

# Accepted Manuscript

The entropic brain - Revisited

Robin L. Carhart-Harris

PII: S0028-3908(18)30117-5

DOI: [10.1016/j.neuropharm.2018.03.010](https://doi.org/10.1016/j.neuropharm.2018.03.010)

Reference: NP 7113

To appear in: *Neuropharmacology*

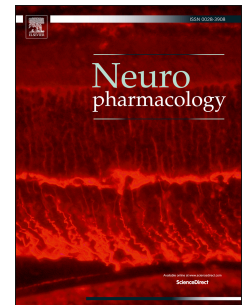
Received Date: 9 January 2018

Revised Date: 15 February 2018

Accepted Date: 12 March 2018

Please cite this article as: Carhart-Harris, R.L., The entropic brain - Revisited, *Neuropharmacology* (2018), doi: [10.1016/j.neuropharm.2018.03.010](https://doi.org/10.1016/j.neuropharm.2018.03.010).

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



**The entropic brain - revisited**

<sup>1</sup>Robin L Carhart-Harris

<sup>1</sup>Psychedelic Research Group, Neuropsychopharmacology Unit, Imperial College London  
[r.carhart-harris@imperial.ac.uk](mailto:r.carhart-harris@imperial.ac.uk)

**Abstract** (162 words)

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.

## 1. Introduction (word count, 7,800)

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 its ‘richness’, 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 synonymous and that entropic-brain-states are experienced as content-rich but unpredictable and therefore uncertain. The theory lends heavily from research with ‘classic’ psychedelic<sup>1</sup> compounds, which have been shown to robustly and reliably increase brain entropy within the ‘psychedelic state’.

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<sup>2</sup>. 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; Carhart-Harris et al., 2017c; Kaelen et al., 2016; Kraehenmann et al., 2015; Kraehenmann et al., 2016; Lebedev et al., 2016; Lebedev et al., 2015; Mueller et al., 2017; Muller et al., 2017; Palhano-Fontes et al., 2015;

---

<sup>1</sup> 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.

<sup>2</sup> 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.

Petri et al., 2014; Preller et al., 2017; Preller et al., 2016; Roseman et al., 2017; Roseman et al., 2014; Roseman et al., 2016; 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; Tagliazucchi et al., 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; Kraehenmann et al., 2016; Mueller et al., 2017; Muller et al., 2017; Preller et al., 2017; Preller et al., 2016; 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; Carhart-Harris et al., 2017c; Kaelen

et al., 2016; Lebedev et al., 2016; Lebedev et al., 2015; Petri et al., 2014; Roseman et al., 2017; Roseman et al., 2014; Roseman et al., 2016; 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 entropy 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).

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 cognitive neuroscientists in the same way that the remarkable psychological effects and clinical potential of psychedelics have piqued the interest of philosophers (Milliere, 2017; Letherby, 2016), psychologists (Watts et al., 2017) and psychiatrists (Carhart-Harris and Goodwin, 2017b).

### **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., 2013b; 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 thinking and focus (Carter et al., 2005; Kuypers et al., 2016).

It is proposed here that, to a critical point, beyond which the ability to consciously reflect 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 our view 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., 2013a; Massimini et al., 2009) or responses within specific behavioural paradigms, may have 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 considerable 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’; 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, ‘on-going’ 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 (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 (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; Scharfner 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’ (*dēlein*, *δηλεῖν*) - to lay emphasis on their *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., 2017; 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<sup>3</sup> (Nutt et al., 2013), let alone testing such an abstract and paradigm-challenging idea<sup>4</sup>. 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)<sup>5</sup>. This measure

---

<sup>3</sup> 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”.

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

<sup>5</sup> 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.

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 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 discrete epochs under psychedelics. If we accept this possibility, how then might we capture such epochs and assess their relationship to insight?

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 over-hanging 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 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 choice, 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 minutes, and complete scanning sessions cover a period of approximately 60 minutes. 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 seconds). Although unconventional, if using fMRI for example, one might dedicate an entire scanning session of e.g. approximately 45 minutes 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 un conducive 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 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. increased 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 'brain-storming' 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 followed by more protracted processes of 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., 2015; Bedi et al., 2014). 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 displayed via ‘noisier’ brain-to-mind 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., 2013b; 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. (Casali et al., 2013b) 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 entropy 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., 2013b). An even more recent study showed that the same Lempel-Ziv measure applied to spontaneous (i.e. resting-state, 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 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 conservatism and cynicism, 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 lent support to the association between the phenomenology of the psychedelic state and the dream state (Kraehenmann et al. 2017; Sanz & Tagliazucchi, 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, 2017a), 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 ‘micro-dosing’ 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<sup>6</sup> 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

---

<sup>6</sup> A zone poised between complete order and disorder within a complex dynamical system, at which certain signature properties are exhibited such as a maximal repertoire of dynamic sub-states, fractal ‘self-similarity’ or power-law scaling, and maximal sensitivity to perturbation (Bak, 1997).

established (Hahn et al., 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 ‘order’ or sub-criticality within this zone than ‘disorder’ or super-criticality (Atasoy et al., 2017; Priesemann et al., 2013; Priesemann et al., 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 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., 2017a; Carhart-Harris et al., 2016a; 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. 2015; Akar et al. 2015) – although contradictory evidence (e.g. Méndez et al. 2012) suggests that the relationship between entropy and depression may be subtype and state specific (e.g. see Akar et al. 2015 and Zhang et al. 2015), 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 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 mania-related symptoms such as 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 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 (Freckska 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 (Waldman, 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) - but we should also be mindful of some of the conceptual dangers of super-criticality raised above, namely mania and ‘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 (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 and test them.

