Psychedelic Psychiatry's Brave New World

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After a legally mandated, decades-long global arrest of research on psychedelic drugs, investigation of psychedelics in the context of psychiatric disorders is yielding exciting results. Outcomes of neuroscience and clinical research into 5-Hydroxytryptamine 2A (5-HT2A) receptor agonists, such as psilocybin, show promise for addressing a range of serious disorders, including depression and addiction.

Introduction—Why the Psychedelic Revolution in Psychiatry?

Research leading to the discovery of new pharmacological treatments for psychiatric disorders has been painfully slow. With a few exceptions, including the use of orexin antagonists for insomnia, current medicines are derivatives of drugs discovered in the 1950s through serendipity and refined through pharmacological modifications. For these reasons, most major pharmaceutical companies have retreated from researching brain targets, threatening to halt a progression in research knowledge and possibly inducing the same sort of dark age that antibiotic research has found itself in.

One way out is to revisit drugs that were once used but fell out of use because of political machinations, especially the war on drugs (Nutt, 2015). Cannabis was the first to be resurrected and the glutamate receptor antagonist anesthetic ketamine has recently been shown to have antidepressant properties, leading to the enantiomer esketamine becoming licensed in the USA and Europe. Now, serotonergic psychedelics, particularly psilocybin (the active compound in "magic mushrooms") are being resurrected as potential treatments for a range of different psychiatric disorders (Rucker et al., 2018). These drugs include LSD, ayahuasca (a drink that contains dimethyltryptamine [DMT] and a monoamine oxidase inhibitor that prevents its breakdown in the gut), as well as 5-MeO-DMT (from the Sonora toad) and mescaline (from the peyote cactus). In the 1950s and 1960s, LSD was widely researched and was considered to achieve major breakthrough treatments by many psychiatrists. At the same time, psilocybin was an experimental medicine supplied by Sandoz as "Indocybin". However, once LSD became used recreationally by young people, it was banned and most other psychedelics were sucked into the legislation; research on their potential therapeutic efficacy ground to a halt. In the past decade, research on these compounds has been re-established by a few groups around the world, culminating in new centers for psychedelic research at Imperial College London and Johns Hopkins University.

Because psilocybin is a Schedule 1 controlled drug, meaning that it has been defined as having high potential for abuse with limited therapeutic utility, it took several years of battling with regulators and ethics committees to gain permission to do clinical research with it, but the struggle was worth it. Its effects on patients suffering from depression were remarkable—e.g., two experiences with psilocybin improved depression scores for weeks, and in some people, years (Carhart-Harris et al., 2018), positioning it as one of the most powerful therapeutics for treatment-resistant depression. There have also been three placebo-controlled trials of psilocybin for anxiety and depression related to end-of-life diagnoses (reviewed in Rucker et al., 2018). Based on this body of positive findings, at least two companies have been set up to take psilocybin to the clinic, funding multi-center dose-finding studies of psilocybin in depression (U.S. National Library of Medicine, 2020a; 2020b). In parallel, we will soon be completing a double-blind trial of psilocybin versus the selective serotonin reuptake inhibitor (SSRI) escitalopram in depression (U.S. National Library of Medicine, 2020c). There have also been studies showing efficacy in alcoholism and tobacco dependence (Rucker et al., 2018), and similar studies in anorexia, obsessive-compulsive disorder (OCD), chronic pain, and opioid use disorder are being developed.

This might seem a strange and disparate set of disorders for a single medicine to work in, and this speaks to the innovative nature of psychedelic therapy. In most studies, the psychedelic is given just once (though in a few studies, twice or three times over a period of weeks) as part of an ongoing psychotherapy course, in complete contrast to currently available medications, which are given at least daily, often with little therapeutic support. We suggest one way of looking at the difference between them is that current medicines suppress symptoms in a similar way that insulin suppresses hyperglycemia in diabetes. Standard antidepressants protect against the stressors that lead to and perpetuate depression, but don't directly access and remedy underlying biopsychosocial causes. In contrast, psychedelic therapy harnesses a therapeutic window opened up by the brain via the effects of the drugs to facilitate insight and emotional release and, with psychotherapeutic support, a subsequent healthy revision of outlook and lifestyle (Carhart-Harris and Nutt, 2017).

