The entropic brain - Revisited

by

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Neuropharmacology (2018), doi: 10.1016/j.neuropharm.2018.03.010.
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Received: 9 January 2018. Received in revised form: 15 February 2018. Accepted: 12 March 2018.

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Abstract

The entropic brain hypothesis proposes that within upper and lower limits, after which consciousness may be lost, the entropy of spontaneous brain activity indexes the informational richness of conscious states. Here the hypothesis is revisited four years on from its original publication. It is shown that the principle that the entropy of brain activity is elevated in the psychedelic state is increasingly well supported by separate and independent studies and analyses, and evidence for greater brain criticality under psychedelics is also highlighted. It is argued that heightened brain criticality enables the brain to be more sensitive to intrinsic and extrinsic perturbations which may translate as a heightened susceptibility to "set" and "setting". This updated version of the original entropic brain hypothesis now offers more concrete information on specific measures of brain entropy and suggests new studies to scrutinise it further, as well as examine its utility for describing and informing the treatment of psychiatric and neurological conditions such as depression and disorders of consciousness.

Keywords: Psychedelics, Serotonin, Criticality, 5-HT_{2A}, Depression, Entropy.

1. Introduction

This review aims to revisit and update a previous theory of conscious states, namely the 'entropic brain' hypothesis (Carhart-Harris *et al*., 2014). The entropic brain proposes that the 'qualia' or subjective quality of any given conscious state, and specifically the 'richness' of its content, can be indexed by a quantitative measure of the magnitude of entropy (in the information theoretic sense) in a given parameter of spontaneous brain activity, such as oscillations in electrical potentials recorded with EEG or MEG. The hypothesis was, and is, heavily influenced by basic principles of information theory and more specifically, the notion that entropy indexes simultaneously both our uncertainty about the future behaviour of a dynamic system and its information content - such that greater entropy equals greater uncertainty and information-content. Thus, the entropic brain maintains that uncertainty and information-content are near equivalents and that entropic-brain-states are experienced as content-rich but unpredictable and uncertain. The theory lends heavily from research with 'classic' psychedelic[1] compounds, which have been shown to robustly and reliably increase brain entropy within the 'psychedelic state'.

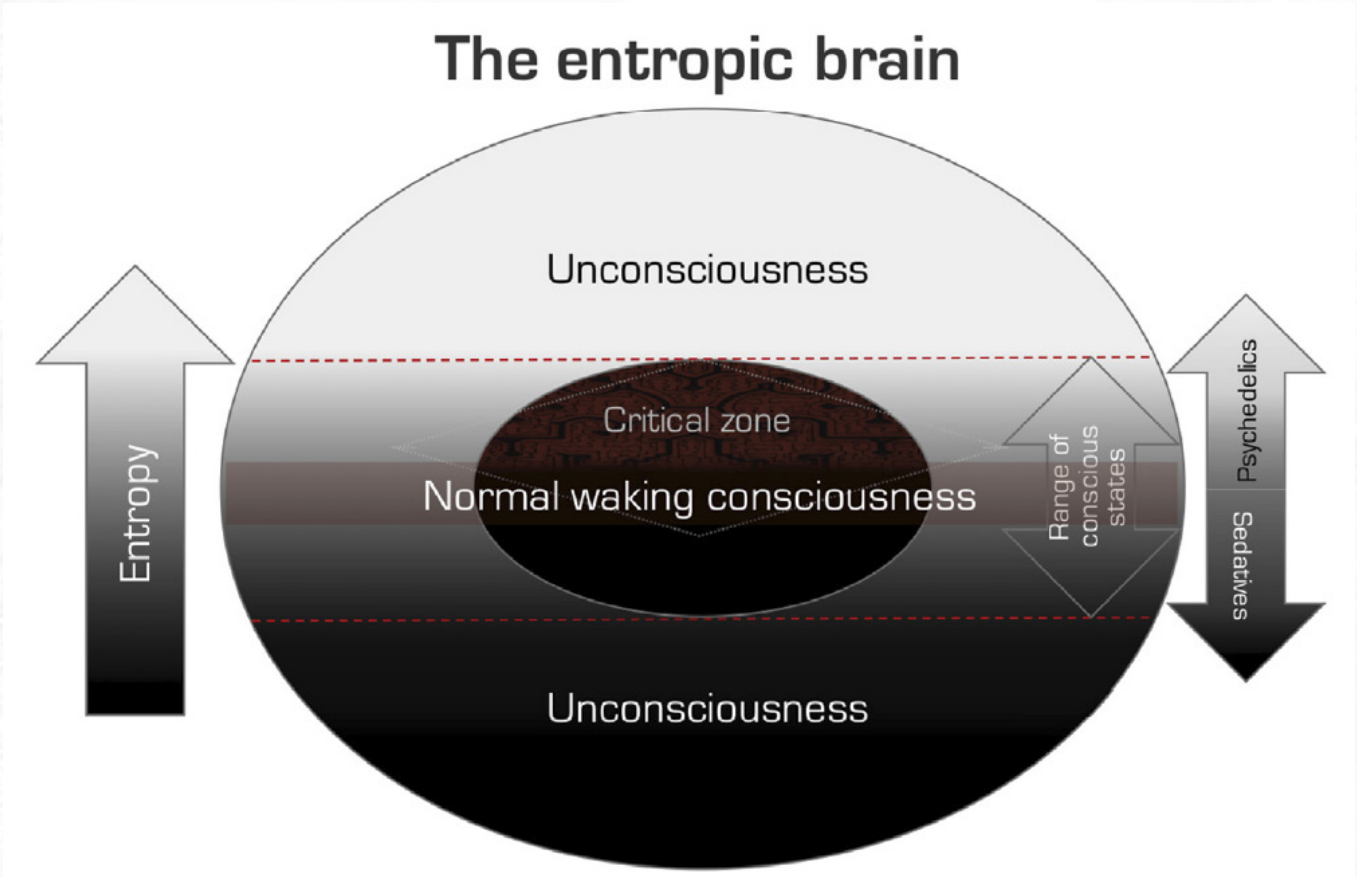

Fig. 1. The entropic brain. Consciousness is proposed to arise within a critical zone at which the entropy or complexity of brain activity is neither too ordered nor disordered. Normal waking consciousness is proposed to inhabit a band within this zone, albeit towards its upper end. Psychedelic compounds are proposed to shift brain entropy and conscious content upwards, higher within the zone of criticality, towards greater conscious content, flexibility of mind and emotional lability but with a trade-off on the preservation of assumptions or beliefs and the sense of familiarity and assuredness they confer. Brain entropy (and criticality) may reach an upper limit at which consciousness is effectively lost - perhaps because phenomenal experience cannot be preserved beyond this point and thus, remembered. Sedatives and anaesthetics shift the brain downwards, i.e. into a subcritical zone and eventual unconsciousness, through loss of content and phenomenal experience. N.B. This figure is intended to be a working schematic; no hard claims are made about the relative scale or dimensions of each domain.

