An introduction to psychedelic neuroscience

by

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Abstract

This chapter is an introduction to the volume "Psychedelic Neuroscience" of Elsevier's Progress in Brain Research addressing the neurobiological mechanisms of psychedelic drugs, the resulting changes in brain activity and integration of traditional viewpoints. As the field is relatively new, there are discrepancies in the literature related to classification, composition and effects of the various psychedelics. Currently, psychedelics are grouped according to their neuro-receptor affinities into classic and atypical psychedelics, each with individual treatment potentials and abilities to elicit potent acute experiences and long-lasting changes in neurobiology through concurrent activation of several neuromodulatory systems. There is disparity in psychedelic brain imaging studies, delineating what is neural activity and hemodynamic needs further investigation for us to understand the brain "state" changes that are apparent. The psychedelic brain "state" is often compared to acute psychosis and we review the psychedelic animal models of psychosis and human brain imaging studies and contrast these to psychosis. The term "psychedelic" means mind-revealing and psychedelics have exceptional anti-amnesic effects and are able to "make conscious" that which was previously unconscious through changes in brain "state," but also there is growing evidence which demonstrates the role of epigenetic mechanisms. This supports traditional therapeutic use of psychedelics to heal ancestral trauma. Details of these mechanisms are provided along with suggestions for further research.

Keywords Psychedelic medicine, Consciousness, Psychosis, qEEG, MEG, fMRI, Neurobiology, Microdosing, Combination psychedelic therapy, Neuromodulators, Epigenetics

1. What are psychedelics?

The field of psychedelic neuroscience has witnessed a recent renaissance following decades of restricted research due to their legal status. As this is a relatively new field, there are incongruences in the literature related to terminology, classification, content and effect of the various psychedelics.

The currently accepted classification of psychedelics includes classic psychedelics and atypical/non-traditional/non-classical psychedelics. Classic psychedelics are the phenethylamines such as 3,4,5-trimethoxy-phenethylamine (mescaline, derived from *Cactaceas* plant family including peyote cactus), tryptamines such as 5-methoxy-dimethytryptamine (5-MeO-DMT; which can be synthetically produced, but also found in *Bufo alvarius* toad venom and several plants including *Anadenanthera peregrina*, derivative colloquially referred to as Amazonian yopo snuffs), *N,N*-dimethyltryptamine (*N,N*-DMT; found in ayahuasca a brew made with *Banisteriopsis caapi* vine and other ingredients), *N,N*-dimethyl-4-phosphoryloxytryptamine (*Psilocybe* genus of mushrooms) and ergolines such as lysergic acid diethylamide (LSD; derived from lysergic acid extracted from ergot fungus) (Barsuglia *et al*., 2018; Murnane, 2018). Atypical psychedelics can be further divided into dissociative psychedelics (N-methyl-D-aspartate receptor-NMDA antagonists), e.g., phencyclidine (PCP; original synthesis was toward an anesthetic), ketamine (an amnesic surgical anesthetic) and ibogaine (derived from *Apocynaceae* family of plants), as well as cannabinoid agonists (e.g., Δ9-tetrahydrocannabinol (Δ9-THC) from cannabis), muscarinic receptor antagonists (e.g., scopolamine initially synthesized for anesthesia), and entactogens (e.g., 3,4-methylendioxymethampheamineMDMA-"ecstasy").

Problematic in the field, perhaps more so than in other fields, is the issue of conflicting results, likely due to the limited research. For example, there is conflicting evidence as to whether or not the low 5-HT$_{2A}$ affinity of ibogaine has any functional relevance. Ly *et al*. (2018) found that the 5-HT$_{2A}$ receptor antagonist, ketanserin, blocked the effect of noribogaine on structural plasticity yet both ibogaine and noribogaine failed to induce head-shake response in rats, a behavior which is seen to be comparable to hallucinations in humans and mediated by 5-HT$_{2A}$ activation (Barsuglia *et al*., 2018; González *et al*., 2018; Murnane, 2018). González *et al*. (2018) suggest that this result supports the subjective experiences in humans, where ibogaine does not produce the typical interferences in thinking, identity distortions, and space-time alteration, which are produced by the classic psychedelics. A second example, where there is confusion is the literature regarding 5-MeO-DMT. 5-MeO-DMT is described as being a constituent of ayahuasca (Murnane, 2018; Riga *et al*., 2014), while it is evidenced that ayahuasca holds a high concentration of *N,N*-DMT, 5-MeO-DMT concentration is either non-existent or negligible in most brews (Barsuglia *et al*., 2018; McKenna, 2004; McKenna *et al*., 1984; Pires *et al*., 2009) and the ayahuasca psychedelic experience bears little to no resemblance to an experience with 5-MeO-DMT. Then cannabis research is possibly the best example of conflicting psychedelic research. As reviewed in Colizzi and Bhattacharyya, 2018, evidence as to whether cannabis use is associated with adverse effects to mental health or cognition in humans is equivocal. There are also many divergent results in the functional human neuroimaging studies as detailed by Müller *et al*. (2018). Indeed, this is a new and growing field of research and more research is required to uncover the various psychedelics drugs, their active components and neurobiological effects.

2. Neurobiology of psychedelic therapy for depression and addiction

Classic psychedelics and dissociative psychedelics are known to have rapid onset antidepressant and anti-addictive effects, unlike any currently available treatment. Randomized clinical control studies have confirmed antidepressant and anxiolytic effects of classic psychedelics in humans (De Gregorio *et al*., 2018; Murnane, 2018). Ketamine also has well established antidepressant and anti-addictive effects in humans mainly through its action as an NMDA antagonist (Gass *et al*., 2018). Ibogaine has demonstrated potent anti-addictive potential in pre-clinical studies and is in the early stages of clinical trials to determine efficacy in robust human studies (Barsuglia *et al*., 2018; Corkery, 2018).