Arguably all of the conditions in which psychedelics have been shown to work share the common feature of being internalizing disorders. In depression, patients continually ruminate about their failings, reiterate thoughts of guilt, and engage in self-critical inner narratives. In addictions, the object of addiction takes on the role

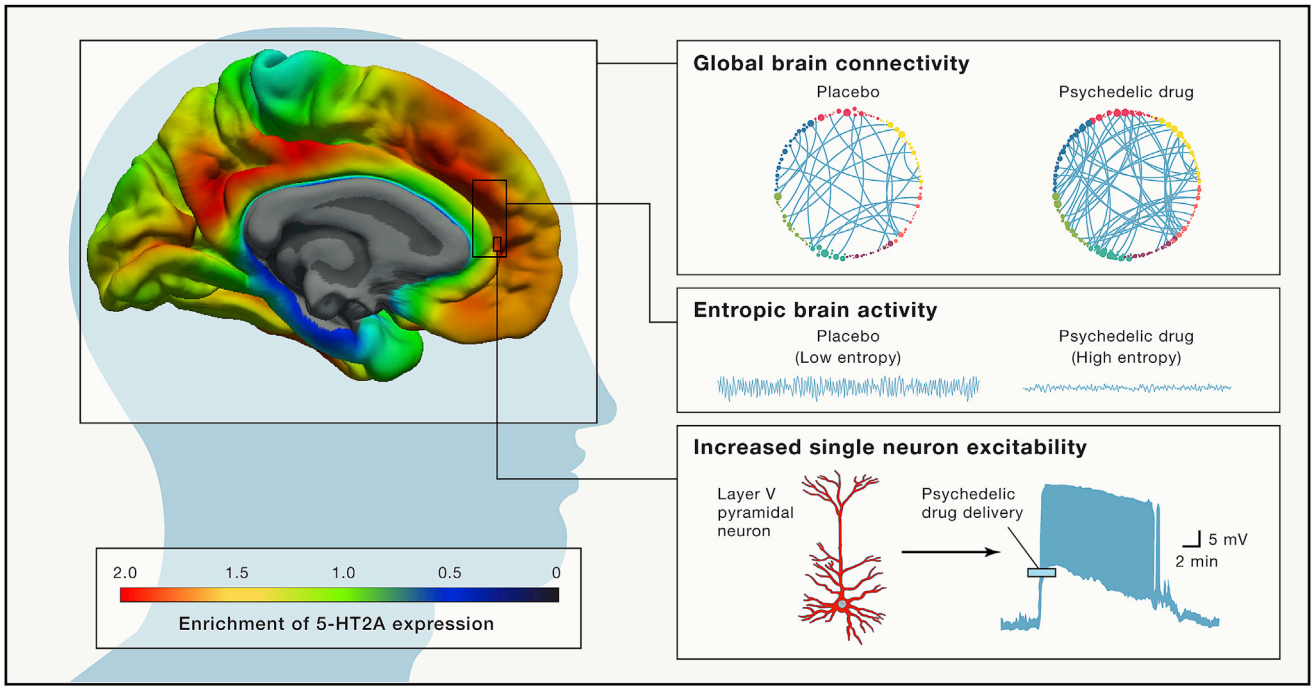

Figure 1. The Three Levels of Activity of Psilocybin

Psilocybin, along with other serotoninergic psychedelics, acts to stimulate 5-HT2A receptors in the cortex, particularly layer 5 pyramidal cells. This leads to massive depolarization and thence rapid repeated firing of these neurons (lower inset). Because these neurons are responsible for organizing cross-cortical integration, this activity results in a profound alteration of cortical signaling. Both magnetoencephalography and electroencephalography measures reveal a major loss of typical rhythmical activity, resulting in a state of extreme desynchronization or enhanced entropy (middle inset). Also, these layer 5 neurons mediate the "top down" perceptual and cognitive predictions (so called "priors"), which form the basis of normal brain processing. Thus, under psychedelics the brain "escapes" from its usual tightly constrained and predictable ways of working; this leads to a global increase in connectivity (top inset) that allows new insights into past behavior, memories, actions, feelings, and beliefs. These in turn can lead to therapeutic changes in conditions such as depression and addiction, which are driven by dysfunctional brain processing. Average density map for 5-HT2A receptor adapted from Beliveau et al. (2017).

of negative thinking in depression, driving behavior that is specific, narrow, and rigid; addicts ruminate on relief afforded by the object, how to get it, how to pay for it, etc. The rationale for using psychedelics in OCD and anorexia is consistent given that there is rumination on intrusive thoughts, e.g., about contamination or calorie mismanagement. Psychedelics likely work by dysregulating activity in systems and circuits that encode these habits of thought and behavior (Carhart-Harris and Friston, 2019), allowing them to recalibrate as the acute effects of the drugs subside. Despite this potential for efficacy across a range of disorders and the initial promising results, many questions remain.

Is 5-HT2A Stimulation the Therapeutic Mechanism of Action?