The great merit of applying the measure of entropy in cognitive neuroscience is that it is uniquely adept at bridging the physical and subjective divide; mere flip sides of the same coin - but different sides nonetheless.[2] Since publication of the initial entropic brain paper in 2014 (Carhart-Harris *et al*., 2014), a number of new functional brain imaging studies with psychedelics have been published (Alonso *et al*., 2015; Atasoy *et al*., 2017; Barrett *et al*., 2017; Bouso *et al*., 2015; Carhart-Harris *et al*., 2016b, 2017c; Kaelen *et al*., 2016; Kraehenmann *et al*., 2015, 2016; Lebedev *et al*., 2015, 2016; Mueller *et al*., 2017; Muller *et al*., 2017; Palhano-Fontes *et al*., 2015; Petri *et al*., 2014; Preller *et al*., 2016, 2017; Roseman *et al*., 2014, 2016, 2017; Sampedro

et al., 2017; Sanches *et al*., 2016; Schartner *et al*., 2017; Schenberg *et al*., 2015; Schmidt *et al*., 2017; Speth *et al*., 2016; Tagliazucchi *et al*., 2014, 2016b; Timmermann *et al*., 2017; Valle *et al*., 2016a; Viol *et al*., 2017). These, plus time, reflection, and the publication of new imaging studies on other altered states e.g. (Schartner *et al*., 2015) plus new research on serotonin function (e.g. (Matias *et al*., 2017), have motivated the present revision.

Key components of this revision include: 1) a more explicit statement that the qualia of time-averaged conscious states can be predicted by brain entropy, 2) reference to specific measures of entropy thought to meaningfully index the qualia of conscious states, 3) a specific example of an important empirical, therapeutically relevant question that may be tackled by the hypothesis, 4) a specific example of a clinical problem (namely disorders of consciousness) where the hypothesis may inspire a novel intervention, 5) new data and thoughts on properties of brain criticality in the psychedelic state, 6) how heightened brain criticality confers maximal sensitivity to perturbation via intrinsic or extrinsic sources ("set" and "setting), 7) how there may be an upper bound to the entropic brain principle beyond which unconsciousness occurs (Fig. 1), and 8) how recent findings on brain serotonin encoding behavioural responses to uncertainty mesh well with the entropic brain hypothesis.

2. An update on neuroimaging studies with psychedelics

According to a PubMed search at the time of submission (January 2018), since the 2014 publication of the original entropic brain paper, there have been over 30 new empirical neuroimaging papers published on the effects of psychedelics on the human brain. Since there are relatively few human neuroimaging teams working with these compounds, it is relatively easy to locate where these have come from, namely: Spain (Alonso *et al*., 2015; Bouso *et al*., 2015; McKenna and Riba, 2017; Sanches *et al*., 2016; Valle *et al*., 2016b), Switzerland (Barrett *et al*., 2017; Kraehenmann *et al*., 2015, 2016; Mueller *et al*., 2017; Muller *et al*., 2017; Preller *et al*., 2016, 2017; Schmidt *et al*., 2017), Brazil (Palhano-Fontes *et al*., 2015; Schenberg *et al*., 2015; Viol *et al*., 2017), and the UK (Atasoy *et al*., 2017; Carhart-Harris *et al*., 2016b, 2017c; Kaelen *et al*., 2016; Lebedev *et al*., 2015, 2016; Petri *et al*., 2014; Roseman *et al*., 2014, 2016, 2017; Schartner *et al*., 2017; Speth *et al*., 2016; Tagliazucchi *et al*., 2016b; Timmermann *et al*., 2017). One aspect of the present task is to digest these recent contributions and summarise what they have added to our understanding of the human brain effects of psychedelics. Given the focus of the present paper, this will be done with specific reference to the entropic brain hypothesis.

The first thing to note is that the theory has received significant empirical support since its introduction in 2014 (Atasoy *et al*., 2017; Lebedev *et al*., 2016; Schartner *et al*., 2017; Tagliazucchi *et al*., 2014; Viol *et al*., 2017). For example, analyses of Lempel-Ziv complexity or entropy (in the extended sense) in MEG-measured spontaneous brain activity under a range of psychedelic (i.e. LSD and psilocybin) and psychedelic-like (i.e. ketamine) drugs revealed consistently increased brain entropy in the psychedelic state (Schartner *et al*., 2017). Moreover, the magnitude of these increases in entropy correlated with the subjective intensity of the drug 'trips' (Schartner *et al*., 2017). It was also found that fMRI-measured brain entropy was elevated acutely under LSD and that the magnitude of this, predicted subsequent changes in personality two weeks later (Lebedev *et al*., 2016). In terms of outside replication, a separate team recently reported increased fMRI-measured brain entropy under a psychedelic, in this case, with the DMT-containing drink, ayahuasca (Viol *et al*., 2017); moreover, an especially recent study by my group recorded increased brain entropy under intravenous DMT, using EEG and the Lempel-Ziv measure (Timmermann *et al*., 2018).

[1] Classic psychedelics are perhaps best defined pharmacologically as drugs that have direct agonist properties at the serotonin 2A receptor sub-type (Nichols, 2016). Classic examples include the major tryptamines: LSD, psilocybin and dimethyltryptamine

[2] The philosophical position that mind and brain are two aspects of or 'ways to look at' the same phenomenon, like two sides of the same coin, is known as 'dual-aspect theory' or 'dual-aspect monism'. The position of *the entropic brain* is that 'mind' is fundamentally 'information' but the informational 'code' is physically and dynamically instantiated in brain activity and can therefore be decoded. Ubiquitous contingencies may be key to how, at least theoretically, we may 'decode' brain to mind - but a difference in *aspect* will always exist, no matter how successful the decoding, as this difference is fundamental.

Another notable recent contribution relates to the novel application of connectome harmonics to the psychedelic state (Atasoy *et al*., 2017). Consistent with the entropic brain hypothesis (Carhart-Harris *et al*., 2014), as well as previous analyses with fMRI and psilocybin (Tagliazucchi *et al*., 2014), this approach revealed

an expanded repertoire of brain states under LSD, and again, this effect correlated with the intensity of the subjective experience (Atasoy *et al*., 2017). To our knowledge, this is the first time that a property of brain criticality under a psychedelic has been clearly and intentionally measured (here the power law distribution of connectome-harmonic brain states) and the results were intriguing, with an apparent enhancement of criticality under LSD relative to the normal waking state (Atasoy *et al*., 2017). As with findings of increased brain entropy under psychedelics (e.g. Schartner *et al*., 2017), increased brain criticality relative to normal waking consciousness (or indeed any other state of consciousness) is an anomaly in the scientific literature (Atasoy *et al*., 2017), and may therefore speak to the exceptionalness of the psychedelic state, something that is widely recognised by those who have experienced their remarkable subjective effects (Huxley, 1959) - but not so much by the broader cognitive neuroscience community. It would be encouraging to think that these novel neurobiological findings may pique the interest of mainstream 'psychedelic-experience-naive' cognitive neuroscientists in the same way that the remarkable psychological effects and clinical potential of psychedelics have piqued the interest of philosophers (Milliere, 2017; Letheby, 2016), psychologists (Watts *et al*., 2017) and psychiatrists (Carhart-Harris and Goodwin, 2017), regardless of firsthand experience.

