ARTICLE

How do hallucinogens work on the brain?

Robin Carhart-Harris, Mendel Kaelen and **David Nutt** consider a big question on several levels

What do we know about how hallucinogens work on the brain to produce their characteristic subjective effects? This question can be approached from a number of different levels. At the lowest functionally relevant level, how do the hallucinogenic compounds themselves interact with a certain neurotransmitter receptor to alter neuronal activity? Then at the neuronal population level, how does a drug-induced change in neuronal firing interact with the integrated oscillatory activity of large populations of neurons? Finally, how does this all play out at the level of large-scale systems or networks in the brain; and of how do changes in the functional behaviour of these systems map on to specific psychological experiences?

questions

Does self-organised activity in the default mode network underlie our sense of self or ego?

Do hallucinogenic drugs produce a waking-dream state?

resources

Carhart-Harris, R.L., Leech, R., Tagliazucchi, E. et al. (2014). The entropic brain. *Frontiers in Human Neuroscience, 8*, 20.

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The 'classic' hallucinogens – such as LSD (derived from ergotamine found in ergot fungi), dimethyltryptamine (DMT, the major hallucinogenic component of ayahuasca) and psilocybin (from magic mushrooms) – possess a unique and arguably unrivalled potential as scientific tools to study the mind and the brain. For those of us who are currently fortunate enough to be researching them, there is a real sense that we are exploring something destined to become the 'next big thing' in psychopharmacology. But how much do we really know about how they act on the brain to produce their many unusual effects? Here, we summarise the relevant research, beginning at the level of single neurons and moving towards networks in the brain.

Hallucinogens 'stimulate' serotonin 2A receptors

The level of single neurons

All classic hallucinogens stimulate a particular serotonin receptor subtype expressed on neurons in the brain, the serotonin 2A receptor. This receptor appears to be central to the action of hallucinogens because blocking it (with another drug called ketanserin) abolishes the occurrence of the hallucinatory state (Vollenweider et al., 1998). Also, the affinity (or 'stickiness') of different hallucinogens for the serotonin 2A receptor correlates positively with their potency, or 'strength'; for example, LSD has an extremely high affinity for the serotonin 2A receptor and is remarkably potent (Glennon et al., 1984). That hallucinogens 'stimulate' serotonin 2A receptors means that they mimic the action of serotonin at the receptor by binding to it, altering its conformation or 'shape', and ultimately altering the internal conditions and therefore behaviour of the neuron it sits on. For the serotonin 2A receptor, the key functional effect of its stimulation is an increase in the excitability of the hosting neuron.

Serotonin 2A receptors are primarily expressed on an important type of neuron or brain cell in the brain, excitatory pyramidal neurons. More specifically, serotonin 2A receptors are especially highly expressed on excitatory pyramidal neurons in 'layer 5' of the cortex. The cortex is organised into layers of different cell types, like the different layers of a cake, and layer 5 is a deep layer, nearer the base than the icing (Weber & Andrade, 2010). Layer 5 pyramidal neurons are especially important functional units in the brain as they are the principal source of output from a cortical region. They project to hierarchically subordinate, or 'lower', cortical and subcortical regions (e.g. from a visual association region to the primary visual cortex). Layer 5 pyramidal neurons project heavily onto inhibitory interneurons and so the net effect of their excitation seems to be inhibitory (Bastos et al., 2012). This is important because hallucinogen-induced excitation of layer 5 pyramidal cells has been interpreted by some as evidence of a more general

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excitatory effect of these drugs, but as will be discussed in the forthcoming sections, recent animal electrophysiological and human neuroimaging recordings have cast further doubt on the assumption that hallucinogens have a general excitatory effect on cortical activity (Carhart-Harris et al., 2012; Wood et al., 2012). Captured by the idiom 'failing to see the woods for the trees', these results are a reminder that one should not be too hasty to extrapolate from the activity of certain single units in the brain, since the interconnected nature of cortical circuits means that local excitation can translate into net inhibition, or rather 'disorder', at a higher level of the system. If John Donne was a neuroscientist, he might have said: 'no neuron is an island, entire of itself'.

