Francesco Castellet y Ballarà: Comment on psychedelic treatment

Villiger D, (2022). How Psychedelic-Assisted Treatment Works in the Bayesian Brain. Front. Psychiatry 13:812180. doi: 10.3389/fpsyt.2022.812180

I have chosen to present and comment on this stimulating review of the most recent research on psychedelics associated with psychotherapy, because it can help us to better understand the revolutionary explanatory power of the predictive or Bayesian model of our mind-brain. A model guiding so much of neuroscience research, which has received and given great impetus to the so-called ‘renaissance' of research into psychedelic substances, perhaps the most promising research into the therapy of resistant depression.

Psychedelic therapy is by no means only psychopharmacological but, on the contrary, indispensably includes a fundamental psychotherapeutic contribution. Villiger even proposes to consider “psychedelics themselves ... as ... a psychotherapeutic and not a psychiatric intervention”.

Beyond the limits of dichotomous thinking, as when we speak of the fundamental unity of mind-body and mind-brain, it almost seems as if we are making a philosophical exercise of it, while at the level of psychoanalytic and psychotherapeutic praxis we mostly continue to use the old model of classical Freudian metapsychology. Perhaps only now with a unifying model such as the Bayesian model does this dichotomy seem to be truly surmountable.

To speak, then, of psychopharmacological therapy should be taken literally as an advancement in the right direction and not as a betrayal of the “true” psychoanalytic endeavor. On the contrary, the curiosity to understand more who we are and how we function, should not allow fences to be built against any serious and documented contribution even if it comes from different languages and epistemologies.

The very history of psychedelics and their original function in the shamanic and religious spheres is a splendid example to be known and explored, as it shows how ancient intuitions about “psycho-pharmaceutical-therapeutic” praxis and the functioning of the mind-brain are now validated by our current knowledge.

According to Villiger, the Bayesian brain hypothesis promotes the idea that the brain is not a passive organ driven by stimuli, but an active probabilistic prediction machine.

Predictive processing (also called predictive coding), which is closely related to Karl Friston's Free Energy principle, is the most influential and best-studied Bayesian approach to the brain. It has been

supported by a wide range of theoretical and experimental studies of both primary sensory processes and higher-level cognitive processes, such as naturalistic speech understanding and decision-making.

The author structures his work as follows: First, in a pharmacological view of psychedelic-assisted treatment he introduces the REBUS (Carhart-Harris &Friston, 2019) hypothesis. Next, in a psychological view of psychedelic-assisted treatment he analyses the role of so-called common factors in all psychotherapies and describes how psychedelics interact with them.

Finally, an integrative view of psychedelic-assisted treatment links the previous two sections and examines how the mechanisms described in the REBUS hypothesis interact with the factors common to all psychotherapies.

The hypothesis of weakened beliefs under psychedelics (REBUS: Relaxed Believes Under psychedelics) is based on the principle of free energy formulated by Karl Friston (Friston, 2010), which is closely related to hierarchical processing of predictions: a theory of brain organization and functioning.

In contrast, the common factor theory of psychotherapy has been used to explain the psychological aspects of psychedelic-assisted treatment.

This paper provides the first comprehensive account of psychedelic-assisted treatment, considering both pharmacological and psychological effects and their interaction.

The most commonly used psychedelics are: d-lysergic acid diethylamide (LSD), psilocybin and N,N-dimethyltryptamine (DMT). From a phenomenological point of view, all three cause profound changes in perception and mood, including ego and mood dissolution, death-like and rebirth-like experiences, paranoid and delusional thoughts, vivid autobiographical memories, altered perception of time, and more. In retrospect, such psychedelic experiences are often described as highly significant.

All these three psychedelics exert their effects primarily through agonism of serotonin 2A receptors (5- HT2AR). Consequently, taking a 5-HT2AR antagonist before taking a psychedelic substantially attenuates its typical phenomenological effects.

To understand the neurological role of 5-HT2ARs, we must look at how the brain is organized and then discuss the first theory on which the REBUS hypothesis is based: the free energy principle. The free energy principle derives from the second law of thermodynamics and provides a mathematical answer to the intrinsic drive of organisms towards self-organization. The basic idea is that, in order to survive, all living organisms must resist entropy, i.e. self-dissolution. This resistance is achieved

by minimizing so-called free energy. Free energy is an information theoretical quantity and can be regarded as the difference between the states that an organism 'considers' necessary for its adaptation, survival and reproductive success and the organism's actual states. Thus, an organism that manages to minimize free energy resists entropy by avoiding unexpected or uncertain states, which in turn enables it to maintain homeostasis.

According to the REBUS hypothesis, psychedelics preferentially act by stimulating 5-HT2ARs on deep pyramidal cells. By doing so, they disinhibit or sensitize these cells, thus easing the accuracy of predictions. In turn, the relative accuracy of ascending prediction errors increases, leading to a greater influence of bottom-up sensory input.

The densest expression of 5-HT2ARs is found in the cortex and, in particular, in the visual cortex and high-level association regions, such as those that are part of the so-called default-mode network (DMN). Consequently, these are the areas in which psychedelics should most influence the accuracy weighting of top-down predictions.