3. The functional meaning of 'increased brain entropy'?

The first thing to note is that there is strong evidence that the entropy of spontaneous brain activity is reduced during states of reduced consciousness (Olofsen *et al*., 2008; Schartner *et al*., 2015; Zhang *et al*., 2001; Burioka *et al*., 2005) and that entropy measures can be used to accurately distinguish between waking consciousness, loss of consciousness and even the minimally conscious state (Casali *et al*., 2013; Schartner *et al*., 2015; Zhang *et al*., 2001). In this context, the discovery of a state in which brain entropy is elevated above its already high level at normal waking consciousness is truly noteworthy (Schartner *et al*., 2017). If entropy indexes the 'level of consciousness', does it not follow that higher entropy in the psychedelic state relates to an increase in some quality of consciousness above its (already high) level during the normal awake state? It is important not to romanticise the psychedelic experience here, with mystical-sounding notions of 'expanded-consciousness', but equally, one should not be shy of the result nor its functional implications. Accordingly, it seems entirely reasonable to infer that there is an expansion in some key property of consciousness under psychedelics, while another may be compromised, e.g. analytical and convergent thinking (Carter *et al*., 2005; Kuypers *et al*., 2016).

It is proposed here that, to a critical point, beyond which the ability to preserve phenomenal experience and thus consciously reflect on it may be entirely lost, the property of consciousness that is most reliably indexed by brain entropy and enhanced under psychedelics is its *richness*. Other terms that could refer to the same property might be: 'content', 'complexity' and 'information'. These largely interchangeable terms harmonise well with the nomenclature of the measures themselves. Indeed, this easy mapping between the measures' names and the subjective feeling states they invoke, was, and remains, an inspiration behind the original *entropic brain* idea. It is maintained that this mapping is robust against charges of category conflation as there is actually little extrapolation being done; even in the strictest mathematical sense, *entropy is uncertainty* (Ben-Naim, 2007). The interpretation of entropy as 'information' (in its familiar sense) may depend, in part, on the process of decoding, i.e. that a decoder be able to 'make sense' of the potentially rich information content of a complex, unpredictable phenomenon (Gleick, 2011). As with 'uncertainty', reference to entropy as 'information' (Shannon, 1949), has led to charges of anthropomorphism (Gleick, 2011). In this context, a key challenge for the entropic brain hypothesis is to decipher the complex code instantiated by brain activity in order to may make more specific and compelling mappings to the feeling states they encode.

4. How might we better test the entropic brain theory?

4.1. Specific challenges

Improving our mappings between spontaneous brain and mind phenomena is a major scientific challenge. Doing so will enable us to better characterise and predict properties of different conscious states, and where appropriate, treat psychiatric and neurological disorders. Since it is the spontaneous brain activity underlying conscious states about which we are most interested, our techniques for realising this mapping will benefit most from retaining an intimacy to the original phenomena of interest. By implication, the study of stimulus-

evoked transients, including discrete perturbations - such as brain stimulation (Casali *et al*., 2013; Massimini *et al*., 2009) or responses within specific behavioural paradigms, may have relatively limited explanatory potential due to their being detached from the central phenomena of interest, i.e. spontaneous 'states' - naturally unfolding across time. In contrast, improving our methods of sampling spontaneous mind and brain states in situ may yield more relevant insights.

Studying spontaneous processes comes with major challenges however; for example, in contrast to carefully controlled manipulations, experimental control is ceded when we choose to sample spontaneous phenomena in their natural form. A related challenge, perhaps best known in the context of physics, is that in sampling phenomena, we may cause an unintended perturbation and thus confound what inferences can be made on the phenomenon of interest. This is known as 'the observer effect' and more strictly, 'the uncertainty principle', and it is not an easy problem to resolve.

> "*Nature is sensitive to our experiments*." (Gleick, 2011)

Moreover, in the context of psychedelic research, it has proved apparent that instructing participants to engage in certain behaviours or with certain stimuli tends to suppress the intensity of the basal, 'ongoing' psychedelic state. Another issue is that interpretations of results based on controlled experimental perturbations should carry important caveats - and these are not always stated. More specifically, likely due to a generalised inability to engage with stimuli that are relatively unengaging and/or difficult to focus on when in the throes of an intrinsically stimulating psychedelic 'trip', it is typical for such experiments to yield (arguably uninteresting) negative findings - e.g. see (Muthukumaraswamy *et al*., 2013; Timmermann *et al*., 2017) for relevant discussions. Similar critiques have been made of findings of impaired cognition and brain responsiveness in pathological conditions such as schizophrenia and/or major depressive disorder - since the most plausible (but less exciting) interpretation of such negative findings is that the patient is simply less able and/or willing to engage with tasks and stimuli in question, and thus, the impairment(s) are generalised rather than specific. Caution is therefore advised when choosing to employ conventional behavioural paradigms in the context of acute administration studies with psychedelics, as this may encourage specific inferences to be made on what are in actuality, non-specific negative outcomes.

4.2. Proposed solutions

In the mid 1990s cognitive neuroscientist Francisco Varela conceded that no simple 'theoretical fix' or 'missing ingredient' could magically bridge the ontological divide between brain/ objective and mind/subjective phenomena (Varela, 1996). In conceding this simple but essential point, he was then able to promote a pragmatic approach to the problem. He proposed that it is still very much possible to make meaningful mappings between irreducible 'mind-stuff' and intimately associated 'brain-stuff' - such that translations between them become relatively seamless, and differences, unobvious. In making this point, Varela cited Edmund Husserl's notion of 'fundamental correlation' and he named his approach 'neurophenomenology' (Varela, 1996).

The pragmatism of *neurophenomenology* chimes well with that of *the entropic brain*. However, it is recognised that significant improvements must be made in our sampling of both brain and mind, if more compelling and specific *fundamental correlations* are to be discovered. Moving beyond the supportive findings that have already been cited (Atasoy *et al*., 2017; Lebedev *et al*., 2016; Schartner *et al*., 2017; Tagliazucchi *et al*., 2014;Viol *et al*., 2017), a significant advancement for the entropic brain will be to go beyond the general but important statement that entropy is a (perhaps uniquely) powerful mind-brain bridge, to highlight specific cases where it bridges in a way that other measures do not. To help with this, it is encouraging to note that significant progress is being made in functional neuroimaging to develop more dynamically sensitive measures, such as sliding windows (Nakai *et al*., 2006), point-process (Tagliazucchi *et al*., 2012) and intrinsic ignition (Deco *et al*., 2017; Deco and Kringelbach, 2017) analyses; and with regards to subjective measures, experience sampling (Christoff *et al*., 2009) and so-called 'microphenomenology' (Petitmengin, 2017) hold much promise, particularly if combined with the aforementioned dynamic brain measures.

5. Do psychedelics facilitate emotional insight, and if so, how?

In the interests of encouraging the testing of the entropic brain hypothesis, it may be especially constructive to offer a specific example here of a particular problem felt to be deserving of special attention and about which a potential solution may be proposed.