Psychedelics are not only known to have rapid onset but their effects persist long after their acute effects; this includes changes in mood and brain function (Barsuglia *et al*., 2018; Colizzi and Bhattacharyya, 2018; Corkery,

2018; De Gregorio *et al.*, 2018; Erritzoe *et al.*, 2018; Ly *et al.*, 2018; Murnane, 2018). These effects are suggested to result from their unique receptor affinities which affect neurotransmission (Barsuglia *et al.*, 2018; Corkery, 2018; De Gregorio *et al.*, 2018; Murnane, 2018) via neuromodulatory systems which then serve to modulate brain activity, i.e., neuroplasticity (Atasoy *et al.*, 2018; Barsuglia *et al.*, 2018; Colizzi and Bhattacharyya, 2018; Müller *et al.*, 2018). These lasting effects are reported to promote cell survival, be neuroprotective, and modulate neuroimmune systems of the brain (De Gregorio *et al.*, 2018; Inserra, 2018; Ly *et al.*, 2018). The mechanisms which lead to these long-term neuromodulatory changes have been linked to epigenetic modifications and gene expression changes (De Gregorio *et al.*, 2018; Inserra, 2018). These psychedelic drug effects, previously under-researched, may potentially provide the next-generation of neurotherapeutics, where treatment resistant diseases, e.g., depression and addiction, may become treatable with attenuated pharmacological risk profiles (Ly *et al.*, 2018; Murnane, 2018).

Classic psychedelics have been shown to stimulate the serotonergic system mainly via 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_7 receptors, with the dopaminergic system primarily via D2 receptors, and indirectly with the glutamatergic and GABAergic systems (Barsuglia *et al.*, 2018; De Gregorio *et al.*, 2018). There is significant cross-talk between these neuromodulatory systems and classic psychedelics, and activation of 5-HT_{1A} and 5-HT_{2A} receptors modulates glutamatergic and dopaminergic neurotransmission in brain networks associated with depression and addiction (Barsuglia *et al.*, 2018; De Gregorio *et al.*, 2018; Guiard and Di Giovanni, 2015; Ly *et al.*, 2018; Murnane; Sampedro *et al.*, 2017). Then activation of 5-HT_{2C} receptors localized in dopaminergic and GABAergic neurons in the ventral tegmental area (VTA) regulates motivation by modulating transmissions to the nucleus accumbens (NAc) and altered balance in this 5-HT_{2C} receptor-associated network is postulated to cause reward-related disorders, such as schizophrenia, depression, and addiction (Sumiyoshi *et al.*, 2014). Further, it is acknowledged that classic psychedelics have an extremely low potential for abuse (Nutt *et al.*, 2007, 2010; UNODC, 2018), and it is suggested that stimulation of 5-HT_{2C} receptors limits their potential for addiction and that their therapeutic effects are mediated by acute 5-HT_{2C} receptor stimulation followed by sustained downregulation of 5-HT_{2A} and 5-HT_{1A} receptors (De Gregorio *et al.*, 2018; Murnane, 2018). Investigation into the complex mechanisms of action of classic psychedelics which lead to its anti-depressant and anti-addiction properties via the serotonergic system continues to gain momentum, e.g., minimal research has investigated the role of 5-HT_7 activation by psychedelics, but has been suggested to play a role in classic psychedelic anti-addiction properties, specifically 5-MeO-DMT in alcohol use disorder (Barsuglia *et al.*, 2018).

The classic psychedelics act directly via the serotonergic system whereas certain atypical psychedelics have direct affinity for numerous neuromodulatory systems. A remarkable example, ibogaine, addressed by Corkery and Barsuglia *et al.* (2018), demonstrates novel pharmacological mechanisms of action to be considered in the potential treatment of substance use disorders and depression (Alper, 2001; Barsuglia *et al.*, 2018) through simultaneous activation of multiple neurotransmitter systems (Baumann *et al.*, 2001a,b). This alkaloid has low micromolar affinity for mu and kappa opioid receptors, SIGMA-1 and SIGMA-2 receptors (SIGMAR1; SIGMAR2), serotonin reuptake transporter (SERT) and dopamine transporter (DAT), is an antagonist to NMDA and α3β4 nicotinic acetylcholine (nAChR) receptors and a weak 5-HT_{2A} receptor agonist (Alburges *et al.*, 2000; Barsuglia *et al.*, 2018; Brown and Alper, 2017; Jacobs *et al.*, 2007; Lavaud and Massiot, 2017; Mash *et al.*, 1998). Drugs with similar NMDA affinity (e.g., such as ketamine and memantine) or NMDA regulators (e.g., such as acamprosate) have shown promise in reducing symptoms of substance use disorders and depression (Barsuglia *et al.*, 2018; Corkery, 2018; Gass *et al.*, 2018; Ron and Wang, 2009). The mu-opioid receptor has demonstrated a functional role in drug reward (Mendez and Morales-Mulia, 2008) as well as craving (Nutt, 2014). Further, ibogaine possesses an opiate replacement mechanism of action as reported for compounds such as methadone (Barsuglia *et al.*, 2018; Baumann *et al.*, 2001a,b; Corkery, 2018; Mash *et al.*, 1995; Zubaran *et al.*, 1999). However, neither ibogaine nor its principle psychoactive metabolite, noribogaine, activate G-proteins associated with morphine administration, or produce signs and symptoms of opioid intoxication in opioid naïve persons; therefore, it seems that ibogaine is able to produce a neuroadaptive effect on endogenous opioid systems which reverses opioid tolerance and may be implicated broadly in its "addiction-interrupting" effects (Barsuglia *et al.*, 2018; Corkery, 2018).

