Scanning the new frontier of mental health: psychedelic brain imaging

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The use of psychoactive substances for ritual, spiritual and medicinal purposes stretches back into prehistory and has been a common feature of many diverse cultures and societies globally. Psychedelics, with their unique ability to amplify feelings of connectedness and openness, may have also served as tools for promoting tribal cohesion and trust in ancient cultures. Psychedelic is a broad term derived from the Greek words 'psyche', meaning soul or mind, and 'deloun', which means to manifest. Classic psychedelics, such as psilocybin (the active ingredient in magic mushrooms), act directly on the serotonin 5-HT2A receptor, while atypical psychedelics, such as MDMA and ketamine, have different pharmacological modes of action and tend to have less of a hallucinogenic effect. They all produce (as the origin of their name suggests) a profound shift in consciousness, generally positive emotional states and feelings of connectedness and openness. Lysergic acid diethylamide (LSD) is in many ways the prototypical psychedelic and began the first wave of psychedelic research in western medicine after it was first synthesized in the early 1940s. By the 1960s, thousands of patients had received LSD therapy in the USA, the UK, Czech Republic and elsewhere for depression, anxiety, addiction and a number of other disorders. This period concurrently saw the development of other key psychiatric drugs such as monoamine oxidase inhibitors as antidepressants and dopamine antagonist drugs as antipsychotics. This revolution in psychiatric treatment ushered in a wave of research and entirely new perspectives on the biological mechanisms underpinning psychiatric disorders.

Brief history of western psychedelic use

However, unlike the more 'standard' psychiatric drugs, LSD soon leaked out of clinical settings and began to be used recreationally. Psychedelic use among young people was widely perceived to be fuelling the counter-cultural and anti-Vietnam war movements in the 1960s. The reaction from the establishment in the USA was President Nixon's 'War on Drugs' which began in the early 1970s and produced a declaration by the United Nations which effectively banned psychedelics worldwide. Clinical use of psychedelics and associated research was halted overnight. In the aftermath of the ban, psychiatric research and drug development arguably lost much of its momentum. With the notable exception of selective serotonin reuptake inhibitors (SSRIs) for depression, the subsequent decades saw a stark absence of novel psychiatric medicines. This period of relative stagnation unfortunately coincided with a global surge in psychiatric disorders, marked by escalating rates of depression and suicide in many countries. Reasons for this are still debated, but the rise in individualism in the libertarian 1980s, coupled with a diminished sense of community, and a consequent epidemic of loneliness are plausible factors.

The contemporary wave of psychedelic research which began in the early 2000s represents the resurgence of the psychedelic work from the mid-20th century, a second psychedelic renaissance emerging after decades of prohibition and suppression of the research findings. Early-phase clinical trials are showing powerful clinical effects on depression, addiction, post-traumatic stress disorder and a range of other problems and we may be on the cusp of a true revolution in psychiatric treatment. The current wave of work has developed in a markedly different landscape. Neuroscientific research methods in the 1960s for both animal/pre-clinical and human/clinical work were relatively unsophisticated. Some early work was performed using electroencephalography (EEG), which measures synchronization of large neuronal assemblies from electrodes placed on the scalp; however, most studies were carried out using only visual inspection of recordings, without modern quantitative methods. In contrast, research conducted in the 21st century has included up-to-date neuroimaging techniques from its inception, both for basic science work with healthy controls, and incorporated into clinical studies. Today, we have a number of methods for

examining the (human) brain *in vivo*, including functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG), which empower scientists to explore the intricate processes unfolding within the brain in real time. This unprecedented capability offers a glimpse not only into the profound neurofunctional changes occurring as a result of therapy in psychiatric disorders but also into the emotional and visual experiences of individuals undergoing an acute psychedelic experience. This approach has produced a great leap forward in our understanding of the effects of these uniquely powerful compounds.

Neuroimaging psychedelics

The majority of contemporary psychedelic research has been performed using fMRI, a tool which images the whole brain and its activity, with no radioactive tracer or contrast injection required. fMRI can be used in conjunction with a task to show how the brain responds to specific stimuli or with the subject at rest to image patterns of baseline brain function and connectivity between separate brain areas. Resting-state studies in healthy participants have revealed significant insights into the acute brain-network effects of compounds like psilocybin, LSD and MDMA. Notably, classic psychedelics profoundly disrupt normal large-scale network patterns of brain connectivity (Figure 1). These findings have led to contemporary theories on the acute and long-term effects, such as the relaxed beliefs under psychedelics (REBUS) model. This suggests that psychedelics promote a reduction in top-down processing, meaning a decrease in the influence of higher-level inhibitory control brain regions. Psychedelics may induce a state where prior expectations, beliefs and perceptual models of the world are relaxed, allowing for novel perceptions and experiences, contributing to the unique and altered state of consciousness associated with psychedelic trips.

