

Beyond *Phantastica*. Analyzing and reframing the debate on subjective and beneficial effects of psychedelics

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Abstract: The question of the relationship between the subjective and beneficial effects of psychedelics is one of the most hotly debated in current research on these substances. This question concerns both the mechanism of action of psychedelics and the kind of therapy we should be focusing on in the future. While proponents and opponents of the necessity of subjective effects clash over questions of value as much as over questions of fact, the characterization of “subjective” effects and that of “hallucinogens” remain imprecise. I suggest that the current debate ignores the possibility of therapies in which subjective effects independent of those usually considered would play a role, and that a better knowledge of subjective effects is needed if the various options are to be properly evaluated.

Keywords: psychedelics, subjective effects, psychoplastogens

1. *Introduction*

It is beyond doubt that we are currently facing a renewal of medical research on psychedelics (psilocybin mostly, but also LSD and DMT), a set of substances credited with a significant therapeutic potential (Pollan, 2018; Nutt *et al.*, 2020) although some observers recommend a cautious approach and point out a risk of disillusionment (van Elk & Fried, 2023). Among all the issues currently discussed in this burgeoning field, the role of “subjective effects” in the therapeutic process is probably one of the most intensely debated (Atik *et al.*, 2024). For many researchers, it would be under the description “hallucinogens” or “eliciting mystical experiences” (whatever these

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I want to thank Héroïse Athéa for her many valuable suggestions, and also Fabrizio Turoldo and the audience of a conference at Ca' Foscari University, Venice for their feedback on a presentation related to this paper.

may be) that psychedelics count as therapeutic tools, not simply as molecules that produce myriads of effects within the brain. For others, in the therapeutic process, psychedelics act mainly as a source of neuroplasticity and related neurobiological changes, and subjective effects do not have the importance that is usually ascribed to them.

In this paper, I shall examine this debate, make explicit what is at stake, but also suggest a possible alternative to the options that are currently under scrutiny. The debate on the relationship between subjective and beneficial effects, which concerns facts and explanation, is also a debate on which type of treatment or molecules we should favor in the future, which concerns preferences and possible choices between alternative options. It is difficult to settle these questions for two types of reasons. First, determining which type of psychedelic-assisted therapy is our best option involves, in principle, a description of the mechanisms (Machamer *et al.*, 2000; Craver, 2007) responsible for the occurrence of long term, beneficial effects of psychedelics— as it is rational to choose what preserves or maximizes such effects. But the least we can say is that how exactly psychedelics act on the brain is far from being completely elucidated (Van Elk and Yaden, 2022), which means that there is currently no consensual list of the relevant factors of a beneficial psychedelic therapy. Secondly, it is safe to assume that what constitutes a better explanation of psychedelic action depends on background epistemic values, just as what constitutes a better choice in matter of therapy depends on non-epistemic values. Different values (and different hierarchies between them) guide different choices (Kuhn, 1979), and it is important to acknowledge that even if our knowledge of the action of psychedelics becomes more complete, differences in perspectives and preferences may well subsist.

In section 1, I analyze the arguments presented by two key players in the debate, Griffiths and Olson, in favor or against what I shall call hereafter the Necessity Thesis - according to which subjective effects are a necessary antecedent of the occurrence of full beneficial effects (1.1). I point out that the difference between these authors cannot be reduced to a difference in the appraisal of the therapeutic potential of psychedelics without acute subjective effects. I insist rather on the importance of values in this debate, like fairness - in regards to the question of access to treatment, and parsimony - in regards to the explanation of the beneficial effects (1.2). In section 2, my proposal is to replace the question: “do we need subjective effects to obtain beneficial effects with psychedelic-like substances?” by another question: « could it be the case that *some* subjective effects of psychedelics do contribute to the explanation of their beneficial effects, while other subjective effects – the most conspicuous, the ones current research focuses on most of the time – are truly epiphenomenal?”. In this case, the characterization of psychedelics as

Phantastica (Lewin, 1964), that is, sources of sensory illusions and visions, would not identify correctly what explains their therapeutic potential. First, I underline the ambiguity of the notions of “subjective effects” and of “hallucinogenic substances” and I sketch a typology of subjective effects (2.1). Second, I consider two types of psychological effects that could matter in the explanation of beneficial effects, mind-wandering and emotional change (2.2). It could be that Olson’s goal – safer psychedelics for a larger population of patients, could be achieved, not (only) with psychedelics without subjective effects, but simply with psychedelics with more limited subjective effects. In the conclusion, I stress the importance of renewed tools for analyzing subjective effects, a prerequisite for progress in the field. I also offer comments on the common resistance to Olson’s project, which prevents a more serene examination of alternatives in the field.

1.1. *Griffiths versus Olson: what is it all about?*

In 2021, the journal *ACS Pharmacology and Translational Science* has published an instructive exchange of views between the late Roland Griffiths, one of the researchers that have played a major role in the re-appraisal of psychedelics in scientific medicine, and David E. Olson a chemist particularly committed to the search for new therapeutic strategies derived from classic psychedelics. The quite dogmatic title of the paper co-published by Yaden and Griffiths is “The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects” (Yaden and Griffiths, 2021) while the more cautious title chosen by Olson is “The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effect” (Olson, 2021). Griffiths expresses an orthodox and widely shared view, while Olson on the other hand challenges this view and considers an alternative possibility. Although there are other significant publications along the same lines as Olson’s (e.g. Hessegrave *et al.*, 2021; Moliner *et al.*, 2023), it seems appropriate to focus on the direct exchange between Griffiths and Olson in order to present the debate on the relationship between subjective and beneficial effects of psychedelics. To defend the Necessity Thesis, Yaden and Griffiths use two main arguments. According to the first argument, the correlation between the occurrence of subjective effects and long-term beneficial or curative effects is sufficiently robust to suggest a causal link between the two. In particular, the intensity of mystical experiences under psychedelics would be the best predictor of positive changes afterwards. According to the second argument, we have reason to interpret the correlation between subjective and beneficial effects in a causal sense, because this relationship is intelligible: the nature of psychedelic experiences and the changes they bring about are likely

