How do psychedelics work?

Robin L. Carhart-Harris[a,b]

Purpose of review
Psychedelics are reawakening interest from psychiatry, cognitive neuroscience and the general public with impressive outcomes in small-scale clinical trials, intriguing human brain imaging work and high-impact journalism.

Recent findings
This brief opinion piece offers a perspective on how psychedelics work in the brain that may help contextualize these developments. It attempts to link various scales of action, from the molecular (serotonin 2A receptor agonism) through to the anatomical and functional (heightened plasticity) and up to the dynamic (increased brain entropy), systems level (network disintegration and desegregation) and experiential.

Summary
It is proposed that psychedelics initiate a cascade of neurobiological changes that manifest at multiple scales and ultimately culminate in the relaxation of high-level beliefs. The purpose of psychedelic therapy is to harness the opportunity afforded by this belief-relaxation to achieve a healthy revision of pathological beliefs.

Keywords
5-HT2A, dimethyltryptamine, lysergic acid diethylamide, psilocybin, psychedelic, psychedelics, serotonin

INTRODUCTION

Psychedelics such as lysergic acid diethylamide, psilocybin and dimethyltryptamine are unique among brain drugs. It is difficult to think of another category of drugs that have inspired interest across such a broad a range of disciplines, from chemistry [1], molecular biology [2], neuropharmacology and neurophysiology [3], to cognitive neuroscience [4], psychology [5], sociology [6], ecology [7], anthropology [8], philosophy [9] and the arts [10]. It is perhaps because of this breadth of appeal that psychedelics were able to impact on Western culture so significantly in the 1960s [6], spawning a new approach in psychiatry [11], genre of music and art [10], and perhaps even a way of thinking and living [6]. We now find ourselves in the midst of a second wave of significant interest in psychedelics in the West [12]. These compounds have a history of shaking not just individual minds but also the highest echelons of power [6,12,13], and now, with the benefit of several decades of scientific advance, it is timely to take stock and ask a basic scientific question: how do they work?

A PHARMACOLOGICAL DEFINITION OF CLASSICAL PSYCHEDELICS

Classical psychedelics can be defined most concretely by their pharmacology. They all share agonist actions at the serotonin 2A receptor subtype (5-HT2AR), a property that has been established most convincingly in humans via a number of antagonist pretreatment studies [14–16] – see also [17▪]. It is a remarkable testimony to science, and nature, that the effects of these compounds, which include the triggering of deeply profound, potentially life-changing existential experiences [18], can be traced to an initial action at the molecular level (5-HT2AR), and it is a grounding truth for those liable to metaphysical, supernatural perspectives on psychedelics – that if this receptor is blocked, none of their fantastical effects can occur.

PSYCHEDELICS HAVE A 'HIGH-LEVEL' LOCUS OF ACTION

We now know that 5-HT2AR signaling opens a window of plasticity as demonstrated by a number

[a]Centre for Psychedelic Research, Department of Psychiatry, University of Oxford, Oxford and [b]Psychedelic Research Group, Department of Psychiatry, Imperial College London, London, UK

Correspondence to Robin L. Carhart-Harris, Department of Psychiatry, Psychedelic Research Group, Imperial College London, London, UK.
E-mail: r.carhart-harris@imperial.ac.uk

Curr Opin Psychiatry 2019, 32:16–21
DOI:10.1097/YCO.0000000000000467

KEY POINTS

- Psychedelics relax high-level priors or 'beliefs' through a hierarchically high-level locus of action.
- 5-HT2AR-initiated belief-relaxation begets potential belief-revision that, if properly mediated, can be conducive to improvements in mental health.
- Trauma and associated uncertainty may trigger the tightening of certain implicit beliefs that express as symptoms of psychiatric disorder.
- Psychedelic therapy has the potential to remediate such aberrant beliefs via a process of belief relaxation and revision.

of different molecular [19], anatomical [20▪▪], functional and behavioral markers [21,22▪]. Anatomically, 5-HT2A receptors are most densely expressed in the cortex, especially in high-level association cortex [23▪▪], and particularly on layer 5 pyramidal neurons [24] – key cortical information-integration units [25]. It fits therefore that 5-HT2AR-induced plasticity is most pronounced in the cortex [19] and that the experiential effects of psychedelics are felt at a high level, as a fundamental change in consciousness.