Task fMRI data from these studies has provided clinically relevant insights, including the impact of LSD on the brain's response to positive stimuli like music, the effects of psilocybin on social and emotional processing and the influence of MDMA on the recall of emotional memories. Once the safety and tolerability of psychedelics was proven in healthy subjects, the next stage was to investigate changes in disease states. The first clinical trial to use fMRI with psilocybin for treatment-resistant depression was conducted at Imperial College London. Importantly, decreased depressive symptoms were observed in all 19 patients at 1 week post-treatment and 47% still met the criteria for response at 5 weeks post-treatment. As well as providing landmark clinical results in this very severely depressed, difficult-to-treat cohort, the study identified changes in blood flow to the amygdala that correlated with changes in depression scores. In the same cohort, increased connectivity was identified post-treatment between the hippocampus and the frontal cortex, a network associated with memory formation and consolidation. These brain imaging findings therefore provided new insights into not only psychedelic drug actions, but also the pathophysiology of severe depression.

Furthermore, data from this trial and a subsequent trial comparing psilocybin with a current first-line treatment for depression (escitalopram; an SSRI) were re-analysed in order to examine large-scale changes in resting-state fMRI data. This study showed that, in both cohorts, the acute

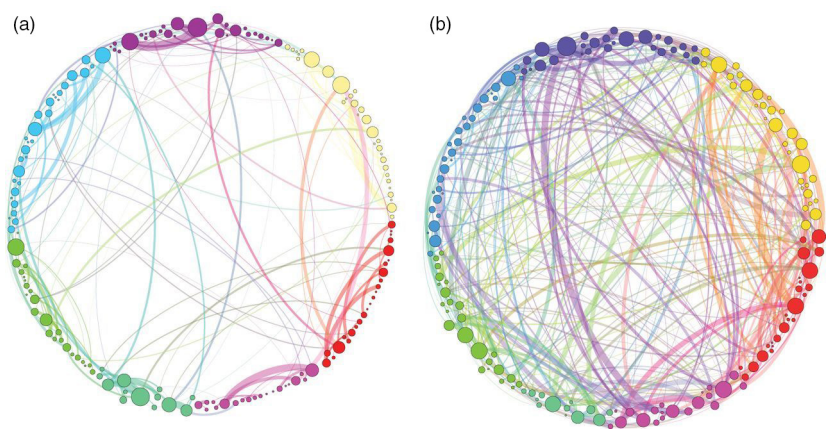

Figure 1. Diagram of the brain's connectivity, produced by analysis of functional magnetic resonance imaging (fMRI) data. Each major brain network is represented as a different colour around the edge of each circle. Under placebo (left), there are strong connections within the network, but relatively few/weak connections between the networks. Under psilocybin (right), there are weaker connections within the networks and many more connections across the networks. Psilocyin, therefore, produces a profound breakdown in the standard pattern of coherent brain-network function. Figure reproduced from Petri et al. (2014) under an open-access licence.

effects of psychedelics on brain organization are somewhat persistent and residual effects can still be seen 1 day (first cohort) and 3 weeks (second cohort) after therapy. This reduction in brain 'modularity' was also related to longer-term clinical results, with the patients showing the largest change in their brain organization tending to show better outcomes. Supporting results from a similar trial at Johns Hopkins University have shown increases in cognitive and neural flexibility up to 1 month after therapy. This suggests a possible clinical mechanism where these disrupted patterns of brain connectivity open a therapeutic window, where (with proper guidance) neural pathways associated with dysfunctional thoughts or behaviours may be degraded and new pathways associated with more functional outcomes may be strengthened. This further suggests that other disorders where patients are stuck in unhealthy patterns of thought and/or behaviour (such as addiction, anorexia nervosa or obsessive-compulsive disorder) may also benefit from the 'rewiring' or 'rebooting' effects of psychedelics on the brain.

Studies using PET have been much less common, partly because of the much higher associated difficulty and costs of PET studies and also because of (until recently) a lack of availability of appropriate radiotracer compounds. PET is a molecular imaging technique that detects and maps the distribution of radiolabelled tracers, which emit positrons as they decay. These positrons collide with electrons in the body, producing γ-ray photons that are detected by the PET scanner, allowing for the visualization and quantification of metabolic and biochemical processes in tissues (Figure 2). Recently, initial studies have been performed in Copenhagen and London with a radiotracer called [11C]CIMBI-36, which is relatively selective for the 5-HT2A receptor. The Copenhagen [11C]CIMBI-36 PET study with psilocybin has shown that the acute subjective effects of psilocin (the active metabolite of psilocybin) are closely associated with receptor occupancy at the 5-HT2A receptor, that is, increased occupancy is associated with a stronger 'trip'. PET, therefore, provides complementary data to functional brain imaging methods like fMRI and the two methods can potentially be combined in a new generation of PET/MR scanners, providing simultaneous molecular-level and functional readouts. In addition, a number of studies have used EEG or MEG, sometimes combined with fMRI. These include recent work from Imperial College on the first brain imaging data to show the effects of *N*,*N*-dimethyltryptamine (DMT) a highly potent and very short-acting classic psychedelic. EEG is becoming a popular method in psychedelic clinical trials because of its ease of use, low cost and non-invasive nature, but its overall signal-to-noise ratio is relatively poor and it is also unable to effectively record data from deep brain structures, which may be important in both acute and clinical effects of psychedelics.