to explain why long-term benefits are observed. There is undoubtedly more than one description of subjective effects in the literature, and more than one conception of their role. One can emphasize the role of mystical experiences themselves (as Yaden and Griffiths) or primarily the importance of insight and belief change that accompany them (Letheby, 2021). But in any case, it seems impossible to Yaden and Griffiths to eliminate the contribution of the occurrence and content of the psychedelic experience (as a source of change of perspective on oneself and the world) from the explanation of the therapeutic effects of psychedelics. For them, to hold that subjective effects are not a mere epiphenomenal byproduct of the curative action of psychedelics leads to a crucial prediction: if these substances were administered in a state of unconsciousness due to deep sleep, they would not produce their full effect. Symmetrically, the occurrence of long-lasting beneficial effects in such a case would be the only direct proof the absence of a causal role for subjective effects (although, as noted by Atik *et al.*, 2024, we should consider the possible positive effect of anesthetic agents on neuroplasticity as a confounding factor).

For his part, Olson is convinced that the explanation of the beneficial effects of psychedelics is of a different nature, and that their future can be thought of in a different way. According to him: 1. psychedelic therapies without massive subjective effects are desirable; 2. psychedelic therapies without massive subjective effects are conceivable; 3. finally, preliminary results suggest that developing new psychedelic therapies in which subjective effects are not a prerequisite for beneficial effects is a promising avenue of research.

When it comes to desirability, Olson implicitly endorses a utilitarian point of view. Basically, the reasoning goes as follows: it is preferable to have psychedelic therapies that can be offered to the greatest possible number of patients; however, because of their subjective effects, psychedelic therapies cannot be offered to many patients who could nevertheless benefit from them; consequently, it is rational to seek to develop non-hallucinogenic psychedelics. According to Olson, there are three main causes that concur to prevent a wider use of psychedelics (Peters and Olson, 2021). The first has to do with apprehensiveness about the psychedelic experience: patients may be reluctant to take psychedelics because of the risk of a bad trip, or simply because of the perceptual distortions involved in the psychedelic experience and its emotionally disturbing nature. The second restriction stems from exclusion criteria linked to co-morbidities: in many cases (like heart disease, or schizophrenia), the patient's condition leads us to consider that he or she is not eligible for therapy based on hallucinogenic substances. The third restriction derives from the cost of therapies which require a relatively expensive substance and a suitable environment with a qualified staff to monitor the experience. To sum up, not everyone is simultaneously intrepid, lucky and

wealthy, and psychiatry must be at least as concerned about the ones that are not as it is about those who are. And it is plausible that non-subjective psychedelics would be less frightening, that they would pose fewer problems for patients with co-morbidities, and that their medical use would be less costly because of fewer requirements. What reasons do we have then to consider that what is desirable is also possible? Olson has proposed to use a new concept, that of psychoplastogen (Olson, 2018), to characterize the effects of classic psychedelics on the brain. A psychoplastogen is a substance that promotes neuronal and cerebral plasticity and does so in such a way that there may be a psychological benefit. While this concept does not apply exclusively to psychedelics, both *in vivo* and *in vitro* studies have highlighted the fact that psychedelics promote both dendrite growth and synapse formation (Ly *et al.*, 2018). In relation to this, Olson also points out that some psychiatric illnesses such as depression are associated with structural changes in brain regions like the prefrontal cortex (retraction of dendrites, loss of dendritic spines and synapses), changes that can be understood as having harmful consequences on affective regulation (Olson, 2018; Olson, 2022). It is therefore possible to conceive the beneficial effect of psychedelics as a consequence of their power as psychoplastogens, as they would restore structures and activity within regions that are damaged and impaired by pathological processes. In this case, the subjective effects of psychedelics should be conceived as non-essential, merely epiphenomenal correlates of their therapeutical action. And it becomes conceivable that in the future, newly designed psychedelic drugs might retain their core beneficial effects as psychoplastogens while lacking the subjective effects of classic psychedelics. At this point, Olson faces a methodological problem: when it comes to predicting the efficacy and safety of a new pharmacological agent, preclinical studies play a crucial role. But measuring the absence of subjective effects of a given substance in a non-human organism is a particularly difficult challenge. One solution is the definition of behavioral criteria of psychedelic experience. Even if they are largely forgotten, proposals for criteria of this type have been around since the first wave of psychedelic medicine (Athéa, 2024). For instance, Barry Jacobs, a researcher based in Harvard, suggested studying visual tracking of unseen objects as a form of “hallucinatory-like behavior” (Jacobs *et al.*, 1977). In the recent literature, however, it is the Head Twitch response (HTR) that has become the commonly used index of psychedelic experience in non-human animals due to a fairly robust correlation between the ability of psychedelics to produce acute subjective effects in human subjects and their ability to produce HT responses in animals, responses that are considered as specific i.e. not observed when other molecules are administered (Halberstadt *et al.*,

2020)¹. On the basis of this criterion (presence or absence of HTR), Olson believes it is possible to tell whether a substance combines the two properties of being non-hallucinogenic and having the capacity to produce beneficial effects. In order to establish that it is possible to develop new non-hallucinogenic psychedelics with therapeutic potential, Olson started with ibogaine, a molecule structurally similar to DMT, which is thought to have anti-addictive properties - reduction of cravings and prevention of relapse (Cameron *et al.*, 2018). However, ibogaine's cardiotoxicity and hallucinogenic properties have prevented the development of its therapeutic use. Olson's team has designed and synthesized an ibogaine-like substance close to the alkaloid tabernanthine, which they named Tabernanthalog (TBG). Olson and colleagues have shown that TBG has no deleterious effects on zebrafish development, while it promotes neuroplasticity in rats, and does not cause HTRs. Using a mouse model of addiction (with a self-administration protocol), they have also shown that tabernanthalog reduces heroin-seeking behavior (Cameron *et al.*, 2018). Olson believes he has thus demonstrated the therapeutic potential of tabernanthalog and, more generally, in direct opposition to Griffiths's view, the possibility of developing psychedelics whose therapeutic effects do not depend on their subjective effects.