*“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-free ‘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 (Matias et al., 2017). This matter is particularly intriguing as averaged surprise is formally equivalent to uncertainty, and is therefore synonymous with entropy (Bestmann et al., 2008). Key questions then ensue, why does this happen, and what function does it serve?<sup>7</sup>

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 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 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.

---

<sup>7</sup> 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).

*"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)

## 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., 2013b), pharmacologically induced loss of consciousness (Schartner et al., 2015; Zhang et al., 2001) and psychedelic-induced 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. 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 in the interests of parsimony and concision. What is left out of the present paper should not be considered ‘retracted’ but rather side-stepped 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 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 and can now be revised, is 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. 2017) – although intuitively, this possibility seems unlikely, as indirect evidence tentatively suggests (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, deliriant 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 of entropy (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.

Relatedly, brain entropy has been treated here as a global brain phenomenon but there are reasons to 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. 2016) 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 unstable’ 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 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 not to an upper, as well as a lower limit (figure 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 exploited. 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.

Insert figure here

Figure 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. Psychedelic compounds are proposed to shift brain entropy and conscious content upwards, i.e. 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 assuredness they confer. Sedatives and anaesthetics shift the brain downwards, i.e. into a subcritical zone and eventual unconsciousness. 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.

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 also 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., 2013b; 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 be critical for (access) consciousness – it is felt that the key properties of such integration, necessary for consciousness, have not yet been properly established - 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 single, coherent, large-scale spatiotemporal configuration can dominate the brain for a sufficiently long-enough for access consciousness to occur.

All models are incomplete and the entropic brain is no exception - but it was conceived and intended to be 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 utility. 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 this 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 has 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) are particularly advanced. This is a shared idea which we hope to pursue further in the future, pending funding and the relevant approvals.

## References

- Abasolo, D., Simons, S., Morgado da Silva, R., Tononi, G., Vyazovskiy, V. V., 2015. Lempel-Ziv complexity of cortical activity during sleep and waking in rats. *J Neurophysiol* 113, 2742-2752.
- Alonso, J. F., Romero, S., Mananas, M. A., Riba, J., 2015. Serotonergic psychedelics temporarily modify information transfer in humans. *Int J Neuropsychopharmacol* 18.
- Atasoy, S., Roseman, L., Kaelen, M., Kringelbach, M. L., Deco, G., Carhart-Harris, R. L., 2017. Connectome-harmonic decomposition of human brain activity reveals dynamical repertoire re-organization under LSD. *Sci Rep* 7, 17661.
- Baars, B. J., 1993. How does a serial, integrated and very limited stream of consciousness emerge from a nervous system that is mostly unconscious, distributed, parallel and of enormous capacity? *Ciba Found Symp* 174, 282-290; discussion 291-303.
- Bak, P., 1997. *How nature works : the science of self-organized criticality*. Oxford University Press, Oxford.
- Barrett, F. S., Preller, K. H., Herdener, M., Janata, P., Vollenweider, F. X., 2017. Serotonin 2A Receptor Signaling Underlies LSD-induced Alteration of the Neural Response to Dynamic Changes in Music. *Cereb Cortex*, 1-12.
- Barttfeld, P., Uhrig, L., Sitt, J. D., Sigman, M., Jarraya, B., Dehaene, S., 2015. Signature of consciousness in the dynamics of resting-state brain activity. *Proc Natl Acad Sci U S A* 112, 887-892.
- Basar, E., Guntekin, B., 2009. Darwin's evolution theory, brain oscillations, and complex brain function in a new "Cartesian view". *Int J Psychophysiol* 71, 2-8.
- Bedi, G., Carrillo, F., Cecchi, G. A., Slezak, D. F., Sigman, M., Mota, N. B., Ribeiro, S., Javitt, D. C., Copelli, M., Corcoran, C. M., 2015. Automated analysis of free speech predicts psychosis onset in high-risk youths. *NPJ Schizophr* 1, 15030.
- Bedi, G., Cecchi, G. A., Slezak, D. F., Carrillo, F., Sigman, M., de Wit, H., 2014. A window into the intoxicated mind? Speech as an index of psychoactive drug effects. *Neuropsychopharmacology* 39, 2340-2348.
- Beliveau V, Ganz M, Feng L, Ozenne B, Højgaard L, Fisher PM, Svarer C, Greve DN, Knudsen GM., 2017. A High-Resolution In Vivo Atlas of the Human Brain's Serotonin System. *J Neurosci* 37(1):120-128.
- Ben-Naim, A., 2007. *Entropy demystified : the second law reduced to plain common sense*. World Scientific, Hackensack, N.J.

