"Introduction"

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1. Philosophy and Psychedelic Psychiatry

We first contemplated this volume in 2019 as a response to the "psychedelic renaissance", a term that refers to widespread renewed interest in the use of psychedelic drugs to enhance psychological well-being. That interest was shared not only by individuals who experienced benefits but by neuroscientists and psychiatrists interested in understanding how the mechanisms of drug action (primarily serotonin-2a receptor agonism) could produce (i) profound changes to the nature of sensation and cognition and (ii) apparently long term beneficial psychological changes, including in cases that are often resistant to other forms of clinical intervention. The idea that a psychedelic experience could lead to the alleviation of distressing and disabling symptoms clearly recommends an assessment of its clinical value. So the psychedelic renaissance involves not just the use of psychedelics but the mainstreaming of discussion and debate about the nature of psychedelic therapy and its efficacy, safety, and prospects for incorporation into the mainstream repertoire of psychiatric treatments. Part of that discussion has involved a critical re-evaluation of attitudes and policies that initially led to the discontinuation of research into psychedelics as a viable form of treatment. The aim of that discussion was to lay the groundwork for a research program that incorporated and integrated research extending from the molecular level to the world of lived experience, to explain how psychedelics can produce adaptive psychological change.

Our aim was to collect material that could provide a sound philosophical and methodological framework for assessing the explanation of psychedelic experience and its many implications, which range from the epistemological to the ethical. In particular, such a framework needs to mediate in a principled way the connection between mechanisms and experience. The world of psychedelic research contains sophisticated reports of the nature of psychedelic experience from the point of view of the subject and there are also many accounts that explain subsequent adaptive change in terms of the nature of the experience.

An example is the idea that a psychedelic experience of "ego dissolution", in which the subject loses a sense of the boundary between herself and the world, allows for a productive "reset" (Carhart-Harris et al., 2017). In such experiences, perception of the external world often remains, but is no longer attached, phenomenologically, to a perceiving entity (Letheby & Gerrans, 2017). The transitory experience of sensation not filtered through a pre-existing sense of self can be psychologically illuminating to someone whose life has been dogged by a maladaptive self-image. At the same time, we know a lot about mechanisms of psychedelic action at molecular, cellular, and circuit levels (Kwan et al., 2022). But this knowledge does not help explain why and how, for example, changes to the functional connectivity of nodes of the Default Mode Network (DMN) lead to the characteristic experience and psychological changes. There is nothing wrong with calling the result a "reset", but this is an intuitive folk-psychological interpretation, not a viable component of a multi-level integrative explanation.

Of course, one might say that this does not matter: We have neural correlates of psychedelic experience and therefore a basis for increasingly fine-grained clinical interventions. Not only are there are many clinical trials proceeding on this basis but the use of psychedelics in treatment of some disorders has now been approved in Australia, on the ostensible basis that such interventions correlate with statistically significant remission of symptoms (Nogrady, 2023). Similar changes have occurred in the United States, with multiple states decriminalizing psychedelics and some legalizing their therapeutic use (Siegel et al., 2023).

However, it is also true that the kind of knowledge we are interested in here remains elusive. Accumulating correlations is important but ultimately explanation depends on detailed multilevel models that explain the role of mechanisms in producing experience. In other words, we need to know how neurobiological processes generate the experience of psychological stability and coherence and how this generation changes under different conditions (Gerrans, 2014).

A good example is the experience of pain and suffering. We know a lot about the mechanisms of pain and anaesthesia and there is a vast clinical database about the effects of interventions in a wide variety of cases. But predicting the effects of levels of anaesthesia depends on a model of pain processing that treats it as a complex systemic phenomenon. The study of pain has moved from a modular compartmentalised model (nociception and social emotional components) to a matrix model in which the effects of any intervention must be traced across the matrix. Pain theorists are not content to note that (de-) activating specific circuitry has a characteristic effect. They have detailed theories that explain, for example, the time course of opioid activity and its selective neural and phenomenological effects. (Lee et. al., 2011, Betti & Agliotti, 2016).

Another example is electroconvulsive therapy (ECT). ECT is a form of intervention for some of the extreme cases for which psychedelic experience is indicated; for example, severe treatment-resistant depression. We know that some such cases are relieved by ECT and we can trace the effects of ECT at the level of neural circuitry and activity. However, we are not even close to being able to explain why ECT works and its differential effects (i.e. why it works in some patients and not others and why its effects are not always sustained) (Read & Bentall, 2010; Bouckaert et al., 2010; Singh & Kar, 2017). Ideally, we would have a model of the cognitive nature of the mechanisms affected by ECT that would enable us to predict and explain why, how, and in what cases it can relieve depressive symptoms.

ECT is in fact a drastic response to depression for which a less extreme form of treatment is antidepressant medication. Here there is a different kind of analogy with psychedelics. In the 1950s the monoamine imbalance hypothesis launched a wave of research that continues today. The role of serotonin in depression and its relief is, however, still not understood at a level of detail that predicts whether a given regime will succeed (Cowen & Browning, 2015; Jauhar et al., 2023). And this is not because the mechanisms are not well understood, at a certain level of grain. It is because we lack a model that illuminates the connection between mechanistic function, psychology, and phenomenology. As discussions since the 1990s attest, the effects of antidepressants also raise some of the broader ethical and epistemological questions that arise inexorably in the psychedelic case (Kramer, 2023; Stein, 2012).

When we conceived of this volume our aim was to collect some of the best current research bearing on these questions for the case of psychedelics. As the psychedelic renaissance approaches its Florentine period the questions are more, not less, acute.

In the remainder of this introduction we have three main tasks. The first is to review, briefly, the history of psychedelics in psychiatry, including the phenomenological and behavioural effects that first led to their being studied for therapeutic purposes. The second is to give an overview of recent research into the safety, efficacy, and therapeutic mechanism(s) of psychedelic-assisted psychotherapy. The third is to summarise the contributions of each of the chapters collected in this volume and show how they address philosophical issues arising from the new wave of psychedelic psychiatry.

2. Psychedelic Psychiatry: The First Two Waves

Mescaline, which occurs naturally in various cacti, has been called "the oldest psychedelic" (Jay, 2022) in light of archaeological evidence suggesting a five-millennium history of human use. It is also the oldest as far as psychiatric interest is concerned, having come to the attention of Weir Mitchell and Havelock Ellis in the 1890s (Mitchell, 1896, Ellis, 1897). Mitchell and Ellis extolled the aesthetic virtues of the drug's visionary properties and assumed it would become popular for recreational purposes. A small number of psychiatrists began investigating mescaline mainly for its putative psychotomimetic (psychosis-mimicking) properties, likening its perceptual effects to schizophrenic hallucinations and its disruptive effects on the sense of self to depersonalization symptoms (Guttmann, 1936; Guttmann & Maclay, 1936). Some already saw potential utility as an aid to psychoanalysis (Smythies, 1953). The drug's seeming ability to loosen ego defences and boundaries gave a tantalizing hint of therapeutic utility – but the momentum to test this idea properly needed another catalyst to materialise.