Populations of neurons

Much of brain activity is rhythmic or oscillatory in nature and electroencephalography (EEG), magnetoencephalography (MEG) and local field potential (LFP) recordings are techniques that measure the collective, synchronously oscillating activity of large populations of neurons. Studies in animals and humans have found decreases in oscillatory activity in the cortex after the administration of hallucinogens, and in one of our most recent and informative studies with psilocybin we observed a profound desynchronising influence on cortical activity (Muthukumaraswamy et al., 2013). This effect was evident in all of the frequencies recorded by MEG, from the slowest (i.e. 'delta', 1–4 oscillations per second) to the fastest (i.e. 'high gamma', 50–100 oscillations per second). Moreover, when a modelling technique was employed to infer the cellular origin of these effects, the results highlighted excitation of layer 5 pyramidal neurons as the most likely cause (Muthukumaraswamy et al., 2013). Cortical desynchrony has also been found in studies with LSD (Bente et al., 1958) and ayahuasca (Riba et al., 2002) using EEG.

An important question that follows from these findings is: why does excitation of layer 5 pyramidal neurons cause desynchronisation at the population level? Recording simultaneously the activity of presumed layer 5 pyramidals and LFPs in rats has gone some way to answer this (Celada et al., 2008). Specifically, researchers in Barcelona found that layer 5 pyramidal neurons usually fire at a particular phase of cortical oscillations, suggesting that the single units are either entrained by cortical rhythms, exert a pacemaker influence on them, or both. Importantly, when the LSD-analogue hallucinogen DOI was administered to rats, the normal concordance between pyramidal cell firing and the phase of LFP oscillations was abolished, and this decoupling was dependent on serotonin 2A receptor stimulation.

To help illustrate this principle by analogy, the strength of cortical rhythms can be thought of as analogous to the rhythmic sound generated by a population of individuals clapping their hands in synchrony. The presence of an individual clapper among a population of clappers means that his/her rate of clapping becomes quickly entrained by the collective sound generated by the population as a whole. Now imagine that a number of mischievous 'ticklers' are introduced to the scene, inducing sporadic clapping by tickling individual clappers. Although the individuals targeted may be excited into clapping more often, there will be a disruptive effect on the regularity and volume of the sound generated by the population as a whole. The basic principle is that although hallucinogens excite certain excitatory neurons in the cortex to fire more readily, this has a disorganising influence on cortical activity as a whole.

The system level

Much of our own research on hallucinogens has focused on human brain imaging and particularly functional magnetic resonance imaging (fMRI), a technique that measures changes in brain activity at a high spatial resolution. In a pair of related studies, we studied changes in brain blood flow (a reliable proxy of brain activity) and network activity in healthy individuals administered psilocybin intravenously whilst they lay in the fMRI scanner.

The results were remarkable because they showed for the first time that characteristic changes in consciousness brought about by a hallucinogen are related to 'decreases' in brain activity (Carhart-Harris et al., 2012). The decreases were localised to important hub structures in the brain, such as the thalamus, posterior cingulate cortex and medial prefrontal cortex. These structures are important as they are centres for information integration and routing in the brain. Thus, rather than being restricted to the performance of specific functions (e.g. the visual cortex is concerned with visual processing and the motor cortex with motor action) these structures possess a more general, managerial purpose, essentially holding the entire system together; analogous to a capital city in a country, or a chief executive officer of a cooperation. The observed decrease in activity in these regions was therefore interpreted as permitting a more unconstrained mode of brain function (Carhart-Harris et al., 2012).

To further interrogate this idea we subsequently conducted a number of network analyses, testing the principle that the brain operates in a freer, less constrained manner in the hallucinogenic state. The first analyses looked at the integrity of individual networks under psilocybin and found that these were essentially less integrated, or even 'disintegrated', under the drug. Next, we examined how brain networks communicate with each other and found that distinct networks became less distinct under the drug, implying that they communicate more openly but, in doing so, lose some of their own individual 'identity'. Other analyses have

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also supported the principle that the brain operates with greater flexibility and interconnectedness under hallucinogens (Carhart-Harris et al., 2014).

The idea that an increase in system-level flexibility in the brain relates to greater cognitive flexibility is supported by several animal studies that have found enhanced cognitive flexibility and associative learning with serotonin 2A receptor stimulation and a retardation of these things with 2A receptor blockade (Boulougouris et al., 2008; Harvey, 2003; Harvey et al., 2004; Romano et al., 2010; Romano et al., 2006). Increased cognitive flexibility may be useful clinically in terms of enhancing cognitive-based psychotherapies for disorders such as depression, obsessive compulsive disorder and addiction, in which pathological patterns of thought and behaviour become entrenched (Carhart-Harris et al., 2014). Non-clinically, hallucinogens may be explored and exploited as novel nootropics; for example, as enhancers of creative thinking (Harman et al., 1966).