DISRUPTION AT VARIOUS SCALES

At the neurochemical and neurophysiological level, 5-HT2AR agonism has been found to induce an asynchronous mode of glutamate release [26] and a spike-to-field decoherence [3]. This irregular excitation at the single unit level is likely to account for dysregulation appearing at the population level, for example in terms of decreased oscillatory power across a broad range of frequency bands [27]. Recent work has begun to support the idea that prominent cortical rhythms such as those in the alpha and beta frequency bands are involved in top-down predictive processing – effectively carrying 'priors', i.e., predictions, expectations or beliefs [28▪,29]. At the whole-brain network level, the functional integrity of canonical 'resting-state' or 'intrinsic' networks has been found to be markedly compromised under psychedelics [4], as has these networks' functional segregation [4,30,31] – leading to the principle that psychedelics induce an transient *disintegration* and *desegregation* of intrinsic brain networks [4], with desegregation being synonymous with increased global functional integration [32] – nicely exemplified by the graphics shown in Fig. 1 [33].

SYSTEM DISINTEGRATION AND DESEGREGATION AS KEY PRINCIPLES OF ACTION

One can feel confident that these principles of network disintegration and desegregation will prevail; they have been replicated by independent teams [31,34] and correlate with high-level psychological phenomena such as 'ego-dissolution' [4,32] – which is intimately related to the so-called unitive experience – i.e., a profound sense of personal, interpersonal and existential 'oneness' and/or 'interconnectedness' [35–37]. The unitive experience is thought to be the core component of the so-called 'mystical' [35] or 'peak' experience [38], the occurrence of which appears to predict positive mental health outcomes [38]. Time will tell whether a more functionally interconnected brain reflects a more globally interconnected state of consciousness – but there is already indirect evidence to support such a view [32].

THE ENTROPIC BRAIN HYPOTHESIS

A third (perhaps unifying) principle takes inspiration from the dimensionless information or communication theoretic metric of *entropy*. Entropy is a quantitative measure of the unpredictability of a dynamical phenomenon, and thus, our uncertainty about its behavior across time [39]. Outside of the context of psychedelics, entropy-related metrics have been used to predict and describe: levels of consciousness [40], psychopathology [41], intelligence [42] and 'surprise' within a 'free-energy' framework [43]. Within the context of psychedelics, entropy-related metrics have been found to index the intensity of the drug's subjective effects across a range of different psychedelic compounds and studies [44▪,45,46] and to predict longer term psychological changes, such as increases in the personality trait 'openness' [47].

Introduced in 2014 [48] and revised in 2018 [45], the 'entropic brain hypothesis' states that entropy-related metrics of population or network level brain activity such as Lempel–Ziv complexity [45], index the richness-of-content of subjective experience in any given state of consciousness. Here, 'richness' refers to the variety or diversity of subjective experience. The hypothesis originates from psychedelic research and therefore states further that psychedelics increase the entropy of both brain activity and experience, as the two are intimately related flip sides of the same essential system, i.e., mind/brain [45]. Indeed, that this is the case, speaks to the fundamental relevance of entropy for understanding the relationship between mind and brain, perhaps inadvertently recognized by Warren Weaver

