Psychedelics as Medicines: An emerging new paradigm

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75 References
3 Figures

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Abstract

Scientific interest in serotonergic psychedelics (e.g., psilocybin and LSD; 5-HT_{2A} receptor agonists) has dramatically increased within the last decade. Clinical studies administering psychedelics with psychotherapy have shown preliminary evidence of robust efficacy in treating anxiety and depression, as well as addiction to tobacco and alcohol. Moreover, recent research has suggested that these compounds have potential efficacy against inflammatory diseases through novel mechanisms, with potential advantages over existing anti-inflammatory agents. We propose that psychedelics exert therapeutic effects for psychiatric disorders by acutely destabilizing local brain network hubs and global network connectivity via amplification of neuronal avalanches, providing the occasion for brain network "resetting" after acute effects have resolved. Anti-inflammatory effects may hold promise for efficacy in treatment of inflammation-related non-psychiatric as well as potentially for psychiatric disorders. Serotonergic psychedelics operate through unique mechanisms that show promising effects for a variety of intractable, debilitating, and lethal disorders, and should be rigorously researched.

Introduction

Following the passage of the controlled substances act of 1970, clinical research with psychedelic agents essentially ended. Now, after a hiatus of more than two decades, a number of recent clinical studies have employed psychedelics in conjunction with psychotherapy, leading to surprising but apparent robust therapeutic efficacy in treating anxiety and depression, as well as addiction to nicotine and alcohol. This paper will review recent developments, and propose that psychiatry and the treatment of other somatic disorders may be approaching a paradigm shift, given persisting efficacy resulting from only one or a few administrations. Earlier anecdotal reports and uncontrolled studies will not be discussed here, but we refer the reader to a recent comprehensive review.[1]

Anxiety and Depression

One indication under early investigation was treatment of psychosocial distress in dying cancer patients with LSD.[2-4] About two-thirds of cancer patients given LSD had improved mood and reduced anxiety and fear of death. More recently, Grob et al.[5] administered 0.2 mg/kg oral psilocybin versus niacin placebo to 12 patients with advanced-stage cancer having a diagnosis of anxiety related to their cancer. Psilocybin is a small molecular weight compound that occurs in nature. A variety of mushrooms from multiple genera, including the genus *Psilocybe*, produce psilocybin. Figure 1 shows an example of *Psilocybe cubensis*. The study observed no clinically significant adverse events, consistent with earlier trials. With the small sample size, they reported nonsignificant trends for benefits of psilocybin compared with niacin placebo on measures of depression and anxiety. Compared with pretreatment baseline, however, the patients' Spielberger State-Trait Anxiety Inventory (STAI) trait anxiety subscale scores revealed a significant reduction in anxiety at one and three months after treatment. Similarly, the patients'

Beck Depression Inventory (BDI) scores showed an improvement of mood that reached significance at six months compared with baseline.

Figure 1 about here

More recently, Carhart-Harris et al.[6] published the results of an open-label feasibility trial of 12 patients with moderate-to-severe, unipolar, *treatment-resistant* major depression. Subjects received two oral doses of psilocybin (10 mg and 25 mg, seven days apart) in a supportive setting. The study assessed depressive symptoms from one week to three months after treatment, with the 16-item Quick Inventory of Depressive Symptoms (QIDS) serving as the primary efficacy outcome. Because of the lack of a control group in this study, readers should use caution in the interpretation of the results.

QIDS depression scores significantly decreased from baseline at one week and three months post-treatment, with the maximum effect at two weeks. BDI and clinician-administered ratings confirmed these results. All patients showed some reduction in depression severity at one week that was sustained in the majority for three months. According to standard criteria for determining remission (i.e. a BDI score of ≤9), eight (67%) of the 12 patients achieved complete remission at one week, and seven patients (58%) continued to meet criteria for response (50% reduction in BDI score relative to baseline) at three months, with five of them (42%) still in complete remission. STAI-T anxiety and SHAPS anhedonia scores also significantly decreased at one week and three months post-treatment from baseline.

We are aware of two larger randomized placebo-controlled studies recently completed by groups at Johns Hopkins University (JHU), directed by Roland Griffiths and one of the present authors (MWJ),[7] and at New York University (NYU), directed by Stephen Ross.[8] The results of these two studies are in press. Unlike the Carhart-Harris and Grob studies, they are reasonably

large, well-powered phase 2 trials of psilocybin-assisted psychotherapy in patients suffering from cancer-related psychosocial distress (CRPD). These two studies represent the first sufficiently powered, formal double-blind, placebo-controlled assessment of a psychedelic agent for therapeutic effect using modern clinical approaches and assessment instruments. Neither study observed significant adverse events. Both of these studies found remarkable efficacy that is unprecedented for CRPD with any currently available conventional therapies.

The JHU study[7] employed a two-session, double-blind, crossover design to investigate the effects of a high oral psilocybin dose (22 or 30 mg/70 kg; equivalent to ~0.31 and ~0.43 mg/kg, respectively) with a low dose (1 or 3 mg/70 kg; equivalent to ~0.014 and ~0.043 mg/kg, respectively), on outcome measures relevant to anxiety or depressive disorders caused or exacerbated by the cancer diagnosis. Therapeutically relevant outcome measures showing sustained effects at six months included the Hamilton Anxiety Rating Scale (HAM-A), the STAI, the Hamilton Depression Rating Scale (HAM-D), and the BDI. Consistent with persisting positive effects previously observed in healthy volunteers,[9] the immediate post-session mystical experience score showed a significant correlation with therapeutic efficacy. The definition of mystical experience is a subjective experience involving substantial participant endorsement of the following categories: internal unity, external unity, noetic quality, sacredness, positive mood, transcendence of time and space, and ineffability.[10] The study showed that a single psilocybin dose, given under supportive conditions to screened and prepared participants, produced substantial and enduring decreases in anxiety and depression in patients with a life-threatening cancer diagnosis.