The REBUS hypothesis assumes that the brain is a hierarchically organized prediction machine that tries to accommodate sensory input from the bottom up, minimizing prediction error. While at the lower levels of the hierarchy, predictions are spatially and temporally accurate, higher levels become increasingly abstract. At the higher levels, there are predictions that form the basis of our generative model; for example, that we have an ego (these highly abstract predictions are sometimes called hyper-priors). It is hypothesized that psychedelics weaken the accuracy of these highly abstract predictions, leading to a greater influence of bottom-up sensory input. Ultimately, this should lead to well-known psychedelic experiences, such as optical hallucinations or ego dissolution.

The second is the so-called entropic brain hypothesis. It holds that 'within upper and lower limits, beyond which consciousness can be lost, the entropy of spontaneous brain activity indexes the informational richness of conscious states'. Within this entropic range, there is a critical point that marks the transition from order to disorder. In the normal waking consciousness of healthy adult humans, the entropic state of the brain is just a little below criticality, which means that cognition is ordered but still somewhat flexible.

Villiger proposes the term “anarchic brain” to explain how psychedelics work.

The term anarchic implies that bottom-up signaling is less controlled by top-down predictions and is free to flow upwards, with a stronger impact on our perception, cognition and action.

In this case, the bottom-up signaling normally suppressed by lower-level intrinsic systems, such as the limbic system, seems to be particularly involved in the action of psychedelics. In turn, limbic

system disinhibition may explain the intense and uncontrollable emotional experiences that usually accompany taking psychedelics. Overall, it has been found that the anarchic brain is more suggestible, more sensitive to context, and has high plasticity and synaptic efficiency. Therefore, the anarchic brain seems to provide perfect conditions for the revision of high-level predictions or for the transformative and curative effects of psychotherapy.

The REBUS hypothesis tells us that psychedelics induce ideal conditions for the revision of high-level predictions by putting the brain into an anarchic state. But, of course, whether these revisions eventually lead to more functional high-level predictions depends on the bottom-up signaling and thus on the 'environment' that generates it. We could say from the quality of the patient-therapist relationship in a treatment 'environment'.

In the case of psychedelic-assisted treatment, psychedelic experiences are typically embedded in some form of psychotherapy. Consequently, there is an inevitable interaction between the pharmacological and psychological effects of psychedelic-assisted treatment.

THE PSYCHOTHERAPEUTIC POINT OF VIEW OF PSYCHEDELIC-ASSISTED TREATMENT

Human beings are a eusocial species with a fundamental need for social connectedness. There is ample evidence in various areas of research that healthy functioning depends on such social connectedness, be it called social support (e.g., belonging, attachment or the absence of loneliness or the phenomena of transference and countertransference in psychoanalysis).

Referring to the free energy principle, we could say that being socially connected reduces free energy and helps us maintain homeostasis. This is because unexpected or uncertain states become less likely. For example, together one can balance gains and losses, exploit positive interdependencies and test one's beliefs. Indeed, a key element in the evolutionary success of human beings is precisely our ability to cooperate.

According to the Bayesian model of brainmind functioning, the psychotherapeutic setting offers a highly controllable and supportive environment that most likely differs from the patient's other past and present environments. Over time, the patient regularly exposed to this therapeutic environment gradually adapts to it. In doing so, he slowly updates his high-level predictions that were formed in less controllable environments and thus indicate great uncertainty. As the therapeutic environment strongly contradicts the rigid prediction of uncontrollability and uncertainty, the sensory prediction error becomes larger and larger. At some point, sensory inputs that signal safety and support can no longer be explained, initiating a process of updating.

Psychedelics seem to amplify the repair effect of the real relationship. From a psychological point of view, we have already mentioned that psychedelics tend to increase feelings of connection with the therapist. The socializing effect of MDMA is typical.

When taking psychedelics, the precision weighting of our high-level predictions becomes lighter and we become more sensitive to bottom-up sensory input. Consequently, overly precise high-level predictions that indicate uncertainty become revisable.

Since there is a real relationship between a therapist and a patient, the sensory input from this relationship rises to the top of the hierarchy, accompanied by perceptual inference. In this case, we need to think not only about the social interactions that produce the sensory input - such interactions are relatively rare in psychedelic sessions - but about the therapeutic setting more generally that produces it: the patient is in a safe environment (i.e. the psychiatric clinic or therapy room), with a person they know and trust (i.e. the therapist), and is doing something that is well prepared (i.e. taking psychedelics). Moreover, the attenuation of high-level predictions may not end directly after the psychedelic effects have worn off.

How can psychedelics interact with the expectancy pathway? With psychedelics, the brain becomes more suggestible. It is assumed that this happens because high-level expectations no longer significantly constrain the lower levels of the hierarchy. Linked to this is an increase in synaptic plasticity, which is hypothesized to facilitate updating processes. Consequently, induced expectations that have been (partly) suppressed by conflicting higher-level predictions should now be able to move up the hierarchy and alter the generative model.