3. Additional therapeutic mechanisms of action

There is strong evidence suggesting that various psychedelics influence the expression and modulation of genes, which in turn, may lead to long-term neurochemical and neuroplastic changes and modification of epigenetic mechanisms (De Gregorio *et al.*, 2018; Inserra, 2018; Ly *et al.*, 2018). When administered chronically, LSD has been shown to have effects on dopaminergic neurotransmission at the level of gene expression by decreasing the mRNA expression of the dopamine receptor genes DRD1 and DRD2 in the medial prefrontal cortex (mPFC) (De Gregorio *et al.*, 2018; Martin *et al.*, 2014). Classic and dissociative psychedelics lead to structural and functional changes in cortical neurons, with plasticity-promoting properties that rival brain-derived neurotropic factor (BDNF) (Ly *et al.*, 2018). LSD has demonstrated to be extremely potent in this regard possibly due to slow off kinetics of the LSD-bound 5-HT$_{2B}$ crystal structure (Ly *et al.*, 2018; Wacker *et al.*, 2017). Although the molecular targets of classic and dissociative psychedelics differ (5-HT and NMDA receptors, respectively), their plasticity promoting properties are similar and are known to activate TrkB, mTOR, and 5-HT$_{2A}$ signaling pathways, suggesting that these key signaling hubs may serve as potential targets for the development of "psychoplastogens," fast-acting antidepressants, and anxiolytics (Ly *et al.*, 2018). The mTOR signaling pathways may also play a role in certain psychedelics' ability to modify epigenetic mechanisms as mTORC1 is thought to be involved in regulating gene expression through epigenetic mechanisms or by directly affecting RNA stability/degradation (Laplante and Sabatini, 2013). Another relevant receptor involved in epigenetic modification is SIGMAR1 (Inserra, 2018). *N,N*-DMT and ibogaine both activate SIGMAR1 (Barsuglia *et al.*, 2018; Inserra, 2018) and recently, SIGMAR1 has been shown to modulate epigenetic processes by creating a dose-dependent interaction between emerin and histone deacetylase (HDAC)1, HDAC2 and HDAC3, affecting chromatin compaction and gene expression (Demmerle *et al.*, 2012;Inserra, 2018; Tsai *et al.*, 2015). At the nuclear envelope, SIGMAR1 recruits chromatin-remodeling molecules to regulate gene expression (Inserra, 2018; Tsai *et al.*, 2015) and at the synaptic level it interacts with voltage-gated ion channels, which leads to modification and reorganization of several homo- and heteroreceptor complexes which in turn modulates of neurotransmission, reviewed in Inserra (2018).

4. Neurobiology of the psychedelic experience

The psychedelic experience can produce eyes-closed and eyes-open imagery. The imagery can be clear and visual or it can have a dream-like quality with strong emotions and insights. There is also often heightened memory retrieval where long-forgotten memories are retrieved with exceptional clarity and detail. A common experience on ibogaine, for example, is that one's life flashes before their eyes as clear as if they were watching a movie about their life (Barsuglia *et al.*, 2018). The neurophysiological mechanisms that facilitate the psychedelic experience are largely unknown but progress is being made in understanding how the neurochemical profile of psychedelics elicits this effect, bringing that which was previously unconscious to the conscious mind. The differences in the psychedelic state elicited by the various classic and atypical psychedelics hold promise in differentiating the exact neuroreceptor-mind interactions. Neuroreceptors are coded by individual genes and extensive genetic variation exists in the population for these neuromodulatory systems. Variation in the neuroreceptor-mind interactions, thus, holds further promise for psychiatric neurogenomics research as it will uncover how individual genetic variation in the neuromodulatory systems affects different psychedelic states and changes in neurobiology.

The serotonergic system's involvement in the psychedelic state has received the most research attention, and has provided new insights related to the neurochemical mechanisms underlying changes in brain network activity and perfusion (Atasoy *et al.*, 2018; Barsuglia *et al.*, 2018; Colizzi and Bhattacharyya, 2018; De Gregorio *et al.*, 2018; Müller *et al.*, 2018; Murnane, 2018). Serotonin is involved in many neurological (e.g., epilepsy) and psychiatric (e.g., depression) diseases. Serotonin receptors may directly or indirectly depolarize or hyperpolarize neurons by changing the ionic conductance and/or concentration within the cells and is able to change excitability within brain networks (Guiard and Di Giovanni, 2015). For example, pharmacological magnetic resonance imaging (phMRI) in rats indicates that psilocin induces brain signal increases in olfactory and limbic areas and brain signal decreases in somatosensory and motor cortices (Murnane, 2018). 5-MeO-DMT disrupts cortical activity and low frequency cortical oscillations in the frontal cortex of rats with alternating activity in frontal and visual areas associated with psychedelic effects (Murnane, 2018).

In humans, activation of postsynaptic 5-HT$_{2A}$ receptors in layer V of the medial prefrontal cortex mPFC is considered to be responsible for the visual hallucinations produced by classic psychedelics. Cortical 5-HT$_{2A}$ hyper-activation affects corticostriatal-thalamo-cortical circuit functioning and triggers a disruption in the thalamic gating of sensory and cognitive information leading to perceptual distortions (Atasoy *et al.*, 2018; De Gregorio *et al.*, 2018).

Studies point toward not only brain network activity changes but also significant increases in hemodynamics (Coman *et al.*, 2015; Spain *et al.*, 2015). Increased cerebral blood flow has been reflected in temperature record of different brain areas with administration of MDMA, increased blood flow to the cortex correlated with increased neuronal activity as expected, however within the thalamus increased blood flow negatively correlated with increased neuronal activity (Coman *et al.*, 2015). Then a psilocin study reported decreased local field potentials to sensory stimuli while hemodynamic response was enhanced (Spain *et al.*, 2015). These data support a brain "state" change, but also require us to challenge our knowledge of the nature of this differential activity, neural versus hemodynamic, and their interplay which leads to the psychedelic experience (Lewis *et al.*, 2017).