The defining action of classic serotonergic psychedelics is mediated primarily through agonism of the 5-Hydroxytryptamine 2A (5-HT2A) receptor (Figure 1). This is exemplified by recent positron emission tomography research, showing that the psychedelic effects of psilocybin in humans are predicted by the degree of occupancy of the 5-HT2A receptor revealed by displacement of the agonist tracer [11C]Cimbi-36 (Madsen et al., 2019). Moreover, 5-HT2A receptor antagonists such as ketanserin block psychedelic effects (Preller et al., 2017). The 5-HT2A receptor is maximally expressed in the cerebral cortex, and because humans have considerably more cortex than other species, they logically have the highest expression. These receptors show some regional heterogeneity in the cortex, being relatively sparse in the sensorimotor cortex, and especially dense in visual and association cortices—with high expression also noted in the claustrum *in vitro*.

5-HT2A receptors are localized on the cell bodies and apical dendrites of large pyramidal neurons concentrated in layer V of the cortex. There are also found, albeit to a lesser degree, on GABAergic interneurons that regulate pyramidal cell firing (Andrade, 2011). Activation of 5-HT2A receptors appears to increase the excitability of the host neuron, causing a spike to wave decoherence and associated dysregulation of spontaneous activity in cortical populations. This dysregulation reliably manifests as increased entropy in on-going activity recorded via local field or scalp potentials, as well as related changes in the power spectrum, e.g., marked decreases in alpha oscillations. A number of aspects of cortical functioning associated with predictive processing appear to be dysregulated under psychedelics, including the following: functioning of layer V pyramidal neurons; the strength of alpha oscillations; the strength of backward traveling waves; and the integrity, segregation, and hierarchical organization of intrinsic networks. This is consistent with our current hypothesis that the main functional effect of psychedelics is to relax the precision weighting of the predictive models encoded in the brain (Carhart-Harris and Friston,

2019). An earlier model takes a different view: that psychedelics disrupt the normal gating of sensory inputs via the thalamus (Vollenweider and Geyer, 2001), and this leads to altered perceptions. However, given a low density of 5-HT2A receptors in the thalamus, it might be that thalamic effects are driven by psychedelics disrupting cortical activity that projects to the thalamus, so the two theories might not be so different.

The therapeutic benefit we theorize is also mediated via this receptor, but as yet, this has not been established in humans—because to do this would require a trial in which a 5-HT2A receptor antagonist is given before the psychedelic to see whether this blocks its therapeutic effects.