Psychedelics (to some extent) give us what we expect to get from them, like a placebo. This is not a new idea. Weil (1972) described psychedelics as a kind of active placebo: although they certainly do something, most of what is may come from the consumers themselves.

Grof (2008) argues that 'psychedelics function more or less as non-specific catalysts and amplifiers of the psyche'. Finally, Matthew Johnson, (quoted in Pollan, 2018) says about the psychedelic treatment: 'Whatever we are delving into here is in the same realm as placebo. But a placebo on a rocket".

Psychotherapy has also been described as a placebo (in the open). Consequently, we can say that a psychedelic session enhances the placebogenic effects of psychotherapy, making the psychedelic-assisted treatment a kind of super placebo.

Psychotherapy (co)defines a patient's set and setting, i.e. his internal and external environment: it induces repair expectations and provides a safe environment. When the brain enters an anarchic state

due to the supposed effects of psychedelics, the bottom-up signals sent by these internal and external environments become more influential. Thus, the patient should be able to transfer the safety and controllability of the therapeutic environment to his or her own generative model, enhancing the pathway of the real relationship. Similarly, psychedelics also seem to enhance the expectancy pathway.

On the one hand, it is hypothesized that the impact of restorative expectations is less limited by higher-level expectations. Any basic positive feelings and attitudes a patient may have towards a psychedelic experience tend to be amplified with psychedelics.

On the other hand, when integrating the psychedelic experience into his or her life, the patient has sufficient room for interpretation. Thus, if he starts a psychedelic session with corrective expectations, he is likely to find corrective cues in the subsequent interpretation.

Overall, we can assume that the pharmacological effects of psychedelics reinforce and accelerate the psychological effects of psychotherapy.

We can now consider whether the use of the analytic couch, the relative sensory deprivation and analyst's hypnotic tone of voice and prolonged silence, could induce an altered state of consciousness in the analysand similar to that produced by psychedelics. On the one hand, there are certainly some similarities between the effects of sensorial deprivation and hypnosis and those produced by psychedelics. Studies on sensorial deprivation have found that it can lead to a range of experiences, including hallucinations, altered states of consciousness, and changes in perception and cognition (Glicksohn et al., 2017). However, it is worth noting that the degree and nature of these effects can vary widely depending on factors such as the duration and intensity of the deprivation, as well as individual differences in susceptibility to such experiences.Research on hypnosis has similarly found that it can induce a variety of altered states of consciousness, ranging from highly suggestible states in which the individual experiences a sense of detachment from reality to more profound states of dissociation and altered perception (Kihlstrom, 2013). However, again, the extent to which such experiences are induced can vary widely depending on the individual and the specific techniques used.

All three of these factors can lead to changes in perception, cognition, and self-awareness, and all three involve some degree of altered states of consciousness. However, it is worth noting that the intensity and nature of these effects are likely to be quite different. Whereas psychedelics can produce profound and transformative experiences that can last for hours or even days, the effects of sensorial deprivation and hypnosis are typically much more fleeting and context-dependent.

With this background in mind, Moreover, it is important to consider the potential risks and benefits of inducing altered states of consciousness in psychoanalytic practice. While such experiences may be useful in certain contexts, such as in the treatment of trauma or addiction, they can also be unpredictable and potentially destabilizing. There is also a risk of re-traumatization or exacerbation of symptoms in some individuals.

In conclusion, the extraordinary, if further confirmed, results obtained from the current clinical trials could at least in part be attributed to the high expectations of both practitioners and patients, but at the same time, given the millenary use of these substances in the most diverse cultural and ritual contexts, their facilitating effect on psychic change is unquestionable if accompanied by an adequate and, I would say, individualized set (type, dose, etc. of psychedelic) and setting (social environment, i.e., experienced therapists, suitably structured to favor the psychedelic experience).

References

Carhart-Harris RL, Friston KJ. (2019). REBUS and the anarchic brain: toward a unified model of the brain action of psychedelics. Pharmacol Rev. 71:316–44. doi: 10.1124/pr.118.017160

Glicksohn, J., Berkovich-Ohana, A., Mauro, F., & Ben-Soussan, T. D. (2017). Time perception and the experience of time when immersed in an altered sensory environment. Frontiers in Human Neuroscience, 11, Article 487. https://doi.org/10.3389/fnhum.2017.00487

Grof S. (2008). LSD Psychotherapy. 4th ed. San Jose, CA: Multidisciplinary Association for Psychedelic Studies.

Friston K. (2010). The free-energy principle: a unified brain theory? Nat Rev Neurosci. 11:127–38. doi: 10.1038/nrn2787

Johnson M. in Pollan M. (2018). How to Change Your Mind. New York: Penguin Random House.

Kihlstrom, J. F. (2013). Neuro-hypnotism: Prospects for hypnosis and neuroscience. Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 49(2), 365–374. https://doi.org/10.1016/j.cortex.2012.05.016

Weil A. (1972). The Natural Mind. Boston: Houghton Mifflin.

As a useful additional bibliographia reference:

Natalie Gukasyan, Alan K Davis , […], and Roland R Griffin (2022) Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. Journal of Psychopharmacology Volume 36, Issue 2. https://doi.org/10.1177/02698811211073759