That catalyst came in the 1940s in the form of lysergic acid diethylamide, soon to achieve global infamy under the name "LSD". Albert Hoffmann first synthesised his "Problem Child" in the 1930s but did not discover its psychoactive properties until a serendipitous accident on April 16th 1943 (Hofmann, 1980). His first deliberate trip three days later is now enshrined in psychedelic folklore and April 19th is celebrated annually by enthusiasts as "Bicycle Day", in honour of Hoffman's difficult ride home from the lab when the effects of a tiny-seeming dose (250 micrograms) became rapidly and alarmingly intense.

Clearly Hoffman had discovered something remarkable, but what was less clear is what *use* there is there for a drug that induces fantastical visionary experiences. Investigators quickly arrived at the same two answers suggested earlier for mescaline, the irony of their juxtaposition notwithstanding: the mimicking of (psychotic) mental illness and the treatment of (non-psychotic) mental illness. Before long, however, a third and older answer came to the fore: the induction of mystical or religious experiences. It was at the intersection of the drugs' spiritual and medicinal applications – intertwined since antiquity in Indigenous traditions – that some of the most remarkable lines of psychiatric investigation developed.

Throughout the 1950s and 60s, the psychotomimetic paradigm developed apace. Scientists impressed by the similarity between some psychedelic and some psychotic experiences pursued two major applications of this parallel: the study of psychedelics' mechanisms of action, in the hope of uncovering the biochemical bases of mental illness, and the controlled ingestion of psychedelics by psychiatrists, to increase their empathy with their psychotic patients (Osmond, 1957). The discovery of LSD's serotonergic action contributed to the evolving understanding of chemical neurotransmission, and thereby to the "psychopharmacological revolution" and the birth of modern biological psychiatry (Dyck, 2010).

However, studies in the psychotomimetic paradigm soon uncovered anomalies; many subjects' experiences sat uneasily with stereotypical conceptions of psychosis. Rather than distressing hallucinations and dysphoric ego fragmentation, such people described ineffable mystical ecstasies, transcendental states, and new perspectives on life. Despite the well-documented influence of "set and setting" on the psychedelic state, salutary and transformative experiences seemed often to emerge despite contrary expectations. Psychiatrists who attempted to use LSD to induce a safe facsimile of *delirium tremens* in alcoholics found, instead, that their patients reported new perspectives and life-changing epiphanies induced by the drug (Mangini, 1998).

Such findings piqued the interest of intellectuals with prior interests in mysticism, such as Huxley (1954) and Alan Watts (1960), who became eloquent advocates for intentional psychedelic use and cemented its link with Eastern spirituality in the popular imagination.

Thus emerged onto the scientific scene a recognisable cousin of the traditional Indigenous conception of psychedelics: as agents of spiritual experience (Dobkin de Rios, 1984; Harner, 1973; Calabrese, 2013; González-Mariscal & Sosa-Cortés, 2022). Proponents of this conception looked to the drugs for evidence concerning the nature of spontaneous mystical states and even concerning the origins of religion. We can call this an *Entheogenic Conception* of psychedelics (Letheby, 2021), using the term coined by Ruck et al. (1979): *generating the divine within*. The most famous academic application of the Entheogenic Conception was Walter Pahnke's (1963) "Good Friday Experiment", in which psilocybin was administered to divinity students listening to a Good Friday service. Methodological limitation aside, Pahnke's study was a milestone in establishing the possibility of an experimental psychopharmacology of religious experience.

The apparently transformative effects of psychedelic experiences had obvious therapeutic implications, which researchers and clinicians pursued vigorously. Two major therapeutic models emerged. The dominant model in Europe was "psycholytic" (mind-loosening) therapy: repeated sessions of classical psychoanalysis enhanced by low doses of psychedelics (Leuner, 1967). The object was to accelerate therapeutic progress by facilitating access to unconscious material and enhancing the therapist-patient bond. In the United States the "psychedelic therapy" model dominated. This involved fewer but higher doses, with significant preparation and support, the aim being to induce an overwhelming transformative peak or mystical experience (Faillace, 1966). Positive results were reported from this method. Many studies suffered from methodological flaws, but a recent meta-analysis of six randomised controlled trials from the 1950s and 60s found evidence for the efficacy of a single high dose of LSD in the treatment of alcoholism (Krebs & Johansen, 2012).

Besides psychotomimetic, entheogenic, and psychotherapeutic investigations, other lines of research concerned psychedelics' apparent potential to enhance creativity (Sessa, 2008) and their putative epistemic use as a research tool for charting the human psyche (Osmond, 1957). Huxley (1954) saw the "antipodes of the mind" revealed by psychedelics as a subject for disciplined scientific exploration, with Stanislav Grof later comparing the drugs' "potential significance for psychiatry and psychology to that of the microscope for medicine or the telescope for astronomy" (Grof, 1975, pp. 32-3). This approach has connections with the recent interdisciplinary enterprise of "philosophical psychopathology", which uses observations from non-ordinary conditions as a basis for conclusions about the structure and function of the ordinary mind (Graham & Stephens, 1994). This is one prominent rationale for the use of psychedelics in recent cognitive neuroscience.

In a landmark paper which introduced the term "psychedelic" to the scientific lexicon, Humphry Osmond summarised these various lines of investigation:

> Nearly everyone who works with [psychedelics] and allied compounds agrees there is something special about them. Such words as "unforgettable" and "indescribable" abound in the literature. Few workers, however, have emphasized that the unique qualities of these substances must be investigated in many directions at the same time, a consideration that makes work in this field all the more difficult. I shall try to remedy this deficiency by citing several reasons for ascribing importance to them…

> (1) The primary interest of these drugs for the psychiatrist lies in their capacity to mimic more or less closely some aspects of grave mental illnesses, particularly of schizophrenia. The fact that medical men have been preoccupied with transient states resembling mental illnesses that have been called model psychoses, however, does not mean that the only use for these compounds is in the study of pathological conditions…
>
> (2) Psychiatrists have found that these agents have a place in psychotherapy. This practice may sound like carrying the idea of "a hair of the dog that bit you" rather far, but it seems to be justified.
>
> (3) Another potentiality of these substances is their use in training and in educating those who work in psychiatry and psychology, especially in understanding strange ways of the mind.
>
> (4) These drugs are of value in exploring the normal mind under unusual circumstances.
>
> (5) Last, but perhaps most important: there are social, philosophical, and religious implications in the discoveries made by means of these agents.
> (Osmond, 1957, pp. 419-420).

Despite this apparent promise, the heyday of psychedelic science was short-lived. A complex interplay of social, political, and scientific factors led to the prohibition of psychedelics, the demonization of LSD in particular, and the virtual cessation of all human research involving these compounds for some decades.