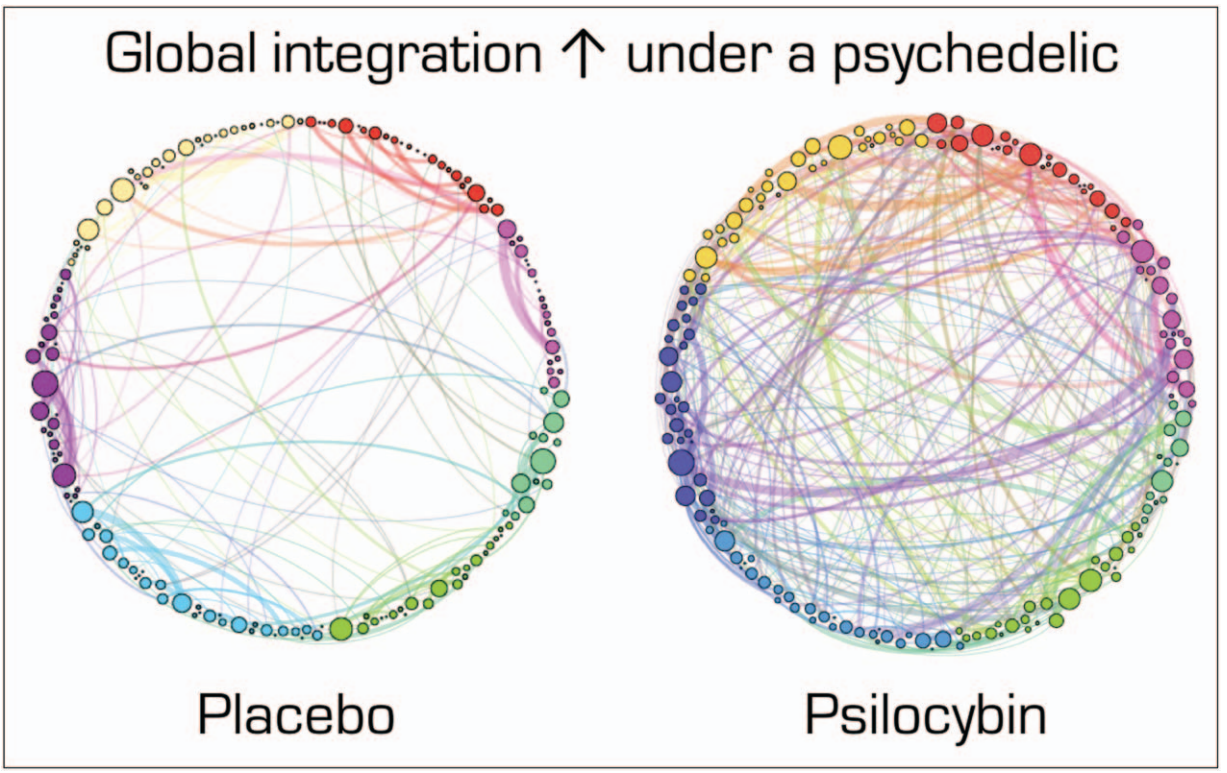

FIGURE 1. Each dot represents a brain region and each color a community of regions that share correlated activity. Lines between dots can be interpreted as evidence that the different regions are communicating above a certain threshold of significance. Ordinarily, most communication is constrained to within a given community (placebo). There is significantly greater between-community communication under psilocybin relative to placebo as reflected by the greater number of lines crossing between the communities. For more details on the methods used to generate these images see [33]. Image reproduced by courtesy of Petri *et al.* [33].

when he said of his colleague, Claude Shannon's, discovery in 1948: 'When one meets the concept of entropy in communication theory, he has a right to be rather excited – a right to suspect that one has hold of something that may turn out to be basic and important.' [49] Shannon used the term 'uncertainty' as a synonym for entropy; applied at the appropriate level, entropy offers a unique bridge across the physical and experiential divide that demands no special extrapolation.

THE ENTROPIC BRAIN MEETS PREDICTIVE PROCESSING

Until recently, this was about as far as things had developed with regards to a unified account of the brain action of psychedelics. However, increasing evidence for an interest in these compounds' therapeutic potential and mechanisms has helped advance thinking on how they work in the brain/mind more generally. Within the last decade especially, predictive processing has emerged as arguably the leading unified model of brain function [50–52]. It has therefore been a matter of some intrigue whether predictive processing could offer a compelling account of the psychedelic experience. Speculated on in a number of past publications [27,53,54], the first focused attempt to provide a predictive processing account of psychedelics' action appeared in 2017 in an intriguing article by Pink-Hashkes *et al.* [55▪]. Here the authors propose that 'decomposed' high-level priors under psychedelics encourages the slippage of prediction error that is processed at a more granular level than would ordinarily be the case, thus accounting for the unusual perceptual and cognitive changes that are characteristic of the psychedelic experience. This model has appeal. 5-HT2ARs are expressed on high-level 'prediction units' (layer 5 pyramidal neurons) in high-level cortex and 5-HT2AR agonism appears to collapse major cortical oscillatory rhythms, such as the alpha rhythm [27] as well as high-level intrinsic networks [4] that are thought to carry and instantiate high-level priors [54]. Hierarchically therefore, psychedelics appear to have a principal locus of action at the high end of the brain's functional hierarchy.