- Bestmann, S., Harrison, L. M., Blankenburg, F., Mars, R. B., Haggard, P., Friston, K. J., Rothwell, J. C., 2008. Influence of uncertainty and surprise on human corticospinal excitability during preparation for action. *Curr Biol* 18, 775-780.
- Block N. Two neural correlates of consciousness. *Trends Cogn Sci*. 2005 Feb;9(2):46-52.
- Bogenschutz, M. P., Johnson, M. W., 2016. Classic hallucinogens in the treatment of addictions. *Prog Neuropsychopharmacol Biol Psychiatry* 64, 250-258.
- Bouso, J. C., Palhano-Fontes, F., Rodriguez-Fornells, A., Ribeiro, S., Sanches, R., Crippa, J. A., Hallak, J. E., de Araujo, D. B., Riba, J., 2015. Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *Eur Neuropsychopharmacol* 25, 483-492.
- Burioka, N., Miyata, M., Cornelissen, G., Halberg, F., Takeshima, T., Kaplan, D. T., Suyama, H., Endo, M., Maegaki, Y., Nomura, T., Tomita, Y., Nakashima, K., Shimizu, E., 2005. Approximate entropy in the electroencephalogram during wake and sleep. *Clin EEG Neurosci* 36, 21-24.
- Carbonaro TM, Johnson MW, Hurwitz E, Griffiths RR., 2017. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. *Psychopharmacology (Berl)*. doi: 10.1007/s00213-017-4769-4.
- Carhart-Harris, R., 2007. Waves of the unconscious: The neurophysiology of dreamlike phenomena and its implications for the psychodynamic model of the mind. *Neuro-Psychoanalysis*.9, pp.
- Carhart-Harris, R., Nutt, D., 2014. Was it a vision or a waking dream? *Front Psychol* 5, 255.
- Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., Nutt, D. J., 2017a. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl)*.
- Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., Nutt, D. J., 2016a. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *Lancet Psychiatry* 3, 619-627.
- Carhart-Harris, R. L., Erritzoe, D., Haijen, E., Kaelen, M., Watts, R., 2017b. Psychedelics and connectedness. *Psychopharmacology (Berl)*.
- Carhart-Harris, R. L., Friston, K. J., 2010. The default-mode, ego-functions and free-energy: a neurobiological account of Freudian ideas. *Brain* 133, 1265-1283.
- Carhart-Harris, R. L., Goodwin, G. M., 2017a. The Therapeutic Potential of Psychedelic Drugs: Past, Present and Future. *Neuropsychopharmacology*.
- Carhart-Harris, R. L., Goodwin, G. M., 2017b. The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. *Neuropsychopharmacology* 42, 2105-2113.
- Carhart-Harris, R. L., Leech, R., Hellyer, P. J., Shanahan, M., Feilding, A., Tagliazucchi, E., Chialvo, D. R., Nutt, D., 2014. The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front Hum Neurosci* 8, 20.
- Carhart-Harris, R. L., Muthukumaraswamy, S., Roseman, L., Kaelen, M., Droog, W., Murphy, K., Tagliazucchi, E., Schenberg, E. E., Nest, T., Orban, C., Leech, R., Williams, L. T., Williams, T. M., Bolstridge, M., Sessa, B., McGonigle, J., Sereno, M. I., Nichols, D., Hellyer, P. J., Hobden, P., Evans, J., Singh, K. D., Wise, R. G., Curran, H. V., Feilding, A., Nutt, D. J., 2016b. Neural

correlates of the LSD experience revealed by multimodal neuroimaging. *Proc Natl Acad Sci U S A* 113, 4853-4858.

Carhart-Harris, R. L., Nutt, D. J., 2017. Serotonin and brain function: a tale of two receptors. *J Psychopharmacol*, 269881117725915.

Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., Nutt, D. J., 2017c. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Sci Rep* 7, 13187.

Carhart-Harris, R. L., Roseman, L., Haijen, E., Erritzoe, D.E., Watts, R., Branchi, I., Kaelen, M., 2018. Psychedelics and the essential importance of context. *J Psychopharm.* Accepted and in press.

Carrillo F, Sigman M, Fernández Slezak D, Ashton P, Fitzgerald L, Stroud J, Nutt DJ, Carhart-Harris RL., 2018. Natural speech algorithm applied to baseline interview data can predict which patients will respond to psilocybin for treatment-resistant depression. *J Affect Disord.* 2018 Apr 1;230:84-86. doi: 10.1016/j.jad.2018.01.006.

Carter, O. L., Burr, D. C., Pettigrew, J. D., Wallis, G. M., Hasler, F., Vollenweider, F. X., 2005. Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. *J Cogn Neurosci* 17, 1497-1508.

Casali, A. G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K. R., Casarotto, S., Bruno, M.-A., Laureys, S., Tononi, G., Massimini, M., 2013a. A theoretically based index of consciousness independent of sensory processing and behavior. *Science translational medicine* 5, 198ra105.

Casali, A. G., Gosseries, O., Rosanova, M., Boly, M., Sarasso, S., Casali, K. R., Casarotto, S., Bruno, M. A., Laureys, S., Tononi, G., Massimini, M., 2013b. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med* 5, 198ra105.

Casarotto, S., Comanducci, A., Rosanova, M., Sarasso, S., Fecchio, M., Napolitani, M., Pigorini, A., A, G. C., Trimarchi, P. D., Boly, M., Gosseries, O., Bodart, O., Curto, F., Landi, C., Mariotti, M., Devalle, G., Laureys, S., Tononi, G., Massimini, M., 2016. Stratification of unresponsive patients by an independently validated index of brain complexity. *Ann Neurol* 80, 718-729.

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., Schooler, J. W., 2009. Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proc Natl Acad Sci U S A* 106, 8719-8724.

Cohen, J. D., McClure, S. M., Yu, A. J., 2007. Should I stay or should I go? How the human brain manages the trade-off between exploitation and exploration. *Philos Trans R Soc Lond B Biol Sci* 362, 933-942.

Cohen, S., 1964. *The beyond within; the LSD story*, by Sidney Cohen. Foreword by Gardner Murphy. New York, Atheneum.