Would Shorter-Acting Psychedelic Drugs Work?

Different psychedelics have very different durations of action. LSD and mescaline are two of the longer lasting (8–14 h), whereas the effects of DMT and 5-MeO-DMT are much shorter, with effects lasting less than 30 min from either a smoked or injected dose, although DMT consumed in ayahuasca will work for about 2–3 h. Psilocybin acts for about 4–5 h after oral ingestion. The oral route is generally considered the most appealing for therapeutic work because the resulting "trip" allows the patient to enter into the psychedelic state with plenty of time for them to explore personal material and potentially experience therapeutic breakthrough (Roseman et al., 2018b). It is theoretically possible, however, that a short trip, such as with i.v. DMT, might "shake-up" and "reset" abnormal patterns of brain activity and so could have some therapeutic benefit. It seems likely that this idea will soon be tested, and if it works, it could significantly reduce the costs of psychedelic therapy by saving on therapist time.

Are the Psychedelic Effects Necessary?

The extensive use of microdosing psychedelics to putatively improve wellbeing and creativity (Kuypers et al., 2019) raises the question of whether a full psychedelic experience is needed. Microdosing involves taking—usually on a regular basis, e.g., 3 times a week—a low dose of a psychedelic that is devoid of subjective psychoactive effects. As yet there have been no trials of microdosing for any psychiatric disorder, and it seems improbable that a single microdose of psilocybin would have as big an effect in depression as the 25 mg psilocybin "macrodose" usually used. Growing evidence suggests the best outcomes from psilocybin are in patients experiencing the most powerful psychedelic effects, variously called breakthrough, peak, or mystical experiences (Roseman et al., 2018b). Additional insight on this question might come from the COMPASS Pathways study (U.S. National Library of Medicine, 2020a), where patients are randomized to either a 1 mg (i.e., a microdose) or to a 10 mg or 25 mg dose (which do have psychedelic effects). The prediction is that the 25 mg dose will be more effective than the 10 mg dose and the 1 mg (microdose) will be ineffective, but the outcomes remain to be seen.

Why Are the Effects So Enduring?

Both the depression and tobacco smoking trials have shown that, in some people, psilocybin can produce clinical remission, in some cases persisting for years. Similar findings are described in the older psychedelic literature, where enduring positive psychological changes were commonly reported. So how does this happen? For now, this question is easier to address from the perspective of psychology, where the key might be how psychedelics relax limiting beliefs and, in parallel, promote insight and an emotional release that can motivate the revision of these beliefs. Indeed, in our depression trial, insight and emotional breakthrough were significant predictors of the longer-term changes (Roseman et al., 2018b). More work is needed to address how insight and emotional release registers in terms of altered brain functioning and anatomy, but several pre-clinical studies have shown that psychedelics promote neural plasticity in key circuits relevant to treating neuropsychiatric disorders, e.g., Ly et al. (2018).

How Much Is "Just Pharmacology"?

Currently, psilocybin therapy for psychiatric disorders is given within a structured psychotherapeutic setting with a considerable therapist input. There is always a preparatory session before drug administration. There are always one, and in some studies two, therapists present during the psychedelic session—which lasts up to 6 h. The next day, and beyond, there are further integration sessions with the same therapists to help patients talk through and thereby "ground" their experiences. This amount of therapist exposure has significant cost implications and therefore naturally leads to the question—is the psychotherapy really necessary? Would just giving the drug alone produce the same clinical benefits? To some extent, this is a false dichotomy, because any effect on the brain is, by implication, an effect on the mind and vice versa, and so the question is more whether there can be an action on the brain and long-term therapeutic effect, without a noticeable mediating subjective experience. A question like this could be addressed either via sub-perceptual microdosing or via giving the psychedelic during sleep or under anesthesia.