3. The Psychedelic Renaissance

In the late 1980s Rick Strassman began human studies of intravenous DMT at the University of New Mexico, breaking a two-decade taboo in the United States. These studies were exercises in basic psychopharmacology, with no attempt to evaluate possible therapeutic effects, but they paved the way for a variety of renewed investigations (Strassman, 2001). Throughout the 1990s German and Swiss laboratories conducted human studies of mescaline and psilocybin, framed in squarely psychotomimetic terms (Hermle et al., 1992, Vollenweider et al., 1997). By the turn of the millennium, scientists were able to set their sights on therapeutic and transformative use once more. Landmark studies of psilocybin's effects on the personality of healthy volunteers (Griffiths et al., 2006, MacLean et al., 2011) and on the symptoms of obsessive-compulsive disorder (Moreno et al., 2006) paved the way for a subsequent explosion of studies. After decades in the shadows, psychedelics are now at the front and centre of psychiatric innovation. What have we learned so far from this remarkable revival of research?

3.1 Safety in Controlled Conditions

Perhaps the most important finding is that psychedelics can be given safely in controlled clinical settings. One key rationale for their prohibition was their allegedly vast harm potential. Media coverage of LSD, in particular, depicted a substance that could cause instant and permanent insanity, genetic defects, and moral corruption (Dyck, 2010; Mangini, 1998).

Recent research has painted a rather different picture. In a review of the literature, Strassman (1984) found that adverse psychological reactions to psychedelics were relatively rare,

typically transient, and usually manageable with interpersonal support. In the relatively few cases of prolonged psychosis, there is often evidence of a pre-existing vulnerability, such as a family history of psychotic illness. The incidence of prolonged psychotic episodes when stringent exclusion criteria are applied seems to be very low.

In an important paper that outlines safety guidelines for human psychedelic research, Johnson et al. summarise the drugs' physiological safety profile as follows:

> Hallucinogens generally possess relatively low physiological toxicity, and have not been shown to result in organ damage or neuropsychological deficits… Nonhuman animal studies have shown MDMA (structurally similar to some classical hallucinogens, but with a substantially different pharmacological mechanism of action) to have neurotoxic effects at high doses, although MDMA has been judged to be safe for human administration in the context of several therapeutic and basic human research studies. In contrast, there is no evidence of such potential neurotoxic effects with the prototypical classical hallucinogens (i.e. LSD, mescaline and psilocybin). Some physiological symptoms may occur during hallucinogen action, such as dizziness, weakness, tremors, nausea, drowsiness, paraesthesia, blurred vision, dilated pupils and increased tendon reflexes… In addition, hallucinogens can moderately increase pulse and both systolic and diastolic blood pressure… However, these somatic effects vary and are relatively unimpressive even at doses yielding powerful psychological effects…
>
> The physical adverse effects of these agents observed in cancer patients were manageable and similar to effects observed in physically healthy individuals. These researchers noted that any other symptoms experienced during sessions with cancer patients were symptoms already associated with their existing illness… Early clinical research also safely administered LSD to chronic alcoholics and cancer patients with considerable liver damage, suggesting hepatic concerns are 'negligible unless the dysfunction is of a critical degree' (Grof, 1980, p. 164).
>
> Participants and review committees may be concerned that LSD or other hallucinogens are associated with chromosomal damage. These concerns stem from an anti-LSD media campaign by the USA government in the late 1960s… However, many follow-up investigations soon squarely refuted the hypothesis that LSD use in humans was a significant risk for chromosomal damage or carcinogenic, mutagenic or teratogenic effects…
> (Johnson et al., 2008, pp. 606-607).

High-dose psychedelic subjects often experience considerable fear or anxiety during the dosing session (Griffiths et al., 2008), but this is typically managed effectively with interpersonal support. In 2016, Ross and colleagues noted that over 2000 doses of psilocybin had been administered in rigorous research trials during a 25-year period, with "no reports of any medical or psychiatric serious [adverse events], including no reported cases of prolonged psychosis or HPPD [hallucinogen persisting perception disorder]" (Ross et al. 2016, p. 1176). In a systematic review of psychedelics' long-term effects, Aday et al. conclude:

> All in all, limited harm has been reported in the new era of research which utilizes extensive safety protocols… and the drugs' potential for dependency is low… In subjective accounts, [patients] with depression… and addiction… have noted the lack

> of long-term adverse side effects as being a considerable benefit over previous treatments they had attempted (e.g., antidepressants).
> (Aday et al., 2020, p. 184)

Of course, safety is one thing, and therapeutic efficacy another.

3.2 Evidence of Therapeutic Efficacy

The three best-studied applications of psychedelic therapy are the treatment of addiction, of depression, and of psychosocial distress accompanying terminal illness. Without attempting a comprehensive review of this literature, we will briefly outline some of the main findings.

As mentioned above, a meta-analysis of RCTs from the 1950s and 60s found that a single high dose of LSD significantly outperformed placebo in the treatment of alcoholism (Krebs & Johansen, 2012). More recently, two open-label pilot studies have addressed the potential of psilocybin to treat alcohol and tobacco addiction, respectively. Bogenschutz et al. (2015) administered one or two doses of psilocybin in conjunction with Motivational Enhancement Therapy to ten volunteers diagnosed with alcohol dependence. During the first four weeks of the programme, while the patients were only receiving therapy, there were no significant changes to drinking behaviour, but the first psilocybin session, at four weeks, was followed by significant improvements in drinking behaviour, as well as reduced craving and increased motivation to quit. Remarkably, the changes were largely maintained at follow-ups 36 weeks after the psilocybin sessions. Meanwhile, Johnson et al. (2014) administered psilocybin to 15 addicted cigarette smokers, each with multiple failed quit attempts. 6 months after receiving a moderate and a high dose of psilocybin in the context of a structured smoking cessation intervention, 12 of the 15 (80%) were verified nicotine-abstinent by biomarkers. One year after the sessions, 10 subjects remained abstinent; more than 16 months after, 9 did (Johnson et al., 2017). Like the alcoholism trial, this open-label study requires replication in larger samples with placebo controls; nonetheless, 80% is a remarkable six-month abstinence rate relative to gold-standard treatments for tobacco addiction (West et al., 2015).