1.2. *Sources of disagreement*

First of all, let's emphasize what the debate is *not* about. Yaden and Griffiths do not deny that *some* beneficial effects can be obtained with future psychedelic therapies independently of their subjective effects. They only argue that subjective effects are the condition for longer-term, more important beneficial effects (Yaden and Griffiths, 2021). In other words, for them, it is not the mere possibility, but rather the *maximization* of beneficial effects that is at stake. Symmetrically, Olson does not deny that a "profound subjective experience" can add something to a "pharmacologically induced state of heightened neural plasticity", i.e. that there is an additional specific effect of this subjective experience and that the beneficial effect of ordinary psychedelic therapies may be the result of the combination of the two (Olson, 2021 p. 565-66). Griffiths has emphasized that in the eventuality of the development of therapies based on non-hallucinogenic substances, patients should retain the option of choosing a therapy with subjective effects (Yaden Earp and Griffiths, 2022). But there is no reason to think that Olson's long-term

¹ The HTR is defined as a "high-frequency paroxysmal head rotation that occurs in rats and mice after 5-HT_{2A} receptor activation" (Halberstadt *et al.*, 2020). Blocking 5-HT_{2A} receptors with an antagonist like ketanserin has the effect of attenuating or suppressing the HTR in rodents, as it is known to prevent the occurrence of the psychedelic state in humans.

aim is to rule out entirely therapies that involve subjective effects; his project is to provide a credible alternative to these therapies, for all the reasons mentioned above. As we can see, the difference between the two points of view, once clarified, might seem minimal and simply concern the degree of therapeutic efficacy that can be predicted with non-hallucinogenic psychedelics (a low degree if we follow Yaden and Griffiths, a more significant and enduring one if Olson is right). Yet the issue is more complex and the difference more profound. We can identify a deeper disagreement on at least three levels: the definition of the best therapeutic option; the background conception of what psychedelic medicine is and should be; and, finally, the epistemic norms according to which we can build an explanation of the power of psychedelics. First of all, the opposition concerns what the default option for therapy should be, and the main values that govern this choice. For Griffiths and colleagues, the best therapeutic option is the one that combines the greatest plausibility of a good outcome with the highest degree of beneficial effects. If we ascribe a low degree to the risk of unpleasant or threatening experiences in the case of therapies relying on classic psychedelics and a “very high likelihood of positive experiences that are weighted as being of exceptional magnitude”, the consequentialist reasoning leads to attribute a higher value to therapies that offer the added benefits of subjective effects (Yaden, Earp and Griffiths, 2022). What I am now focusing on is not the empirical question of whether Griffiths and colleagues are in fact minimizing the risks of adverse effects associated with classic psychedelics, like headaches, nausea, or even suicidal ideation. (Goodwin and al., 2022; van Elk and Fried, 2023). My point is rather to note that Yaden and Griffiths do not give central importance to the value of accessibility (to the greatest number) which is central for Olson. The different answer Griffiths and Olson give to the question of what should be the default option in terms of proposed therapy if we compare strategies with and without subjective effects is not primarily guided by a different assessment of existing therapies, but by a different definition of what constitutes the best option: greater benefits for each patient that receives treatment, including extra-therapeutic ones (Griffiths), benefits that are more widely and fairly distributed in the general population (Olson).

Secondly, it can be argued that there is an important difference in the conception of psychedelic medicine that underlies each account of the role of subjective effects in the therapeutic process. For instance, it is probably impossible to reconstruct the context of the (re)discovery of psychedelics in academic research without mentioning Robert (Bob) Jesse, one of the co-authors of the 2006 study whose rigorous methodology and findings were instrumental in the revival of psychedelic medicine (Griffiths et al, 2006). Robert Jesse is both the founder of the Council on spiritual practices and a person who played a key

role in the evolution of Griffiths' research interests -an evolution that led him to focus on psychedelics (Pollan, 2018). On the one hand, it is worth noting that the mission of this organization is quite explicitly to make the «direct experience of the sacred more available to more people»². On the other hand, laboratory ethnography suggests that psychedelic research at the Johns Hopkins Center for Psychedelic and Consciousness studies is not completely isolated from an underground community of psychonauts (Noorani, 2021). Comparable studies have yet to be carried out in other research centers, and I do not claim that all researchers interested in classic psychedelics and their subjective effects share the same credo, or a covert attraction for the supernatural. However, in some cases at least, therapeutic research on psychedelics is more concerned with taking advantage of the entheogenic properties of psychedelics than with breaking with the spiritual traditions that have used them, a fact which has not failed to elicit concerns among some clinicians who are, for instance, reluctant to see religious icons invade the clinical space (Johnson, 2021). It is quite obvious that the project of Griffiths is rather to add the rigor and respectability of double-blind, randomized, placebo-controlled studies to the use of psychedelics than to establish a watertight barrier between spiritual and curative uses.