Human brain imaging studies are limited, the neurophysiological underpinnings are largely speculative (Müller *et al.*, 2018), while the findings are interesting and need to be further investigated. For example, an LSD functional MRI (fMRI) study found increased hemodynamic activity within brain areas rich in 5-HT$_{2A}$ receptors and globally, the authors conclude that this reflected increased functional connectivity and that this increased activity led to ego dissolution (Tagliazucchi *et al.*, 2016). Then a psilocybin fMRI study found decreased hemodynamic activity within the thalamus and anterior and posterior cingulate cortices, where the decreased activity in the anterior cingulate correlated with the psychedelic experience. They further report a decrease in resting state connectivity between the medial prefrontal cortex and posterior cingulate cortex; the authors conclude that psilocybin reduced connectivity, and this reduction enabled the psychedelic experience (Carhart-Harris *et al.*, 2012). A different psilocybin resting state fMRI study reported that connectivity increased in higher brain networks such as the default mode, executive control, and dorsal attention networks (Tagliazucchi *et al.*, 2014). Then an arterial spin labelling study found that post MDMA, hemodynamics decreased and this was localized to right medial temporal lobe (MTL), thalamus, inferior visual cortex, and somatosensory cortex (Carhart-Harris *et al.*, 2015). Then a spontaneous magnetoencephalographic (MEG) study investigated Lempel-Ziv (LZ) complexity, more commonly applied in EEG studies, to determine diversity of mixed-signal being recorded. Where they found three psychedelic drugs: psilocybin, LSD, and ketamine, increased signal diversity within occipital cortices, this extended over the parietal cortex with LSD, and even further with ketamine over the full cortex, excluding medial frontal brain areas (Schartner *et al.*, 2017), they were also able to support a reduction in alpha MEG activity for all three psychedelics tested. The authors concluded that their findings provide confirmation that psychedelics create a higher level of consciousness which is reflected in MEG LZ complexity (Schartner *et al.*, 2017). A second psychedelic MEG study, which investigated psilocybin, reported reduction in spontaneous cortical activity (1-50 Hz) in posterior association cortices, and (8-100 Hz) in frontal association cortices. Second, they reported hugely significant reductions within the default mode network (Muthukumaraswamy *et al.*, 2013). Then a low-resolution electromagnetic tomography (LORETA) study investigated ayahuasca and found reductions in delta, theta, alpha-2, and beta-1 frequency bands, these changes were predominantly evident over the temporo-parietal-occipital junction (Riba *et al.*, 2004). Overall, the brain imaging studies, which address hemodynamic activity in humans, support acute increases and decreases in several brain regions. Electromagnetic studies report reductions in neural activity, most notably evident for alpha band frequency, and not limited to specific brain areas, but potentially reducing frontal activity and increasing parietal activity. Together these findings support the conclusion Lebedev *et al.* (2015) drew in relation to psilocybin; that psychedelics lead to a "disintegration" of functional connectivity, and this permits ego-dissolution (Lebedev *et al.*, 2015). It is suggested that this "disintegration" is at least in part due to decreased connectivity between of the parahippocampal and retrosplenial cortex, as was reported in a resting state fMRI LSD study (Carhart-Harris *et al.*, 2016), which may serve to support the change in cortical activity.

Psychedelic electroencephalographic research supports a brain "state" change, with evidence of reduced neural activity frontally and support increased activity parietally. A quantitative EEG (qEEG) study, investigated the acute effects of *N,N*-DMT and 5-MeO-DMT, finding significant reductions in global absolute alpha activity, while moderate significant increases were seen in theta and beta (Acosta-Urquidi, 2015;

Barsuglia *et al*., 2018). Then ayahuasca induced decreases in delta, theta, and alpha frequency activity, the power of alpha activity in parietal and occipital cortex was negatively related with the intensity of visual psychedelic experience (Valle *et al*., 2016). Acute dosing of *N,N*-DMT showed reduction in coherence between anterior and posterior EEG recording sites, where anterior coherence decreased, permitting parietal coherence to drive the EEG activity (Alonso *et al*., 2015). Psilocybin was reported to decrease 1.5-20 Hz frequency activity, and using source density EEG the neural networks which showed this decreased connectivity were in the anterior and posterior cingulate cortices and the parahippocampal regions (Kometer *et al*., 2013). The authors also report that the psychedelic experience was related to delta (1.5-4 Hz) activity between the retrosplenial cortex, the parahippocampus, and the lateral orbitofrontal area (Kometer *et al*., 2013). These data together support shifts in brain "state" with changes in cortical control from frontal brain areas to parietal and in part this is related to hippocampal network activity.

Further, EEG studies have investigated and contrasted MDMA, cannabis, and MDMA with cannabis use on EEG frequency where they show that MDMA with or without cannabis use increased delta band frequency, while cannabis use alone was found to increase high alpha band activity (Herning *et al*., 2005). In addition, this study found that MDMA with or without cannabis use showed increased blood flow and diastolic blood velocity (Herning *et al*., 2005). The increased alpha band activity in cannabis-alone users contradicts several papers which support attenuated alpha band activity (Hart *et al*., 2010). Then other cannabis studies report no change in alpha, and only report reductions in delta and beta activity (Zuurman *et al*., 2010). Cannabis has been shown to increase heart rate when alpha band activity is reduced (Hart *et al*., 2010), CB1 antagonism prevents the increase in heart rate produced by cannabis (Zuurman *et al*., 2010); however, this study which tested CB1 antagonism in acute cannabis use reported no change in alpha activity. Then an acute study investigated the effects of MDMA with and without ethanol or Δ9-THC, and MDMA alone was found to decrease theta and alpha power, when a combination of MDMA and Δ9-THC was taken together their attenuation of theta and lower-1-alpha (6.4-8.4 Hz) was less than when given alone, then the combination of MDMA with Δ9-THC lead to significant reduction in lower-2-alpha (8.4-10.4 Hz), but not when administered alone. Then a study in users of MDMA showed an incremental increase in alpha activity (11 Hz) as cumulative doses of ecstasy increased, with no effect on theta activity (Adamaszek *et al*., 2010).