Psychedelics have also been studied for the treatment of depression. In an open-label pilot study, seventeen patients with major depressive disorder received a single dose of ayahuasca[1] and showed significant reductions in depressive symptoms lasting three weeks (Osório et al., 2015, Sanches et al., 2016). Meanwhile, in a double-blind RCT involving 35 patients with treatment-resistant depression, half of the patients showed significant antidepressant effects lasting up to a week after a single dose of ayahuasca (Palhano-Fontes et al., 2019). In another open-label study, 12 patients with treatment-resistant depression each received a moderate and a high dose of psilocybin with non-directive psychological support. Patients showed significant reductions in depressive symptoms (Carhart-Harris et al., 2016) which were largely maintained six months after dosing (Carhart-Harris et al., 2018). Subsequent double-blind studies have reported more equivocal findings. In one trial, psilocybin performed no better than a conventional antidepressant on primary outcome measures in a double-blind, head-to-head comparison (Carhart-Harris et al., 2021), though the proper interpretation of these findings has been debated (Nayak et al, 2023). In another trial, with a large sample, psilocybin treatment led to substantial reductions in depression symptoms, but was associated with more adverse

[1] An Amazonian shamanic beverage typically created by mixing plants containing DMT with plants containing monoamine oxidase inhibitors (MAOIs) that allow the DMT to be orally active, as well as potentially contributing psychoactive effects of their own.

events than in previous trials (Goodwin et al., 2022). Finally, a similarly large trial found substantial reductions in depression, with relatively few adverse events (Raison et al., 2023).

The third major application of psychedelic therapy in recent research has been the amelioration of psychosocial distress in terminally ill patients. Those with a terminal diagnosis undergo many forms of suffering, not least of which is considerable anxiety, depression, and existential distress relating to their illness and impending death. Effective ways of dealing with this distress are badly needed. In the 1960s and 70s, psychedelics were used to ease the psychological suffering of terminally ill patients (Dyck, 2019). Clinicians and patients alike saw the treatment as extremely helpful.

Several clinical trials from this era are reviewed by Reiche et al. (2018). All studies reported positive results. More recently, Grob et al. (2011) reported a pilot study in which 12 patients with anxiety relating to a terminal diagnosis each received one placebo session and one moderate-dose psilocybin session in double-blind fashion. Psilocybin sessions were followed by significant reductions in anxiety lasting three months and reductions in depressive symptoms that reached significance six months after dosing. Similar results were found in a study of LSD in 12 patients with terminal illness (Gasser et al., 2014).

These findings have since been replicated in two larger, double-blind RCTs—one conducted at New York University and the other at Johns Hopkins. Between the two studies, a total of 80 terminal patients with clinically significant anxiety and depression received psilocybin and placebo sessions. High-dose psilocybin, but not placebo, led to significant decreases in anxiety and depression that were sustained six months after treatment (Griffiths et al., 2016, Ross et al., 2016). A long-term follow-up was conducted in the NYU study; over half of the surviving patients who participated in the follow-up still showed significant anxiolytic and antidepressant effects, three to four years post-treatment (Agin-Liebes et al., 2020).

3.3 Therapeutic Mechanisms

The biggest unanswered question about psychedelic therapy is: does it really work? There are difficulties in demonstrating, convincingly, the efficacy of a treatment for which effective blinding is well-nigh impossible (Muthukumaraswamy et al., 2021). Also, most of the promising early findings described above still await replication in larger samples.

The second-biggest unanswered question is: if it does work, *how* does it work? Psychedelic therapy is a far cry from existing psychiatric treatments, given its reliance on a small number of discrete episodes of dramatically altered consciousness. And it is precisely this distinctive factor – the psychedelic experience itself – that provides our strongest clue about the mechanisms involved. Across many studies, the most consistent predictor of positive clinical outcomes is the phenomenological character of the acute drug-induced experience.

Psychedelic experiences vary greatly. The same dosage of the same drug, given to 10 different people, may evoke 10 wildly different experiences – some involving primarily visual or aesthetic phenomena, others dominated by intensified emotional experience, and others centred on philosophical reflections and insights. However, some definite phenomenological patterns can be discerned, especially when “set and setting” are held fairly constant. In particular, one type of experience seems to occur quite frequently in controlled, clinical conditions, and to predict subsequent therapeutic benefits: the so-called *mystical-type* experience.

The notion of mystical experience used in psychedelic research derives originally from the work of William James (1902) and Walter Stace (1960). This concept, based on cross-cultural analyses of religious literature, has been developed into a psychometric construct – the mystical-*type* experience – with six distinct phenomenological dimensions: feelings of unity, transcendence of time and space, ineffability, paradoxicality, sacredness, noetic quality, and positive mood. Simplifying slightly, a "complete" mystical-type experience is defined as one for which a subject scores 60% or higher on each of the corresponding sub-scales of the Mystical Experience Questionnaire (Griffiths et al., 2006). Many studies have found the construct of a complete mystical-type experience, and related constructs, to be the best predictors of lasting symptom reductions in psychedelic therapy (Kangaslampi, 2023).

This correlation between mystical-type experience and therapeutic outcomes is suggestive, but it is far from a complete answer. For one thing, it is compatible with many different hypotheses about the causal mechanisms at play. Some researchers have suggested that psychedelic therapy works mainly by low-level, non-experiential, neurobiological processes, with the remarkable experiences little more than a side-effect (Olsen, 2020). This is a minority position; the correlation between experience types and clinical outcomes suggests to most researchers that the experience itself is causally involved (Yaden & Griffiths, 2020). But this bare assertion underdetermines mechanistic hypotheses: *how*, exactly, does the experience help?

The influential REBUS (Relaxed Beliefs Under Psychedelics) model (Carhart-Harris & Friston, 2019) says that psychedelics' signature effects, especially at the moderate-to-high doses used in psychedelic therapy, result primarily from a weakening or "relaxation" of subjects' unconscious, high-level beliefs about self and world. This model is rooted in the predictive processing theory of brain function, which sees the brain as a hierarchical inference engine constantly generating "best guesses" about the external world and updating these in response to sensory prediction errors (Hohwy, 2013). Carhart-Harris and Friston propose that maladaptive beliefs become deeply entrenched in relevant pathologies; thus, by temporarily "relaxing" these beliefs, psychedelics afford an opportunity to revise them for the better. We have elsewhere developed a similar predictive processing account of psychedelic experience and its therapeutic effects (Letheby & Gerrans, 2017, Letheby, 2021), focusing on the role played by predictive models of the *self*. Albeit speculative and provisional, this self-binding model and the REBUS model both attempt the task mentioned above: linking neurobiological processes to clinical phenomenology via cognitive or computational theory.

Interestingly, the REBUS and self-binding models agree that changes in *metaphysical beliefs*, which sometimes result from mystical-type experiences, are not the main driver of therapeutic change. However, changes in such beliefs are an intuitively plausible mechanism, especially in a palliative care context. Moreover, at least one study has found a correlation between increased non-physicalist beliefs and beneficial psychological changes after a psychedelic experience (Timmermann et al., 2021). This underscores the fact that, while ratings of mystical-type experience are the most consistently identified correlate of therapeutic outcomes, they are not the only such correlate. Other studies have linked good clinical results to feelings of psychological insight (Davis et al., 2020, Peill et al., 2022), feelings of emotional breakthrough (Roseman et al., 2019), and increases in mindfulness-related capacities (Mian et al., 2020). Qualitative research has identified similar themes including insights, changes to self-perception, and emotional breakthrough or catharsis (Breeksema et al., 2020).

