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## How does psychedelic therapy work?

*Philosophy of Psychedelics*, by Chris Letheby, Oxford University Press, 2021, 272pp.,

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Dating back to the late 1990s, the growing popularity of psychedelics is not a recent trend. Psychiatrists, psychologists, and neuroscientists are paying increasing attention to these hallucinogenic substances, which seem to hold great promise for treating a wide range of pathologies - including depression, addiction, anxiety and more (see Nichols, 2016; Nutt & Carhart-Harris, 2021 for example). According to the results of a growing number of clinical trials, these new substances could far surpass existing treatments, in both speed and efficacy, with negligible side effects (e.g. Andersen et al., 2021). But for these substances to be effective, they must not be administered under just any conditions. So-called “psychedelic therapy” usually consists of a single dose taken by the patient after several preparatory sessions, combined with close psychological support during and after administration. Under these controlled conditions, the use of psychedelics would catalyze an intense but brief conscious experience, resulting in beneficial therapeutic effects (Letheby, 2021, p. 11). One of the interesting things about this therapy is that it places at the heart of the treatment process two things that are sometimes seen as conflicting: the biological action of the molecule, and the psychological experience. This “psychedelic experience” is often described by patients as “mystical” or “spiritual”, and empirical evidence suggests that the effects of psychedelics may be mediated through this “mystical experience” (see the detailed empirical review done by Letheby in chapter 2 of his book). However, the relationship between the biological effects of these substances, the psychedelic experience, and therapeutic effects is not well understood (Nutt et al., 2023). This is precisely the subject of the first book by Chris Letheby, *Philosophy of Psychedelics*. Through a combination of empirical evidence and philosophical perspectives, the author argues that the central mechanism of psychedelic therapy lies in the alteration of the “sense of self” triggered by a mystical experience. This review of Letheby’s book aims to summarize and discuss his position in light of the latest findings in fundamental neuroscience.

The book primarily explores the seemingly crucial role of mystical experience in psychedelic therapy. Letheby uses the definition of “mystical experience” of standard psychometric questionnaires, "as involving a sense of unity and transcendence of individual selfhood, as well as noetic feelings of directly encountering ultimate reality, a transcendence of time and space, a sense of sacredness, ineffability, and paradoxicality, and a deeply felt positive mood." (Letheby, 2022, p. 4) According to Letheby, the crucial nature of the mystical experience in psychedelic therapy raises both epistemic and ethical questions. If the therapy works only by inducing metaphysical hallucinations and what could be conceived as irrational beliefs (epistemic aspect), is it not questionable (ethical aspect)? In other words, as Pollan puts it, "Is psychedelic therapy simply foisting a

comforting delusion on the sick and dying?" (2015). This is what Letheby calls the "comforting delusion objection" to psychedelic therapy. The purpose of Letheby's book, then, is twofold: first, to show that this objection fails by taking a naturalistic approach; and second, to propose a working mechanism for this therapy. Letheby's general strategy for dealing with the comforting delusion objection is to first assume that *naturalism is true*, and to admit that if the *epistemic status* of psychedelic therapy is doubtful, we should hesitate to prescribe it. For the latter, this means that "realistic" forms of well-being, based on accurate understanding of reality, are preferable over unrealistic ones based on misrepresentation (Letheby, 2021, p. 30). Letheby's thesis is that the epistemic status of psychedelic therapy is unproblematic: "This treatment, despite first appearances, does not work centrally by inducing comforting metaphysical beliefs, but by changing how patients see themselves and relate to their own minds and lives." (Letheby, 2021, p. 3) And in his view, even if there are epistemic risks, there are offset by significant epistemic benefits.

As we said, Letheby starts by assuming that naturalism is true. According to the author, a robust naturalistic worldview as the one he favors generally implies the rejection of supernatural entities and forces, or disembodied minds, and "the acceptance that the universe is populated solely by the kinds of in principle-detectable entities, processes, properties, and forces studied by the natural sciences. (...)" (Letheby, 2021, p. 28). In short, he adopts a metaphysical doctrine that combines a generic physicalism or materialism concerning the mind with a denial of the existence of non-natural entities or properties (such as God, angels, the soul, etc.). Throughout his book, he will maintain this stance, which manifests itself in particular in a keen interest in the existing empirical literature. Letheby's naturalism is thus also methodological: in his view, philosophical conclusions must be based on and integrated with relevant scientific findings (Letheby, 2022, p. 6). According to Letheby, there is nothing essential about psychedelic medicine that cannot be reconciled with this worldview.