Thankfully, the true origin and meaning of neologism 'psychedelic' is becoming increasingly well recognised and understood. It dates back to the mid 1950s and an exchange between two Brits (one, the famous author - Aldous Huxley) in which they sought to find a more appropriate term for these compounds (Huxley *et al*., 1977). The objective was to devise a word that would better capture their core psychological properties than the relatively shallow and arguably misleading alternative 'hallucinogen'. It was Huxley's interlocuter, the psychiatrist and psychedelic research pioneer Humphrey Osmond who would coin the term 'psychedelic' - combining two ancient Greek words for 'mind' or 'soul' (*psyche*, *ψυχή*) and 'to reveal' or make manifest' or 'visible' (delein, δηλειν) - to lay principal emphasis on these compounds' *mind-revealing* effects.

The notion that a principal property of psychedelics is their ability to reveal aspects of the mind that are normally not fully visible, was (Cohen, 1964; Grof, 1979; Sandison, 1954), and remains (Carhart-Harris and Friston, 2010; Kraehenmann *et al*., 2017a,b; Richards, 2015), widely accepted among those most familiar with their effects, if through direct personal experience, or second or third-hand observation. Remarkably however, that psychedelics do this, remains a mere assumption/hypothesis that has never been systematically measured and tested, and therefore given an opportunity to be verified or falsified.

It seems reasonable to begin by acknowledging that this relatively major oversight may be explainable - if not excusable - by the unreasonable difficulty of conducting human research with psychedelics[3] (Nutt *et al*., 2013), let alone testing such an abstract and paradigm-challenging idea.[4] Tackling this problem pragmatically however, we may begin by deconstructing it into simpler, more concrete and testable components. One such component is that psychedelics facilitate 'emotional insight', i.e. definable as the acquisition of new thoughts, ideas or realisations about one's self (or 'persona' - to use a Jungian term), assumptions and behaviour. Such insights may (or may not) then lead to subsequent *changes* in assumptions, perspectives and behaviour. We may operationally define emotional insight using a revised version of a scale previously devised and employed to test the notion that dreams facilitate emotional insight (Edwards *et al*., 2013).[5] This measure could be employed within a placebo-controlled study with a psychedelic, with the hypothesis that scores would be significantly higher in relation to the psychedelic experience than with placebo. Moreover, to add specificity and thus, potential strength to subsequent inferences, a psychoactive control drug could be introduced, such as a benzodiazepine, stimulant or non-psychedelic dissociative. Interestingly, a recent study largely adhered to such a design and found greater reported psychological insight in relation to the psychedelic (psilocybin) experience than with experiences produced by an active control (dextromethorphan) (Carbonaro *et al*., 2017)

If further positive findings were to be obtained, key questions would then ensue, such as: what underlies such emotional insight (e.g. in terms of brain activity), and are such events amenable to capture and measurement in real-time, i.e. as they arise, as opposed to merely in retrospect? If the insight arises as a discrete event or epoch in time, then it stands to reason that it is amenable to capture, but if it is protracted, even to the extent that it crystallises after the psychedelic 'trip' has ended, then capturing and measuring this seems less feasible. In the interests of pragmatism (and plausibility), let us imagine that the entropic beginnings of emotional insight, do occur in discernable epochs under psychedelics. If we accept this possibility, how then might we capture such epochs and assess their relationship to insight?

[3] The reasons for this are manifold but can perhaps most simply and accurately be traced to stigma and related conservatism affecting key decision makers within governments, funding bodies, ethics boards, mainstream scientific communities and senior institutional figureheads. From experience, psychedelic research is an endeavor the establishment is far readier to say "no" to than "yes".

[4] Paradigm-challenging because expressed in psychoanalytic or psychodynamic terms, it is the principle that the unconscious mind exists and its existence can be tested.

[5] To assist other researchers, a revised, albeit as yet unvalidated emotional insight scale is provided as a supplementary file attached to this paper. This scale is currently in the process of validation - but others are invited to contribute to this process.

Button-press to signify the occurrence of discrete spontaneous events is an approach that has been used in the past, e.g. in relation to auditory hallucinations in psychosis (Leroy *et al*., 2017) and spontaneously arising thoughts (Ellamil *et al*.,2016) but the overhanging psychological influence of the instruction to button press, as well as the subsequent motor actions, associated artefacts and the preceding deliberation on and intention to act, may suppress and/or confound the target phenomenon and therefore create false and/or unreliable attributions. Thus, an alternative to button press may be needed and one such example may be 'experience sampling', i.e. the procedure of cueing participants to report on the content of their recent conscious experience at random or pseudo-random time intervals (Christoff *et al*., 2009). Such reports may be brief and constrained, e.g. delivered in the form of simple ratings, or more open, e.g. delivered through free speech. Due to the importance of brevity and desire not to interfere with the naturally unfolding experience, simple ratings may be the most practical option, particularly if concomitant functional neuroimaging recordings are being made - which are time sensitive and expensive (e.g. especially with fMRI). Thus, a simple brief rating of 'strength of emotion' and/or 'richness of conscious experience' could be used which could be supplemented post-hoc by detailed microphenomenology interviews (Petitmengin, 2017) that seek to evoke the original feeling and probe its nature with strategic questioning.

Importantly, we might improve on this entire approach by twinning the psychedelic experience with conditions known to be especially amenable to emotional arousal and insight. As already touched upon, this is especially pertinent in the context of neuroimaging, and particularly fMRI, where due to expense, as well as mechanical and comfort-related issues, individual scans typically last for approximately 5-15 min, and complete scanning sessions cover a period of approximately 60 min. Thus, introducing conditions in which emotional arousal and insight can be more easily coaxed, would serve a valuable function.

This could be done efficiently with music, structured in such a way that one may predict a priori, where intense experience and related insight may be most likely to occur. Experience sampling could track emotional strength/richness of experience in real-time and cues to rate/report on this could be sufficiently interspersed in time, so as to minimise interfering with the natural experience itself while being sufficiently regular to capture the desired events (e.g. a simple rating every 90-150 s). Although unconventional, if using fMRI for example, one might dedicate an entire scanning session of e.g. approximately 45 min to so-called resting-state scanning with music playing throughout. Inherently varying qualities within the music, such as individual 'songs' or periods within them, may serve as temporal flags to direct post-hoc reporting, which could be complemented by microphenomenology techniques (Petitmengin, 2017). If the spatially confined and auditorily loud nature of fMRI is considered unconducive to immersion in the experience and associated emotional release, then MEG or high density EEG might be more effective modalities.

A critical reader may ask, why such concern for the subjective measures, especially in a paper concerned primarily with a theory on brain function? The simple response to this is that questions of how experience is sampled should be given equivalent weight to questions of how concomitant brain activity is recorded, as the aim is to optimize the strength of our correlations between the two (Petitmengin, 2017). By implication, improving the fidelity of our subjective measures will serve this agenda as effectively as utilising the most powerful neuroimaging technologies and analyses.

How might we tie-in the entropic brain theory to this hypothetical study and its outcomes, and what predictions would we make about the magnitude of brain entropy during periods of intensified experience in which subsequent insight is reported? The clue may be in how the question has been framed, i.e. that there is a temporal sequence to events - with an increase in brain entropy coinciding with a period of intense immersion and 'information download' (which also feels unpredictable, openly explorative and experientially 'rich') followed by a subsequent period of normalisation of or reduction in brain entropy, that relates to a process of 'integrating', 'decoding' or sorting this information - and its subsequent crystallisation as 'insight'. Mechanisms and measures of *self-organisation* may be relevant in this context (Bak, 1997).