PSYCHEDELIC THERAPY CAN TREAT A PAN-DIAGNOSTIC PATHOPHYSIOLOGY

This model has a number of interesting implications. It is intriguing to consider that decomposed or 'relaxed' high-level priors or 'beliefs' may underlie the potential of psychedelics to treat a range of different psychiatric disorders. Psychedelics have been shown to effectively treat depression, in which pervasive negative beliefs or biases have long been thought to be a core feature [56]. Indeed, it was recently shown that overly pessimistic expectations about future life events in treatment-resistant depression could be rectified after treatment with psilocybin therapy [57]. In other small-scale trials, psychedelics have been found to yield improvements in obsessive-compulsive disorder [58], end-of-life existential distress [59,60▪,61,62▪] and addictions [63,64] – and there is anecdotal evidence of ayahuasca being used to treat eating disorders [65].

THE 'TIGHTENED BELIEFS IN RESPONSE' TO UNCERTAINTY MODEL

The above-listed conditions could all be viewed as manifestations of implicit beliefs or biases that have become overly dominant and resistant to revision. In the case of addictions, problematic beliefs may manifest as aberrant *priorities* due to the canalization of implicit associations that compel particular (addictive) behaviors. The sufferer may or may not be conscious that his/her beliefs are unhealthy – but remains compelled by them all-the-same. The mnemonic TIghtened BEliefs in Response to uncertainty (TIBER) is offered to capture this phenomenon. Here 'trauma' is interchangeable with 'uncertainty' – if used in an extended sense to mean any significant acute and/or repeated adversity that is paralleled by significant uncertainty. The basic tenet is that (implicit) beliefs tighten as a defensive response to significant, intolerable stress and uncertainty. Consistent with the 'free-energy principle', organisms are inherently programmed to resist uncertainty – and uncertainty is, in the main, aversive [52].

TOWARD A UNIFIED MECHANISTIC MODEL

Serotonin 2A receptor agonism, heightened plasticity and brain entropy, mirrored by the relaxation of high-level beliefs could be considered the basic mechanistic action of psychedelics [66]. For aberrant beliefs to be 'revised', 'reset' or 'recalibrated' in a healthier way – as seems to occur not infrequently under psychedelics [67], they must first be decomposed or 'relaxed' – which requires a temporary contravention of the free-energy principle [52]. Thus, the *relaxation* of beliefs may be a definitive (acute) action of psychedelics, and the *revision* of beliefs may be a potential longer term outcome that is more contingent on contextual manipulation [68], for example through music-listening [69], priming and suggestion [70], open, empathetic listening [71] and spontaneous and/or coaxed insight [72▪]. Like the occurrence of peak experiences [38], psychological insight under or after a psychedelic appears to be an important predictor of long-term positive mental health outcomes [72▪]. The ability of psychedelics to decompose pathological beliefs that narrow perception and obstruct understanding may lie at the heart of their special value as therapeutic agents. Psychedelics are, by definition, 'mind-revealers' – and it is an ideal of psychedelic therapy that aberrant beliefs be dissolved so that 'clear vision' be possible [57,71].

THE 'RELAXED BELIEFS UNDER PSYCHEDELICS' MODEL AND CONCLUSION

This brief opinion piece has offered a broad overview of current thinking on the brain action of psychedelics. It has highlighted the critical importance of 5-HT2AR agonism and traced its effects through heightened plasticity and brain entropy to the relaxation and potential revision of high-level priors or beliefs. If mediated properly [68], such belief-revision may underlie the rapid and enduring improvements in mental health that are being widely reported with psychedelics [73]. As a second mnemonic to complement the TIBER model, the 'REBUS' model is offered – RElaxed Beliefs Under pSychedelics.

Whatever their intuitive appeal, it is appropriate to caution that the TIBER and REBUS models are, at present, largely conceptual offerings. Significant empirical work and more in-depth discussion is needed to clarify how the various components of these models interrelate and instantiate biologically and dynamically. Crucially, time will tell how useful these models prove to be at describing and predicting various relevant phenomena.