Neurobiological research into psychedelic therapy has focused heavily on the putative role of the celebrated Default Mode Network (Gattuso et al., 2023). Several studies have linked

modulation of this system to acute and lasting effects of psychedelics, though some researchers are wary of overstating its importance relative to the available evidence (Doss et al., 2020). While psychedelics' basic pharmacological mechanism of serotonin-2A receptor agonism is well characterized, the systemic changes that link this mechanism to altered consciousness are still very poorly understood. The REBUS model and its precursor, the "Entropic Brain" hypothesis (Carhart-Harris et al., 2014; Carhart-Harris, 2018) emphasize modulation of the DMN, while other neuroscientific models focus on changes to cortico-thalamo-striato-cortical circuitry (Vollenweider & Geyer, 2001), cortico-claustro-cortical circuitry (Doss et al., 2022) and the Salience Network (Letheby & Gerrans, 2017, Letheby, 2021) – another system implicated in self-representation and in multiple psychiatric disorders (Seth, 2013).

4. Contributions to this Volume

Clearly, the use of psychedelics in psychiatry raises a host of philosophical questions. The contributions to this volume cluster around three broad topics. The first, which we have entitled "Self and Mind", concerns what psychedelic research can contribute to philosophical and scientific theories of the mind, and vice versa. The second, "Science and Psychiatry", focuses most directly on methodological and conceptual issues surrounding the scientific study and psychiatric use of psychedelics. The third, "Ethics and Spirituality", addresses broader questions about the distinctive sorts of themes that arise in psychedelic experience and set this treatment so decisively apart from standard clinical practice.

4.1 Self and Mind

The field of philosophical psychopathology uses reports of non-ordinary conscious experiences as evidence for conclusions about the structure and function of the ordinary mind. Raphaël Millière (chapter 2, this volume) argues that reports of a specific type of psychedelic experience – experiences of *body disownership* – can play an evidential role in an ongoing debate in this field over the existence of a distinct phenomenology of bodily ownership. Realists about such a phenomenology appeal to apparent cases of "phenomenal contrast" between states with the phenomenology and states without it, but the interpretation of relevant reports is highly controversial. Without taking a definitive stance on their correct interpretation, Milliere suggests that reports of drug-induced bodily disownership are highly significant for this debate, as they succumb less readily to anti-realist interpretations.

The second chapter in the "Self and Mind" section, by Philip Gerrans (chapter 3, this volume), uses evidence from the study of psychedelic-induced ego dissolution to shed light on the neurocognitive mechanisms of self-representation and their relations to metaphysical debates about the existence of the self. Gerrans adapts Daniel Dennett's notion of the self as a "centre of narrative gravity" to neurocognitive theory, arguing that the feeling of unified self-awareness emerges from interoceptive processes that model the self as a centre of *allostatic* gravity, and that the feature binding aspects of self-representation previously identified by Letheby and Gerrans (2017) only emerge at higher autobiographical or narrative levels of processing. He also draws out the consequences of this account for ongoing debates over the metaphysics of the self in light of predictive processing and active inference theories.

One longstanding question concerns how psychedelic experience, with its sometimes salutary effects, relates to phenomenologically overlapping but typically detrimental experiences, e.g. in psychosis. A specific instance of this question concerns the difference between beneficial and detrimental disruptions to *self-modelling,* or self-representation. This is the topic of the

contribution by Anna Ciaunica and Adam Safron (chapter 4, this volume): Why are psychedelic-induced changes to the sense of self so often beneficial, and how do they differ from the detrimental changes found in conditions like depersonalization disorder (DPD?) Ciaunica and Safron invoke ideas from the active inference framework to argue that the difference is one of control: since psychedelic experiences of self-loss are under the agent's control, but self-loss in DPD is not, experiences of the former kind promote beneficial flexibility of the self-model whereas the latter lead to deleterious inflexibility and rigidity.

Meanwhile, Berit Brogaard and Dimitria Electra Gatzia (chapter 5, this volume) take aim at the dominant interpretation of psychedelic experience in terms of predictive processing theory. They argue that certain psychedelic effects cannot readily be explained in predictive processing terms but can be explained much more naturally by the alternative *Gist Theory* of perception that they develop in the chapter. The phenomena in question include specific types of perceptual distortions and changes to executive functioning that indicate, to these authors, impairment of attentional mechanisms. So, just as Milliere treats psychedelic experience as a window onto the phenomenology of bodily ownership, Brogaard and Gatzia treat it as a window onto the nature of perceptual processing.

Link Swanson's contribution (chapter 6, this volume) also explores the perceptual effects of psychedelics and how they may best be explained. Here the focus is on visual effects, specifically, which Swanson argues have been unjustly neglected in recent research and may hold important clues to understanding the therapeutic effects and epistemic dimensions of the psychedelic experience. He develops a model of psychedelic visuals based on the novel principle of hypercontextual modulation (HCM), cites evidence in support of this model, and shows how it can illuminate some of the most interesting and academically neglected aspects of the psychedelic experience.

4.2 Science and Psychiatry

Uniquely among the contributions to the volume, the chapter by Jaipreet Mattu and Jacqueline Sullivan (chapter 7, this volume) considers research into the effects of psychedelics on non-human animals. An extensive program of translational research has used rodent models to garner evidence concerning therapeutic effects of psychedelics in depression and biological mechanisms potentially underlying those effects. Mattu and Sullivan argue that there is a mismatch between the research methods that are used in these rodent models and those that are used in human psychedelic studies, and that this renders current investigative techniques unsuitable for mechanistic discovery. They develop a new positive proposal for how to harmonize methods used in animal and human studies and thereby advance the project of psychedelic translational research using rodent models.

The remaining two chapters in this section relate very directly to the experiences of those who receive psychedelics in clinical settings for therapeutic purposes. David Yaden, Sandeep Nayak, and the late Roland Griffiths (chapter 8, this volume) consider the emerging debate about the prevalence, importance, and implications of belief changes occurring in psychedelic therapy. Yaden et al. survey evidence suggesting that belief changes in the direction of metaphysical non-naturalism do sometimes occur. They also offer some guidelines for how clinicians should handle this, distinguishing helpfully between various different scenarios – such as participant-initiated and clinician-initiated discussions of metaphysical beliefs – and drawing on the work of William James as well as that of contemporary philosophers.

Finally, Virginia Ballesteros (chapter 9, this volume) draws on the work of Wittgenstein to develop a new account of how psychedelic experiences can alleviate symptoms of depression. Ballesteros connects the Wittgensteinian notions of "world" and "point of view" to Ratcliffe's influential phenomenology of depression, arguing that the (experiential) world of the depressed patient is characterized by a pervasive lack of beauty, meaning, and possibilities for action and change. Psychedelic experience, Ballesteros suggests, can be world-shifting, for better and worse; when it remediates depression, it does so by shifting the patient into a world that is the polar opposite of the depressed world. This new world is one characterized and permeated by beauty, meaning, unity, and connectedness. Such a shift can facilitate therapeutic acceptance of the contingencies of one's life and the perception of valuable possibilities for action.