There is an absence of reliable ibogaine EEG studies in humans, a single study in cynomologus monkeys reported no effect (Binienda *et al*., 2011), then several rat studies. These studies report increased low-frequency, delta and theta, activity, and found ibogaine pre-treatment lowered cocaine-induced seizure threshold, reflected in alpha1-frequency band activity (Binienda *et al*., 2000, 2011). These data support changes in brain network activity, but are contradictory, and further investigation is needed. There are significant changes in alpha activity, which may be related to changes in thalamocortical gating activities.

Then event-related potential (ERP) EEG studies, which are few, report some discrete neural circuitry psychedelic effects, and the little evidence which is available suggests that exposure to psychedelic drugs impacts the relevant neural circuitry needed for specific cognitive tasks.

In a randomized, double-blind study, psilocybin, the preferential 5-HT$_{2A}$ antagonist ketanserin, or psilocybin with ketanserin was administered acutely, during the completion of a facial recognition task psilocybin enhanced positive mood and attenuated recognition of negative facial expression, which was reflected in P300 wave form amplitude, positive > negative (Kometer *et al*., 2012). A second study by the same group which investigated the spatiotemporal dynamics of a modal object completion task found psilocybin to attenuate the N170 amplitude, particularly apparent during the processing of incomplete objects, while slightly enhancing P100 component (Kometer *et al*., 2012). The authors found the attenuated N170 over right extrastriate and posterior parietal cortices correlated with intensity of visual hallucinations. The authors suggest this reduction in N170 reflects 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor-mediated visual hallucinations (Kometer *et al*., 2012).

Then ERP cannabis studies report on occasional versus heavy cannabis users which completed a divergent attention task with acute administration of Δ9-THC, occasional users showed reduced P100 amplitude; while both occasional and heavy users showed decreased P300 amplitudes, no effect on ERP waveforms were reported for their second task, the stop signal task, a task which measures activation of behavioral inhibitory circuitry (Theunissen *et al*., 2012). A second study, which addressed acute dose-related effects of Δ9-THC on a three-stimulus oddball paradigm, found that with increasing dose of Δ9-THC, P300a increased and P300b decreased, latency of P300 and waveform of the N100 were not affected (D'souza *et al*., 2012). The sparse ERP

wave form findings suggest neural circuit function, versus "state," is dependent on psychedelic exposure and dosing, beyond this further research needs to be conducted to gain better insight to the effects of psychedelics on neural processing during cognition.

As the body of brain imaging and EEG data increase the discrepancies will narrow, refer to more insights from chapters in this volume (Atasoy *et al.*, 2018; Barsuglia *et al.*, 2018; Colizzi and Bhattacharyya, 2018; De Gregorio *et al.*, 2018; Murnane, 2018; Müller *et al.*, 2018).

5. The link between psychosis and the psychedelic state

A population study which investigated psychedelic use in Norway, in 2013, reported that from their 21,967 respondents, 13.4% reported lifetime psychedelic use, and found no significant association with mental health outcomes; in fact there were several instances where psychedelic use was associated with lower rate of mental health problems (Krebs and Johansen, 2013). The use of psychedelics, such as cannabis, when psychosis does develop and persists, is suggested to result from an interaction of genes and the environment, as an example; multiple natural genetic variations interact with cannabis and other environmental factors (stress) to increase the risk of developing psychosis (Cortes-Briones *et al.*, 2015). Ergo psychedelics alone do not produce psychosis or psychotic disorder, as an individual needs to be genetically predisposed or carry a greater risk profile or susceptibility to developing psychosis (Mason *et al.*, 2009).

This being said, basic animal researchers employ acute and chronic dosing of certain psychedelics to induce psychotic-like behaviors in their research animals, usually rat or mouse, to investigate the neurobiological mechanism of psychosis, e.g., NMDA antagonists ketamine and PCP (Forrest *et al.*, 2014). NMDA antagonists disrupt glutamatergic signaling, specifically reducing NMDA receptor function; this is a postulated mechanism which leads to the human psychotic state, at least in part (Colizzi and Bhattacharyya, 2018; Davison *et al.*, 2017; Frohlich and Van Horn, 2014) and conversion to psychosis in ultra-high risk for psychosis (UHR) individuals.

Importantly, for an animal to "serve" as a reliable model of a human condition it needs to meet several validity criteria (Belzung and Lemoine, 2011). Behavioral comparisons between PCP and schizophrenia-like behavior in rodents report, for example, deficits in the cognitive domain which are comparable to schizophrenia executive function deficits; these include deficits in novel object recognition, attentional set shifting and T-maze delayed alternation. Then PCP in primates reduces frequency and duration of social interaction which is comparable to social withdrawal in humans, a negative symptom of schizophrenia. Administration of antipsychotic medications has been shown to reverse these behavioral deficits produced by PCP, specifically deficits in reversal learning and locomotor sensitization (Jones *et al.*, 2011), where it is suggested that this reversal is achieved through the activation of muscarinic-1 receptors (Miyauchi *et al.*, 2017). However, as with all psychiatric animal models, there are limitations in their translation to the human condition, e.g., animals cannot communicate the experience of a hallucination or the retrieval of unconscious memory. Other psychedelic animal models of schizophrenia address serotoninergic dysfunction reported in schizophrenia, and have included acute and chronic administration of mescaline, psilocybin, and LSD (Halberstadt and Geyer, 2013; Marona-Lewicka *et al.*, 2011), and again lack full translation to the human condition.