Apart from the introduction and conclusion, the author's argument unfolds in eight chapters. Chapters 2 and 3 review the history and phenomenology of psychedelic therapy, but focus primarily on the empirical evidence for its efficacy. Chapters 4 and 5 consider possible mechanisms of psychedelic therapy, and chapters 6 and 7 offer a detailed analysis of one such mechanism. Finally, chapters 8 and 9 set forth the reasons why psychedelic therapies would be agents of epistemic benefit.

In chapter 2, Letheby gives a brief history of psychedelic psychiatry, from Hoffman's discovery of the psychoactive effects of LSD in 1943 to the "renaissance" of psychedelic research in the 1990s. This is followed by a review of the contemporary empirical literature, which is continued in chapter 3. This review focuses on the effects in humans of the classical psychedelics, including LSD, psilocybin, DMT, and mescaline, all of which are thought to act on serotonin 2-a receptors (5-HT<sub>2A</sub> receptors). Letheby highlights a pattern: the psychological benefits of psychedelics are correlated with the occurrence of a mystical experience. In other words, subjects who have a mystical experience during the drug's action tend to be those who experience lasting benefits. In the literature, the existence of this pattern has led to the formulation of the comforting delusion objection.

In chapters 4 and 5, Letheby turns his attention to the mechanisms of action of psychedelic therapies. He describes the theory of molecular neuroplasticity, according to which the benefits of psychedelic therapies are epiphenomena of changes in synaptic neuroplasticity. He then introduces the alternative idea that the therapeutic benefits of psychedelics derive directly from their ability to induce transcendental visions of another reality. He points out the limitations of these two mechanistic hypotheses and proposes a third: that the benefits of psychedelic therapies are based on aspects of the psychedelic experience that are independent of non-naturalistic metaphysical ideas. More specifically, at the root of the therapeutic effects would be an “experiential factor” consisting of changes in mental representations of the self. Indeed, changes in the ego state would be one of the most salient features of the psychedelic state and mystical experience - which does not necessarily imply non-naturalistic beliefs. In support of his thesis, and following Carhart-Harris (Carhart-Harris et al., 2014), he mentions the idea that the pathologies for which psychedelic therapy is promising (depression, anxiety, addiction) have all been linked to changes in the representation of the self. Letheby reviews other types of evidence that aim to support his idea. On the one hand, two psychological arguments: the good correlation between experiences of psychological insight and clinical benefit, and the increase in mindfulness capacities. On the other hand, a neural mechanistic hypothesis: therapeutic benefits seem to correlate with the modulation of two networks that some scientists consider to support self-representation (default mode and salience networks).

In chapters 6 and 7, Letheby attempts to bridge the explanatory gap between neuroscientific and psychological explanations. His solution is to appeal to a neurocognitive theory of brain function: the predictive processing theory of cognition. This theory describes the brain as an "organ for prediction error minimization, which builds models of the world and uses these to predict sensory inputs." (Letheby, 2022, p. 11) Letheby draws on and refines the REBUS (RElaxed Beliefs Under pSychedelics) model proposed by Carhart-Harris and Friston (2019). This model suggests that psychedelics alter consciousness by disrupting the neural substrates of the brain's high-level predictive models (encoding beliefs about self, space, time, causality, etc.); resulting in reduced confidence in our most abstract and fundamental beliefs. Letheby adds, among other things, that it is certain specific beliefs that are targeted: the self-related beliefs. According to Letheby, this cognitivist framework helps explain psychedelic therapy in terms of two factors - the induction of some plasticity (neural, cognitive, etc.) on the one hand, and the discovery and appropriation of healthier forms of being oneself on the other.

In the final chapters 8 and 9, Letheby details the knowledge that can be acquired through psychedelic therapy: a certain "know-how" (learning “how to let go” - see Letheby, 2021, p. 178); a certain "knowledge by acquaintance" (of one's own unrealized potential, and of the contingency of the self); as well as a "new knowledge of old facts" (reinterpretation of past facts). He also points to indirect epistemic benefits (e.g. making someone more curious about the world around them and others).

