HOW DO PSYCHEDELIC DRUGS WORK ON THE BRAIN?

Dr Robin CAHART-HARRIS: Ok so I'm a postdoc working for David Nutt at Imperial. I've been working researching psychedelic drugs for the last five years or so. I completed my PhD four years ago and I've been working on really just this subject matter for the last five years. So... I'll try and give you the basics first. We'll start with the term itself psychedelic: what does it mean and where does it come from? When you hear psychedelic, most people think about psychedelic art and really it conjures up ideas of psychedelic culture and so you might think of geometric hallucinations and colourful patterns and this kind of thing, the kind of art and iconography that you associate with the sixties but that's actually quite far from where the term actually originates.

So in the mid 1950s, a British psychiatrist, Humphry Osmond, was carrying out work with mescaline and LSD. Aldous Huxley, the writer and intellectual, learnt of Osmond's work and he was very interested in the idea of these drugs so he sought out Humphrey and asked whether he would provide him with some mescaline and supervise his own psychedelic experience. So, after some deliberation, Osmond was worried about sending the great Aldous Huxley mad but he did actually relent and he provided him with some mescaline and Aldous Huxley had an incredibly profound experience which he writes about in his famous book *The Doors of Perception*. So in conversations between these men after all this that Aldous had experienced, they were looking for a useful word that could define and describe this class of drugs because previously they'd really just been referred to as hallucinogens, they'd also just been looked at in the context of models of psychosis, there was an idea that they generate some of the symptomatology of psychosis or schizophrenia. But these men thought that the current words didn't really capture the essence of what these drugs do and how they change consciousness and maybe how they work in the brain. So Huxley had suggested a term which Osmond wasn't very sort of impressed with and he came out with his own and he actually combined the Greek word for mind or soul, *psyche*, with the word *delos*, apologies for my translation, but er, so 'delos' means to make visible or clear or to manifest so in combination these words described the drugs as mind manifesters or mind revealers. And so already there's something quite interesting, these guys are trying to capture some key property of these drugs and they really think that the primary property is one of making the mind manifest so that, for me, is intriguing in itself, that there should be aspects of the mind which aren't normally available to consciousness and these drugs might be used as tools to get to those aspects of the mind.

So why study psychedelics? Well, there's been some interesting recent work carried out in the US that has administered quite a large dose of psilocybin, the compound found in magic mushrooms, so they've administered a large dose of psilocybin to a relatively large sample of research participants and **they found that** two thirds of these participants described their experience as being one of the most profound of their whole lives, within the top five most profound experiences of their lives. And so when asked what that means, what does that translate to, they would say it was comparable to such things as the birth of their first child or the death of somebody very close, a parent. So it really was up there with, you know, major life events. So again we've got some context here which is helping to communicate really that these drugs profoundly affect consciousness and are interesting scientifically.

This psychiatrist was working with LSD in the 1960s and he was particularly effusive about these drugs and their potential. He said that "psychedelics used responsibly and with proper caution, could be for psychiatry what the microscope is for biology or the telescope is for astronomy. These tools make it possible to study important processes that under normal circumstances are not available for direct observation." So inspired by these findings and particularly Stanislav Grof actually, he's an interesting chap, you know, I become very interested in psychedelics and the question of how they work in the brain. Given that they have such profound psychological effects, it's a natural inference to think that, you know, learning how they change brain activity to produce these effects is gonna tell us some very important things about how consciousness is produced in the brain.

So most of my work's been with psilocybin and this is a compound found in magic mushrooms. Fortunately it's out of season at the moment, it's not mushroom season so you won't be getting your iPhones out and snapping this picture and going hunting at the end of the talk or tomorrow. So what's striking about psilocybin and its metabolite, psilocin, is the similarity of its molecular structure to the endogenous neurotransmitter in the brain, serotonin. So I've got a pointer now... Here's psilocin, this is what psilocybin's broken down to, and here's serotonin so this is found in all of our brains in quite high concentrations and it's a very important neurotransmitter involved in modulating sleep and mood, cognition and lots of things that we do. And it's

really quite striking that only a small change in its molecular structure confers such a profound effect on consciousness when these drugs are administered to people.

In the mid 1980s, **it was found that** there's a strong positive correlation between a psychedelic drug's affinity for a particular serotonin receptor in the brain and its potency. So drugs that are stickier at the serotonin 2A receptor, this subtype of serotonin receptor, are more potent so to help illustrate that rule, the classic psychedelic LSD is particularly sticky at the serotonin receptor, the serotonin 2A receptor and it's also incredibly potent, it's the most potent psychedelic drug whereas mescaline... you require large amounts of it to produce hallucinogenic psychedelic effects and it is significantly less sticky, it has a lower affinity at the serotonin 2A receptor. So already we've got some important clues here about how the drugs work in the brain. **It's also been found that** if you block this subtype of the serotonin receptor, the serotonin 2A receptor, and then you give a psychedelic drug, psilocybin, then you won't get the psychedelic effects that you normally would so it completely attenuates the psychedelic effects of psilocybin.

So this serotonin 2A receptor is important clearly for how these drugs work in the brain so then it's important to know whereabouts in the brain is this receptor. So PET work, PET imaging work in humans has found that the serotonin 2A receptor is particularly highly concentrated in the cortex of the brain so that's the outer layer of the brain rather than the subcortical structures and it's also especially highly expressed in what are referred to as multimodal or high level structures in the cortex. So rather than for instance the visual cortex which has a very specific function or the motor cortex, you know, that are concerned with really only one modality, these high level regions do more sort of general things and there's some interesting work looking at these regions at the moment in the context of consciousness and high level cognitive functions.

So what else about the serotonin 2A receptor? Well the cortex is organised in this layered fashion, there's a number of different layers and there's a particular layer in the cortex, layer 5, where you find again a very high concentration of these serotonin 2A receptors, and these cells here, these large pyramidal cells in layer 5 of the cortex are the primary output layer of the cortex so they're very large and they do a very important function, they're thought to confer sort of top-down information, their activity is supposed to provide contextual information about sensory input and other sensations.

What else? Well what happens when you stimulate the serotonin 2A receptor, when it's activated by the serotonin or by a psychedelic drug? Well the effect of serotonin 2A receptor stimulation is to excite that host cell and make it more likely to fire. So we know that the serotonin 2A receptor is important, we know where it is, we know that when a psychedelic binds and stimulates this receptor, it excites that host cell. So these are some basics. So this is all low-level stuff. What is this really gonna tell us about consciousness? Well most of my work has been looking at functional brain imaging and at this level we get a kind of overview of the brain, we get a macroscopic rather than microscopic picture of brain function and what's going on in the brain. And at this level, at this network level, it's actually easier to make mappings between brain function, brain activity and brain processes to psychological phenomena.

So in our first study we used functional magnetic resonance imaging to measure blood flow in the brain and this study involved fifteen healthy volunteers, they had a mean age of 34, it was an eighteen-minute scan and there was a placebo scan to provide us with a baseline and then the drug scan, psilocybin. They lay in the scanner and there wasn't any behavioural task that they had to carry out, they were simply resting there, in this case with a fixation cross so they were supposed to just relax and look at it. So we gave 2 milligrams of psilocybin, this compares to about 50 milligrams of the drug given orally, which compares to about 20 to 40 liberty cap magic mushroom if you want to put it in a recreational context. So which compares to about 20 to 40 liberty cap magic mushrooms if you want to put it in a recreational context so it's an incredibly rapid onset and the effects are quite profound. And then essentially we make a subtraction: blood flow post infusion of the drug versus blood flow pre infusion and then we see whether there are any changes.