The NYU study[8] used a therapeutic approach and clinical setting that were similar to the one employed in the JHU study, the chief difference being the use of niacin as the active placebo

control instead of low-dose psilocybin. Again, the study documented dramatic symptom reductions, with large effect sizes comparable to the JHU study, and efficacy sustained to six months after treatment. As with the JHU study, the authors safely administered a single moderate psilocybin dose (21 mg/70 kg) in conjunction with psychotherapy to a cohort of patients with life-threatening cancer, and observed acute and sustained anxiolytic and antidepressant effects. Here too, the intensity of the subjective mystical experience correlated with clinical benefit, including improved attitudes toward disease progression and death, improved quality of life, and increased spiritual well-being.

Similarly, Gasser et al.[11] employed LSD-assisted therapy in 12 patients with anxiety related to a diagnosis of life-threatening diseases. Patients received either 200 μg LSD (free base) or a 20 μg active placebo dose of LSD with an open-label crossover to 200 μg LSD after unblinding. There were no serious adverse effects associated with the treatment. Positive trends found using the STAI persisted for 12 months after treatment. Subsequently, Gasser et al.[12] followed up the same participants 12 months later to examine long-term effects on anxiety and explore subjective experiences and lasting psychologic effects. Nine of the original subjects participated. Gasser et al.[12] found that the STAI state and trait scores did not increase after the end of the study. In semi-structured interviews, seven of nine participants reported a sustained reduction in anxiety. None of the participants reported lasting negative effects. The authors concluded that LSD-assisted psychotherapy in patients with life threatening illness demonstrated safety and positive stable treatment outcomes at long-term follow-up.

Recently, in an open-label clinical trial in patients suffering from depression, ayahuasca, a South American plant decoction that contains the hallucinogenic compound *N*,*N*-

dimethyltryptamine (DMT), produced marked improvement in depressive symptoms with no mania or hypomania for up to 21 days after a single dose.[13]

Obsessive-Compulsive Disorder

Anecdotal reports led Moreno et al.[14] to study the effect of oral psilocybin (25, 100, 200, and 300 μg/kg at one week intervals) in obsessive compulsive disorder (OCD) patients in a proof-of-concept pilot study. All nine participants experienced marked symptom reduction during one or more sessions (23%–100% reduction in the Yale-Brown Obsessive Compulsive Scale score), and most experienced relief beyond the expected psilocybin pharmacological life, and beyond the 24-hour assessment. One participant showed long-term remission at six-month follow-up. However, readers should interpret these results cautiously; the fact that the study showed a similar magnitude of symptom reduction at all dose conditions, including the trivial dose intended to serve as an active placebo, suggests that the placebo effect might have accounted for results. Alternatively, psilocybin might have been remarkably effective even at the trivial dose. Results should be followed up with a study that includes a true placebo or a non-psilocybin active comparator.

Addiction

An early focus of psychedelic research from the 1950s to early 1970s was addiction. In the 1950s researchers in Saskatchewan, Canada led by Humphry Osmond and Abram Hoffer were the first to study addiction treatment with psychedelics, specifically using LSD and mescaline to treat alcoholism.[15] Guided by the observation that alcoholics tended to achieve sobriety after experiencing delirium tremens (a toxic and sometimes fatal syndrome prompted by alcohol withdrawal), these researchers initially hypothesized that psychedelics, which were physiologically safe but considered to model psychosis, might prompt a safer delirium that

would occasion sobriety without the fatal risks of delirium tremens. Rather than delirium, however, the researchers observed insightful "mind manifesting" effects (prompting advent of the term "psychedelic," and describing effects that are related to the "mystical" effects mentioned earlier) that prompted sobriety.[16] Although this initial research and some subsequent studies did not involve randomized comparison to a control condition, the research reported promising success. Researchers conducted subsequent randomized trials, with several studies showing non-significant trends favoring improved outcomes for LSD. However, a meta-analysis of six studies involving 325 total participants randomized to LSD (dose ranging from ~210 to 800 μg) or a control condition showed significant decreases in alcohol misuse in the LSD groups compared to control groups, e.g. odds ratio ≈2 at the initial follow-up at least one month post-treatment.[17] In addition to these early alcoholism studies, one study examined whether LSD reduced drug use in the context of opioid addiction. This residential study of heroin-addicted individuals found significantly lower biologically confirmed heroin use in the LSD group (receiving 300–450 μg) compared to the control group at all time frames examined up to 12 months post-treatment.[18] Twelve-month continuous abstinence rates were 25% vs. 5% in the LSD and control groups, respectively. The promising results from both the opioid and alcoholic populations suggest the exciting possibility that psychedelic treatment might be broadly applicable to psychological and/or biological processes in common across addictions, in contrast to typical addictions medications that target specific drug classes by acting at the primary receptor mediating drug effects (e.g., methadone for opioid addiction; nicotine replacement for tobacco addiction).