Importantly, antipsychotic drugs are known to act on the dopaminergic and serotonergic systems; however, their full mechanism of action is still being discovered. Conventional typical antipsychotics have strong affinity to D_2 receptor, which are found in high concentrations within the mesolimbic and mesocortical pathways, which are seen as the primary pathways involved in schizophrenia, if following the dopamine hypothesis, and lead to the presentation of positive psychotic symptoms, i.e., hallucinations and delusions (De Gregorio *et al.*, 2018). New atypical antipsychotics, which are prescribed in lower dosages than typical antipsychotics, make the addition of acting on 5-HT receptors, e.g., 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} subtypes (Sumiyoshi *et al.*, 2014), as do classic psychedelics (De Gregorio *et al.*, 2018; Murnane, 2018). Clozapine, an atypical antipsychotic, which is effective in treating treatment resistant schizophrenia and negative symptoms of psychosis, may act as an inverse agonist on 5-HT_{2C} receptors (Meltzer *et al.*, 2012). Where, the 5-HT_{1A} receptor gene promotor polymorphism (rs6295, C-1019G) has been associated with treatment efficacy of negative symptoms in schizophrenia (Sumiyoshi *et al.*, 2014).

If we return to the atypical psychedelic cannabinoid Δ9-THC, it is known that via activation of opioid receptors it effects changes in several neurotransmitter systems and affects neuromodulation. Comparatively these same neural systems and many of the changes reported are comparable to those in schizophrenia, and include modulation of serotonergic, glutamatergic, and dopaminergic systems (Colizzi and Bhattacharyya, 2018; Lisman *et al.*, 2008; van de Giessen *et al.*, 2017). Clinically the psychotic symptom profile between cannabis-induced psychotic disorder (CIPD) and acute schizophrenia are very similar; however, CIPD report higher levels of antisocial behavior and cognition is less severely affected (El-Serafi and Hewedi, 2014; Núñez and Gurpegui, 2002).

In functional human neuroimaging studies of acute Δ9-THC, to induce the positive symptoms of schizophrenia acutely, report changes in hemodynamic response and these were associated with psychotic symptom experience. First, while completing a verbal learning task, behavioral performance was unaffected, then during the early stages of the task, parahippocampal gyri hemodynamics increased and this response tapered off as the task progressed, then ventrostriatal activation during retrieval of word pairs shortened, where ventrostriatal activation was correlated with psychotic symptoms experienced (Bhattacharyya *et al.*, 2009). Second, while completing an oddball paradigm Δ9-THC improved behavioral response latency and the decreased hemodynamic response within the right caudate was negatively associated with psychotic symptoms experienced (Bhattacharyya *et al.*, 2012). Yet, while completing a response inhibition task, Go/No-Go, with acute administration of Δ9-THC, psychotic experiences reported correlated with inhibition deficits, and were both correlated with decreased hemodynamic response in the left inferior frontal cortex (Bhattacharyya *et al.*, 2015). These hemodynamic changes are similarly reported in studies investigating schizophrenia (Bhattacharyya *et al.*, 2012; Kaladjian *et al.*, 2007; Rubia *et al.*, 2001) being an interplay and change in hemodynamic response within the front cortical brain areas and basal nuclei during processing of inhibition and attention/salience tasks (Murray *et al.*, 2017).

Acute intravenous Δ9-THC infusion in healthy controls reports disruption of neural pathways, as measured by EEG; this includes: increased "randomness" of EEG activity, as measured by the LZ complexity algorithm, the "randomness" or noise produced correlated with the positive symptoms of psychosis, i.e., hallucinations and delusions (Cortes-Briones *et al.*, 2015). A second study reported disruption and decreased power of theta band activity over the frontal hemispheres with reduced hemispheric communication (Henquet *et al.*, 2008). A third study reported disruption of gamma band activity, 40 Hz, coherence between auditory evoked potentials, while no effect was noted at 20 and 30 Hz, where the reduced 40 Hz coherence was associated with the positive symptoms of psychosis (Cortes-Briones *et al.*, 2015). Together these studies suggest a global disruption in expected neuronal activity with acute Δ9-THC, and this carries over to abusers of cannabis (Laprevote *et al.*, 2017), where they suggest that the disruption in frequency band activity and coherence lead to the disinhibition of inhibitory functions in cannabis users (Prashad *et al.*, 2018), supporting the clinical symptoms of CIPD. In schizophrenia and the psychotic disorders, it is purported that there is a disengagement of thalamocortical gating activity (Müller *et al.*, 2018), this is classically and widely accepted to present with a significant increase in delta band activity and reduction in alpha band activity, and this is reported globally during rest and a cognitive active state (Howells *et al.*, 2018). This suggests that the atypical psychedelic, cannabis does not produce a similar signature to schizophrenia, as the relationship between delta and alpha activity is not evident.

Albeit that cannabis may not yield similar electrophysiological signatures to schizophrenia, animal studies in ibogaine, which are incrementally growing, do show brain activity which is more comparable, where it is reported that delta activity increases and changes in alpha band activity are apparent, therefore potentially supporting changes in thalamocortical gating (Binienda *et al.*, 2000, 2011; Govindaiah *et al.*, 2010). Importantly, limited neuroimaging and electrophysiological studies have been conducted in the array of psychedelics due to their legal status. Further research is required as psychedelics may uncover unique biological mechanisms which may aid the development of improved medications to treat psychosis (De Gregorio *et al.*, 2018; Müller *et al.*, 2018).