4.3 Ethics and Spirituality

The three chapters in this section deal with issues of ethics (broadly construed) and spirituality. Samir Chopra and Chris Letheby (chapter 10) take their cue from recent discussions of psychedelics as putative *moral enhancement* agents, asking: if psychedelics can, indeed, promote moral behaviour, how do they do so? In pursuing an answer to this question, they examine the phenomenology of transformative experiences of forgiveness induced by psychedelics. Chopra and Letheby argue, on the basis of their phenomenological investigation, that psychedelics can morally enhance by reducing dissonance between morally relevant beliefs and emotions, and that the way in which they do this vindicates some heterodox ideas about moral psychology developed by Cora Diamond. In particular, Diamond argues that great literature can morally persuade by making "appeals to the intelligence" that are not reducible without remainder to argument; likewise, say Chopra and Letheby, for psychedelic experience.

Eric Steinhart's contribution (chapter 11, this volume) addresses the connection between psychedelic experience and *naturalistic spirituality*. Those who undergo transformative psychedelic experiences often describe these experiences as spiritual, but there are deep philosophical questions about what such descriptions mean and whether undergoing drug-induced spiritual experiences is in tension with the philosophical doctrine of naturalism. Steinhart compares and contrasts three metaphysical interpretations of psychedelic spiritual experiences: a traditional religious approach, a naturalistic approach with a physicalist ontology, and a naturalistic approach with a Platonist ontology. A central point of his contribution is that the commitment to naturalism – a polysemous term – need not entail a commitment to physicalism, and richer resources than physicalism permits may be required to do justice to the spiritual dimensions of psychedelic experience. Steinhart concludes his chapter with a discussion of the ethics of metaphysical belief, echoing the questions addressed by Yaden et al. about how best to handle psychedelic-induced belief changes in clinical situations.

In the final chapter of the volume, Thomas Metzinger (chapter 12, this volume) addresses perhaps the broadest question of all: (how) can the psychedelic experience be integrated into contemporary culture and society in a way that is "rational, evidence-based, and ethically convincing"? He argues that there is an ethical imperative to solve this *Enculturation Problem* and that doing so will require the development of a genuine *Bewussteinskultur*, or culture of consciousness – a notion he has developed in extensive prior work (Metzinger, 2024). Metzinger's guiding assumptions are that the radical approach of immediate, total psychedelic legalization and the conservative approach of persisting with current Drug War policies are equally untenable alternatives. He marshals some sobering data about the need for new policy solutions and sketches a blueprint for a "minimal enculturation protocol" – a way to trial the cultural integration of legal psychedelic experiences that should be acceptable to all parties and

could attract no reasonable opposition. Without some initiative emerging along these lines, Metzinger argues, the ratio of harms and benefits accruing to society from the use of psychedelics and related substances is likely to deteriorate in the near future.

Our hope is that the chapters collected in this volume can collectively make some small contribution to addressing this problem and preventing this eventuality.

References

Aday, J.S., Mitzkovitz, C.M., Bloesch, E.K., Davoli, C.C. & Davis, A.K. (2020). Long- term effects of psychedelic drugs: A systematic review. *Neuroscience & Biobehavioral Reviews*, *113*, 179– 189.

Agin-Liebes, G.I., Malone, T., Yalch, M.M., Mennenga, S.E., Ponté, K.L., Guss, J., Bossis, A.P., Grigsby, J., Fischer, S. & Ross, S. (2020). Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *Journal of Psychopharmacology*, *34*(2), 155–166.

Betti, V. & Aglioti, S.M. (2016). Dynamic construction of the neural networks underpinning empathy for pain. *Neuroscience & Biobehavioral Reviews*, *63*, pp.191-206.

Bogenschutz, M.P., Forcehimes, A.A., Pommy, J.A., Wilcox, C.E., Barbosa, P.C.R. & Strassman, R.J. (2015). Psilocybin- assisted treatment for alcohol dependence: a proof- of-concept study. *Journal of Psychopharmacology*, *29*(3), 289– 299.

Bouckaert, F., Sienaert, P., Obbels, J., Dols, A., Vandenbulcke, M., Stek, M. & Bolwig, T. (2014). ECT: its brain enabling effects: a review of electroconvulsive therapy–induced structural brain plasticity. *The journal of ECT*, *30*(2), 143-151.

Breeksema, J. J., Niemeijer, A. R., Krediet, E., Vermetten, E., & Schoevers, R. A. (2020). Psychedelic treatments for psychiatric disorders: A systematic review and thematic synthesis of patient experiences in qualitative studies. *CNS drugs*, *34*, 925-946.

Calabrese, J. D. (2013). *A different medicine: postcolonial healing in the Native American Church*. Oxford University Press.

Carhart-Harris, R. L. (2018). The entropic brain-revisited. *Neuropharmacology*, *142*, 167-178.

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*(3), 316-344.

Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., ... & Nutt, D. (2014). The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Frontiers in Human Neuroscience*, 20.

Carhart-Harris, R.L., Bolstridge, M., Rucker, J., Day, C.M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J.A., Forbes, B., Feilding, A. & Taylor, D. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619-627.

Carhart-Harris, R.L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J.N., Wall, M.B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K. & Leech, R. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*, *7*(1), 1-11.

Carhart-Harris, R.L., Bolstridge, M., Day, C.M., Rucker, J., Watts, R., Erritzoe, D.E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S. & Rickard, J.A. (2018). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology*, *235*, 399-408.

Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D. & Nutt, D.J. (2021). Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine, 384*(15), 1402-1411.

Cowen, P. J., & Browning, M. (2015). What has serotonin to do with depression?. *World Psychiatry, 14*(2), 158.

Davis, A. K., Barrett, F. S., & Griffiths, R. R. (2020). Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of contextual behavioral science*, *15*, 39-45.

Dobkin de Rios, M. (1984). *Visionary vine: Hallucinogenic healing in the Peruvian Amazon*. Waveland Press. Original work published 1972.

Doss, M.K., May, D.G., Johnson, M.W., Clifton, J.M., Hedrick, S.L., Prisinzano, T.E., Griffiths, R.R. & Barrett, F.S. (2020). The acute effects of the atypical dissociative hallucinogen salvinorin A on functional connectivity in the human brain. *Scientific reports*, *10*(1), 16392.

Doss, M. K., Madden, M. B., Gaddis, A., Nebel, M. B., Griffiths, R. R., Mathur, B. N., & Barrett, F. S. (2022). Models of psychedelic drug action: modulation of cortical-subcortical circuits. *Brain*, *145*(2), 441-456.

Dyck, E. (2010). *Psychedelic psychiatry: LSD from clinic to campus*. Johns Hopkins University Press.

Dyck, E. (2019). Psychedelics and dying care: A historical look at the relationship between psychedelics and palliative care. *Journal of Psychoactive Drugs, 51*(2), 102–107.