More recent studies have followed-up on these early promising results. The first modern laboratory study examining a serotonergic psychedelic for addiction was an open-label pilot

study that employed psilocybin with manualized cognitive behavioral therapy in 15 treatment-resistant tobacco/nicotine dependent smokers, conducted by one of the present authors and colleagues.[19] After four preparatory meetings involving cognitive behavioral therapy for smoking cessation and specific preparation for psilocybin, participants took 20 mg/70 kg psilocybin on the participant's target quit date. Participants received a second and third psilocybin session at two and (optionally) eight weeks post-target quit date. The default dose increased to 30 mg/70 kg in these subsequent sessions although the dose could be maintained at 20 mg/70 kg based on initial session response. Researchers conducted weekly cognitive behavior therapy sessions until 10 weeks post-target quit date. Breath carbon monoxide and urine cotinine results showed abstinence in 12 of 15 participants (80%) at six months post-target quit date. Those who were smoke-free at six months scored significantly higher on a measure of psilocybin-occasioned mystical experience compared to those who had relapsed.[20]

A recent follow-up report of that pilot study showed biologically-confirmed smoking abstinence in 10 of 15 participants (67%) at 12-months post-target quit date.[21] The longest-term follow up, which occurred at a mean of 2.5 years post-target quit date, showed biologically-confirmed abstinence in nine participants (60%). Although the causal role of psilocybin is not conclusive, these results were promising because of the typical low success rate for smoking cessation, which is ~35% at six months for the most effective FDA-approved medication, varenicline. These initial results are currently being followed up by a randomized comparative efficacy study in which participants are assigned to either a psilocybin or nicotine patch group, both with the same cognitive behavioral therapy. The study is also examining fMRI (including RSFC, cue reactivity, and executive function tasks) both before and after psilocybin treatment to identify mechanistic correlates of success.

Following up on early promising alcoholism studies with LSD, as reviewed in the aforementioned meta-analysis of LSD in the treatment of alcoholism,[17] a recent open label pilot study has examined psilocybin in the treatment of 10 participants with a diagnosis of alcohol dependence.[22] Like the tobacco pilot study, treatment involved manualized psychosocial therapy; in this case, a 12-week program of motivational enhancement therapy. After four preparatory sessions participants received 0.3 mg/kg oral psilocybin. Four weeks later they received 0.4 mg/kg by default, with the option to remain at 0.3 mg/kg, depending on earlier response. The study required participants to be abstinent from alcohol for 24 hours before both sessions. Four additional non-drug sessions occurred between the two psilocybin sessions, and an additional four occurred after the last psilocybin session. Compared to pre-psilocybin baseline, self-reported alcohol use decreased significantly following the first psilocybin administration. Mean self-reported alcohol use at 36-week follow-up remained lower than at baseline (>40% of days involving drinking at baseline to <20% of days involving drinking at follow up). Self-reported drug intensity and a measure of mystical experience in regard to the first psilocybin session were positively and significantly correlated with alcohol reductions. The researchers are conducting a larger double-blind study comparing psilocybin to an active placebo, both with motivational enhancement therapy. Like the tobacco trial, fMRI is being conducted before and after treatment to examine correlates of efficacy.

In addition to the carefully controlled laboratory studies described above, recent observational or survey studies have documented purported reductions in the use of alcohol and other drugs, or reductions in addiction severity, resulting from the administration of ayahuasca in sacramental non-laboratory contexts.[23]

Limitation

A limitation of psychedelic-assisted therapy for CNS disorders is the fact that because these substances produce such a profound state of altered consciousness, they should not be prescribed for self-monitored use at home; therapy sessions require supervision. Patients must be carefully screened for a history of mental illness, and receive a number of hours of psychotherapy prior to drug administration. The therapy room is comfortably furnished, and two specially trained therapists are present during the sessions. Specific guidelines for the safe use of psychedelics in therapy have been published.[24]

Inflammation

Although researchers have recognized the unique CNS effects of psychedelics for a long time, only recently have they discovered that serotonergic psychedelics also have potential efficacy against inflammatory diseases. Diseases related to inflammatory mechanisms or having inflammation as a major component are leading causes of death, disability, and reduced quality of life around the world and include coronary artery disease, diabetes, asthma, inflammatory bowel disease, and rheumatoid arthritis. Inflammation in the brain has been linked to several psychiatric disorders including depression, addiction, and neurodegenerative disorders such as Parkinson's and Alzheimer's disease.[25,26] A complex immune system that has evolved to protect the host organism from infection mediates inflammation. Scientists generally recognize pathological inflammation resulting in disease states as dysfunction in the immune system, where it has become overactive to the point of damaging the host.

The main participants in the immune response include innate immune cells such as macrophages that are the scavengers of debris and invading microorganisms, and adaptive immune cells derived from bone marrow, including T-helper cells and other lymphocytes, which

recognize foreign invaders and can secrete antibodies. Current therapies fall into three distinct categories. The first comprises non-steroidal anti-inflammatory drugs (NSAIDs) that act by blocking the activity of cyclooxygenase, an enzyme that produces intracellular molecules that help to signal a cell to mount an inflammatory response. The second is represented by steroid drugs like prednisone, which are immunosuppressant. They primarily act to prevent cells from synthesizing pro-inflammatory molecules called cytokines by inhibiting their gene expression. The third class is biologics, which are antibodies or antibody-like molecules that act as sponges to "soak up" proinflammatory cytokines and prevent them from propagating immune signals from one cell to another.