In partial support of these ideas, we have previously found that acute entropy under a psychedelic predicts sub-acute and potentially long-term changes in personality (i.e. increases in the personality trait 'openness' to experience) (Lebedev *et al*., 2016), and certain qualities of brain activity (i.e. functional connectivity) have been found to change in an opposite direction after a psychedelic experience than during it (Carhart-Harris *et al*., 2017c). These mechanisms might be likened to those discussed in relation to the creative process (Lubart, 2001), in which an experience of insight is preceded by planning (intention), free-association-like

'brainstorming' and a subsequent, delayed process of evaluation or verification (integration). Loosely, these mechanisms might also be related to the phenomena of divergent versus convergent thinking (Guilford, 1967; Kuypers *et al*., 2016) as well as exploratory versus exploitative search (Cohen *et al*., 2007), in which there is an initial entropic state that is exploratory and divergent in nature which is then followed by more protracted processes of cognitive convergence and 'exploitation'.

Before concluding this section, it is worth considering a couple of additional novel analytical approaches, i.e. in addition to applying information theoretic measures of entropy to brain data, it may be possible to measure the entropy of subjective experience itself, e.g. through the richness of the language used to describe it and in properties such as the rarity of the adjectives and phrases used and contingencies between words, phrases and categories or themes. Efforts are currently being made to explore how this can be done in a useful and meaningful way - but serving as inspiration are the impressive developments in natural speech analytics that have been made in psychiatry and psychopharmacology in recent years (Bedi *et al*., 2014, 2015). Relatedly, one may also apply validated measures of cognitive bizarreness to accounts of the psychedelic experience, as has been done recently (Kraehenmann *et al*., 2017).

Both brain and free-speech data might also be combined with machine learning methodologies with the aim of predicting new datasets and outcomes (e.g. see Carrillo *et al*., 2018) - however, by implication, entropic brain and mind states will be harder to predict, and perhaps also to derive predictions from; thus, the unreliability of machine learning algorithms to predict entropic brain states may be a specific hypothesis of the entropic brain theory itself - and this effect could be visually displayed via 'noisier' brain-to-mind visual reproductions (Naselaris *et al*., 2009).

6. Can psychedelic-induced consciousness-enrichment be used to treat disorders of consciousness?

Beyond what has just been discussed, let us consider another specific example of an area in which the entropic brain theory may be effectively applied. Brain entropy or 'complexity' has been found to reliably index conscious level in healthy people during normal waking consciousness versus the anaesthetised state, as well as in disorders of consciousness (Casali *et al*., 2013; Olofsen *et al*., 2008; Schartner *et al*., 2015; Zhang *et al*., 2001). Perhaps the most impressive research in this regard has been performed by Casali *et al*. (2013) who used transcranial magnetic stimulation (TMS) to perturb the brain in healthy individuals and patients with disorders of consciousness of varying degrees of severity. The Lempel-Ziv measure was then applied to EEG recordings of TMS-pulsed brain activity to yield the so-called perturbational-complexity index or PCI; for detailed explanations of Lempel-Ziv measures of brain activity, see (Schartner *et al*., 2015; Zhang *et al*., 2001). This PCI approach was remarkably reliable at differentiating between disorders of consciousness, e.g. with vegetative state patients scoring lowest, followed by patients in the minimal conscious state, the emerging from minimally conscious state and finally, locked-in syndrome and healthy controls during normal wakefulness (Casali *et al*., 2013). An even more recent study showed that the same Lempel-Ziv measure applied to spontaneous (i.e. restingstate, non-TMS perturbed) brain activity effectively differentiated between consciousness and unconsciousness in healthy individuals (Schartner *et al*., 2015), and in a separate earlier study, the same basic measure was found to index depth of anaesthesia with an almost 100% sensitivity and specificity (Zhang *et al*., 2001).

To our knowledge, until recently, it was generally thought that normal waking consciousness represents the (conscious) state of maximal brain entropy, since all comparison states characterised by a relative loss of consciousness, such as sleep, the anaesthetised and sedated states and disorders of consciousness, feature a corresponding reduction in brain entropy (Burioka *et al*., 2005; Schartner *et al*., 2015). It was a remarkable discovery therefore that the psychedelic state bucks this trend, with robust increases in brain entropy exceeding the levels associated with normal waking consciousness observed with different psychedelic compounds (Schartner *et al*., 2017).

In addition to questions about what we are to make about these findings, are questions about what we are to do with them? Interventions for disorders of consciousness are relatively ineffective and/or unreliable and range from the pharmacological to surgical (Giacino *et al*., 2014). If reductions in consciousness relate to

reductions in brain entropy (Schartner *et al*., 2015), and psychedelics robustly and reliably increase brain entropy (Schartner *et al*., 2017), then does it not follow that psychedelics may be used to elevate conscious content in patients with disorders of consciousness?

Pragmatics and need, rather than cynical conservatism, should dictate how we proceed with this idea. One logical place to start might be with non-human animal research where the hypothesis that psychedelics lift entropy and thus, conscious content, from a sedated baseline may be tested. However, since it is difficult to assess conscious content in non-human animals, and anaesthesia to assist with recordings can confound interpretations, a logical advance on this would be to test whether psychedelics can lift both conscious content and entropy from a sedated baseline in humans. We might also extend this line of enquiry to sleep, with the hypothesis that psychedelics lift entropy and conscious content in NREM sleep, perhaps by switching the sleeper into dreamful REM sleep. Support for the REM-promoting effects of acutely administered psychedelics can be found in literature from the 1960s (Muzio *et al*., 1966; Torda, 1968) and recent work has leant support to the association between the phenomenology of the psychedelic state and the dream state (Kraehenmann *et al*., 2017; Tagliazucchi and Sanz, 2018) - see also (Carhart-Harris, 2007; Carhart-Harris and Nutt, 2014).

If these proof-of-principle experiments were to yield positive results, we might then consider taking the intervention to patients with disorders of consciousness. The normal procedure for informed consent in such patients would apply, and given the positive safety profile of psychedelics, and association with positive mental health outcomes (Carhart-Harris and Goodwin, 2017), albeit with important caveats related to context of use (Carhart-Harris *et al*., 2018), a logical and ethical case could be made in favour of conducting such a study. Again, if positive results were to be found, considerations may then turn to how the intervention could be given in a more manageable way, e.g. via adherence to a 'microdosing' protocol (Fadiman, 2017), where threshold perceptible doses of psychedelics are given 2-3 times per week to (putatively) modulate improvements in mood and cognition. Moreover, where there is sufficient residual consciousness for this to be appropriate, such a dosing regimen might also be combined with conventional rehabilitation therapy.