Deco, G., Tagliazucchi, E., Laufs, H., Sanjuán, A., & Kringelbach, M. L. 2017. Novel intrinsic ignition method measuring local-global integration characterizes wakefulness and deep sleep. *Eneuro*, 4(5), ENEURO-0106.

Deco, G., Kringelbach, M. L., 2017. Hierarchy of Information Processing in the Brain: A Novel 'Intrinsic Ignition' Framework. *Neuron* 94, 961-968.

Edwards, C. L., Ruby, P. M., Malinowski, J. E., Bennett, P. D., Blagrove, M. T., 2013. Dreaming and insight. *Front Psychol* 4, 979.



- Ellamil M, Fox KC, Dixon ML, Pritchard S, Todd RM, Thompson E, Christoff K., 2016. Dynamics of neural recruitment surrounding the spontaneous arising of thoughts in experienced mindfulness practitioners. *Neuroimage* 136:186-96.
- Fadiman, J. 2017. Microdosing. Presentation at Psychedelic Science conference. Oakland, California.
- Fagerholm, E. D., Lorenz, R., Scott, G., Dinov, M., Hellyer, P. J., Mirzaei, N., Leeson, C., Carmichael, D. W., Sharp, D. J., Shew, W. L., Leech, R., 2015. Cascades and cognitive state: focused attention incurs subcritical dynamics. *J Neurosci* 35, 4626-4634.
- Freksa, E., More, C. E., Vargha, A., Luna, L. E., 2012. Enhancement of creative expression and entoptic phenomena as after-effects of repeated ayahuasca ceremonies. *J Psychoactive Drugs* 44, 191-199.
- Gallimore, A. R., 2015. Restructuring consciousness -the psychedelic state in light of integrated information theory. *Front Hum Neurosci* 9, 346.
- Giacino, J. T., Fins, J. J., Laureys, S., Schiff, N. D., 2014. Disorders of consciousness after acquired brain injury: the state of the science. *Nat Rev Neurol* 10, 99-114.
- Gleick, J., 2011. *The information : a history, a theory, a flood*. Fourth Estate, London.
- Grof, S., 1979. *Realms of the human unconscious : Observations from LSD research*. Souvenir Press, London.
- Guilford, J. P., 1967. *The nature of human intelligence*. New York: McGraw-Hill Book Co.
- Hahn, G., Ponce-Alvarez, A., Monier, C., Benvenuti, G., Kumar, A., Chavane, F., Deco, G., Guldenmund P, Vanhaudenhuyse A, Boly M, Laureys S, Soddu A., 2012. A default mode of brain function in altered states of consciousness. *Arch Ital Biol.* 150(2-3):107-21.
- Fregnac, Y., 2017. Spontaneous cortical activity is transiently poised close to criticality. *PLoS Comput Biol* 13, e1005543.
- Harman, W. W., McKim, R. H., Mogar, R. E., Fadiman, J., Stolaroff, M. J., 1966. Psychedelic agents in creative problem-solving: a pilot study. *Psychol Rep* 19, 211-227.
- Hartogsohn, I., 2016. Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *J Psychopharmacol* 30, 1259-1267.
- Hesse, J., Gross, T., 2014. Self-organized criticality as a fundamental property of neural systems. *Frontiers in systems neuroscience* 8, 166.
- Huxley, A., 1959. *The Doors of Perception and Heaven and Hell*. Penguin Books, Harmondsworth.
- Huxley, A., Palmer, C., Horowitz, M., 1977. *Moksha : writings on psychedelics and the visionary experience (1931-1963)*. Stonehill, New York.
- Janiger, O., Derios, M. D., 1989. LSD and Creativity. *J Psychoactive Drugs* 21, 129-134.
- Kaelen, M., Roseman, L., Kahan, J., Santos-Ribeiro, A., Orban, C., Lorenz, R., Barrett, F. S., Bolstridge, M., Williams, T., Williams, L., Wall, M. B., Feilding, A., Muthukumaraswamy, S., Nutt, D. J., Carhart-Harris, R., 2016. LSD modulates music-induced imagery via changes in parahippocampal connectivity. *Eur Neuropsychopharmacol*.
- Kaelen, M., Giribaldi, B., Raine, J., Evans, L., Timmerman-Slater, C., Rodriguez, N. Roseman, L., Feilding, A., Nutt, D., Carhart-Harris, R. 2018. The hidden therapist: Evidence for a central role of music in psychedelic therapy. *Psychopharmacology* (Springer). Accepted. In Press.
- Klonowski, W., Jernajczyk, W., Niedzielska, K., Rydz, A., Stepień, R., 1999. Quantitative measure of complexity of EEG signal dynamics. *Acta Neurobiol Exp (Wars)* 59, 315-321.
- Kotchoubey B, Merz S, Lang S, Markl A, Müller F, Yu T, Schwarzbauer C., 2013. Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. *J Neurol* 260(4):975-83.