Although ethically challenging to implement, giving individuals a psychedelic under anesthesia and assessing its subsequent effect on a mental-health-relevant outcome might help resolve debate about the importance of the psychological components of psychedelic therapy, as well as the imperfection of current blinding procedures. Ours' and others' data do suggest that there is a positive interaction between the neuroplastic effects of 5-HT2A receptor agonism and what is done with that plasticity (Roseman et al., 2018b). Indeed, part of the core drug action seems to be to make people exceptionally sensitive to what lies beyond their (ego) boundaries, whether this be material percolating up from their inner world, e.g., in terms of emotions and memories, or coming into the brain from the outer world, e.g., in terms of the therapist(s) present and music heard.

What Are the Brain Mechanisms through Which Psychedelics Remedy Psychiatry Disorders?

There is great current interest from both neuroscience and clinical perspectives in understanding how psychedelics remedy psychiatry disorders. Knowing "the answer" would not only help reassure sceptics that psychedelics are more than just a powerful placebo but would also help maximize their therapeutic benefit—particularly in directing interventional processes to maintain wellness.

Table 1. A Brief Summary of the Many Factors that Together Make the Case for Psychedelic Research in Psychiatry

Supporting points	Supporting references
Massive mental health burden, Limited breakthrough treatments, Industry pull-out from psychiatry	Carhart-Harris and Friston (2019) Carhart-Harris and Nutt (2017) Rucker et al. (2018)
Growing evidence of safety & efficacy for psychedelics	Carhart-Harris et al. (2018) Carhart-Harris and Nutt (2017) Rucker et al. (2018)
Limited abuse potential (e.g. not addictive)	Nutt (2015)
Novel action	Carhart-Harris and Friston (2019) Carhart-Harris and Nutt (2017)
Rapid action. Enduring action. Transdiagnostic action	Carhart-Harris et al. (2018) Rucker et al. (2018)
New, plausible multi-level models of action	Andrade (2011) Barrett et al. (2020) Carhart-Harris and Friston (2019) Roseman et al. (2018a) Vollenweider and Geyer (2001)
Bridges psychotherapy and pharmacology	Carhart-Harris et al. (2018)
New level of institutional support (new research centres)	Imperial College London and John Hopkins
Area attracting venture investment	COMPASS Pathways, Usona
Long heritage of medicinal use (unlike modern medicines)	Nutt (2015) Rucker et al. (2018)

This is the prime need right now because, despite the impressive immediate effects of psilocybin on depression, about half of patients relapse within 6 months. Why this is is presently unknown, but it supports the idea that, in some people, depression can become a persistent, intractable, problem that might influence thinking processes forever. In others, it might be a defense against a traumatic event or loss that psychedelics uncover and help the patient process and move on from. More work is needed to test our assumption that the most severe presentations might require more than just a single-dose treatment.

As described above, the 5-HT2A receptor is likely the key molecular mediator of cases of major psychological change. This receptor seems to have a low level of basal activity in normal brain states because its complete blockade with 5-HT2A antagonists has almost no effect on daytime mind and brain functioning. Interestingly 5-HT2A antagonists do enhance deep (stages 3–4) sleep (Idzikowski et al., 1987), a state of heightened brain synchronicity, the exact opposite of the entropic brain state seen with psychedelics (Carhart-Harris and Friston, 2019). We suggest that in states of extreme stress, when novel behavioral responses are vital, the 5-HT2A system might be activated to provide solutions to the crisis and also help lay down new, more adaptive behavioral and cognitive patterns (Carhart-Harris and Nutt, 2017). The "resetting" of normal functioning in intrinsic brain networks, like the default-mode network, might be related to this adaptive mechanism (Carhart-Harris et al., 2017).