One of us (C.D.N) recently discovered that psychedelics comprise a fourth class of anti-inflammatory drug that acts through activation of the serotonin 5-HT_{2A} receptor. Although not yet in human trials for inflammation, research has shown profound effects in animal models of human inflammatory-related diseases. Scientists have long recognized serotonin as a molecule associated with inflammation, with elevated serotonin levels and an increased number of serotonin receptors in inflamed tissues. In the brain, researchers have linked serotonin to neuroinflammation, and have shown treatment with SSRI antidepressants to be anti-inflammatory.[27] Whether or not increased levels of serotonin and its receptors are causative or reactive has not been established. Depending on the tissue and site of inflammation, studies have found serotonin to have both pro- and anti-inflammatory effects.[28]

Interestingly, the primary protein target for psychedelics, the 5-HT_{2A} receptor, is the most widely expressed serotonin receptor in the mammalian body. Its presence has been detected in nearly every tissue and cell type examined, including all the major types of immune-related cells. It also is found in epithelial and endothelial cells, which serve as the barriers between the

environment and our body and are integral for normal immune responses. Despite the 5-HT_{2A} receptor being the most widely expressed serotonin receptor in the body, nearly all focus on its functions has been its role in the CNS. Only relatively recently have non-CNS and peripheral roles been identified that include cell differentiation and proliferation, vasoconstriction, and immune regulation. Whereas research has associated serotonin itself with proinflammatory mechanisms through the 5-HT_{2A} receptor,[29] research has also demonstrated psychedelics to have profound anti-inflammatory properties mediated by 5-HT_{2A} receptor activation.

The initial study reported that psychedelics, including LSD, potently and selectively prevented inflammation elicited by the master inflammatory cytokine Tumor Necrosis Factor alpha (TNF-α) in smooth muscle cells isolated from rat aorta.[30] Whereas all psychedelics tested from several different structural classes demonstrate anti-inflammatory activity about as potent as steroidal drugs (IC_{50} values between 1-35 nM), the research found one drug (*R*)-DOI to be extraordinarily potent; it had an EC_{50} of 15 *picomolar* in preventing TNF-α mediated inflammation in aortic smooth muscle cells. Interestingly, (*R*)-DOI has little effect on inflammation stimulated by lipopolysaccharide (LPS), indicating that the anti-inflammatory action of 5-HT_{2A} receptor activation is selective for TNF-α mediated inflammation.

Next, systemically administered (*R*)-DOI was examined for its ability to block the effects of systemic TNF-α in mice. Once again, (*R*)-DOI had potent anti-inflammatory effects mediated through activation of 5-HT_{2A} receptors.[31] These effects were particularly potent in vascular and intestinal tissues, with therapeutic levels much lower than those necessary to produce any behavioral effects. We hypothesize that, unlike biologics such as etanercept, which simply act as a sponge to soak up circulating TNF-α, psychedelics initiate anti-inflammatory signaling cascades from the 5-HT_{2A} receptor that directly interfere with communication between activated

TNF-α receptors and their downstream effectors like NFκβ. As such, psychedelics, and (*R*)-DOI in particular, represent the first small molecule inhibitors of TNF-α–mediated inflammation. Further, these anti-inflammatory effector pathways are different from those that are recruited to the receptor by serotonin activation through functionally selective mechanisms.

Following up on these results, studies examined efficacy in a mouse model of a human inflammatory disease, allergic asthma. Asthma is a significant health issue, with about 10% of the population affected. On average, children and minorities have higher rates of asthma, as well as more attacks per year. The main symptoms of asthma are airways hyperresponsiveness, pulmonary inflammation, and mucus hyperproduction. The pathogenesis of asthma involves activation of several immune related cells in the lung, including lymphocytes, macrophages, and eosinophils.[32,33] Current therapies include β2-adrenergic receptor agonists, which are not disease modifying but simply produce bronchodilation, and glucocorticoids, which are immunosuppressants that present with their own health risks. Several biologics directed against cytokines involved in the pathology of asthma have been in clinical trials but with mixed success, at best.[34] Currently there are only two FDA-approved biologics to treat asthma, but they are approved only for a small subset of asthma sufferers, those with more severe symptoms who also are resistant to steroid treatment.

In the aforementioned mouse model of allergic asthma, which shares several pathological similarities to human allergic asthma, psychedelics showed the ability potently to prevent the development of pulmonary inflammation and other asthma related symptoms at doses far below those minimally required to produce behavioral effects.[35] The lowest dose tested, 0.01 mg/kg, was able completely to prevent airways hyperresponsiveness, eosinophilia, and pulmonary inflammation. Because drug was administered nose-only by nebulization, the actual amount of

drug reaching the lung surface is only a fraction of the dose that was delivered, underscoring its potency. Although (*R*)-DOI was the compound most characterized by Nau et al.,[35] other related psychedelics tested also were able to block the development of allergic asthma (unpublished data).

Figure 2 about here

Cellular analysis indicates that (*R*)-DOI blocks the recruitment of Th2 cells and eosinophils to the lung, and suppresses the production of proinflammatory cytokines from Th2 cells and innate immune cells like macrophages.[35] Interestingly, (*R*)-DOI blocks the production of only some (e.g. IL5, IL13, GMCSF), but not all (e.g. IL4), proinflammatory cytokines and chemokines (see Figure 2). This finding indicates that, unlike general immunosuppressants, (*R*)-DOI leaves critical aspects of immune function intact, and that 5-HT_{2A} receptor agonist therapy will likely be less associated with opportunistic infections than are steroids and biologics. Research is continuing to define further the molecular basis of the anti-inflammatory effects of 5-HT_{2A} receptor activation, and it is likely that it extends beyond simple blockade of TNF-α. Research is also pursuing the efficacy of (*R*)-DOI in additional inflammatory disease models such as atherosclerosis.

In summary, animal models of human diseases indicate that psychedelics in general, and (*R*)-DOI in particular, may be an effective therapy for asthma, atherosclerosis, coronary artery disease, and inflammatory bowel disease. There are several other inflammatory conditions that we believe also may benefit from (*R*)-DOI therapy, including rheumatoid arthritis and diabetes.