- Kraehenmann, R., Pokorny, D., Aicher, H., Preller, K. H., Pokorny, T., Bosch, O. G., Seifritz, E., Vollenweider, F. X., 2017. LSD Increases Primary Process Thinking via Serotonin 2A Receptor Activation. *Front Pharmacol* 8, 814.
- Kraehenmann, R., Preller, K. H., Scheidegger, M., Pokorny, T., Bosch, O. G., Seifritz, E., Vollenweider, F. X., 2015. Psilocybin-Induced Decrease in Amygdala Reactivity Correlates with Enhanced Positive Mood in Healthy Volunteers. *Biol Psychiatry* 78, 572-581.
- Kraehenmann, R., Schmidt, A., Friston, K., Preller, K. H., Seifritz, E., Vollenweider, F. X., 2016. The mixed serotonin receptor agonist psilocybin reduces threat-induced modulation of amygdala connectivity. *Neuroimage Clin* 11, 53-60.
- Kraehenmann R, Pokorny D, Vollenweider L, Preller KH, Pokorny T, Seifritz E, Vollenweider FX., 2017. Dreamlike effects of LSD on waking imagery in humans depend on serotonin 2A receptor activation. *Psychopharmacology (Berl)*. (13):2031-2046. doi: 10.1007/s00213-017-4610-0.
- Kuypers, K. P., Riba, J., de la Fuente Revenga, M., Barker, S., Theunissen, E. L., Ramaekers, J. G., 2016. Ayahuasca enhances creative divergent thinking while decreasing conventional convergent thinking. *Psychopharmacology (Berl)* 233, 3395-3403.
- Leary, T., Litwin, G. H., Metzner, R., 1963. Reactions to Psilocybin Administered in a Supportive Environment. *J Nerv Ment Dis* 137, 561-573.
- Lebedev, A. V., Kaelen, M., Lovden, M., Nilsson, J., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., 2016. LSD-induced entropic brain activity predicts subsequent personality change. *Hum Brain Mapp*.
- Lebedev, A. V., Lovden, M., Rosenthal, G., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., 2015. Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Hum Brain Mapp* 36, 3137-3153.
- Letheby C., 2016. The epistemic innocence of psychedelic states. *Conscious Cogn* 39:28-37. doi: 10.1016/j.concog.2015.11.012.
- Leroy, A., Foucher, J. R., Pins, D., Delmaire, C., Thomas, P., Roser, M. M., Lefebvre, S., Amad, A., Fovet, T., Jaafari, N., Jardri, R., 2017. fMRI Capture of Auditory Hallucinations: Validation of the Two-Steps Method. *Hum Brain Mapp* 38, 4966-4979.
- Liu J, He T, Zheng C, Huang Y., 1997. Measuring EEG complexity for studying the state of mental load. *Sheng Wu Yi Xue Gong Cheng Xue Za Zhi*. 14(1):33-7.
- Lubart, T., 2001. Models of the Creative Process: Past, Present and Future. *Creativity Research Journal*. 13. 295-308.
- Massimini, M., Boly, M., Casali, A., Rosanova, M., Tononi, G., 2009. A perturbational approach for evaluating the brain's capacity for consciousness. *Prog Brain Res* 177, 201-214.
- Masters, R. A., 2010. *Spiritual bypassing : when spirituality disconnects us from what really matters*. North Atlantic Books, Berkeley, Calif.
- Mateos DM, Guevara Erra R, Wennberg R, Perez Velazquez JL, 2018. Measures of entropy and complexity in altered states of consciousness. *Cogn Neurodyn* 12(1):73-84.
- Matias, S., Lottem, E., Dugue, G. P., Mainen, Z. F., 2017. Activity patterns of serotonin neurons underlying cognitive flexibility. *Elife* 6.
- McGlothlin, W., Cohen, S., McGlothlin, M. S., 1967. Long lasting effects of LSD on normals. *Arch Gen Psychiatry* 17, 521-532.
- McKenna, D., Riba, J., 2017. *New World Tryptamine Hallucinogens and the Neuroscience of Ayahuasca*. *Curr Top Behav Neurosci*.
- Meisel, C., Storch, A., Hallmeyer-Elgner, S., Bullmore, E., Gross, T., 2012. Failure of adaptive self-organized criticality during epileptic seizure attacks. *PLoS Comput Biol* 8, e1002312.



