainly found that high amygdala reactivity is a marker of

more depressive symptoms but now you show that psilocybin treatment for depression is also related to higher amygdala reactivity. Any chance of integrating these two findings?

Lea: Yeah that's a tough one! As I already said, one plausible explanation is this regained emotionality or emotional reconnection that in the end leads to better treatment response. But it's also important to consider the time point of scanning in the trials. That was the morning after the high dose session, which usually means the morning after an intense and emotionally charged psychedelic experience. Maybe the increased amygdala reactivity together with the decreased functional connectivity is just a response to this significant experience.

I am curious to see what the situation would look like one week or six weeks later, though. Especially because I believe that the effects of psychedelic therapy work in phases. You have this acute, highly significant psychedelic experience and everything that comes with that (e.g. mystical experiences, re-experiencing traumas, visionary states), and maybe there is an increased amygdala reactivity at this point because everything is still not really processed.

But then weeks pass, and people integrate the experience and, with this, their situation can change also on the neural level! I am really amazed by the idea that psychedelic therapy may have different effects across different time points. That is why I think that there is so much more research needed to investigate different effects across time. For example, there is a lot of acute data that gives us an idea of how psilocybin and LSD work acutely but what underlies the treatment effects at different time points is really unknown.

Lukas: Since we have a lot of students reading the blog who might be thinking: I want to do what she does! Can you give any advice to students looking to follow the same path you took?

Lea: Well, I worked hard during my studies, figured out what I wanted and pursued my interests, but also had a bit of luck! For example, I got into the research group at Imperial, which was amazing, and when I decided to go back to Germany it was not clear that I would find a professor that would conduct psychedelic research with me. I am very thankful that I reached out to Prof. Gründer because there was no other psychedelic research in Germany happening, so I would not have been able to conduct this work otherwise.

In general, my advice would be to stay motivated and to try to get in contact with the people you would want to work with. For example, get involved with the MIND Foundation and just reach out to researchers like me or my supervisor and people you could imagine yourself working with. We are all very open and willing to carry out research projects involving undergraduates and graduate students.

But I really have to stress that it is not that easy, it's a long process. I have this big poster in my office saying "good things take time" which I bought to cheer myself up in phases of low motivation, just to keep myself on track. I have to say that it is definitely not easy to conduct good scientific work with illegal substances and to establish clinical trials without the involvement of the pharmaceutical industry. There is a lot of regulatory stuff and hurdles you have to overcome so you need to be very, very motivated and dedicated, that is the current reality.

Lukas: So, considering all the dedication, good luck, and motivation needed to be a scientist in this field: Is it worth it?

Lea: For me, it is definitely worth it. I love what I am doing and I love to be part of this growing field! But I would also say if you are interested in psychedelic substances and psychedelic research that does not mean other topics are boring and might not be an option.

For example, if you want to do a PhD and there is no vacancy for you in psychedelic research maybe ask yourself: Why am I interested in this kind of research? What would I like to investigate? And maybe when you think deeper about what is it that intrigues you, you can find a related topic. Maybe it is in a slightly different field but still related. I do not think it is a good idea to be too narrow-minded by saying I only want to do psychedelic research because, in the end, you might miss the big picture regarding all the things we do not know in psychiatry and neuroscience!

Lukas: Very good point! Last question: What is next for you?

Lea: On the research side, I am a PhD student and my big task – I always call it my baby – is the clinical trial with psilocybin for treatment-resistant depression which we are conducting together with the MIND Foundation and the Charité in Berlin as a second study site. I am kind of the project manager at the moment, which is a lot of work, but I hope we will start at the end of this year, at least that is the plan.

Besides that, I have been involved in some pre-clinical psychedelic work at the Central Institute of Mental Health7 but I think now I am actually too busy with other things to continue my involvement in that. However, it was a super interesting experience to see the benefits of pre-clinical work, for example, that you can conduct pre-clinical work so much quicker and with fewer hurdles compared to clinical studies. For now, however, I am going to focus on the clinical trial and my psychotherapy training and I hope to get my PhD at some point during this process.

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