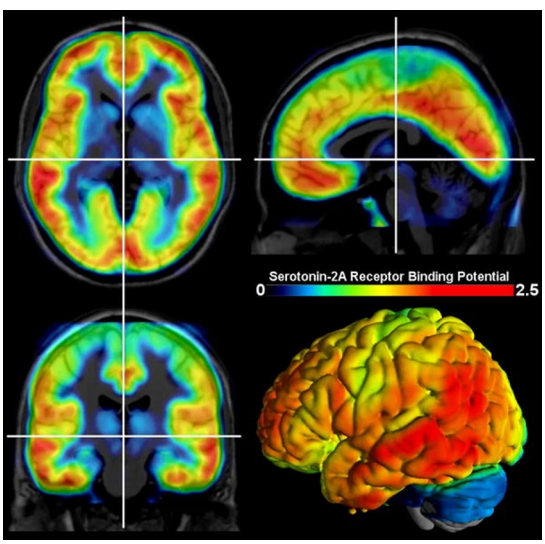

Figure 2. Distribution of the serotonin/5-HT2A receptor in the human brain, as measured with PET. The 5-HT2A is predominantly localized to high-level regions of the cortex with relatively few receptors present in sub-cortical regions. Image reproduced from Saulin et al. (2012) under an open-access licence.

Future research and clinical development

There is currently strong interest in developing psychedelic treatments from both the commercial and clinical/academic sectors. Psychedelics have already been licensed as medicines in Australia, and it is likely that MDMA will become a licensed treatment for PTSD in the USA in 2024, with psilocybin for depression following closely behind. With the tools and research methods available now, there is, therefore, an important and almost unprecedented opportunity – to develop these novel treatments for widespread clinical us, and, concurrently, to conduct detailed neuroscientific work to explore their therapeutic mechanisms. Never before have we had such a range of powerful and applicable research techniques available at this point in the development of a new class of psychiatric treatments. Ideally, these two streams of work will be inter-dependent and complementary; the basic science work can help guide the further refinement of these treatments as they are deployed more widely, and the clinical experience gained may influence the direction of the neuroscientific research.

There are a host of vital unanswered questions. So far, no study has examined how the acute (molecular/functional) effects translate into longer-term (clinically relevant) brain effects in the same cohort of subjects. There is also intriguing data suggesting that psychedelics have strong effects on neuroplasticity, with pre-clinical work showing extremely strong affinity for both LSD and psilocybin at the TrkB receptor, a key receptor for brain-derived neurotrophic factor (BDNF). Data showing

neuroplasticity effects in humans is currently lacking, and it is unknown to what extent neuroplasticity may play a role in the therapeutic effects of these treatments. If psychedelics are found to be able to promote neural or synaptic growth in humans, they may conceivably have a useful role in neurological conditions such as Alzheimer's disease or other dementias. To tackle these issues we need concerted efforts to conduct advanced multi-modal (PET/fMRI) imaging studies, with PET tracers such as [11C]CIMBI-36 and [11C]UCB-J (a marker of synaptic density; useful for neuroplasticity investigations). By using multimodal imaging, we can build a conceptual bridge between the low-level molecular effects and higher-level functional effects of these drugs (over extended time-scales) and then extend that bridge further into clinical translation.

Undeniable challenges, including adequate financing, stigma and generalization across certain psychiatric populations, lie ahead. Studies like this use cutting-edge techniques and are technically challenging, as well as being extremely costly in terms of both money and time. Furthermore, the stigma and difficult legal situation surrounding psychedelics mean that research is much more demanding and costly than similar research with compounds which are not stigmatized or legally prohibited. Strong clinical trial results have led to legal restrictions being gradually relaxed in some jurisdictions though, and a high level of public awareness of these potential treatments is helping to push politicians further in the direction of further easing of prohibition, at least for research purposes. Deploying these treatments at a wider scale in the general population will also provide unique logistical challenges, and developing them as effective long-term treatments (outside of the confines of the relatively short-lived clinical trials) is also a significant obstacle. We hope our continuing efforts to understand the uniquely powerful effects of psychedelics on modifying human consciousness will eventually lead to them taking their place as a standard treatment in the toolbox of psychiatry and neurology and perhaps may even lead to profound and vital insights into the nature of consciousness itself. ■

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