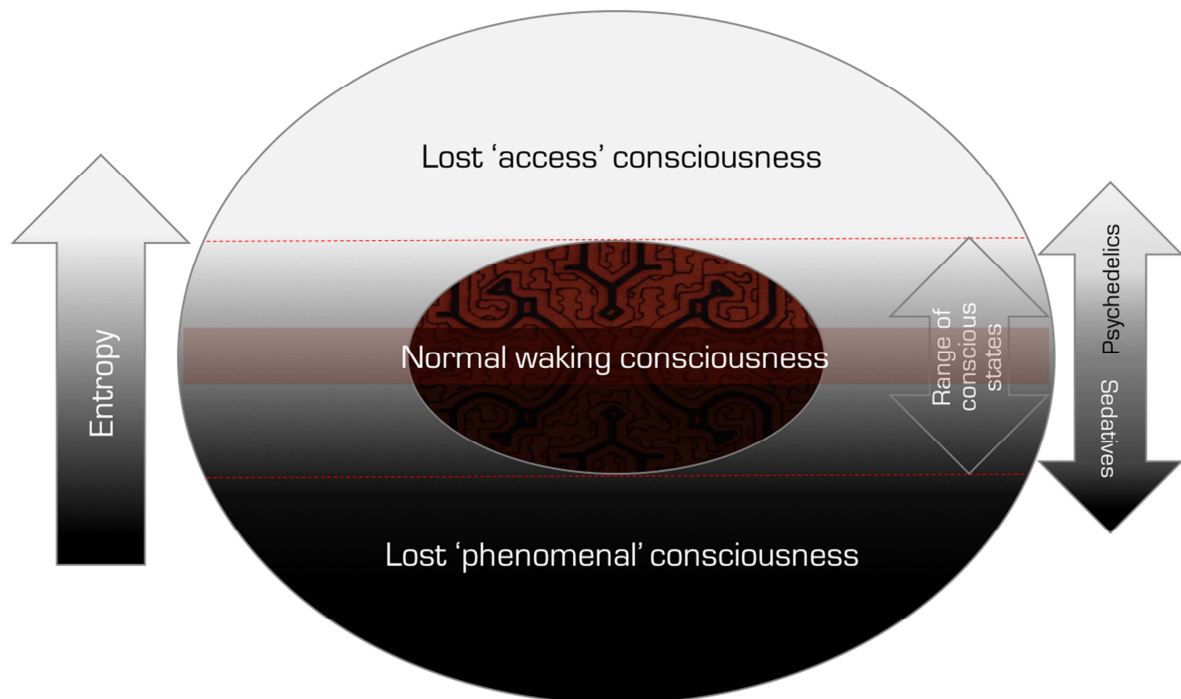
- Méndez MA, Zuluaga P, Hornero R, Gómez C, Escudero J, Rodríguez-Palancas A, Ortiz T, Fernández A., 2012. Complexity analysis of spontaneous brain activity: effects of depression and antidepressant treatment. *J Psychopharmacol* 26(5):636-43.
- Milliere, R., 2017. Looking for the Self: Phenomenology, Neurophysiology and Philosophical Significance of Drug-induced Ego Dissolution. *Front Hum Neurosci* 11, 245.
- Moreno, F. A., Wiegand, C. B., Taitano, E. K., Delgado, P. L., 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry* 67, 1735-1740.
- Moretti, P., Munoz, M. A., 2013. Griffiths phases and the stretching of criticality in brain networks. *Nature communications* 4, 2521.
- Mueller, F., Lenz, C., Dolder, P. C., Harder, S., Schmid, Y., Lang, U. E., Liechti, M. E., Borgwardt, S., 2017. Acute effects of LSD on amygdala activity during processing of fearful stimuli in healthy subjects. *Transl Psychiatry* 7, e1084.
- Muller, F., Lenz, C., Dolder, P., Lang, U., Schmidt, A., Liechti, M., Borgwardt, S., 2017. Increased thalamic resting-state connectivity as a core driver of LSD-induced hallucinations. *Acta Psychiatr Scand* 136, 648-657.
- Muthukumaraswamy, S. D., Carhart-Harris, R. L., Moran, R. J., Brookes, M. J., Williams, T. M., Erritzoe, D., Sessa, B., Papadopoulos, A., Bolstridge, M., Singh, K. D., Feilding, A., Friston, K. J., Nutt, D. J., 2013. Broadband cortical desynchronization underlies the human psychedelic state. *J Neurosci* 33, 15171-15183.
- Muzio, J. N., Roffwarg, H. P., Kaufman, E., 1966. Alterations in the nocturnal sleep cycle resulting from LSD. *Electroencephalogr Clin Neurophysiol* 21, 313-324.
- Nakai, T., Bagarinao, E., Matsuo, K., Ohgami, Y., Kato, C., 2006. Dynamic monitoring of brain activation under visual stimulation using fMRI--the advantage of real-time fMRI with sliding window GLM analysis. *J Neurosci Methods* 157, 158-167.
- Nandrino, J. L., Pezard, L., Martinerie, J., el Massioui, F., Renault, B., Jouvent, R., Allilaire, J. F., Widlocher, D., 1994. Decrease of complexity in EEG as a symptom of depression. *Neuroreport* 5, 528-530.
- Naselaris, T., Prenger, R. J., Kay, K. N., Oliver, M., Gallant, J. L., 2009. Bayesian reconstruction of natural images from human brain activity. *Neuron* 63, 902-915.
- Nichols, D. E., 2016. Psychedelics. *Pharmacological Reviews*, 68, 264-355.
- Nutt, D. J., King, L. A., Nichols, D. E., 2013. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 14, 577-585.
- Olofsen, E., Sleight, J. W., Dahan, A., 2008. Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect. *British Journal of Anaesthesia* 101, 810-821.
- Palhano-Fontes, F., Andrade, K. C., Tofoli, L. F., Santos, A. C., Crippa, J. A. S., Hallak, J. E. C., Ribeiro, S., de Araujo, D. B., 2015. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. *PLoS One* 10, e0118143.
- Papo, D., 2016. Commentary: The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front Hum Neurosci* 10, 423.
- Petermann, T., Thiagarajan, T. C., Lebedev, M. A., Nicoletis, M. A., Chialvo, D. R., Plenz, D., 2009. Spontaneous cortical activity in awake monkeys composed of neuronal avalanches. *Proc Natl Acad Sci U S A* 106, 15921-15926.
- Petitmengin, C., 2017. Enaction as a Lived Experience Towards a Radical Neuropsychophenomenology. *Constructivist Foundations* 12, 139-147.