When thinking in terms of brain regions and circuits underpinning clinical responses, a lot of work in recent years has focused on the role of the amygdala in unconscious threat processing, as well as prefrontal control of this. Amygdala response to threat cues (e.g., a fearful face) measured with fMRI is significantly increased in depressed people. A range of different drug treatments for depression have been shown to suppress this hyperresponsivity and this has become a prime theory for how these medicines work. Recently, psilocybin has been shown to do something similar in healthy volunteers 1 week after psilocybin (Barrett et al., 2020), but an opposite effect was seen in treatment-resistant patients (TRDs) 1 day after psilocybin therapy (Roseman et al., 2018a), which potentially implies a complex, non-linear process of change. We also found evidence of decreased "resting-state" blood flow in the temporal cortex, which contains the amygdala, 1 day after psilocybin for TRDs that was predictive of positive outcomes (Carhart-Harris et al., 2017). Our current trial of psilocybin versus the SSRIs escitalopram in major depressive disorder (U.S. National Library of Medicine, 2020c) aims to more comprehensively address this matter after a standard treatment with each.

Protecting Research

Major hurdles facing research with psychedelics include the burden that their Schedule 1 status incurs and a lack of mainstream funding, and we suspect these things are related. The Schedule 1 status of psychedelics led to vastly increased regulations on research, associated costs, and damaging stigma that likely deterred governmental agencies, other reputable funding bodies, and companies from backing the relevant research. Before LSD was banned, the US NIH funded over 130 studies exploring its clinical utility; however, since the ban, it has funded none and until a few years ago, no company was committed to manufacturing medical grade psychedelics and thus procurement of the required drugs for clinical trials was almost impossible (Nutt, 2015).

Nowadays, both COMPASS Pathways and Usona are making psilocybin at scale with others starting. Natural plant-based products such as ayahuasca, peyote, and magic mushrooms are now legal in some South American countries and are becoming decriminalized in a few US cities. Moreover, magic mushrooms could be legalized in the US state of Oregon later this year. Magic truffles, which contain the same active compound, are legal in the Netherlands, and this loophole, combined with a growing interest in the therapeutic potential of psilocybin, has led to fast-growing industry in Dutch truffle retreats. Some finance journalists have begun predicting a "shroom boom" to rival the "green rush" seen with medicinal cannabis (Raphael, 2018). This escalating recreational use presents an opportunity to collect "Big Data" for educational and harm-reduction purposes, and we have set-up an online

platform for doing this, called psychedelicsurvey.com.

It is possible to make new 5-HT2A receptor agonist ligands that would, at the time of synthesis, be outside national or UN Conventions. However, based on recent examples, the risk of them becoming restricted would be very high. In the UK, the ultra-restrictive 2016 Psychoactive Substances Act makes all novel psychoactive compounds illegal, and some of the newer 5-HT2A receptor agonists (e.g., the NBOMeS) have been found to be more toxic than the older ones, a situation similar to that seen with the growth of legal but more harmful synthetic cannabinoids.

Overall, it seems the best way forward to fostering research and therapeutic application is to press for a rescheduling of psychedelics with proven therapeutic utility, especially psilocybin. That psilocybin was made Schedule 1 (i.e., having no medical value) on the shirt-tails of politically motivated banning of LSD has had an immense negative effect on treatment and research (Nutt, 2015). A campaign to re-schedule psilocybin is now underway in the UK, led by the charity DrugScience.org.uk and has international, scientific support.

Summary

The resurrection of research into the neuroscience and therapeutic application of psychedelics represents one of the most important initiatives in psychiatry and brain science in recent decades. It rectifies decades of global research paralysis that emerged as collateral damage from the war on drugs and that has become one of the worst examples of censorship of human research in the history of science. The past ten years have seen the first green shoots of recovery with a number of teams across several continents beginning human neuroimaging and clinical trials that have delivered remarkable insights into brain function and instigated an exciting new approach to the treatment of a range of psychiatric disorders (Table 1). What is now needed is a combined, multi-level, multidisciplinary program of research into the mechanisms underpinning these findings.

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