Nothing could be further from Olson's concerns. The redefinition of psychedelics as psychoplastogens characterizes them through their ability to initiate low-level material processes within the brain of patients, processes that can receive, in principle, a complete account from a third-person perspective. This difference in perspective also affects the way in which the available evidence is taken into account. Griffiths relies essentially on the results of clinical research, whereas in a project like Olson's, animal models are of crucial importance. It is hardly surprising that Griffiths should use the reference to narrative medicine to criticize the search for new-generation psychedelics with no subjective effects, on the grounds that this research remains locked into an exclusively biological conception of illness (Yaden, Earp and Griffiths, 2022). The disagreement, then, concerns the relation between psychedelic medicine and spiritual practices: should psychedelic medicine be conceived as a secularized equivalent of such practices (an encounter with the sublime, or a journey within oneself), or should the link between the two be severed once for all.

Finally, there is the question of the epistemic values that determine the type of explanation of beneficial effects that is preferred. In the perspective adopted by Olson, one crucial value is parsimony. Regarding the relationship between subjective and beneficial effects, for Olson and other researchers the default strategy is to try to suppress the subjective effects and to challenge Griffiths' necessity thesis. This is the inspiration, for example, behind studies

² <https://csp.org/docs/home>.

in which 5-HT_{2A} receptors are blocked in animal models of the therapeutic action of psychedelics (Hesselgrave *et al.*, 2021). On the one hand, that the activation of 5-HT_{2A} receptors is crucial in the production of subjective effects (hallucinations, etc.) is one of the best established results in psychedelic research (Vollenweider *et al.*, 1998). On the other hand, the fact that the beneficial effects of psilocybin (anti-anhedonic effect, for example) are nonetheless maintained when 5-HT_{2A} receptors are blocked (Hesselgrave *et al.*, 2021) creates a problem for all those who place the psychedelic experience at the heart of therapy (Athéa, 2023). What interests me at present is not the evidential value of these studies but their common approach, an approach well known in other areas of scientific investigation. For instance, when he proposed his doctrine of uniformitarianism in geology, Lyell used an argument of this type: it is preferable to begin by trying to explain the present profile of the earth's relief with familiar causes (erosion and so on) and to see where this leads us, before postulating the intervention of extraordinary causes (such as catastrophes) in the past (Lyell, 1832; Gould, 1987). Olson and others apply a similar strategy when they suggest starting by trying to account for the beneficial effects of psychedelics through low-level structural and functional changes in the brain, rather than through mystical experiences and their content. Invoking the role of subjective effects before exhausting the resources of explanations that involve exclusively better-understood factors would be like appealing to catastrophes before exhausting the resources of explanations involving ordinary causal factors in geology. Griffiths and Olson have different ideas as to what constitutes the best therapeutic strategy (depending on whether the value of accessibility to the greatest number of people is emphasized to a greater or lesser extent), different conceptions of the relationship between spiritual and medical uses of psychedelics, and they do not give parsimony the same role in the choice of the right explanatory strategy. For all these reasons, the difference between Griffiths and Olson appears to be far more important than a simple difference in prediction regarding the potential of Tabernanthalog and other psychedelics without subjective effects in tomorrow's medicine.

1.3. *Which subjective effects are we speaking of?*

To sum up, the Necessity thesis (NT) is difficult to reconcile with several findings. Besides Olson's research, as we have seen, some studies suggest that beneficial effects of psychedelics are compatible with the blockade of 5-HT_{2A} receptors in animal models of mental disorders (Hesselgrave *et al.*, 2021). Moreover, we have to take into account the beneficial effects of non-hallucinogenic doses of LSD and psilocybin (Anderson *et al.*, 2018) even if

in this case expectation bias may play a significant role. And we have to take into account human cases where the therapeutic effects – for instance the antidepressant effects of psilocybin, are not accompanied by “psychedelic effects” (Rosenblat *et al.*, 2023). However, these elements do not provide an easy victory for Olson. First, there is the problem of the lack of specificity of the “psychoplastogen” view. Positive effects on neuroplasticity is a common feature of many substances and it is difficult to reduce the distinctive therapeutic power of psychedelics to their characterization as psychoplastogens (Van Elk & Yaden, 2022). Secondly, there is a persistent lack of integration between known effects of psychedelics on BDNF production and neural plasticity, and modifications of the brain caused by psychedelics at a higher level of integration like the activity of the Default Mode Network. Thirdly, from a methodological point of view, the inference in animal studies from the absence of HTR to the non-hallucinogenic power of a given substance is less secure than it is sometimes assumed – false negatives and false positives have been both reported (for a review, Athéa, 2024). The debate is also plagued by the underdetermination of key concepts, a phenomenon that hinders further progress in the field, or, to be more specific, that prevents the formulation and examination of alternative hypothesis, some of them not currently considered. First, we could distinguish between several types of “subjective effects” – some of them potentially separable from others. Second, it is not difficult to establish that in the existing literature, the term “hallucinogenic” is equivocal and as a consequence, what is meant by a “non-hallucinogenic substance” is equivocal too. All of this raises the interesting possibility that Griffiths’ Necessity Thesis could be false if we speak of “subjective effects” in general, but true (or nearly true) if we consider, if not the necessity, at least the significance of *some* of these effects in the therapeutic process and its enduring benefits. And it would be also possible that “non-hallucinogenic” means in some contexts “deprived of *some* subjective effects”. In particular, what Olson calls “safer psychedelics” would not be psychedelics without (any kind of) subjective effects, but psychedelics that do not raise the probability of the occurrence of visions, ego dissolution and other features of mystical experience. And instead of Griffiths’ Necessity Thesis, we would have a more modest hypothesis where some subjective effects would be a welcomed ingredient of the beneficial effects – for instance because therapy is about the possibility of change, and effects that are subjective, i.e. that can be introspectively accessed, make the very possibility of change known to the patient. Because of this, specific kinds of subjective effects will play an important role in the process of the cure. I develop these ideas in section II.