- Petri, G., Expert, P., Turkheimer, F., Carhart-Harris, R., Nutt, D., Hellyer, P. J., Vaccarino, F., 2014. Homological scaffolds of brain functional networks. *J R Soc Interface* 11, 20140873.
- Pezard, L., Nandrino, J. L., Renault, B., ElMassioui, F., Allilaire, J. F., Muller, J., Varela, F. J., Martinerie, J., 1996. Depression as a dynamical disease. *Biol Psychiatry* 39, 991-999.
- Preller, K. H., Herdener, M., Pokorny, T., Planzer, A., Kraehenmann, R., Stampfli, P., Liechti, M. E., Seifritz, E., Vollenweider, F. X., 2017. The Fabric of Meaning and Subjective Effects in LSD-Induced States Depend on Serotonin 2A Receptor Activation. *Curr Biol* 27, 451-457.
- Preller, K. H., Pokorny, T., Hock, A., Kraehenmann, R., Stampfli, P., Seifritz, E., Scheidegger, M., Vollenweider, F. X., 2016. Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. *Proc Natl Acad Sci U S A* 113, 5119-5124.
- Priesemann, V., Valderrama, M., Wibral, M., Le Van Quyen, M., 2013. Neuronal avalanches differ from wakefulness to deep sleep--evidence from intracranial depth recordings in humans. *PLoS Comput Biol* 9, e1002985.
- Priesemann, V., Wibral, M., Valderrama, M., Propper, R., Le Van Quyen, M., Geisel, T., Triesch, J., Nikolic, D., Munk, M. H., 2014. Spike avalanches in vivo suggest a driven, slightly subcritical brain state. *Front Syst Neurosci* 8, 108.
- Richards, W. A., 2015. Sacred knowledge : psychedelics and religious experiences. Columbia University Press, New York.
- Roseman, L., Demetriou, L., Wall, M. B., Nutt, D. J., Carhart-Harris, R. L., 2017. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. *Neuropharmacology*.
- Roseman, L., Leech, R., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., 2014. The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Front Hum Neurosci* 8, 204.
- Roseman, L., Sereno, M. I., Leech, R., Kaelen, M., Orban, C., McGonigle, J., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., 2016. LSD alters eyes-closed functional connectivity within the early visual cortex in a retinotopic fashion. *Hum Brain Mapp*.
- Roseman L, Nutt, D.J., Carhart-Harris, R.L. 2018. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Frontiers in Pharmacology*. Accepted. In Press.
- Sampedro, F., de la Fuente Revenga, M., Valle, M., Roberto, N., Dominguez-Clave, E., Elices, M., Luna, L. E., Crippa, J. A. S., Hallak, J. E. C., de Araujo, D. B., Friedlander, P., Barker, S. A., Alvarez, E., Soler, J., Pascual, J. C., Feilding, A., Riba, J., 2017. Assessing the Psychedelic "After-Glow" in Ayahuasca Users: Post-Acute Neurometabolic and Functional Connectivity Changes Are Associated with Enhanced Mindfulness Capacities. *Int J Neuropsychopharmacol* 20, 698-711.
- Sanches, R. F., de Lima Osorio, F., Dos Santos, R. G., Macedo, L. R., Maia-de-Oliveira, J. P., Wichert-Ana, L., de Araujo, D. B., Riba, J., Crippa, J. A., Hallak, J. E., 2016. Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study. *J Clin Psychopharmacol* 36, 77-81.
- Sandison, R. A., 1954. Psychological aspects of the LSD treatment of the neuroses. *J Ment Sci* 100, 508-515.
- Schartner, M., Seth, A., Noirhomme, Q., Boly, M., Bruno, M. A., Laureys, S., Barrett, A., 2015. Complexity of Multi-Dimensional Spontaneous EEG Decreases during Propofol Induced General Anaesthesia. *PLoS One* 10, e0133532.

- Schartner, M. M., Carhart-Harris, R. L., Barrett, A. B., Seth, A. K., Muthukumaraswamy, S. D., 2017. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. *Sci Rep* 7, 46421.
- Schenberg, E. E., Alexandre, J. F. M., Filev, R., Cravo, A. M., Sato, J. R., Muthukumaraswamy, S. D., Yonamine, M., Waguespack, M., Lomnicka, I., Barker, S. A., da Silveira, D. X., 2015. Acute Biphasic Effects of Ayahuasca. *PLoS One* 10, e0137202.
- Schmidt, A., Muller, F., Lenz, C., Dolder, P. C., Schmid, Y., Zanchi, D., Lang, U. E., Liechti, M. E., Borgwardt, S., 2017. Acute LSD effects on response inhibition neural networks. *Psychol Med*, 1-13.
- Schultz, W., 2016. Dopamine reward prediction error coding. *Dialogues in clinical neuroscience* 18, 23-32.
- Seth, A. K., Barrett, A. B., Barnett, L., 2011. Causal density and integrated information as measures of conscious level. *Philos Trans A Math Phys Eng Sci* 369, 3748-3767.
- Shannon, C. E., 1949. The mathematical theory of communication. The University of Illinois Press, [S.I.].
- Shew, W. L., Plenz, D., 2013. The functional benefits of criticality in the cortex. *Neuroscientist* 19, 88-100.
- Speth, J., Speth, C., Kaelen, M., Schloerscheidt, A. M., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., 2016. Decreased mental time travel to the past correlates with default-mode network disintegration under lysergic acid diethylamide. *J Psychopharmacol* 30, 344-353.
- Sun L, Wang YF, He H, Chen J., 2007. Changes of the alpha competitive structure after administration of single dose methylphenidate in different subtypes of attention deficit hyperactivity disorder boys. *Beijing Da Xue Xue Bao Yi Xue Ban* 39(3):289-92.
- Tagliazucchi, E., 2017. The signatures of conscious access and its phenomenology are consistent with large-scale brain communication at criticality. *Conscious Cogn* 55, 136-147.
- Tagliazucchi, E., Balenzuela, P., Fraiman, D., Chialvo, D. R., 2012. Criticality in large-scale brain FMRI dynamics unveiled by a novel point process analysis. *Front Physiol* 3, 15.
- Tagliazucchi, E., Carhart-Harris, R., Leech, R., Nutt, D., Chialvo, D. R., 2014. Enhanced repertoire of brain dynamical states during the psychedelic experience. *Hum Brain Mapp* 35, 5442-5456.
- Tagliazucchi, E., Chialvo, D. R., Siniatchkin, M., Amico, E., Brichant, J. F., Bonhomme, V., Noirhomme, Q., Laufs, H., Laureys, S., 2016a. Large-scale signatures of unconsciousness are consistent with a departure from critical dynamics. *J R Soc Interface* 13, 20151027.
- Tagliazucchi, E., Roseman, L., Kaelen, M., Orban, C., Muthukumaraswamy, S. D., Murphy, K., Laufs, H., Leech, R., McGonigle, J., Crossley, N., Bullmore, E., Williams, T., Bolstridge, M., Feilding, A., Nutt, D. J., Carhart-Harris, R., 2016b. Increased Global Functional Connectivity Correlates with LSD-Induced Ego Dissolution. *Curr Biol* 26, 1043-1050.
- Tagliazucchi, E., Sanz, C. 2018. The experience elicited by hallucinogens presents the highest similarity to dreaming within a large database of psychoactive substance reports. *Frontiers in Neuroscience*. Accepted. In Press.
- Thomasson, N., Pezard, L., 1999. Dynamical systems and depression: a framework for theoretical perspectives. *Acta Biotheor* 47, 209-218.
- Thomasson, N., Pezard, L., Allilaire, J-F., Renault, B.m Martinerie, J. 2000. Nonlinear EEG Changes Associated with Clinical Improvement in Depressed Patients. *Nonlinear Dynamics Psychology and Life Sciences*. 4. 203-218.