Ellis, H.L. (1897). A note on the phenomena of mescal intoxication. *The Lancet*, *149*(3849), 1540-1542.

Faillace, L.A. (1966). Clinical use of psychotomimetic drugs. *Comprehensive Psychiatry, 7*(1), 13– 20.

Gasser, P., Holstein, D., Michel, Y., Doblin, R., Yazar- Klosinski, B., Passie, T. & Brenneisen, R. (2014). Safety and efficacy of lysergic acid diethylamide- assisted psychotherapy for anxiety associated with life-threatening diseases. *Journal of Nervous and Mental Disease, 202*(7), 513– 520.

Gattuso, J. J., Perkins, D., Ruffell, S., Lawrence, A. J., Hoyer, D., Jacobson, L. H., ... & Sarris, J. (2023). Default mode network modulation by psychedelics: a systematic review. *International Journal of Neuropsychopharmacology*, *26*(3), 155-188.

Gerrans, P., 2014. *The measure of madness: Philosophy of mind, cognitive neuroscience, and delusional thought.* MIT Press.

González-Mariscal, J. M., & Sosa-Cortés, P. E. (2022). Insights for Modern Applications of Psilocybin Therapy from a Case Study of Traditional Mazatec Medicine. *Anthropology of Consciousness*, *33*(2), 358-384.

Goodwin, G.M., Aaronson, S.T., Alvarez, O., Arden, P.C., Baker, A., Bennett, J.C., Bird, C., Blom, R.E., Brennan, C., Brusch, D. & Burke, L. (2022). Single-dose psilocybin for a treatment-resistant episode of major depression. *New England Journal of Medicine*, *387*(18), 1637-1648.

Graham, G. & Stephens, G.L. (eds.) (1994). *Philosophical Psychopathology*. MIT Press.

Griffiths, R. R., Richards, W. A., McCann, U., & Jesse, R. (2006). Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology*, *187*, 268-283.

Griffiths, R.R., Richards, W.A., Johnson, M.W., McCann, U.D. & Jesse, R. (2008). Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *Journal of Psychopharmacology*, *22*(6), 621– 632.

Griffiths, R.R., Johnson, M.W., Carducci, M.A., Umbricht, A., Richards, W.A., Richards, B.D., Cosimano, M.P., & Klinedinst, M.A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life- threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology*, *30*(12), 1181– 1197.

Grob, C.S., Danforth, A.L., Chopra, G.S., Hagerty, M., McKay, C.R., Halberstadt, A.L. & Greer, G.R. (2011). Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry*, *68*(1), 71– 78.

Grof, S. (1975). *Realms of the Human Unconscious: Observations from LSD Psychotherapy*. Viking.

Guttmann, E. (1936). Artificial psychoses produced by mescaline. *Journal of Mental Science*, *82*(338), 203-221.

Guttmann, E., & Maclay, W. S. (1936). Mescalin and depersonalization: therapeutic experiments. *Journal of Neurology and Psychopathology*, *16*(63), 193.

Harner, M. J. (1973). *Hallucinogens and shamanism*. Oxford University Press.

Hermle, L., Fünfgeld, M., Oepen, G., Botsch, H., Borchardt, D., Gouzoulis, E., Fehrenbach, R.A. & Spitzer, M. (1992). Mescaline-induced psychopathological, neuropsychological, and neurometabolic effects in normal subjects: experimental psychosis as a tool for psychiatric research. *Biological Psychiatry*, *32*(11), 976-991.

Hofmann, A. (1980). *LSD: My Problem Child*. Trans. Jonathan Ott. McGraw.

Hohwy, J. (2013). *The predictive mind*. Oxford University Press.

Huxley, A. (1954). *The Doors of Perception.* Reprint: HarperCollins, 2009.

Jauhar, S., Arnone, D., Baldwin, D. S., Bloomfield, M., Browning, M., Cleare, A. J., ... & Cowen, P. J. (2023). A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression. *Molecular Psychiatry*. DOI: 10.1038/s41380-023-02095-y

James, W. (1902). *The varieties of religious experience*. Reprint: Penguin, 1983.

Jay, M. (2019). *Mescaline: a global history of the first psychedelic*. Yale University Press.

Johnson, M.W., Garcia- Romeu, A., Cosimano, M.P. & Griffiths, R.R. (2014). Pilot study of the 5- HT2AR agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology, 28*(11), 983– 992.

Johnson, M.W., Garcia- Romeu, A. & Griffiths, R.R. (2017). Long-term follow-up of psilocybin-facilitated smoking cessation. *American Journal of Drug and Alcohol Abuse*, *43*(1), 55– 60.

Kangaslampi, S. (2023). Association between mystical-type experiences under psychedelics and improvements in well-being or mental health–A comprehensive review of the evidence. *Journal of Psychedelic Studies*, *7*(1), 18-28.

Kramer, P. D. (2023). *Listening to Prozac: The Landmark Book About Antidepressants and the Remaking of the Self*. Penguin. Original work published 1993.

Krebs, T.S. & Johansen, P.Ø. (2012). Lysergic acid diethylamide (LSD) for alcoholism: Meta-analysis of randomized controlled trials. *Journal of Psychopharmacology, 26*(7), 994–1002.

Kwan, A.C., Olson, D.E., Preller, K.H. & Roth, B.L. (2022). The neural basis of psychedelic action. *Nature Neuroscience*, *25*(11), 1407-1419.

Lee, M., Silverman, S.M., Hansen, H., Patel, V.B. & Manchikanti, L. (2011). A comprehensive review of opioid-induced hyperalgesia. *Pain physician*, *14*(2), p.145.

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

Letheby, C., & Gerrans, P. (2017). Self unbound: ego dissolution in psychedelic experience. *Neuroscience of Consciousness*, *2017*(1), nix016.

Leuner, H. (1967). Present state of psycholytic therapy and its possibilities. In Abramson, H.A. (ed.) *The Use of LSD in Psychotherapy and Alcoholism*, 101– 116. Bobbs- Merrill.

MacLean, K.A., Johnson, M.W. & Griffiths, R.R. (2011). Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *Journal of Psychopharmacology, 25*(11), 1453– 1461.

Mangini, M. (1998). Treatment of alcoholism using psychedelic drugs: A review of the program of research. *Journal of Psychoactive Drugs*, *30*(4), 381– 418.

Metzinger, T. (2024). *The elephant and the blind: The experience of pure consciousness: Philosophy, science, and 500+ experiential reports*. MIT Press.

Mian, M. N., Altman, B. R., & Earleywine, M. (2020). Ayahuasca's antidepressant effects covary with behavioral activation as well as mindfulness. *Journal of Psychoactive Drugs*, *52*(2), 130-137.

Mitchell, S.W. (1896). Remarks on the effects of Anhelonium lewinii (the mescal button). *British Medical Journal*, *2*(1875), 1625-1629.