The highest density of 5-HT_{2A} receptor expression is in the brain, and it is reasonable to expect that psychedelics also may have anti-inflammatory activity at multiple sites in the brain, including neuronal and non-neuronal cells. Within the context of the therapeutic mechanisms

proposed for psychiatric disorders described later in this review, whereby psychedelics "reset" resting state functional connectivity (RSFC), it seems possible that anti-inflammatory mechanisms may play an important role in the long-lasting therapeutic actions of psychedelics. In the short term, therapeutic effect may be achieved through resetting of RSFC, but pre-existing and persisting neuroinflammation may drive the brain back into a pathological state after weeks to months. By blocking neuroinflammation comorbid with certain psychiatric disorders, the brain may be able to maintain its healthy state once networks reset, to produce long lasting beneficial effects. Supporting this hypothesis, several studies (reviewed by Mayfield et al.[36]) indicate blockade of inflammatory mechanisms reduces addiction and drug self-administration in animal models.

Mechanism of Action in the Brain

If continuing clinical studies further validate the use of psychedelic-assisted therapy for all of the above discussed CNS indications, it begs the question, "How can the same single treatment approach lead to improvement in such a diverse range of dysfunctions?" This question deserves serious consideration, which we shall now attempt to address, and is at the core of what is suggested in the title as "a new paradigm." We emphasize that the ideas to be discussed here represent untested hypotheses, but are consistent with presently known results.

Neuroscientists and clinicians often tend to think of the brain from a reductionist perspective, being constructed of anatomical modules that are regulated by discrete neurotransmitter pathways. These modules are somehow "wired" together and interact with other anatomical sites through neuronal projections. Prior to recent advances in neuroimaging, it has been virtually impossible to envision how all of these "modules" might interact and influence each other.

For example, SSRI type antidepressants enhance synaptic levels of serotonin, norepinephrine, or both (e.g. SNRIs). Physicians often treat anxiety disorders with benzodiazepines, which target the GABA/chloride channel. In these cases, and all other CNS disorders, a specific chronic receptor/transmitter-based pharmacotherapy is indicated for a particular psychiatric condition. Empirical research has largely derived these therapies, and no one has been able to explain satisfactorily how such pharmacotherapies actually lead to therapeutic improvement. For psychedelics, the brain serotonin 5-HT_{2A} receptor is the presumed target; yet classical notions of a correlation between various psychiatric disorders and specific 5-HT_{2A} receptor/neurotransmitter systems generally fail as an explanation for their therapeutic effects.

Within the past 10-15 years, however, advances in brain imaging technologies have revealed that resting-state brain activities are organized into multiple large-scale functional networks, called resting-state networks (RSNs). The statistical association/dependency among two or more anatomically distinct time-series is known as functional connectivity (FC); RSFC analyses can discover which regions are coupled, and compare patterns, especially between patient or subject groups. They can reveal brain network dynamics that can account for emergent psychological phenomena that could not be revealed by studying underlying receptor and neuronal activity.

Analysis of human brain connectivity has identified sets of regions that are essential for enabling efficient neuronal signaling and communication. These 'brain hubs' are centrally-embedded within anatomical networks, and participate in functional roles across a range of cognitive and affective tasks with widespread dynamic coupling within and across functional networks. As central hubs, however, they are susceptible to disconnection and dysfunction in

various brain disorders. Data from numerous empirical and computational studies supports the idea that brain hubs are crucial for integrating information that serves as the basis for various aspects of complex cognitive function.

Importantly, studies in patient populations have shown that blood oxygen level dependent (BOLD) fMRI can be used to detect altered functional connectivity in individuals suffering from a variety of CNS diseases. Further, patients can often be distinguished from healthy controls with high sensitivity and high specificity. In addition, research has shown connectivity strength to be correlated with severity of disease symptoms, with recovery of connectivity observed following pharmacological treatment.[37] These connectivity networks can be disturbed in various psychiatric conditions such as anorexia nervosa,[38] obsessive-compulsive disorder,[39] depression,[40-42] anxiety,[43,44] bipolar disorder and hypomania,[45] trauma,[46] and addiction,[47,48] among others. These citations are by no means exhaustive, but demonstrate that a large number of psychiatric disorders are associated with disturbances in RSFC.

If we think of neurotransmitters/neuromodulators and their receptors more as components of neuronal circuits, in the same way that resistors, capacitors, inductors, etc. are functional elements in electrical circuits, then we can view receptor-based pharmacotherapy more as tinkering with the components of a circuit that is malfunctioning and empirically replacing various components in attempts to find a drug that will restore proper (healthy) function to the neuronal circuit.

From a global perspective, research has shown that healthy brain networks have a characteristic organization that enables optimal cognitive function at a low wiring cost, characterized by a combination of high clustering (a measure of local connectedness) and short path length (indicative of global integration). Recent studies have found that network

organization in neurological disease nearly always deviates from this optimal pattern. Local rerouting of networks can therefore be viewed as a local outgrowth of new connections and has been referred to as "hub failure." Importantly, Stam[49] proposes that connectivity hub overload and failure, resulting in a disruption of the normal hierarchical architecture of brain networks, is a potential final common pathway of several neurological diseases.