Acknowledgements

RC-H would like to thank Shamil Chandaria for discussions on related themes and Karl Friston, with whom he will soon contribute a more substantial piece on these ideas and the REBUS model in particular.

Financial support and sponsorship

The author is supported by the Alex Mosley Charitable Trust and the Ad Astra Chandaria Foundation.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Shulgin AT, Shulgin A. Tihkal: the continuation. Berkeley, CA: Transform; 1997.
2. Gonzalez-Maeso J, Sealfon SC. Agonist-trafficking and hallucinogens. Curr Med Chem 2009; 16:1017–1027.
3. Celada P, Puig MV, Diaz-Mataix L, Artigas F. The hallucinogen DOI reduces low-frequency oscillations in rat prefrontal cortex: reversal by antipsychotic drugs. Biol Psychiatry 2008; 64:392–400.
4. Carhart-Harris RL, Muthukumaraswamy S, Roseman L, *et al.* Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc Natl Acad Sci U S A 2016; 113:4853–4858.
5. Carhart-Harris RL, Kaelen M, Bolstridge M, *et al.* The paradoxical psychological effects of lysergic acid diethylamide (LSD). Psychol Med 2016; 46:1379–1390.
6. Stevens J. Storming heaven: LSD and the American dream. London: Paladin; 1987; 1989.
7. Forstmann M, Sagioglou C. Lifetime experience with (classic) psychedelics predicts pro-environmental behavior through an increase in nature relatedness. J Psychopharmacol 2017; 31:975–988.
8. Labate BC. Ayahuasca shamanism in the Amazon and beyond. Oxford, New York: Oxford University Press; 2014.
9. Letheby C. The epistemic innocence of psychedelic states. Conscious Cogn 2016; 39:28–37.
10. Johnson K. Are you experienced?: How psychedelic consciousness transformed modern art. Munich, London: Prestel; 2011.
11. Aaronson BS, Osmond H. Psychedelics: the uses and implications of hallucinogenic drugs. London: Hogarth Press; 1971.
12. Pollan M. How to change your mind: the new science of psychedelics. London: Penguin; 2018.
13. Lee MA, Shlain B. Acid dreams: the complete social history of LSD, the CIA, the sixties and beyond. London: Pan; 2001.
14. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Babler A, *et al.* Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 1998; 9:3897–3902.
15. Kraehenmann R, Pokorny D, Aicher H, *et al.* LSD increases primary process thinking via serotonin 2a receptor activation. Front Pharmacol 2017; 8:814.
16. Valle M, Maqueda AE, Rabella M, *et al.* Inhibition of alpha oscillations through serotonin-2a receptor activation underlies the visual effects of ayahuasca in humans. Eur Neuropsychopharmacol 2016; 26:1161–1175.
17. ■ Deco G, Cruzat J, Cabral J, *et al.* Whole-brain multimodal neuroimaging model using serotonin receptor maps explains nonlinear functional effects of LSD. Curr Biol 2018; 28:3065–3074.e6.

Anatomy-informed modeling shows how the spatial distribution of serotonin 2A receptors can predict that functional brain effects of lysergic acid diethylamide.

18. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology 2006; 187:268–283; discussion 284-292.
19. Vaidya VA, Marek GJ, Aghajanian GK, Duman RS. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J Neurosci 1997; 17:2785–2795.
20. ■■ Ly C, Greb AC, Cameron LP, *et al.* Psychedelics promote structural and functional neural plasticity. Cell Rep 2018; 23:3170–3182.

Shows clear increases in synaptogenesis in various forms with a variety of different psychedelic compounds.

21. Boulougouris V, Glennon JC, Robbins TW. Dissociable effects of selective 5-HT2A and 5-HT2C receptor antagonists on serial spatial reversal learning in rats. Neuropsychopharmacology 2008; 33:2007–2019.
22. ■ Carhart-Harris RL, Nutt DJ. Serotonin and brain function: a tale of two receptors. J Psychopharmacol 2017; 31:1091–1120.