One of the merits of this book is that it is well informed about some of the existing empirical literature. However, while it claims to take into account the “empirical literature”, it should be pointed out that this is not just any literature. There is a field that is overlooked in this book, but which is nevertheless a key player in the renaissance of psychedelic research: basic neuroscience and most importantly, preclinical research. For example, Letheby omits all the recent preclinical trials on non-hallucinogenic psychedelics, such as those conducted by Cameron et al. (2021). As part of this research, scientists aim to synthesize non-hallucinogenic psychedelic analogs that have therapeutic benefits without causing acute mind-altering effects. The goal is to produce safer molecules that do not generate a psychedelic or mystical state, reducing the associated risks of such therapies (such as bad trips), and making them more widely accessible. If these molecules prove to be effective in clinical trials, these results would provide a serious counter-argument to Letheby's position that the phenomenological effects are the key to therapeutic success, or, as he said, the “primary cause of the effects on well-being and symptomatology” (2021, p. 207). Although Letheby briefly acknowledges this point, he seems not to be taking the possibility seriously (2021, p. 207). However, there are at least two reasons why he might do so.

First, there are recent case reports of successful treatment with psychedelic drugs in humans in the absence of psychedelic experience (e.g. Rosenblat et al., 2023). If such cases multiply, it should lead us to re-examine the centrality of the psychedelic experience in healing. Second, when it comes to neuroscience proper, the author's position is based on a state of the art that sometimes seems simplified compared to the most recent reports. For example, the author assumes that psychedelics work by interacting with 5-HT<sub>2A</sub> receptors (2021, p. 9, p. 118). But the situation appears to be somewhat more complex: recent literature shows that the therapeutic effects of psilocybin in mouse models of depression do not depend on serotonin 5-HT<sub>2A</sub> receptors. Moreover, these studies suggest that the hallucinogenic effects of psychedelic compounds can be dissociated from their therapeutic and plasticity-promoting effects (see Hesselgrave et al., 2021; Moliner et al., 2023).

Thus, this combination of neuroscientific and clinical findings may call into question the importance of the psychedelic experience in psychedelic therapy. In other words, the role of the “experiential factor” in the efficacy of such treatments would become uncertain if non-hallucinogenic psychedelic molecules that do not produce psychedelic experiences show therapeutic efficacy.

Letheby's broad view of neuroscience probably explains why the main argument for rejecting what he calls “the pure neuroplasticity theory” seems incomplete (2021, p. 65). The author argues that while neuroplastic effects likely contribute to the therapeutic potential of psychedelics, they are not the central mechanism. His argument is simple: “across multiple studies with different populations and different psychiatric conditions, the strongest predictor of lasting therapeutic benefits is not the dosage of the drug, but the occurrence of a mystical-type experience.” (Letheby, 2022, p. 7) But this argument needs to be supplemented, because the lack of correlation between dose and effect may well be

explained by another factor: the difference in sensitivity between individuals. And this difference could be explained by molecular mechanisms. It may be that the concentration of 5-HT<sub>2A</sub> receptors or other receptors available per individual, or their binding potential, could be sufficient to predict both the intensity of the psychedelic experience and the therapeutic effects. Overall, his argument does not seem to rule out the possibility that brain mechanisms may be sufficient to explain therapeutic benefits.

Likewise, the three mechanistic models discussed by Letheby in chapters 4 and 5 are not the only ones being considered by scientists today. There are other mechanistic models of psychedelic action at the neural or cognitive level - such as the cortico-striato-thalamocortical model, the strong prior model, and the cortico-claustro-cortical model (see Kwan et al., 2022). It might be interesting for Letheby to include them in his discussion.

In short, one wonders how Letheby's theoretical proposal will develop as research programs on psychedelics progress. Nevertheless, for those interested in psychedelics from a philosophical perspective, this book is a good starting point. In addition to the interesting questions raised, it also provides the reader with a clear, if partial, overview of the complex contemporary debates in the field of psychedelic empirical research. This is both the strength and the weakness of Letheby's proposal: based on a specific empirical corpus, his conceptual framework will have to be re-evaluated in the light of the very next discoveries, especially the results of preclinical research.

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