7. Criticality

It was an original hypothesis of the initial entropic brain paper (Carhart-Harris *et al*., 2014) that psychedelics tune the brain even closer to criticality[6] than is evident in normal waking consciousness and importantly, recent findings with fMRI and LSD do seem to support this idea (Atasoy *et al*., 2017). That the brain exhibits characteristics of criticality is now well established (Hahn *et al*., 2012; Fregnac, 2017; Tagliazucchi, 2017; Tagliazucchi *et al*., 2016a), and there is some evidence to suggest that the brain ordinarily resides towards the sub-critical end of a general 'zone of criticality' (Priesemann *et al*., 2014), i.e. brain criticality may be better thought of as 'zone' than a discrete critical 'point' (Moretti and Munoz, 2013) and the waking brain seems to be positioned closer to 'extreme order' or sub-criticality within this zone than 'extreme disorder' or super-criticality (Atasoy *et al*., 2017; Priesemann *et al*., 2013, 2014). Brain dynamics have been shown to shift towards sub-criticality with increasing cognitive load (Fagerholm *et al*., 2015) and into super-criticality in epileptic seizure (Meisel *et al*., 2012). As with entropy, cases of enhanced criticality above the already high level associated with the normal waking brain are relatively unheard of in the scientific literature; thus, by implication, increased criticality under psychedelics is exceptional (Atasoy *et al*., 2017).

What then are we to make of this? Criticality is known to confer functional advantages to a system in terms of maximising the capacity and efficiency of information processing through optimizing adaptability while preserving order (Shew and Plenz, 2013), and it stands to reason that a system moving closer to criticality and/or shifting closer to the super-critical end of a critical zone is likely to favour flexibility and susceptibility to perturbation over preservation - as well as exploration over exploitation (Cohen *et al*., 2007). Reflecting on some of the recent findings with psychedelics, this principle makes sense: for example, psychologically supported treatment with psychedelics has been associated with impressive improvements in psychiatric conditions such as addictions (Bogenschutz and Johnson, 2016), obsessive-compulsive disorder (Moreno *et al*., 2006), and depression (Carhart-Harris *et al*., 2016a, 2017a; Sanches *et al*., 2016). Moreover, several of these conditions have been associated with brain sub-criticality (Carhart-Harris *et al*., 2014) - particularly depression (Pezard *et al*., 1996; Thomasson and Pezard, 1999; Thomasson *et al*., 2000, 2002; Zhang *et al*., 2001; Akdemir Akar *et al*., 2015) - although contradictory evidence (e.g. Méndez *et al*., 2012 ; Akdemir Akar *et al*., 2015) suggests that the relationship between entropy and depression maybe be subtype and state specific (e.g. see

Akdemir Akar *et al*., 2015 and Zhang *et al*., 2001), as well as sensitive to medication status (Méndez *et al*., 2012).

Regarding the dynamics of mood itself, it is intriguing to entertain the thought that, within certain bounds, the super-critical end of the zone of criticality may favour positive mood - and perhaps even be a fundamental property of it (Carhart-Harris and Nutt, 2017; Thomasson *et al*., 2000, 2002), although there may be a tipping point, where the hyper-flexible (instable) individual may become vulnerable to a mania-related condition exhibiting behaviours such as agitation, inappropriate elation and grandiosity. It is noteworthy that such symptoms can sometimes be seen acutely and even sub-acutely with psychedelics (e.g. see https://erowid.org/experiences/), perhaps most commonly when the experience has been poorly integrated (Carhart-Harris *et al*., 2017b). The notion of 'spiritual bypassing' may be relevant here, in which transpersonal and/or 'spiritual' notions and ideals are (unconsciously) used to distract ourselves from and thus avoid directly working on painful personal material and/or developmental needs (Masters, 2010).

One of the signature properties of a critical system is a maximal sensitivity to perturbation (Bak, 1997; Hesse and Gross, 2014; Tagliazucchi *et al*., 2016a). By this token, we may ask whether and how this translates to the psychedelic experience? The importance of 'set' and 'setting' to the quality of a psychedelic trip has long been raised (Leary *et al*., 1963, and see also Hartogsohn, 2016) and a recent perspective piece on the assumed importance of context, both to the quality of the acute psychedelic experience and subsequent long-term psychological outcomes, has recently been published (Carhart-Harris *et al*., 2018). Intriguingly, as discussed above, it seems that not all stimuli have added impact in the psychedelic state - but are dependent on being sufficiently captivating and immersive for the individual (Kaelen *et al*., 2018). For example, in a recent clinical trial of psilocybin for depression, music played to patients during the treatment session that was well liked and in resonance with their underlying emotional state was found to be strongly associated with the occurrence of so-called 'peak experience' and positive therapeutic outcomes; however, if the music was out-of-synch with the patient's tastes and or emotional state, then positive clinical outcomes were diminished (Kaelen *et al*., 2018) - see also (Roseman *et al*., 2018).

There have been a small number of recent (Frecska *et al*., 2012; Kuypers *et al*., 2016) and historical reports (Harman *et al*., 1966; Janiger and Derios, 1989; McGlothlin *et al*., 1967) on enhancements in creative thinking in relation to psychedelics. However, this effect appears to be reserved for the divergent, explorative component of the creative process rather than the convergent aspect (Kuypers *et al*., 2016), which may depend more on critical thinking - and which may be impaired (at least acutely) under psychedelics (Carter *et al*., 2005; Kuypers *et al*., 2016). Bold claims have been made about the potential of so-called psychedelic 'microdosing' to enhance cognition (Waldmana, 2017; Fadiman, 2017) but as yet, there has been no published scientific verifications of this. If evidence was to accrue however, attunement of brain dynamics closer to criticality and an associated flexibility of thought could be considered a candidate mechanism - see (Carhart-Harris and Nutt, 2017) for relevant discussions. We should also be mindful of some of the conceptual dangers of super-criticality raised above however, namely (hypo)mania and so-called 'spiritual bypassing'.

Lastly, it is worth reflecting whether enhanced criticality under psychedelics (Atasoy *et al*., 2017) may express in other functionally useful ways. As touched on earlier, the ability of psychedelics to relax prior assumptions may provide the necessary preconditions for the emergence of spontaneous insight. Conceptually, it seems reasonable to suppose that attunement of brain activity towards criticality may be a mechanism underlying spontaneous insight under psychedelics (Atasoy *et al*., 2017). Avalanche-phenomena and/or cascading processes in responses to intrinsic perturbation are signatures of critical systems (Petermann *et al*., 2009) and may be involved in the disinhibition and associated 'release' of previously inhibited information under psychedelics (Alonso *et al*., 2015; Carhart-Harris *et al*., 2014; Kaelen *et al*., 2016). The collapse of functional hierarchies that serve to maintain the status quo may also be key, enabling freer communication between the different levels - such as between the evolutionarily older emotional circuitry of the brain (e.g. the limbic system) and the cortex, perhaps through periodic cascades propogating through the system (e.g. see Kaelen *et al*., 2016). These matters are speculative but deserving of discussion - if only to earmark them for the future when it is easier to formulate our hypotheses more clearly and test them accordingly.

