MIND FOUNDATION

Schedule 1 Drugs or breakthrough therapies?

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> *“To soar beyond the human cannot be described in words. Let the example be enough to one for whom grace holds this experience in store.”Paradiso I, 70-72*

Recently C.J. Büche wrote an in-depth analysis of the role of particular representations of psychedelics in popular media in the “psychedelic renaissance”1. In addition to his work, different ways of describing psychedelics can also be examined in scientific discourse. Paying attention to language choices may offer significant insight into the cultural and personal assumptions of the authors. With due exceptions: in some cases, researchers may have been constrained by funding agencies and ethical committees to describe psychedelics in negative terms, regardless of their own convictions, as a precondition to carry out and publish their studies.

Much like in general media, a variety of contrasting descriptions of psychedelics can be found in scientific media. At least three kinds of language can be identified: in the first, psychedelics are described as with no medical utility and high potential for abuse (“Schedule 1” drugs in all respects)2. In the second , they are considered potentially key to a better understanding of brain function3 and breakthrough treatments4 for otherwise untreatable psychiatric conditions. In the third kind of language, psychedelics are described only or mainly as “psychosis-inducing drugs”5, and considered medically useful in the study of psychotic disorders such as schizophrenia. This subdivision is of course a simplification to some degree: the same authors may use different language in different papers, and “mixed” accounts are also possible.

Schedule 1 drugs

The first kind of language, summarized by the statement that psychedelics are drugs with a high potential for abuse and no medical utility, has little to no scientific basis[6]. This stigmatized view of psychedelics can be traced back to a political heritage of the 1970 Controlled Substances Act and the subsequent War on Drugs, and is rapidly disappearing from scientific publications in light of more recent and more rigorous evidence. Nonetheless, it is important to note that:

1) Contemporary clinical trials have been carried out with small sample sizes, highly restrictive screening processes, under constant professional medical supervision, and not always with the possibility of a fully double-blind placebo condition[7]. All these factors may have contributed to their success. This is not to diminish the impressive results of these rigorous and difficult studies (particularly in treatment-resistant populations); but rather to suggest avoiding hasty conclusions, such as that psychedelics may be risk-free panaceas for any and all psychiatric disorders.

2) While there is evidence that at the population level, the risks of psychedelics have been overstated[8], there is no conclusive evidence for the safety of psychedelics at the *individual* level, and particularly little understanding of persisting effects such as HPPD[9]. Non-professional "therapeutic" practices involving the use of psychedelics outside clinical settings therefore present a significant amount of risk. This risk is potentially higher than with recreational use, not only because of the high variance in subjective and environmental factors already intrinsic in psychedelic experiences, but particularly because these practices target populations with potentially unaddressed neurobiological issues and high psychological sensitivity.

Tools and medicines

The second kind of language, which describes psychedelics as useful medicines and important tools for scientific research, (re-)emerged recently with the contemporary and less politically-constrained wave of psychedelic research led by groups at Imperial College London and Johns Hopkins University, among others. The term "psychedelic renaissance" commonly refers to these lines of research, whose merits are many, undeniable, and documented extensively elsewhere[10]. In this context, it is worthwhile only to remark that some of these studies may also be criticized for using culturally specific terms (e.g. "mystical experiences", "ego-dissolution") under the implicit assumption that they reflect somewhat universal or biologically-grounded phenomena, which need not be the case.

For example, non-western cultures using psychedelics may lack the concept of a contemplative "mystical experience", or the dualistic views of subject/object and internal/external implied by "ego-dissolution". Therefore, they might experience and interpret the same neurological phenomena according to an entirely different ontology. Influential cognitive theories, such as predictive coding, indeed suggest that cultural and personal expectations (as well as language itself[11]) should powerfully shape the content and interpretation of psychedelic experiences, in agreement with a long history of observations[12].

Models of schizophrenia-like psychosis

The third kind of language is particularly interesting, because it has been and still is quite widespread, despite raising a host of scientific and philosophical questions of its own. Does it make sense to characterize psychedelics only or mainly as "psychosis-inducing drugs"? Is their psychiatric utility only or mainly to be found as models of "schizophrenia-like psychosis"[5]?

The canonical definition of psychosis is based on hallucinations, aberrant salience, and delusional beliefs, and appears water-tight in identifying pathological cases. However, it is only so because it relies on a

specific, shared set of beliefs and assumptions. Language characterizing psychedelics only or mainly as “psychosis-inducing drugs” cannot be fully justified empirically, but instead has to rely on a very specific *a priori* judgement about the content of psychedelic experiences, as well as unstated assumptions about what constitutes *real*, how much of it is socially constructed, and importantly in this context, *how much of it is accessible through language*.

These questions have been the subject of intense philosophical debate for millennia, but are glanced over in some scientific papers using this kind of language. “Reality” is implicitly assumed to be deterministic, mechanistic, and fully encompassed by analytic language and mathematical laws: a worldview still prevalent in life sciences today, inherited from 19th-century physical sciences. However, even physical sciences have long since moved away from this view: Gödel’s incompleteness theorem and the quantum mechanical uncertainty principle, like modern Pillars of Hercules, pose fundamental limits to the systematically knowable reality. Furthermore, the social sciences inform us that much of what we commonly refer to as “real”, or at least acceptable, is determined by societal consensus, not by scientific examination. The humanities posit that language itself, let alone reality, has countless possible interpretations (with the escape of pragmatism: not all interpretations are equally useful).