Argues that postsynaptic 5-HT1AR agonism in limbic regions aids stress moderation and characterizes the main action of selective serotonin reuptake inhibitors, whereas psychedelics depend on 5-HT2AR agonism primarily and a mental plasticity conducive to effective psychotherapy. Also links this to endogenous function, with 5-HT2AR becoming more significant for serotonin function under conditions of significant stress.

23. ■■ Beliveau V, Ganz M, Feng L, *et al.* A high-resolution in vivo atlas of the human brain's serotonin system. J Neurosci 2017; 37:120–128.

First images of 5-HT2AR distribution in the living human brain using a 5-HT2AR agonist tracer.

24. Jakab RL, Goldman-Rakic PS. 5-Hydroxytryptamine2a serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Natl Acad Sci U S A 1998; 95:735–740.
25. Larkum ME, Nevian T, Sandler M, *et al.* Synaptic integration in tuft dendrites of layer 5 pyramidal neurons: a new unifying principle. Science 2009; 325:756–760.
26. Aghajanian GK, Marek GJ. Serotonin, via 5-HT2A receptors, increases EPSCs in layer v pyramidal cells of prefrontal cortex by an asynchronous mode of glutamate release. Brain Res 1999; 825:161–171.
27. Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, *et al.* Broadband cortical desynchronization underlies the human psychedelic state. J Neurosci 2013; 33:15171–15183.
28. ■ Mayer A, Schwiedrzik CM, Wibral M, *et al.* Expecting to see a letter: alpha oscillations as carriers of top-down sensory predictions. Cereb Cortex 2016; 26:3146–3160.

Intriguing evidence that the alpha rhythm carries visual and language-related priors.

29. Fries P. Rhythms for cognition: communication through coherence. Neuron 2015; 88:220–235.
30. Roseman L, Leech R, Feilding A, *et al.* The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. Front Hum Neurosci 2014; 8:204.
31. Muller F, Dolder PC, Schmidt A, *et al.* Altered network hub connectivity after acute LSD administration. Neuroimage Clin 2018; 18:694–701.
32. Tagliazucchi E, Roseman L, Kaelen M, *et al.* Increased global functional connectivity correlates with LSD-induced ego dissolution. Curr Biol 2016; 26:1043–1050.
33. Petri G, Expert P, Turkheimer F, *et al.* Homological scaffolds of brain functional networks. J R Soc Interf 2014; 11:20140873.
34. Palhano-Fontes F, Andrade KC, Tofoli LF, *et al.* The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. PLoS One 2015; 10:e0118143.
35. Stace WT. Mysticism and philosophy. London: Macmillan; 1961.
36. Nour MM, Evans L, Nutt D, Carhart-Harris RL. Ego-dissolution and psychedelics: validation of the ego-dissolution inventory (EDI). Front Hum Neurosci 2016; 10:269.
37. Carhart-Harris RL, Erritzoe D, Haijen E, *et al.* Psychedelics and connectedness. Psychopharmacology 2018; 235:547–550.
38. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 2017; 8:974.
39. Ben-Naim A. Entropy demystified: the second law reduced to plain common sense. Hackensack, NJ: World Scientific; 2007.
40. Schartner M, Seth A, Noirhomme Q, *et al.* Complexity of multidimensional spontaneous EEG decreases during propofol induced general anaesthesia. PLoS One 2015; 10:e0133532.
41. Pezard L, Nandrino JL. Dynamic paradigm in psychopathology: 'Chaos theory', from physics to psychiatry. Encephale 2001; 27:260–268.
42. Saxe GN, Calderone D, Morales LJ. Brain entropy and human intelligence: a resting-state fMRI study. PLoS One 2018; 13:e0191582.
43. Schwartenbeck P, Fitzgerald T, Dolan RJ, Friston K. Exploration, novelty, surprise, and free energy minimization. Front Psychol 2013; 4:710.
44. ■ Schartner MM, Carhart-Harris RL, Barrett AB, *et al.* Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Sci Rep 2017; 7:46421.

Compelling evidence that psychedelics increase brain entropy.