2. *Kinds of effects and the vagueness of the category of “hallucinogens”*

I shall begin this section with a very basic distinction between three possible *kinds* of subjective effects. The first kind is what I shall call content-related effects (CRE). Psychedelics are known to provide unusual experiences, that is, especially, experiences whose intentional content is itself unusual, or exceptional: because of the distortion of space perception, for instance, because of the uncommon vividness of sensory impressions, because of the modification of the bodily image, or because of a new sense of unity with the external world. Hallucinations are only one kind of such CRE. The second kind is what I shall call affect-related effects (ARE). The intensity of emotions during psychedelic episodes, the fluctuation from one state with a positive valence to another with a negative one (both extreme), as well as the emotions linked to the content of the episodes (for instance the feeling of awe in a mystical experience) all qualify as ARE. But there is also a more subtle kind of subjective effect, that I shall call process-related effects (PRE). We could illustrate this with the classic description of the varieties of the psychedelic experience offered by Robert Masters and Jean Houston, first published in 1966 (Masters and Houston, 2020). Among the “psychological effects” of LSD and peyote, these authors count changes not only in the content of thought but also in its “rate”. In the first, first-person account of psychedelic experience presented in the book, it is said that “within consciousness, MORE simultaneous mental processes operate without any one of them interfering with the awareness of others” (ibid., p.11). One of the key chapters on the book is called “the voyage inward”, inviting us to pay attention to the central dimension of the mental modifications induced by psychedelics: the progressive exploration of a mental landscape that is caused by “mind manifesting” drugs. Process-related effects are subjective effects related to the dynamics of thought. Another way of characterizing PRE would be to consider them as the subjective counterpart of acquired behavioral flexibility, one important characterization of the effects of psychedelics on nonhuman organisms (Hibicke *et al.*, 2020). PRE, or fluidified mental processes (with a distinct phenomenology) would supervene on the neural basis of extended behavioral flexibility. They would provide access of new contents of thought, for sure, but they would not alter basic perceptual and self-knowledge like CRE. If we accept the distinction between these three kinds of subjective effects, one hypothesis is that even if CRE, ARE and PRE occur frequently together, or are frequently reinforcing each other, they are not necessarily inseparable, and they are not necessarily related in the same manner to therapeutics or more generally to beneficial effects. For instance, in the therapeutic use of MDMA, it is its ability to boost

empathy and social feelings (a specific kind of ARE) that is emphasized, without any reference to CRE, that is, unusual contents of conscious experience (Danforth *et al.*, 2018). One possibility, then, is that psychedelic-like substances that are believed to induce no subjective effects (like TBG) would be psychedelics without CRE (or minimal CRE), but not without subjective effects in general. This possibility, if true, would call into question the relevance to therapeutics of the most salient, most often described features of psychedelics (so-called “acute effects”, the ones that have been central to their description as entheogens) but this would not mean that the power of psychedelics has to be described in a purely biological vocabulary. In this context, we should remember that the meaning of “hallucinogen” is far from constant, which means that the list of effects that are both necessary and sufficient to justify that a drug D is called “hallucinogenic” is not fixed. For Louis Lewin (Lewin, 1924) within his influential taxonomy of modifiers of cerebral activity, hallucinogens are classified as *Phantastica* in opposition to *Euphorica* (products that reduce mental activity and induce subjective well-being), *Inebriantia* (sources of intoxication), *Hypnotica* (sedatives and soporific agents), and *Excitantia* (psychostimulants). The main effects of *Phantastica* are sensation distortion, the presence of hallucinations, illusions and visions, which means that Lewin puts very clearly the emphasis on CRE in the definition of hallucinogens. Very often, the meaning of “hallucinogen” encompasses a larger range of phenomena: for instance, in its online edition, the *Encyclopedia Britannica* associates hallucinogens both with spiritual, dream-like and psychotic experience: “Hallucinogen, substance that produces psychological effects that tend to be associated with phenomena such as dreams or religious exaltation or with mental disorders such as schizophrenia”, before adding that “hallucinogens produce changes in perception, thought, and feeling³”⁴ (CRE, ARE and maybe PRE). According to Halberstadt and Geyer, “hallucinogens are a class of pharmacological agents that increase the intensity and lability of affective responses and produce profound distortions of perceptual processes encompassing the visual, auditory and tactile modalities” (Halberstadt and Geyer, 2011), a combination of ARE and CRE with no special reference to hallucination *per se*. Finally, some researchers have pointed out that “the term *hallucinogen* derives from the late latin *alucinari*, meaning to wander in mind, talk idly or prate” (Abraham and al., 1996). In this last case, to be “hallucinogenic” would have much more to do with PRE (switching from one topic to another, making mental digressions) than with CRE. This variation is itself innocuous, as long as the definition of “hallucinogen” and “hallucinogenic” that we have in mind is made explicit. But in the literature on psychedelics, it seems that the presence or absence of “subjec-

³ <https://www.britannica.com/science/hallucinogen>

tive effects” or the hallucinogenic (or non- hallucinogenic) power of a given substance have not to do with perceptible, conscious effects in general but with what we have called CRE, or content-related effects – a radical change in the representation of the world, and/or of the self. In this sense, for a given substance to be classified as “non-hallucinogenic” it would be sufficient that it does not cause distortions in external and bodily perception, and that it does not give rise to a mystical experience. This would not preclude that ARE (that are not themselves dependent on CRE) and PRE do occur with “non hallucinogenic-C” substances; and this would not preclude that these effects would contribute (in some measure) to the beneficial effects. In the next section the question I would like to answer is what kind of subjective effects could play such a role, and under what conditions.