To summarise, we have learned that the first site of action of hallucinogens is the serotonin 2A receptor and that their stimulation causes important neurons to fire out of phase with the rhythmic oscillations of large populations of neurons in the cortex. This disruption of cortical rhythmicity extends to large-scale brain networks, where a generalised decrease in system organisation and constraint is observed. We discuss these ideas more fully in a recent review article that characterises the hallucinatory state as 'entropic' (i.e. disordered, in relation to normal waking consciousness) (Carhart-Harris et al., 2014).

Drugs that act on the brain have been studied quite extensively with the aim of understanding the neurobiology of consciousness; however, the majority of this research has focused on anaesthetics and sedatives that cause a general reduction in the level of consciousness. However, in our opinion, reducing wakefulness via anaesthetics is a relatively limited strategy for studying human consciousness. In contrast, hallucinogens are much more powerful tools, since they profoundly alter the quality of consciousness whilst leaving arousal or wakefulness intact. In our working model of different dimensions of consciousness and their sensitivity to modulation via different neurotransmitter systems, we suggest a consideration of:

- Level: The GABA-A system regulates cortical arousal and when stimulated produces sedation.
- Focus: The dopamine system modulates attentional and goal-directed behaviours and enhances alertness.
- Flexibility: Serotonin 2A receptor stimulation increases cognitive flexibility.

Hitherto, we have characterised hallucinogens as agents of disorganisation; however, it must be acknowledged that the picture presented is somewhat incomplete. Specifically, it fails to address some of the most prominent and intriguing psychological properties of hallucinogens, such as their ability to produce complex visual hallucinations (de Araujo et al., 2012) or 'ego-disintegration' in the promotion of 'peak-type' experiences (Griffiths et al., 2006). Thus, in the final two sections of this article we will offer some empirically informed insights on what may be occurring in the brain to account for such phenomena.

Chaos above, anarchy below

The discussion so far has focused almost exclusively on decremental changes in brain activity brought about by hallucinogens (e.g. decreased oscillatory activity, blood flow and network integrity); however, it is important to note that disinhibitory effects have also been observed in certain brain regions.

Before the advent of non-invasive neuroimaging, the only means of recording neuronal activity below the surface of the cortex was to surgically insert wire electrodes deep into target brain tissue. Remarkably, in the 1950s and 60s, under the pretence of research on psychosis, such procedures were carried out in human subjects who were administered hallucinogenic drugs such as mescaline and LSD. Despite the ethically questionable nature of these experiments, they did reveal some interesting clues about the neurobiology of the hallucinatory state. Specifically, phasic discharges in medial temporal lobe (MTL) circuitry (i.e. the hippocampus, amygdala and septal nuclei) appeared in recordings during periods of marked hallucinosis, while the more familiar cortical desynchrony associated with hallucinogens was also present (Monroe & Heath, 1961; Schwarz et al., 1956).

Intriguingly, a similar cortical/MTL dichotomy has been observed in rodents administered a DMT-like compound (Riga et al., 2014) and in our fMRI research with psilocybin. Specifically, in our psilocybin studies, in addition to decreased blood flow, oscillatory activity and network integrity in the cortex, we also observed an increase in the amplitude of low-frequency signal fluctuations in the hippocampus and parahippocampus (Carhart-Harris et al., 2014). Increased medial temporal lobe activity is a major characteristic of rapid eye movement (REM) sleep, which is strongly correlated with dreaming (Aserinsky & Kleitman, 1953), and the increases in hippocampal activity detected in our own analyses correlated positively with volunteers' ratings of the dreamlike quality of their experiences (Carhart-Harris & Nutt, 2014). LSD given just before waking or during sleep has been found to promote REM sleep and dreaming (Carhart-Harris & Nutt, 2014; Muzio et al., 1966), and with eyes-closed, the hallucinogenic state has often been compared to dreaming (Carhart-Harris & Nutt, 2014).