Returning to the mechanisms of psychedelic therapeutics, it has been observed that the most favorable outcomes in treating anxiety and depression resulting from a life-threatening diagnosis,[50,51] as well as nicotine addiction[20] are associated with subjects undergoing a powerful transcendent experience, sometimes referred to as a mystical, or peak experience. In fact, investigators have known for about half a century that psychedelic-induced mystical/religious experiences can be profoundly transformative.[52,53] That has spawned debate among researchers studying psychedelic-assisted therapy as to whether the therapeutic improvements seen are due to some receptor-based change in neurochemistry, or whether the transcendent/mystical/religious experience is itself the change agent. Both of these points of view may miss the mark, however, as we will argue here that the mystical or transcendent experience may actually be a behavioral marker for the underlying therapeutic mechanism of psychedelics.

In a series of studies with psilocybin, Carhart-Harris and colleagues[54,55] have reported that psilocybin led to decreased connectivity (i.e. disintegration) within a key brain network known as the default mode network (DMN). Using BOLD fMRI they observed decreased activity in the posterior cingulate cortex (PCC), one of the key hubs of the DMN, which normally has high resting state metabolic activity. Psilocybin also caused decreased activity in the medial prefrontal cortex (mPFC), which is intriguing in relation to the psilocybin treatment of depression, mentioned earlier, because increased activity and connectivity within this region

of the DMN has been shown in individuals with depression,[56,57] a pattern that is attenuated following depression treatment.[58]

In their recent neuroimaging study of subjects given LSD, Carhart-Harris et al.[59] also observed drug-induced disintegration of the DMN. They observed decreased RSFC between the parahippocampus, retrosplenial cortex, and PCC.[59] They also calculated within-RSN or "integrity", and between-RSN or "segregation" for 12 functionally familiar RSNs. The investigators observed that decreased integrity within the DMN correlated with ratings of ego dissolution, and observed decreased segregation (increased connectivity) between eight pairs of the RSNs. Using magnetoencephalography (MEG), they also observed a significant decrease in delta and alpha power, which were correlated with ego-dissolution. They conclude that psychedelics reduce the stability and integrity of well-established brain networks,[55] and simultaneously reduce the degree of segregation between them.[60] These effects are consistent with a more general principle they have formulated that cortical brain activity becomes more "entropic" under psychedelics.[61] That is, psychedelics lead to a brain state where there is a greater repertoire of connectivity motifs that form and fragment over time. It should be pointed out that psychedelics do not simply make the brain more random, but rather after the normal organization is disrupted, strong, topologically long-range functional connections emerge that are not present in the normal state.[62] This effect is illustrated in Figure 3, a circular connectogram showing how connectivity is primarily between local regions in the placebo condition, but has expanded outward after psilocybin to include more global connectivity with many other brain areas.[59]

Figure 3 about here

If we follow Stam's hypothesis,[49] discussed earlier, disintegration of RSN organization, i.e. local connection outgrowth, or "hub failure" in neurological diseases, reflects a deviation from an optimal connectivity pattern. Based on the brain imaging done to date on how psychedelics act in the brain, we speculate that, following psychedelic-induced disintegration within local networks, as well as increased global interconnectivity, connections responsible for psychiatric-disorder-associated hub failures are disrupted and broken by the emergence of strong, topologically long-range functional connections. Then, as the effect of the drug wears off, networks can reconnect in "healthy" ways, in the absence of the pathological driving force(s) that originally led to hub failure and disease. We propose that this beneficial "rewiring" of brain networks is more likely to occur in environments such as those used in therapeutic psychedelic sessions, in which the patient is encouraged to focus on her/his inner experience and discuss/reflect on the experience in the days following the psychedelic session. In essence, the brain is able to restore its network connectivity to a pre-disease state, in much the same way that a computer can be rebooted when its operation becomes sluggish.

This discussion has not been comprehensive, but we believe these ideas cannot be far from the mark in discerning how psychedelics exert therapeutic improvement in such a wide variety of psychiatric disorders. The authors are aware of four human trials now underway with psilocybin where investigators are using fMRI to map RSFC both before and after psilocybin treatment. The results of these trials will constitute important tests of the foregoing hypotheses.

What drives changes in functional connectivity?

The final mechanistic question is how psychedelics are able to produce profound and widespread disruptions in functional connectivity. Here is the place where one can appropriately focus on a receptor-based mechanism. Psychedelics are agonists or partial agonists at the brain

serotonin 5-HT_{2A} receptor subtype (see recent review by Nichols.[1]) This receptor is a member of the Family A type G protein-coupled receptors (GPCRs), and is widely expressed throughout the brain, being particularly dense on apical dendrites of layer 5 cortical pyramidal cells. Its canonical signaling occurs through coupling to Gαq, activating phospholipase C, resulting in phosphoinositide hydrolysis, formation of diacylglycerol, and leading to mobilization of intracellular calcium.

Activation of 5-HT_{2A} receptors on glutamatergic neurons within the brain generally does not lead to depolarization and the generation of action potentials; the cells simply become more excitable. The claustrum has the highest expression of 5-HT_{2A} receptors in the brain , but there is also significant expression in Layer 5 in the medial prefrontal cortex, the reticular nucleus of the thalamus, ventral tegmental area, the locus coeruleus, amygdala, and a few other key regions. In addition, psychedelics suppress raphe cell firing in the brain stem either directly (LSD and similar compounds) or indirectly (by phenethylamines), an effect that also leads generally to cortical cell excitation.[63] Widespread changes in neuronal excitability resulting from activation of 5-HT_{2A} receptors in these key brain regions would be expected to have marked effects on cognition.