6. Future research

The neuroimaging and electrophysiological research that has been performed clearly reports that there are changes in brain "state" and authors suggest that this may be related to de-coupling of certain brain networks, yet to be fully identified. One such network which is of interest is the para-hippocampal network (Carhart-Harris *et al.*, 2014). The hippocampus is a densely connected region that may coordinate interhemispheric cortical connectivity and sensory functioning (Chan *et al.*, 2017). The hippocampus forms part of the limbic system along with regions such as the cingulate gyrus, insular cortex, subcallosal gyrus, amygdala, septal nuclei, thalamic nuclei (e.g., anterior thalamic nucleus (ATN)), hypothalamus and the reticular formation in the brainstem (Mtui *et al.*, 2015). These are regions implicated in psychiatric disorders and the psychedelic state and many of them express the 5-HT$_{2A}$ receptor (Bombardi, 2014). An important limbic circuit which has received little attention in relation to the psychedelic state is the Papez circuit. The Papez circuit is a series of connections between the cingulate cortex, the entorhinal cortex, the hippocampus proper, the fornices of the hippocampus, the mammillary bodies, the mammillo-thalamic tract and the ATN (Mtui *et al.*, 2015). The ATN forms a pivotal part of the Papez circuit, with widespread limbic connections forming an "extended hippocampal formation" (Jankowski *et al.*, 2013). Studies of diencephalic amnesia reinforce the crucial role of the ATN for memory, although the ATN is also considered important for the pathophysiology of epilepsy and serves as a possible target for deep brain stimulation (DBS) treatment in this condition (Balak *et al.*, 2018; Jankowski *et al.*, 2013). The presence of slow- and fast-spiking bursting anterior thalamic units, which discharge within the theta frequency, suggests that the anterior thalamus is involved in the propagation of theta signals through the Papez circuit and such theta propagation could have resulting mnemonic functions (Jankowski *et al.*, 2013). In future research, it would be interesting to investigate the involvement of this circuit following psychedelic administration in animals.

The identification of non-psychedelic compounds with similar serotonergic and glutamatergic receptor affinities as psychedelics has been proposed to be an important area for future research, with view to potential anti-neuroinflammatory properties (De Gregorio *et al.*, 2018; Ly *et al.*, 2018; Murnane, 2018). An example given by Murnane is how DOI induces profound anti-inflammatory effects at doses below those required to induce rodent head-twitch behavior. If non-psychedelic agonists that share the anti-inflammatory effects of DOI could be developed, this may have significant therapeutic implications (Murnane, 2018) as would the identification of non-psychedelic analogs capable of promoting plasticity in the prefrontal cortex (Ly *et al.*, 2018). Such compounds would also be critical in resolving the debate as to whether the psychedelic state is necessary for their therapeutic effects (Ly *et al.*, 2018). As reviewed by Barsuglia *et al.*, 2018, the intensity of the mystical experience is a key predictor of therapeutic outcomes in psilocybin-assisted treatment of alcohol dependence. Perhaps, for certain disorders (inflammatory disorders or degenerative disorders, for example), non-psychedelic compounds would be effective. More research needs to focus on psychedelic "microdosing," as it is known in the field. As mentioned by Murnane, sub-psychedelic doses of psychedelic compounds have been found to assist with certain disorders or conditions which is common practice within the psychedelic communities; however, there is only one human study in the literature which demonstrated that microdosing psilocybin had a positive effect on creativity (Prochazkova *et al.*, 2018). Additional controlled studies in this area could be of tremendous value in the field.

Another promising line of research would be into ibogaine's ability to reverse opioid tolerance, ergo development of non-addictive chronic pain medication. It is suggested that ibogaine is able to produce a neuroadaptive effect on endogenous opioid systems likely due to its ability to reverse the effects of opiates on gene expression, returning the receptors to pre-addiction condition (Barsuglia *et al.*, 2018; Corkery, 2018). Ibogaine administered together with morphine potentiates the analgesic effects of morphine as well as reduce developing tolerance (Corkery, 2018; Kroupa and Wells, 2005; Schneider, 1957). Uncovering these mechanisms would be of great value to the field of pain management.

Another area that requires further research is combination psychedelic therapy. Traditional practitioners often use psychedelics in combination and have been doing so for many generations. Barsuglia *et al.* (2018) propose a theory as to how 5-MeO-DMT and ibogaine used in sequential administration would be more effective in treating addiction than either one on its own. The combined neurotransmitter profile of the two compounds would likely have an augmented effect when used in combination but as this is the first study of its kind assessing combined psychedelic therapy, more research is needed to uncover poly-psychedelic pharmacology.

Psychedelics remain largely illegal in many countries; limiting human research, the research findings to date suggest that psychedelics hold therapeutic benefit to several human conditions, psychiatric through to chronic pain. There would be benefit from preclinical studies in which multimodal neuroimaging and electrophysiological recordings are taken, while within a solid research design, which manages the diversity of human behavior (Murnane, 2018). Longitudinal research investigating single/multiple administration and at various doses, including microdosing, would greatly enhance our understanding. In humans, this longitudinal research design could be coupled with genomic analyses to understand inter-subject variation in acute and chronic psychedelic effect (Colizzi and Bhattacharyya, 2018).

7. The mystery

Wisdom requires not only the investigation of many things but contemplation of the mystery.
Jeremy Narby

Science is at the early stages of understanding psychedelic molecular mechanisms and even further from understanding the psychedelic state as any scientist who has experienced it is aware. Let us contemplate the mystery and try to imagine how psychedelics are able to "make conscious" previously subconscious information, which forms part of traditional practitioners' imperative in administering psychedelics for therapeutic purposes over the millennia. This may provide insight to the relevant brain changes needed to promote attenuation of anxiety and promote anti-addictive brain states.