The definition of psychosis is therefore at least as much culturally and socially determined as it is scientific. Psychedelic experiences, too, are heavily influenced by culture, both in their content and its interpretation. This suggests that particularly in scientific papers regarding psychedelics, all assumptions (e.g. what constitutes “real”, how much of it can be conveyed through language) and constructs (e.g. “psychosis”, “mystical experience”) should not be taken for granted as if they were empirically determined scientific facts, but rather carefully examined to avoid potential confounds.

Is the psychiatric utility of psychedelics only or mainly to be found in modeling “schizophrenia-like psychosis”? At first glance, psychedelic experiences can indeed share common features of schizophrenic psychoses: hallucinations, mania, paranoia. However, research shows that there is no straightforward link between any substance model and schizophrenia13. From a metacognitive viewpoint, after taking psychedelics, most people maintain a sense of the induced experience being somehow different from the ordinary reality of everyday life (note that both may be experienced as “real”, but real *in different ways*)14. Some schizophrenic patients do exhibit such a “double bookkeeping” pattern, or the ability to distinguish between the ordinary and hallucinatory realities they experience. But this is not true in all cases: in “single-bookkeeping” schizophrenic psychoses, hallucinations and ordinary reality are *not* distinguishable, and both are automatically taken at face value. In such cases, other substance classes, for example anticholinergic hallucinogens15, would provide a more accurate model. Furthermore, auditory verbal hallucinations, an important hallmark of schizophrenic psychoses16, are not a prominent feature of psychedelic experiences. Once again, a different class of substances (amphetamines) and modality of use (chronic rather than acute) may provide a more suitable model17.

A fortiori, the evidence showing long-term, population-level positive effects of psychedelics on suicidality and mental distress18, as well as the recent clinical trials on depression in terminally ill cancer patients19, clearly show that the psychiatric utility of psychedelics goes far beyond modeling psychosis6. Even if the premise is accepted that psychedelics are only or mainly "psychosis-inducing drugs", one would have to concoct a convincing explanation for why inducing a "schizophrenia-like psychosis" turns out to be a positive choice for mental health, both at the statistical level in the general population and in medically controlled clinical trials. The available scientific evidence therefore suggests that there is more to psychosis (and even more so to complex psychotic disorders such as schizophrenia) than psychedelics can teach us about it; and vice versa, there is far more to psychedelics than what they can teach us about psychoses and psychotic disorders.

The conclusion seems warranted that language characterizing psychedelics only or mainly as drugs inducing "schizophrenia-like psychosis", or suggesting any straightforward relation between the two, is at best a limited account, at worst misleading, and based upon unstated and questionable assumptions. For completeness, it is worth remarking that a similar line of criticism could be raised against language characterizing psychedelics only or mainly as "mystical-experience-inducing drugs" or "ego-dissolving drugs"; but this has not been the case in any serious scientific publication to date, hence why the criticism here was directed specifically towards the language of "psychosis-inducing drugs". The same goes for any other attempt to oversimplify these complex phenomena and reduce them to a single aspect without taking potential cultural and linguistic confounds into account.

Language and mechanisms: the ineffable medicine

For sake of brevity, let's not discuss the languages of "unifying" theories of psychedelic effects20, which ultimately require a unified theory of conscious experience, an incredibly interesting but extremely difficult task for all the obvious reasons. There is no consensus in the scientific community when it comes to the specific mechanisms that should mediate the potential benefits of psychedelics for psychiatric conditions. Some researchers propose that they are due to reduced inflammation21, others to increased neuroplasticity22, others again (among which the key groups of the psychedelic renaissance) suggest that reaching an ineffable "mystical experience"19 or "ego-dissolving"23 psychological state is actually the crucial factor in the therapeutic process. Back to language again: *"The Tao that can be spoken of is not the eternal Tao".* This age-old remark becomes relevant again in the context of psychedelic research. What is the most appropriate language to scientifically study experiences for which perhaps the most common subjective report is that the experience itself lies "beyond" or "outside" of language? Is there anything at all we can say about such ineffable concepts and experiences24?

The emerging picture is fascinatingly complex and far from settled. In the future, language choices will play a crucial role25, as they can build both bridges and walls between (apparently) contrasting theories. Psychedelics seem to resist all attempts at simplistic, systematic, complete characterization: even the most widely accepted neurophysiological mechanism of action (agonism at the 5HT-2A receptor26) does not directly explain why substances with entirely different receptor affinity profiles can have highly overlapping effects with those of psychedelics, for example Salvinorin A27, a kappa-opioid receptor agonist and the active compound in the plant *Salvia Divinorum*; or ketamine, an NMDA-receptor antagonist with hallucinogenic properties at specific doses28, capable also of increasing neuroplasticity22 and showing great promise in the treatment of depression29. Furthermore, the downstream effects of functional selectivity at the 5HT-2A receptor are still being worked out30, and recent analyses31 show that affinities for muscarinic and opioid receptors may also be relevant for predicting the reported subjective effects. These difficulties might discourage the scientific study of psychedelics, but seen in a different light, they greatly increase the potential contributions of these substances to science and medicine.

In conclusion, these reflections suggest a few general points that, if implicitly understood and explicitly implemented, might be useful to productively move forward in the field of psychedelic research:

1. All assumptions and constructs should be double-checked with particular care to diminish cultural and linguistic confounds.
2. Different scientific descriptions may be valid at the same time, although differing in scope and degree of supporting evidence.
3. Theories should be treated as models and perspectives rather than complete and definitive explanations.

Psychedelic research is already stretching the boundaries of scientific language and methods. One might speculate that a paradigm shift in the way we view the relationship between brain processes and subjective experiences will be necessary in order to obtain a fully satisfactory, naturalistic account of these remarkable phenomena.

Or perhaps even that won't do.

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