Béïque et al.[64] had reported on a subpopulation of large neurons in deep layers of the cortex that was highly sensitive to 5-HT and that responded with strong membrane depolarizations that were capable of initiating spiking activity. The nature of this cell population remained unknown until 2016, when Martin & Nichols[65] purified psychedelic-activated neurons from rat brain for the first time and demonstrated that psychedelics directly activated a small subset of 5-HT_{2A}-expressing excitatory neurons (< 5% of the total brain neuronal population) in key brain regions, including the prefrontal cortex and the claustrum. Interestingly, the neurons

activated by psychedelics expressed significantly higher levels of the gene for the 5-HT_{2A} receptor and are therefore more sensitive to psychedelics than other neurons. They also found that the nature of how psychedelics activated these neurons differed, depending on the specific brain region where they resided. Martin and Nichols hypothesize that this small population of directly responding neurons represents a "trigger population," and that activation of these neurons initiates the cellular events leading to recurrent activity, cortical network destabilization, and the host of perceptual and cognitive behaviors associated with psychedelics. For example, these activated neurons subsequently recruit other select cell types including small subpopulations (< 10%) of somatostatin and parvalbumin inhibitory GABAergic interneurons. The differential activation of subsets of both excitatory and inhibitory neurons to disparate extents than would normally occur in a normal conscious brain is predicted to alter the basic function of a given brain area and its ability to communicate with other regions. Because distinct regional cellular populations respond differently to psychedelics, different brain regions will be more or less sensitive to their effects. These cellular effects of psychedelics, therefore, likely underlie the alterations in brain network communication observed by imaging studies.

Another interesting finding by Martin and Nichols[65] is that psychedelics also activate astrocytes and glia. Astrocytes function as an interface between synaptic activity and the vasculature, helping to serve the metabolic needs of the neurons. We speculate that the effects of psychedelics on astrocytes could be contributing to alterations in cortical blood-flow and metabolism detected by BOLD-fMRI and PET imaging, and that blood-flow and metabolism may be de-coupled through astrocyte activation.

With the highest density of 5-HT_{2A} receptor expression in the entire brain, the claustrum is a particularly intriguing brain structure. As noted above, its exact functions remain unclear,

but recent studies have begun to examine its role. For example, based on patterns of retrograde tracing in non-human primates, Reser et al.[66] have suggested that the claustrum is ideally positioned as a modulator that could desynchronize or terminate correlated activation of DMN-related areas. Seeley et al.[67] also propose that the connectivity and anatomy of the claustrum place it ideally to control temporal structure of network activity over component cortical areas of the salience network.

Using in vivo diffusion tensor imaging tractography and graph theoretical analytics, Torgerson et al.[68] quantitatively examined the structural connectivity of the claustrum. They found it to be widely connected, with the highest density of fiber connections per unit volume of *all* brain regions examined. Their network theoretical analyses revealed that (a) the claustrum is a primary contributor to global brain network architecture, and that (b) significant connectivity dependencies exist between the claustrum, frontal lobe, and cingulate regions. They conclude that the claustrum occupies a unique, and presumably critical, location in the overall architecture of network connectivity in the brain and is ideally located within the human central nervous system connectome to serve as the putative "gate keeper" of neural information for conscious awareness.

Spontaneous activity in the brain alternates between periods of relative quiescence interspersed with short bursts of activity that recruit a spatially delimited population of neurons. In one mode of activity, these bursts, called neuronal avalanches, follow a power-law distribution, in which bursts recruiting a small number of neurons occur much more frequently than larger ones.[69] The branching ratio (σ) characterizes a branching process for neuronal avalanches, which is defined as the average ratio of current to past activity.[70] If the branching ratio is smaller than one ($\sigma < 1$), activity dies out before it has propagated far, whereas a ratio

larger than one ($\sigma > 1$) leads to an explosion of activity, called an amplifying avalanche. These networks are termed sub- and super-critical, respectively.

The empirical demonstration of brain resting-state activity simultaneously exhibiting functional segregation and integration has led to the suggestion that the cortex normally resides at a critical state, manifested by spontaneous, scale-invariant, cascades of activity known as neuronal avalanches, and that the human brain as a whole behaves as a system at criticality.[71,72] Indeed, investigators have thought that the brain spends most time at an activity level that corresponds to the critical point, that is, fluctuating around a phase transition.[73] This conjecture has, however, been challenged by Priesemann et al.[74] who analyzed in vivo spiking activity from three mammalian species and local field potential recordings from human brain. Their results provide evidence that mammalian nervous systems operate in a driven, sub-critical regime, but which nevertheless actually deviates only little from a self-organized critical (SOC) state, and whose computational capabilities may still be close to optimal.

Theoretical models have replicated power-law avalanches by assuming the presence of functionally feedforward connections (FFCs) in the underlying dynamics of the system. Thus, a feedforward chain of activation that persists despite being embedded in a larger, massively recurrent circuit generates avalanches.[75] Vincent et al.[75] studied functional connectivity of cultured cortical neurons plated onto multielectrode arrays (MEAs) and investigated whether pharmacologically-induced alterations in avalanche dynamics were accompanied by changes in FFCs. Bath application of glutamate receptor antagonists abolished synchronized activity, whereas the $GABA_A$ receptor antagonist picrotoxin increased its occurrence. The strength of FFCs for control recordings was significantly higher than for recordings after glutamate receptor antagonists, and significantly lower than for recordings after picrotoxin, demonstrating that the

strength of FFCs can be modulated by pharmacological agents. Their results indicate that removal of inhibitory GABA tone in networks leads to amplifying avalanches, accompanied by an increase in the strength of FFCs compared to controls. Hence both the distribution of avalanches and the strength of FFCs are concomitantly modulated by drug treatments. Given that psychedelics increase extracellular cortical glutamate, and have an excitatory effect on cortical cells through activation of 5-HT_{2A} receptors, one could predict that psychedelics also would lead to amplifying neuronal avalanches. This prediction is confounded by the fact that psychedelics also activate inhibitory GABA interneurons, but it seems likely that unopposed activation of neuronal 5-HT_{2A} receptors might result in seizure activity.