At a 2-month follow-up, approximately 70 of the participants rated the psilocybin experience as among the most personally meaningful of their lives. A subsequent study documented that administration of psilocybin led to increases in the openness domain of personality that was stable for at least a year. This was notable because few, if any, previous studies had demonstrated that any discrete experimental manipulation was capable of yielding long-lasting changes in personality.
Murnane

The 5-MeO-DMT state "began with images of floating through the universe and being surrounded by the stars. He also described seeing a 'universal cosmic matrix' that had a central column of electric light and spiritual beings merging into the light. 'It's just love. Everything. All of it. That is all that exists. Love is it.' Upon debriefing from his session several hours afterwards, he believed this experience was the single-most peak transformational experience of his life. He reported he lost all sense of his body and surroundings, and was 'transformed on a cellular level into infinite energy and pure love,' and described, 'all of [his] stress and difficulties throughout [his] life felt like they occurred for a meaningful purpose, and the traumas of [his] past were washed over by an infinitely loving energy'" (Barsuglia *et al.*, 2018)

In individuals with substance use disorders, ibogaine stimulates heightened memory retrieval specifically related to drug abuse, the perception of one's own future with or without drug use, and visions which reveal powerful insights into the nature of the addiction such as personal traumas.
Barsuglia *et al*.

Psychedelics are known to have exceptional anti-amnesic effects where memories are retrieved in great detail. In fact, all psychedelics have the ability to make conscious/reveal/retrieve that which was previously unconscious and the term, psychedelic, means mind-revealing.

The neurophysiological mechanisms that facilitate this anti-amnesic effect are largely unknown but progress is being made in identifying the molecular and cellular mechanisms and brain networks involved.

The anti-amnesic effect of psychedelics has also been supported in rodent studies where administration of ibogaine facilitated spatial memory retrieval (Popik, 1996), and low dose Δ9-THC has been shown to improve memory in aged rodents (Sarne *et al*., 2018), and to enhance synaptic marker proteins and increase hippocampal spine density (Bilkei-Gorzo *et al*., 2017). The anti-amnesic effect of ibogaine and ayahuasca is, partly, due to the SIGMAR1 affinity of both compounds. SIGMAR1 activation has been shown to reverse experimental-induced amnesia in rodents, via enhancement of the cholinergic and glutamatergic systems

(Antonini *et al.*, 2009; Earley *et al.*, 1991; Inserra, 2018; Maurice *et al.*, 1998). Peak densities of SIGMAR1 are found in brain areas relevant to traumatic memory formation, retrieval and updating, such as the amygdala and the hippocampal formation (Inserra, 2018).

Psychedelics also enhance synaptic plasticity and increase neurogenesis, processes known to be involved in memory reconsolidation and fear extinction (Inserra, 2018; Ly *et al.*, 2018). The fear response triggered by the memory can be reprogramed and/or extinguished through synaptic plasticity and changes in gene expression mediated by epigenetic modification via 5-HT$_{2A}$ and SIGMAR1 activation (Corkery, 2018; De Gregorio *et al.*, 2018; Inserra, 2018; Ly *et al.*, 2018).

Subsequently, the memory is reconsolidated and stored with updated significance via cortical mechanisms. As suggested, there is a change in cortical control from frontal brain areas to parietal brain areas and, in part, this is related to hippocampal network activity. For example, varying doses of PCP have been shown to change the functional connectivity (phMRI) between several brain areas, including the fronto-cortical and hippocampal brain regions (Paasonen *et al.*, 2017). Atasoy *et al.* (2018) report that changes in brain activity occur in a frequency-specific manner with LSD and psilocybin, and that these changes in power-law components lead to an expansion of the repertoire of active brain states and the emergence of more complex brain dynamics which heightens information processing capabilities.

Perhaps a similar mechanism may be involved in ancestral communication.

> *Higher doses of ibogaine generate its psychoactive effects, including hallucinations and the facilitation of communion with the spirits of the ancestors in rites of passage. Ibogaine ingestion in a religious context allows a bonding across time and space between consumers and their ancestors and fellow community members through a shared common experience of a distinctive system of belief and consciousness.*
> **Corkery**

Ayahuasca and ibogaine are the psychedelics most commonly associated with ancestor communication. Ayahuasceros and Bwiti tribesman summon the ancestors during ceremony. The Basotho people of southern Africa use *Boophone disticha*, a psychedelic bulb for ancestor communication as well. This may be culturally-specific interpretation but an alternate hypothesis proposed here is that the same mechanisms that are involved in psychedelics' anti-amnestic properties, i.e., their ability to retrieve and reconsolidate memories via changes in gene expression and brain activity, are the same mechanisms involved in "making conscious" information in our DNA and inherited epigenetic information. Genetic memory is a field of psychology and epigenetic modification from ancestral experience and/or trauma is now known to be heritable and able to affect offspring for many generations afterward (Klosin *et al.*, 2017; Mitchell *et al.*, 2016; Wei *et al.*, 2015). More research is required but if changes to our mind, memories and personality are due to changes in gene expression and epigenetic mechanisms and if psychedelics are able to "make conscious" stored neural information that is coded by genes and epigenetics, then it may be possible for information stored in our DNA and in our epigenome to be "made conscious" and in the case of the epigenome, reconsolidated in the same way as memories are. This is not a new concept in the psychedelic community. Psychedelics are said to heal ancestral trauma. After spending many years researching ayahuasca in South America, Narby (1999) concluded that ayahuasca used by shamans in the Western Amazon affords them access to knowledge coded in DNA. As more and more research uncovers the molecular mechanisms of psychedelic neuroscience, this does not seem like an impossible idea. Early psychedelic use in South America and Africa may be the origin of modern ancestor worship.

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Further reading

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