Moreno, F.A., Wiegand, C.B., Taitano, E.K. & Delgado, P.L. (2006). Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive- compulsive disorder. *Journal of Clinical Psychiatry*, *67*(11), 1735– 1740.

Nayak, S. M., Bari, B. A., Yaden, D. B., Spriggs, M. J., Rosas, F. E., Peill, J. M., ... & Carhart-Harris, R. (2023). A Bayesian reanalysis of a trial of psilocybin versus escitalopram for depression. *Psychedelic Medicine*, *1*(1), 18-26.

Nogrady, B. (2023). Australia's approval of MDMA and psilocybin for PTSD and depression is premature, say critics. *BMJ*, *2023*(382), 1599. http://dx.doi.org/10.1136/bmj.p1599

Olson, D. E. (2020). The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science*, *4*(2), 563-567.

Osmond, H. (1957). A review of the clinical effects of psychotomimetic agents. *Annals of the New York Academy of Sciences*, *66*(3), 418-434.

Osório, F.D.L., Sanches, R.F., Macedo, L.R., dos Santos, R.G., Maia- de- Oliveira, J.P., Wichert- Ana, L., de Araujo, D.B., Riba, J., Crippa, J.A., and Hallak, J.E. (2015). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. *Revista Brasileira de Psiquiatria*, *37*(1), 13– 20.

Pahnke, W.N. (1963). *Drugs and mysticism: An analysis of the relationship between psychedelic drugs and the mystical consciousness: A thesis* (Doctoral dissertation, Harvard University).
https://maps.org/images/pdf/books/pahnke/walter_pahnke_drugs_and_mysticism.pdf. 5th August 2023.

Palhano- Fontes, F., Barreto, D., Onias, H., Andrade, K.C., Novaes, M.M., Pessoa, J.A., Mota- Rolim, S.A., Osório, F.L., Sanches, R., dos Santos, R.G. & Tófoli, L.F. (2019). Rapid antidepressant effects of the psychedelic ayahuasca in treatment- resistant depression: A randomized placebo- controlled trial. *Psychological Medicine*, *49*(4), 655– 663.

Peill, J. M., Trinci, K. E., Kettner, H., Mertens, L. J., Roseman, L., Timmermann, C., ... & Carhart-Harris, R. L. (2022). Validation of the Psychological Insight Scale: A new scale to assess psychological insight following a psychedelic experience. *Journal of Psychopharmacology*, *36*(1), 31-45.

Raison, C. L., Sanacora, G., Woolley, J., Heinzerling, K., Dunlop, B. W., Brown, R. T., ... & Griffiths, R. R. (2023). Single-dose psilocybin treatment for major depressive disorder: A randomized clinical trial. *JAMA*, *330*(9), 843-853.

Read, J. & Bentall, R. (2010). The effectiveness of electroconvulsive therapy: a literature review. *Epidemiology and Psychiatric Sciences*, *19*(4), 333-347.

Reiche, S., Hermle, L., Gutwinski, S., Jungaberle, H., Gasser, P., & Majić, T. (2018). Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review. *Progress in Neuro-psychopharmacology and Biological Psychiatry*, *81*, 1– 10.

Roseman, L., Haijen, E., Idialu-Ikato, K., Kaelen, M., Watts, R., & Carhart-Harris, R. (2019). Emotional breakthrough and psychedelics: validation of the emotional breakthrough inventory. *Journal of psychopharmacology*, *33*(9), 1076-1087.

Ross, S., Bossis, A., Guss, J., Agin- Liebes, G., Malone, T., Cohen, B., Mennenga, S.E., Belser, A., Kalliontzi, K., Babb, J. & Su, Z. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life- threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology*, *30*(12), 1165– 1180.

Ruck, C.A., R. G. Wasson, Bigwood, J., Ott, J. & Staples, D. (1979). Entheogens. *Journal of Psychedelic Drugs*, *11*(1- 2), 145– 146.

Sanches, R.F., de Lima Osório, F., Dos Santos, R.G., Macedo, L.R., Maia- de- Oliveira, J.P., Wichert- Ana, L., de Araujo, D.B., Riba, J., Crippa, J.A.S. & Hallak, J.E. (2016). Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: A SPECT study. *Journal of Clinical Psychopharmacology*, *36*(1), 77– 81.

Sessa, B. (2008). Is it time to revisit the role of psychedelic drugs in enhancing human creativity? *Journal of Psychopharmacology*, *22*(8), 821– 827.

Seth, A. K. (2013). Interoceptive inference, emotion, and the embodied self. *Trends in Cognitive Sciences*, *17*(11), 565-573.

Siegel, J. S., Daily, J. E., Perry, D. A., & Nicol, G. E. (2023). Psychedelic drug legislative reform and legalization in the US. *JAMA psychiatry*, *80*(1), 77-83.

Singh, A. & Kar, S.K. (2017). How electroconvulsive therapy works?: understanding the neurobiological mechanisms. *Clinical Psychopharmacology and Neuroscience*, *15*(3), 210.

Stace, W.T. (1960). *Mysticism and philosophy*. Reprint, Jeremy P. Tarcher.

Stein, D. J. (2012). *Philosophy of psychopharmacology*. Cambridge University Press.

Strassman, R. J. (1984). Adverse reactions to psychedelic drugs. A review of the literature. *The Journal of nervous and mental disease*, *172*(10), 577-595.

Strassman, R. (2001). *DMT: The spirit molecule: A doctor's revolutionary research into the biology of near-death and mystical experiences*. Simon and Schuster.

Smythies, J.R. (1953). The mescaline phenomena. *The British Journal for the Philosophy of Science, 3*(12), 339-347.

Timmermann, C., Kettner, H., Letheby, C., Roseman, L., Rosas, F. E., & Carhart-Harris, R. L. (2021). Psychedelics alter metaphysical beliefs. *Scientific Reports*, *11*(1), 22166.

Vollenweider, F.X., Leenders, K.L., Scharfetter, C., Maguire, P., Stadelmann, O. & Angst, J. (1997). Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology*, *16*(5), 357-372.

Vollenweider, F. X., & Geyer, M. A. (2001). A systems model of altered consciousness: integrating natural and drug-induced psychoses. *Brain research bulletin*, *56*(5), 495-507.

West, R., Raw, M., McNeill, A., Stead, L., Aveyard, P., Bitton, J., Stapleton, J., McRobbie, H., Pokhrel, S., Lester-George, A. & Borland, R. (2015). Health-care interventions to promote and assist tobacco cessation: A review of efficacy, effectiveness and affordability for use in national guideline development. *Addiction*, *110*(9), 1388– 1403.

Watts, A.W. (1960). The new alchemy. In *This is It, and Other Essays on Zen and Spiritual Experience*, 127–153. Pantheon.

Yaden, D. B., & Griffiths, R. R. (2020). The subjective effects of psychedelics are necessary for their enduring therapeutic effects. *ACS Pharmacology & Translational Science*, *4*(2), 568-572.