45. Carhart-Harris RL. The entropic brain – revisited. Neuropharmacology 2018. [Epub ahead of print]
46. Viol A, Palhano-Fontes F, Onias H, *et al.* Shannon entropy of brain functional complex networks under the influence of the psychedelic ayahuasca. Sci Rep 2017; 7:7388.
47. Lebedev AV, Kaelen M, Lovden M, *et al.* LSD-induced entropic brain activity predicts subsequent personality change. Hum Brain Mapp 2016; 37:3203–3213.
48. Carhart-Harris RL, Leech R, Hellyer PJ, *et al.* The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci 2014; 8:20.
49. Shannon CE, Weaver W. The mathematical theory of communication. Penguin, London: University of Illinois Press; 1949.
50. Clark A. Surfing uncertainty: prediction, action, and the embodied mind. 2017.
51. Hohwy J. The self-evidencing brain. Nous 2016; 50:259–285.
52. Friston K. The free-energy principle: a unified brain theory? Nat Rev Neurosci 2010; 11:127–138.
53. Timmermann C, Spriggs MJ, Kaelen M, *et al.* LSD modulates effective connectivity and neural adaptation mechanisms in an auditory oddball paradigm. Neuropharmacology 2017. [Epub ahead of print]
54. Carhart-Harris RL, Friston KJ. The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. Brain 2010; 133(Pt 4):1265–1283.
55. ■ Pink-Hashkes S, van Rooij I, Kwisthout J. Perception is in the details: a predictive coding account of the psychedelic phenomenon. Amsterdam, New York: CogSci; 2017.

Curious narrative review that offers a predictive processing account of the brain action of psychedelics.

56. Beck AT. Depression; causes and treatment. Philadelphia: University of Pennsylvania Press; 1972.

57. Lyons T, Carhart-Harris RL. More realistic forecasting of future life events after psilocybin for treatment-resistant depression. Front Psychol 2018. doi: 10.3389/fpsyg.2018.01721.

58. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 2006; 67:1735–1740.

59. Grob CS, Danforth AL, Chopra GS, *et al.* Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 2011; 68:71–78.

60. ■ Griffiths R, Johnson MW, Carducci M, *et al.* Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmcol 2016; 30:1181–1197.

One part of a dual publication on psilocybin for end of life distress. Rigorous double blind randomised control trial (RCT) with clear positive outcomes.

61. Gasser P, Holstein D, Michel Y, *et al.* Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 2014; 202:513–520.

62. ■ Ross S, Bossis A, Guss J, *et al.* Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmcol 2016; 30:1165–1180.

One part of a dual publication on psilocybin for end of life distress. Rigorous double blind RCT with clear positive outcomes.

63. Bogenschutz MP, Forcehimes AA, Pommy JA, *et al.* Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 2015; 29:289–299.

64. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 2014; 28:983–992.

65. Lafrance A, Loizaga-Velder A, Fletcher J, *et al.* Nourishing the spirit: exploratory research on ayahuasca experiences along the continuum of recovery from eating disorders. J Psychoactive Drugs 2017; 49: 427–435.

66. Carhart-Harris RL. Serotonin, psychedelics and psychiatry. World Psychiatry 2018; 17:358–359.

67. Haijen EC, Kaelen M, Roseman L, *et al.* Predicting responses to psychedelics: a prospective study. Front Pharmacol 2018; 9:897.

68. Carhart-Harris RL, Roseman L, Haijen E, *et al.* Psychedelics and the essential importance of context. J Psychopharmacol 2018; 32:725–731.

69. Kaelen M, Giribaldi B, Raine J, *et al.* The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology 2018; 235:505–519.

70. Carhart-Harris RL, Kaelen M, Whalley MG, *et al.* LSD enhances suggestibility in healthy volunteers. Psychopharmacology 2015; 232: 785–794.

71. Watts R, Day C, Krzanowski J, *et al.* Patients' accounts of increased 'connectedness' and 'acceptance' after psilocybin for treatment-resistant depression. J Humanist Psychol 2017; 57:520–564.

72. ■ Carhart-Harris RL, Bolstridge M, Day CMJ, *et al.* Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology 2018; 235:399–408.

First focused study of psilocybin for treatment-resistant depression.

73. Carhart-Harris RL, Goodwin GM. The therapeutic potential of psychedelic drugs: past, present and future. Neuropsychopharmacology 2017; 42: 2105–2113.