- Thomasson, N., Pezard, L., Boyer, P. et al. (2002). Nonlinear EEG Changes in a 48-Hour Cyclic Manic-Depressive Patient. *Nonlinear Dynamics Psychol Life Sci* 6: 259.
- Timmermann, C., Spriggs, M. J., Kaelen, M., Leech, R., Nutt, D. J., Moran, R. J., Carhart-Harris, R. L., Muthukumaraswamy, S. D., 2017. LSD modulates effective connectivity and neural adaptation mechanisms in an auditory oddball paradigm. *Neuropharmacology*.
- Tononi, G., Boly, M., Massimini, M., Koch, C., 2016. Integrated information theory: from consciousness to its physical substrate. *Nat Rev Neurosci* 17, 450-461.
- Timmermann, C., Roseman, L., Williams, L., Scharfner, M., Leech, R. Feilding, A., Nutt, D.J., Carhart-Harris, R. L. 2018. Enter the void: EEG correlates of the DMT experience. In prep.
- Tononi, G., Edelman, G. M., 1998. Consciousness and complexity. *Science* 282, 1846-1851.
- Tononi, G., Sporns, O., Edelman, G. M., 1994. A measure for brain complexity: relating functional segregation and integration in the nervous system. *Proc Natl Acad Sci U S A* 91, 5033-5037.
- Torda, C., 1968. Contribution to serotonin theory of dreaming (LSD infusion). *N Y State J Med* 68, 1135-1138.
- Valle, M., Maqueda, A. E., Rabella, M., Rodriguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mananas, M. A., Barker, S., Friedlander, P., Feilding, A., Riba, J., 2016a. Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology* 26, 1161-1175.
- Valle, M., Maqueda, A. E., Rabella, M., Rodriguez-Pujadas, A., Antonijoan, R. M., Romero, S., Alonso, J. F., Mananas, M. A., Barker, S., Friedlander, P., Feilding, A., Riba, J., 2016b. Inhibition of alpha oscillations through serotonin-2A receptor activation underlies the visual effects of ayahuasca in humans. *Eur Neuropsychopharmacol* 26, 1161-1175.
- Varela, F. 1996. Neurophenomenology: A methodological remedy for the hard problem. *J Consciousness Studies* 3: 330-49.
- Viol, A., Palhano-Fontes, F., Onias, H., de Araujo, D. B., Viswanathan, G. M., 2017. Shannon entropy of brain functional complex networks under the influence of the psychedelic Ayahuasca. *Sci Rep* 7, 7388.
- Waldman, A. a., 2017. A really good day : how microdosing made a mega difference in my mood, my marriage, and my life.
- Watts, R., Day, C., Krzanowski, J., Nutt, D., Carhart-Harris, R., 2017. Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *Journal of Humanistic Psychology* 57, 520-564.
- Zarjam P, Epps J, Lovell NH, Chen F., 2012. Characterization of memory load in an arithmetic task using non-linear analysis of EEG signals. *Conf Proc IEEE Eng Med Biol Soc* 3519-22.
- Zhang, X. S., Roy, R. J., Jensen, E. W., 2001. EEG complexity as a measure of depth of anesthesia for patients. *IEEE Trans Biomed Eng* 48, 1424-1433.

## The entropic brain



**The entropic brain - revisited****Highlights**

- 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.
- 8) how recent findings on brain serotonin encoding behavioural responses to uncertainty mesh well with the entropic brain hypothesis.

ACCEPTED MANUSCRIPT