2.1 . *Two potential factors of change*

In this section I want to consider two examples of psychological effects of psychedelics that could possibly contribute to their beneficial effects. One is *mind-wandering* and the other is *positive emotions and moods*. Before examining them more closely, I want to make explicit under which conditions these effects may deserve our attention in the present context. First, they should have a genuine subjective (experiential) dimension. Second, it must be plausible that they can occur without the presence of CRE, and acute subjective effects associated to them (and possibly, that they could have some kind of equivalent in a nonhuman animal). Thirdly, it must be plausible that they could by themselves boost the therapeutic process. Fourthly, it must be possible to explain their occurrence by the known effects of psychedelics on the brain. If they meet all of these conditions, such effects could be combined with the purely neurobiological effects of molecules that do not produce acute subjective effects. Within Olson’s larger project (safer psychedelics for a larger population) we should then look for molecules that are not hallucinogenic-C, but we could welcome other molecules that are hallucinogenic-P (or hallucinogenic-A, or both). Let’s consider first mind wandering. Mind-wandering has been defined as “a mental state where thoughts arise spontaneously, relatively free from constraints and intentions” (Christoff *et al.*, 2016). As recalled by Christoff and colleagues, William James compared our thought to a bird’ life, an alternation of “flights”, the transition from one mental state to another, and “perchings” – the fixation of thought on a given content (James, 1890). Mind-wandering would correspond to a combination of spontaneous, unhindered phases of “flights”, and “perchings” that are linked to the consideration of different, rather than recurring contents – which makes mind-wandering the antidote to rumination. Several stud-

ies exist on the effect of classic psychedelics on mind-wandering (Wiesser *et al.*, 2021), or on the relation between mind-wandering and neuromodulation in general (O’Callaghan *et al.*, 2020). According to our definitions, a hallucinogen-P would be a promoter or enhancer of mind-wandering. It would not give rise to out-of-the ordinary experiences, but it would increase and facilitate mental fluidity, and the consideration of new and unexpected thoughts⁴. I want to propose that an increase of mind-wandering meets the above requirements for a promising, *sui generis* subjective effect of psychedelic-like substances different from acute subjective effects. First, it is plausible that increased mind-wandering has a distinctive phenomenology – the feeling of being unconstrained for instance in the process of association of thoughts, possibly with an affective component like surprise. Second, it is plausible that mind-wandering can be beneficial, for instance in the context of depression and obsessive thoughts, but also of addiction. For instance, the occurrence of unexpected thoughts about alternative rewards and possible expectations about the future would promote changes in patterns of behavior. It is true that some kinds of mind-wandering have been associated with negative affect (Stawarczyk *et al.*, 2012), but in itself, this is no reason to think that mind wandering is always detrimental. Thirdly, outside the field of psychedelic research, mind-wandering is known to be independent of perceptual distortions or mystical thinking and it is compatible with a robust sense of the (minimal) self. Fourthly, we can think of different alterations of the brain under psychedelics – from low-level neuroplasticity to the destabilization of network hubs (Nichols, 2017) that can promote mind-wandering in addition to other subjective effects. It remains to be seen if new molecules, or the combination of 5-HT_{2A} receptor antagonists and classic psychedelics can result in a dissociation of mind wandering and well-known acute subjective effects of psychedelics.

Another possible case of promising subjective effect of psychedelics is their influence on one’s affective life. First, even the researchers that defend the Necessity Thesis about the role of mystical experiences recognize that emotional change, or the ability to overcome challenging emotions (“emotional breakthrough”) could be a possible “primary determinant of long-term psychological outcomes” (Roseman *et al.*, 2019). For instance, some patients have reported the “evaporation” of negative emotions, like rage and anger,

4 The ideas presented about mind-wandering in this section have certainly a family resemblance with the widely discussed REBUS Model of Carthart-Harris and Friston (Carthart-Harris and Friston, 2019). A detailed comparison would exceed the scope of the present paper, but I see no reason to focus exclusively on changes related to beliefs and not to consider other changes, related to other kinds of mental states.

under psychedelics (*ibid.*). A good predictor of a positive change in well-being, the presence of an emotional breakthrough could be considered as a distinct component of the psychedelic experience” (*ibid.*). Second, among the enduring effects of psilocybin, the diminution of negative emotions and anxiety, and the presence of elevated levels of positive affect have both been reported, with corresponding modification in the patterns of brain activation (Barrett *et al.*, 2020). To the best of my knowledge, it is not currently known if in the case of the administration of psychedelics combined with the blockade of 5-HT_{2A} receptors, the above-mentioned effects on negative or positive affect do persist in the absence of hallucinogenic-C effects, and in what measure. And it is not known if substances derived from classic psychedelics, besides their known effects on neurogenesis and neuroplasticity, could include these effects on subjective well-being not simply as a later outcome of the therapeutic process, but as a primary source of the long-term benefits of such a process. If it were the case, these subjective effects -probably combined with adequate set and setting, to prevent negative emotions and anxiety would probably not act simply as “mood brighteners”. A similar suggestion can be found in a paper by Peter Hendricks (Hendricks, 2018). Hendricks builds on the definition of awe given by Kelter and Haidt (2003) which adds to the reference of “vastness” as a formal object of the emotion of awe, a reference to what they call the “need for accommodation” – the adjustment of one’s mental structure and habits to an experience that is new and disconcerting. In a similar manner, positive affective changes, even not related to an awe-inspiring experience, would by their very occurrence open a new space of mental possibilities of which the therapeutic process will benefit.