> "The unconscious is a thing of nature." (Carl Jung)
>
> "In all chaos there is cosmos, in all disorder, a secret order." (Carl Jung)

8. Serotonin and the entropic brain

Before concluding this paper, it seems appropriate to link in recent advances in serotonin research to the entropic brain hypothesis. A particularly exciting development is the discovery that unlike the dopamine system (Schultz, 2016), serotonin appears not to encode classic reward/punishment information but rather value-nonspecific 'surprise' (Matias *et al*., 2017). More specifically, optogenetic techniques in mice have revealed that serotonin expressing neurons within the dorsal raphe nuclei fire in response to unexpected outcomes independent of their value sign (Matias *et al*., 2017). This matter is particularly intriguing as averaged surprise is formally equivalent to uncertainty, and is therefore effectively synonymous with entropy (Bestmann *et al*., 2008). Key questions then ensue, why does this happen, and what function does it serve?[7]

One possible interpretation is that serotonin works to relax prior assumptions so as to weaken perseverative/habitual responding (Carhart-Harris and Nutt, 2017; Matias *et al*., 2017). This relaxation of prior assumptions may be done to facilitate new learning, in conditions where prior assumptions become counterproductive and/or when the agent's environmental conditions are so volatile and changeable that heightened flexibility and exploration become the optimal strategies (Carhart-Harris and Nutt, 2017). Related ideas were recently discussed in a major review paper on brain serotonin function, where the significant pro-plasticity effects of serotonin were ascribed to increased signalling at the excitatory serotonin 2A receptor subtype (Carhart-Harris and Nutt, 2017). Indeed, signalling at other serotonin receptors (e.g. the postsynaptic serotonin 1A receptor subtype) may similarly encode behavioural responses to uncertainty, albeit in a different way, e.g. through enhancing one's endurance of uncertainty through stress-moderation, rather than adaption to it through changes in outlook and behaviour (Carhart-Harris and Nutt, 2017). Mechanistically, serotonin 2A receptor signalling has been hypothesised to serve a function analogous to 'annealing' in metallurgy or system 'reset' in computing (Carhart-Harris and Nutt, 2017; Carhart-Harris *et al*., 2017c) where through enhanced excitability, the influence of prior beliefs is relaxed - as per a flattened energy landscape - so that new learning can occur.

> "Your assumptions are your window on the world, scrub them off every once in a while, or the light won't come in." (Isaac Asimov)

[7] N.B. Even though psychedelics have been shown to suppress raphe firing, the consequences of such firing are mimicked by direct serotonergic agonism via the psychedelic (Nichols, 2016).

9. Discussion

This article has revisited the so-called entropic brain hypothesis (Carhart-Harris *et al*., 2014). It has cited increasing empirical support for the idea since it was originally published in early 2014 (Carhart-Harris *et al*., 2014) and highlighted a particularly promising measure of brain entropy, Lempel-Ziv, that has proved to be informative about conscious level in disorders of consciousness (Casali *et al*., 2013), pharmacologically induced loss of consciousness (Schartner *et al*., 2015; Zhang *et al*., 2001) and psychedelicinduced consciousness 'enrichment' (Schartner *et al*., 2017). It has attempted to tackle the question of *what* increased entropy in the brain relates to in terms of conscious experience, proposing that richness of conscious experience, *information content* and *subjective uncertainty* are all close relatives - if not direct counterparts - of increased brain entropy (at least within a critical zone). Specific challenges for the entropic brain theory, and ideas about how it may be tested and advanced, were discussed. Two specific examples were provided of how the entropic brain might be clinically applied, i.e. through using psychedelics to facilitate emotional insight and/or treat disorders of consciousness. The former may be likened to the use of free-association in psychoanalysis, where an open, free-flowing mindstate is encouraged so that the likelihood of spontaneous insight is enhanced. Closing sections focused on properties of criticality in the brain and how these may be accentuated under psychedelics (Atasoy *et al*., 2017) as well as recent advances in serotonin research that chime well with *the entropic brain* and may be usefully combined with it to solve a major riddle in psychopharmacology, namely *what is brain serotonin for*? The proposed solution being: to differentially encode behavioural responses to uncertainty. See (Carhart-Harris and Nutt, 2017) for a more focused discussion of this matter.

Like the original entropic brain paper (Carhart-Harris *et al*., 2014), this updated version can be considered

speculative and forward looking. This approach is vulnerable to critique (Papo, 2016) but may also be a strength. It is worth reflecting that the major arguments and hypotheses of the original entropic brain paper have stood up well to empirical scrutiny, e.g. that brain entropy is enhanced under psychedelics (Lebedev *et al*., 2016; Schartner *et al*., 2017; Tagliazucchi *et al*., 2014; Viol *et al*., 2017) and that the 'psychedelic-brain' exhibits more pronounced signatures of criticality than normal waking consciousness (Atasoy *et al*., 2017).

It may be noted however, that some of the themes and terminology used in the original paper, e.g. 'primary and secondary consciousness', 'the ego' and the default-mode network, have been omitted from the present contribution. There is no conscious agenda behind this, other than a desire to focus on the most pertinent and timely topics, done in the interests of parsimony and concision. What is left out of the present paper should not be considered 'retracted' but rather side-stepped for the time being, in the interests of expediency. It should be clearly stated however, that the position that psychedelic research offers a unique opportunity for major principles of psychoanalytic theory to be tested, verified and revived is still very much maintained. There is a door ajar here for psychoanalytically-minded experimental psychologists and neuroscientists to open and walk through.

> "Until you make the unconscious conscious it will direct your life and you will call it fate." (Carl Jung)

> "These substances [psychedelics] function as unspecific amplifiers that increase the energetic niveau in the psyche and make the deep unconscious dynamics available for conscious processing. This unique property of psychedelics makes it possible to study psychological undercurrents that govern our experiences and behaviors to a depth that cannot be matched by any other methods and tools available in modern mainstream science." (Stanislav Grof)

Briefly, one specific hypothesis contained in the original paper (Carhart-Harris *et al*., 2014) that has not stood the test of time, can now be revised, namely that the brain during seizure is sub-critical in relation to normal waking consciousness; in fact, evidence suggests it is super-critical (Meisel *et al*., 2012) - which, with the benefit of hindsight, makes much more sense.

About the specific limitations of the present paper, it has been selective in its focus, and unlike the original (Carhart-Harris *et al*., 2014), has said little about other altered states of consciousness in which entropy may be elevated above the normal waking baseline. Befitting its richer content and emotional tone, it has been shown that REM sleep is more entropic than NREM sleep (Abasolo *et al*., 2015; Burioka *et al*., 2005) but what about psychosis? The variegated nature of this disorder means we must be cautious about making too general and therefore misleading statements about it. For example, we can speculate that whereas entropy/uncertainty/content may be elevated in manic states (e.g. see Thomasson *et al*., 2002) and early and acute psychotic episodes, it may be suppressed once a fixed delusion has formed - and/or an antipsychotic and/or mood-stabilising medication is introduced and becomes effective - for example see (Méndez *et al*., 2012) for evidence of decreased brain entropy after treatment with mirtazapine for depression.