The depolarization of cortical trigger subpopulations of cells by 5-HT_{2A} receptor activation in the claustrum, as well as in numerous key brain areas noted earlier, would seem to be consistent with the notion that claustral cell firing would be, at the least, catalytic in initiating profound alterations in global network connectivity, potentially producing a supercritical brain state and amplifying neuronal avalanches.[75]

With all that in mind, one now has a basis for understanding how psychedelics might exert their therapeutic effects. Activation of the 5-HT_{2A} receptor occurs in various important brain hubs, including cortical regions, leading primarily to a reduction in the threshold for cortical cell depolarization (i.e. the cells become more sensitive). The small subset of excitatory trigger neurons depolarizes and initiates recurrent activity that spreads throughout specific regions, which then recruit subpopulations of inhibitory and non-neuronal cells to a supercritical state. That leads to generation of amplifying neuronal avalanches and destabilization of local network hubs, with subsequent changes in global connectivity. Further, it seems possible that one key region, the claustrum, with its extensive connectivity throughout the brain, acts as a

central hub in maintaining balance of the resting-state network, akin to the conductor of an orchestra. The effects of psychedelics on this structure may disrupt ability to maintain the balance between excessive cortical integration and complete segregation in the brain, and brain connectivity falls from criticality to a new, more chaotic (or entropic) state, which reverses only after the drug has cleared the system. As proposed earlier, networks can then reconnect in "healthy" ways, without the pathological force(s) that originally led to hub failure and disease. Potential anti-inflammatory effects of psychedelics could then facilitate stabilization of the brain in its renewed healthy state.

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Figure Legends

Figure 1. *Psilocybe cubensis*, one of the species of mushrooms that naturally produce psilocybin, the psychedelic medicine used for most of the recent clinical trials. (Image from the *Mushroom Observer*; http://mushroomobserver.org/observer/intro)

Figure 2. A proposed mechanism for the anti-inflammatory effects of psychedelics. Under normal conditions, TNF-α (green) binding to its receptor (blue) initiates signaling cascades that lead to the dissociation of the inhibitor of NFκB (IκBα) (purple) from the NFκB/IκBα complex and its degradation (small purple). The active NFκB complex (p65+p50) (pink) translocates to the nucleus and initiates the transcription of proinflammatory genes that together lead to inflammation. Activation of 5-HT_{2A} receptors (red) with psychedelics initiates signal transduction pathways that include recruitment of PKC. The primary hypothesis is that the specific isoforms of PKC recruited by psychedelics interfere with activation of the TNFR or the ability of the TNFR to signal downstream to NFκB, preventing TNFR-mediated inflammation.

Figure 3. A circular connectogram showing that communication is normally confined to particular communities or hubs in the brain (on placebo) but that there is markedly increased inter-community cross-talk after psilocybin. Each node is one region in the brain parcellation used in reference 62, and the colors refer to the communities found on the placebo scaffold. The same colors are used on the psilocybin scaffold to show how the normal modular structure changed dramatically between the two conditions. The plots represent aggregated information from 15 subjects. The width of the links is proportional to their weight and the size of the nodes is proportional to their strength. Note that the proportion of heavy links between communities is both much higher and very different in the psilocybin group, suggesting greater global integration. (Image courtesy of Dr. Robin Carhart-Harris, from data in reference 62.)

Figure 1

Figure 2

Figure 3.

DOI

NH_3^+

5-HT_{2A}

α

β

γ

CO_2H^-

TNFα

TNFR

PLCβ (?)

PKC

p65

IkBα

p50

Inflammation

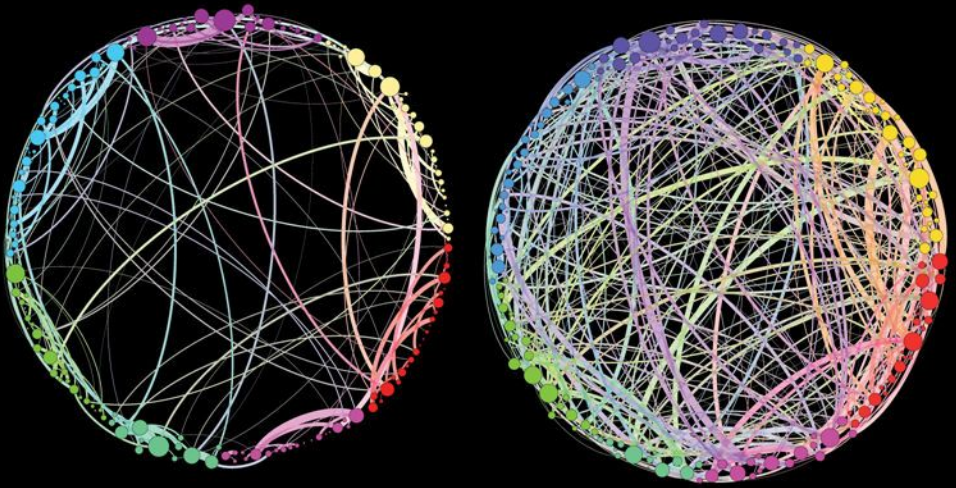
(IL-6, ICAM1, MCP1, etc.)

p65

p50

nucleus

Brain communication patterns



placebo

psilocybin