Conclusion

We still don’t know to what extent the beneficial effects of psychedelics depend on their subjective effects. One reason for this is that in preclinical studies, the criteria for defining a substance as “non-hallucinogenic” are vague. As a consequence, evidence of dissociation between the two types of effects remains weak. Another reason is that in human studies, very few data are available to determine whether the action of psychedelics on the brain, in the absence of 5-HT_{2A} receptor activation has, besides their known neurobiological effects, more subtle subjective effects, independent of well-studied acute subjective effects, and what would be their nature and possible role. To make some progress on this question, it would be profitable in animal studies to supplement HTR measures with other operational criteria of being “hallucinogenic” or “non-hallucinogenic” (Athéa, 2024) – for instance, a revised

version of the study of visual tracking of unseen objects (see above, 1.1.). Research would need also to investigate what happens with human patients under psychedelic influence when 5-HT_{2A} receptors are blocked, or, in the case analogs of TBG were used in clinical trials – to focus less exclusively on acute subjective effects and scales of mysticism – for instance, by using measures of mind-wandering like the Amsterdam Resting State Questionnaire (ARSQ, Wiessner et al, 2021) combined with measures of emotional effects like the Emotional Breakthrough Inventory (Roseman et al 2019), or derived tools. This could allow us to distinguish substances without subjective effects and hallucinogens-P or hallucinogens-A, and to compare their respective therapeutic potential, a potential susceptible to vary from one mental disorder to another (the same subjective effect may not matter in the same manner in the case of addiction and major depression). Making such methodological suggestions is just one application of what Reichenbach called the advisory task of epistemology (Reichenbach, 1938). If it proved possible to develop psychedelic therapies with less subjective effects, this prospect would undoubtedly meet the same resistance that proponents of non-subjective psychedelics have already encountered. The question would be asked again: if classic psychedelics provide experiences that many patients consider to be among the “most positive and meaningful” of their entire lives (Yaden *et al.*, 2022), why should we want to deprive them of such exceptional episodes of their life? To this question, it is probably not sufficient to answer that usual forms of psychedelic therapy would remain a possible choice for the patients each time they are sufficiently safe for them, and also that we have seen that there is no consensus in favor of the Necessity Thesis. What can be added is that there are different possible understandings of the principle of beneficence in medical ethics, linked to different conceptions of health. If for instance we adopt a view of health according to which health is associated with minimal happiness and autonomy of the agent (Nordenfelt, 2000), there is nothing to object to a therapy that promotes effectively minimal happiness, rather than states of bliss, especially if minimal happiness is for the greater number and bliss for the happy few. With this background in mind, we can think of the minimally happy agent as healthy, even if he finds life absurd rather than meaningful. While differences of opinion regarding well-being and normative medical ethics are there to stay, the assimilation of psychedelics to *Phantastika* is not inevitable and other paths may be open to psychedelic medicine than the one traced by Griffiths, paths not necessarily similar to the one suggested by Olson.

References

- Abraham, H. D., Aldridge, A.M., Gogia, P. (1996), *The psychopharmacology of hallucinogens*, "Neuropsychopharmacology", 14, 4, 1996, pp. 285-298.
- Anderson, T., Petranker, R. *et al.* (2019), *Microdosing psychedelics: Personality, mental health, and creativity differences in microdosers*, "Psychopharmacology", 236, 2, 2019, pp. 731-740.
- Athéa, H. (2024), *Une enquête philosophique sur les modèles animaux*, Unpublished dissertation.
- Athéa, H. (2023), *How does psychedelic therapy work?*, "Philosophical Psychology", 2023, pp. 1-5.
- Atik, M., *et al.* (2024), *Disentangling the acute subjective effects of classic psychedelics from their enduring therapeutic properties*, "Psychopharmacology", DOI: 10.1007/s00213-024-06599-5, 2024.
- Barrett, F.S., Doss, M.K., Sepeda, N.D., Pekar, J.J., Griffith, R.R. (2020), *Emotions and brain function are altered up to one month after a single high dose of psilocybin*, "Scientific Reports", 10, 2020, p. 20214.
- Cameron, L. P., *et al.* (2018), *A non-hallucinogenic psychedelic analogue with therapeutic potential*. "Nature", 589, 2018, pp. 474-479.
- Carhart-Harris, R.L., Friston, K.J. (2019), *REBUS and the anarchic brain: Toward a unified model of the brain action of psychedelics*, "Pharmacological Reviews", 71, 2019, pp. 316-344.
- Christoff, K., Irving, Z.C., Fox, K.C.R., Spreng, R.N., Andrews-Hanna, J.R. (2016), *Mind-wandering as spontaneous thought: A dynamic framework*, "Nature Reviews", 17, 2016, pp. 718-731.
- Craver, C. (2007), *Explaining the brain*, Oxford University Press, Oxford.
- Danforth, A., *et al.* (2018), *Reduction of social anxiety after MDMA-assisted therapy with autistic adults: A randomized, double-blind, placebo-controlled pilot study*, "Psychopharmacology", 235, 2018, pp. 3137-3148.
- Earp, B., Griffiths, R. (2022), *Ethical issues regarding nonsubjective psychedelics as standard of care*, "Cambridge Quarterly of Healthcare Ethics", 31, 4, 2022, pp. 464-471.
- Gould, S.J. (1987), *Time's Arrow, Time's Cycle: Myth and Metaphor in the Discovery of Geological Time*, Harvard University Press, Cambridge.
- Goodwin, G.M., *et al.* (2022), *Single-dose psilocybin for a treatment-resistant episode of major depression*, "The New England Journal of Medicine", 387, 2022, pp. 1637-1648.
- Jacobs, M.E., Trulston, M.E., and Stern, W.C. (1977), *Behavioral effects of LSD in the cat: Proposal of an animal behavior model for studying the actions of hallucinogenic drugs*, "Brain Research", 132/2, pp. 301-314.
- James, W. (1890), *The Principles of Psychology*, Henry Holt and Company.
- Halberstadt, A.L., and Geyer, M.A. (2011), *Multiple receptors contribute to the*

behavioral effects of indoleamine hallucinogens. "Psychopharmacology", 61, 3, 2011, pp. 364-381.