Also, while the literature is replete with studies applying entropy/complexity measures to EEG data recorded in the context of anaesthetics and sedatives, it is surprisingly difficult to find studies in which the same measures have been applied to EEG data recorded after acute administration of a stimulant (although see - Sun *et al*., 2007). Stimulants would be particularly interesting controls for psychedelics, in terms of demonstrating the specificity of the proposed relationship between brain entropy and richness of conscious experience and subjective uncertainty. Until such comparisons are made, it is not possible to reject the possibility that brain entropy is merely an index of "alertness" or "arousal" - as has been suggested previously (Mateos *et al*. 2018) - although indirect evidence tentatively suggests that this alternative explanation is not compelling (Sun *et al*., 2007; Liu *et al*., 1997; Zarjam *et al*., 2012). It seems more reasonable to suppose however, that altered states of consciousness induced by non-serotonergic psychedelics, deliriants and/or dissociatives, that share some of the phenomenological features the classic serotonergic psychedelics, e.g. enriched and changeable contents of consciousness and a sense of uncertainty, might also exhibit heightened entropic brain activity, as was recently demonstrated with the NMDA receptor antagonist ketamine for example (Schartner *et al*., 2017).

Another limitation of the present paper is that although explicit mention has been given to the Lempel-Ziv

measure (Schartner *et al*., 2015), only general statements about it have been made - for greater detail see (Schartner *et al*., 2015; Zhang *et al*., 2001). For example, perhaps there are reasons to focus on the compressibility of signals detected from specific spatial locations when studying specific subjective phenomena (e.g. occipital sensors and visual phenomena) or to improve the temporal precision of our sampling so as to more accurately map between neurophysiological and phenomenological events or epochs - as discussed above. It is hoped that more nuanced hypotheses arising from the entropic brain theory can be tested in the future.

rain theory can be tested in the future. Relatedly, brain entropy has been treated here as a global brain phenomenon but there are reasons to be believe that spatial localisation is relevant to both the action of psychedelics and the neurobiology of consciousness. For example, the serotonin 2A receptors that appear to be the key trigger receptors for the psychedelic experience (Nichols, 2016) have their densest expression in high-level cortical regions belonging to the default-mode network (Beliveau *et al*. 2017) and this network, as well as other fronto-parietal networks, have been closely implicated in consciousness regulation (Guldenmund *et al*., 2016) - as they have in the psychedelic state (Tagliazucchi *et al*., 2016b; Carhart-Harris *et al*., 2016b).

Another key issue deserving of focus before closing, is the matter of the relationship between entropy and criticality. It seems reasonable to infer that such a relationship exists but nothing specific has yet been said about this. Is it more accurate to describe the psychedelic brain as 'critical' or 'dynamically instable' than 'entropic'? Is there a limit to the rule that increased brain entropy relates to increased richness of conscious content? The answer to this last question is "probably yes", and more specifically, it seems likely that there is a zone of criticality (Moretti and Munoz, 2013) above which any further increases in brain entropy create a state of mind and brain that is incapable of integrating information into coherent 'wholes' (Gallimore, 2015). Anecdotal reports of complete and/or near-complete loss of consciousness under psychedelics can be found (https://erowid.org/experiences/) but are rare. Thus, generally speaking, the entropic brain principle, that increased brain entropy relates to an increased richness of conscious experience, may be said to stand, but only within an upper as well as a lower limit (Fig. 1). It is interesting to reflect that identifying the point at which conscious awareness is lost with psychedelics may be informative about consciousness itself - in the same way that anaesthetic-induced loss of consciousness has been well used to study consciousness so effectively. Questions about the ethics and safety of giving sufficiently high enough doses of psychedelics to achieve loss of consciousness may preclude this work from ever being done however - at least for the foreseeable future; although potent short-acting psychedelics such as DMT and 5-MeO-DMT may help surmount this issue. Another intriguing question is whether so-called "access consciousness" is more readily lost than "phenomenal consciousness" (Block, 2005) in the extreme, high-entropy psychedelic state.

Finally, but importantly, it must be conceded that applying entropy measures to brain physiology is not a new endeavour (Klonowski *et al*., 1999; Nandrino *et al*., 1994; Papo, 2016; Zhang *et al*., 2001) and theories on the relationship between brain functional complexity and subjective experience have a history that should be properly acknowledged (Barttfeld *et al*., 2015; Basar and Guntekin, 2009; Seth *et al*., 2011; Tononi and Edelman, 1998; Tononi *et al*., 1994). Perhaps the most influential theory on the brain basis of consciousness, is the so-called 'integrated-information theory' of consciousness (Tononi *et al*., 2016), and this includes as one part of it, a measure of brain entropy/complexity. Indeed, it has been said in a critique of the original entropic brain paper that entropy/complexity measures applied to brain function merely 'depurate' the integration term from the integrated-information theory (Papo, 2016). This charge is readily accepted but the position is taken here that the entropy/complexity component of the integrated-information theory provides the major share of its explanatory power. This position is empirically substantiated, since it is arguably the complexity/entropy more than the integration measures per se that are so impressively predicting conscious level (Casali *et al*., 2013; Casarotto *et al*., 2016; Schartner *et al*., 2015; Zhang *et al*., 2001). While the requirement for integration is not disregarded (e.g. see the discussion on entropy and criticality in the previous paragraph) and may indeed by critical for access consciousness particularly - it is felt that the key properties of such integration, necessary for consciousness, have not yet been clearly delineated - although see the Global Workspace theory (Baars, 1993) for an appealing model on the importance of integration to conscious experience, as well as more recent work on large-scale (Tagliazucchi *et al*., 2016a) and long-range connectivity (Kotchoubey *et al*., 2013). It also remains possible that a role for integration may be implied within entropy/complexity measures; for example, future work may discover the point or zone within which entropy exceeds a critical threshold at which no one coherent, large-scale spatiotemporal configuration can dominate the brain for a sufficiently long-enough for access consciousness to be possible.

All models are incomplete and the entropic brain is no exception - but it was conceived and intended to offer a simple and useful heuristic, enabling relatively seamless translations to be made between a quantitative measure of the richness of brain activity and the richness of subjective experience.

10. Conclusions

In summary, four years on from the publication of the original entropic brain hypothesis, the present paper has sought to reflect on its influence, reliability and future scientific and clinical value. The position is maintained that entropy represents a uniquely powerful bridging tool for human neuroscience that will enable a better understanding of the mind-brain relationship and mechanics of consciousness, including how we may treat its abnormalities.

Acknowledgements

Imperial College London's neuroscientific research with psychedelics has been funded entirely through charitable donations. In this regard, deserving special credit for their early and enduring support is the Beckley Foundation, and particularly its Founder and Director Amanda Feilding. The author is presently supported by the Alex Mosley Charitable Trust. He is deeply grateful to Professor David Nutt for his support for his research, and also grateful to Leor Roseman and Christopher Timmermann for reading and commenting on an earlier draft of this manuscript. Christopher Timmermann's comments on neurophenomenology and microphenomenology have been particularly helpful. The author would also like to acknowledge conversations with Enzo Tagliazucchi, Jacobo Sitt, Robert Leech and Gregory Scott regarding the idea of using psychedelics to elevate conscious content in disorders of consciousness. Conversations with Dr Scott (NIHR clinical lecturer) have been particularly advanced. This is a shared idea which we hope to pursue further in the future, pending funding and the relevant approvals.

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