Electrical stimulation of the medial temporal lobe circuitry has long been known to produce complex dreamlike

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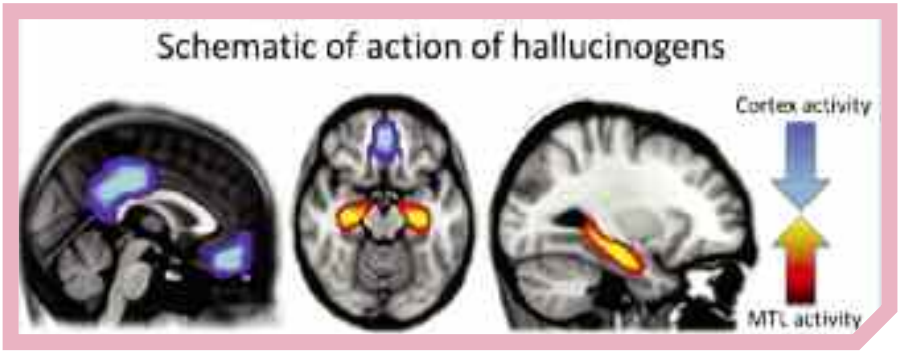

Differential effect of a hallucinogen on the default mode network regions (blue) and the medial temporal lobes (orange). 'Disorganised' activity in the former permits the latter to operate more autonomously: 'chaos above, anarchy below'.

visions of a similar sort to those associated with dreaming and the hallucinogenic drug state, and direct stimulations of the parahippocampal face and place sensitive regions have recently been found to produce visual distortions/hallucinations such as 'melting' faces and visions of complex scenes (Megevand et al., 2014), similar in many respects to reports of hallucinogen-induced visual hallucinations. Thus, it makes sense to look more closely at changes in the activity and network behaviour of the MTL structures in the future, as well as the relationship between REM sleep dreaming and the hallucinogenic drug state, in order to develop our understanding of the neurobiology of the hallucinatory state.

Finding the self by losing the self

One of the most common yet abstract experiences described in relation to the hallucinogenic drug state is a disintegration or dissolution of the self or ego. Such an experience is difficult to fathom from the vantage of normal waking consciousness, where an integrated sense of self is felt as pervasive and permanent. It is perhaps not surprising therefore that the experience of ego-disintegration is described as profoundly disconcerting and unusual (Griffiths et al., 2006). Classic accounts of so-called 'mystical' or 'spiritual' experiences have placed emphasis on the necessity for self or ego disintegration for their occurrence (James & Bradley, 2012). Thus, in order to investigate the neurobiological basis of ego-disintegration and mystical-type experiences, it is useful to first examine the neural correlates of self-awareness.

Evidence has accumulated in recent years highlighting a relationship between a particular brain system and so-called 'ego functions' such as self-reflection (Carhart-Harris & Friston, 2010). This network is referred to as the 'default mode network' because it has a high level of ongoing activity that is only suspended or interrupted when one's attention is taken up by something specific in the immediate environment, such as a cognitive task (Raichle et al., 2001). It was a matter of great intrigue to us therefore that we observed a marked decrease in brain activity in the default mode network under psilocybin (Carhart-Harris et al., 2012) whilst participants described experiences such as: 'Real ego-death stuff! I only existed as an idea or concept… I felt as though I was kneeling before God!'

To scrutinise this phenomenon further, we looked at correlations between decreases in oscillatory activity in a certain frequency band (i.e. 'alpha'), in a certain part of the default mode network (the posterior cingulate cortex, PCC – the major cortical hub) and ratings of 'ego-disintegration' post-psilocybin. In what is perhaps our most intriguing and potentially important finding on the neurobiology of the hallucinogenic drug state to date, we found a highly significant correlation between the magnitude of decreases in oscillatory activity in the PCC and reports of ego-disintegration (Carhart-Harris et al., 2014; Muthukumaraswamy et al., 2013). Thus, those participants that showed the most dramatic collapses in rhythmic activity in their PCCs reported the most extreme ego-disintegration. Adding to the intrigue, alpha oscillations develop to a maximal level in mature adult humans and have been hypothesised to be a marker or 'signature' of high-level human consciousness (Basar & Guntekin, 2009). Could PCC alpha rhythms be critical for the development and maintenance of one's sense of self, and if 'yes', what specific functions do they subserve? These are important questions for future research.

Conclusions

So, stimulation of the serotonin 2A receptor disrupts coupling between the firing of certain cells types and the rhythmic oscillations of larger populations of neurons in the cortex. Hallucinogens have a disorganising influence on cortical activity which permits the brain to operate in a freer, less constrained manner than usual.

These are exciting times, with much still to learn. Unfortunately, this research is unusually difficult to conduct, being fraught with regulatory obstacles and other challenges. However, in the inspiring words of John F. Kennedy about another endeavour that was ultimately accomplished almost half a century ago: 'We choose to do these things, not because they are easy, but because they are hard.'

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