Halberstadt, A.L., *et al.* (2020), *Correlation between the potency of hallucinogens in the mouse head-twitch response assay and their behavioral and subjective effects in other species*. "Neuropharmacology", 167, 2020, e107933.

Hendricks, P.S. (2018), *Awe: A putative mechanism underlying the effects of classic psychedelic-assisted psychotherapy*, "International Review of Psychiatry", 30, 4, 2018, pp. 331-342.

Hesselgrave, N., *et al.* (2021), *Harnessing psilocybin: Antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT_{2R} activation in mice*, "PNAS", 118, 17, 2021, e2022489118.

Hibicke, M., *et al.* (2020), *Psychedelics, but not ketamine, produce persistent antidepressant-like effects in a rodent experimental system for the study of depression*, "ACS Chemical Neuroscience", 11, 2020, pp. 864-871.

Johnson, M.W. (2021), *Consciousness, religion, and gurus: Pitfalls of psychedelic medicine*, "ACS Pharmacology and Translational Science", 4, 2021, pp. 578-581.

Keltner, D., Haidt, J. (2003), *Approaching awe: A moral, aesthetic, and cognitive emotion*, "Cognition and Emotion", 17, 2, 2003, pp. 297-314.

Kuhn, T.S. (1979), *Objectivity, value judgment, and theory choice*, in T.S. Kuhn, *The Essential Tension: Selected Studies in Scientific Tradition and Change*, University of Chicago Press, Chicago, pp. 329-339.

Letheby, C. (2021), *Philosophy of psychedelics*, Oxford University Press, Oxford.

Lewin, L. (1964), *Phantastica: Narcotic and stimulating drugs. Their use and abuse*, Dutton & Company, New York.

Ly, C., *et al.* (2018), *Psychedelics promote structural and functional neural plasticity*, "Cell Reports", 23, 11, 2018, pp. 3170-3182.

Lyell, C. (1832), *The principles of geology*, J. Murray, London.

Machamer, P., Darden, L., Craver, C. (2000), *Thinking of mechanisms*, "Philosophy of Science", 67, 1, 2000, pp. 1-25.

Masters, R., Houston, J. (2000), *The varieties of psychedelic experience*, Rochester, Park Street Press.

Moliner, R., *et al.* (2023), *Psychedelics promote plasticity by directly binding to BDNF receptor TrkB*. "Nature Neuroscience", 26, 2023, pp. 1032-1041.

Nichols, D.E., *et al.* (2017), *Psychedelics as medicines: An emerging new paradigm*, "Clinical Pharmacology and Therapeutics", 101, 2, 2017, pp. 209-219.

Noorani, T. (2021), *Containment matters: Set and setting in contemporary psychedelic psychiatry*. "Philosophy, Psychiatry, and Psychology", 28, 3, 2021, pp. 201-216.

Nordenfelt, L. (2000), *Action, ability, and health*, Springer, Berlin.

Nutt, D., Errizoe, M., Carhart-Harris, R. (2020), *Psychedelic psychiatry's brave new world*, "Cell", 81, 2020, p. 24-28.

O'Callaghan, C., Walpole, I.C., Shine, J.M. (2021), *Neuromodulation of the mind-wandering brain state: The interaction between neuromodulatory tone, sharp wave ripples, and spontaneous thought*, "Philosophical Transactions B", 376, 1817, 2021, 20190699.

Olson, D.E. (2018), *Psychoplastogens: A promising class of plasticity-promoting neurotherapeutics*, "Journal of Experimental Neuroscience", 12, 2018, pp. 1-4.

Olson, D.E. (2021), *The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects*, "ACS Pharmacology and Translational Science", 4, 2021, pp. 563-567.

Olson, D.E. (2022), *Biochemical mechanisms underlying psychedelic-induced neuroplasticity*. "Biochemistry", 61, 3, 2022, pp. 127-136.

Peters, J., Olson, D. (2021), *Engineering safer psychedelics for treating addiction*, "Neuroscience Insights", 16, 2021, pp. 1-4.

Pollan, M. (2018), *How to change your mind: The new science of psychedelics*, Penguin, London.

Reichenbach, H. (2006), *Experience and prediction*, Notre Dame University Press, Notre Dame.

Roseman, L., Haijen, E., et al. (2019), *Emotional breakthrough and psychedelics: Validation of the Emotional Breakthrough Inventory*, "Psychopharmacology", 33, 9, 2019, pp. 1076-1087.

Rosenblat, J.D., et al. (2023), *Antidepressant effects of psilocybin in the absence of psychedelic effects*, "American Journal of Psychiatry", 180, 5, 2023, pp. 395-396.

Stawarczyk, D., Majerus, S., Van der Linden, M., D'Argembeau, A. (2012), *Using the daydreaming frequency scale to investigate the relationships between mind-wandering, psychological well-being, and present-moment awareness*, "Frontiers in Psychology", 3, A363, 2012, pp. 1-15.

Van Elk, M., Fried, E.I. (2023), *History repeating: Guidelines to address common problems in psychedelic science*, "Therapeutic Advances in Psychopharmacology", 14, 2023, pp. 1-20.

Vollenweider, F.X. (1998), et al., *Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action*, "NeuroReport", 9, 17, 1998, pp. 3897-3902.

Wiessner, I., Falchi, M. et al. (2021), *Low-dose LSD and the stream of thought: Increased discontinuity of mind, deep thoughts, and abstract flow*, "Psychopharmacology", 2021, pp. 1-13.

Yaden, D.B., Griffiths, R. (2021), *The subjective effects of psychedelics are necessary for their enduring therapeutic effects*, "ACS Pharmacology and Translational Science", 4, 2021, pp. 568-572.

Yaden, D.B. (2022), *Pharmacological, neural, and psychological mechanisms underlying psychedelics: A critical review*, "Neuroscience and Biobehavioral Reviews", 140, 2022, e104793.

