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Research on psychedelic substances

The term 'psychedelic' (i.e. mind-manifesting) was coined by Humphrey Osmond to characterize a group of substances that are capable of liberating human perception from cultural conditioning, providing an opening to the transcendent qualities of being human. Osmond claimed that LSD and similar drugs may give people insightful experiences that enable them to better understand themselves and their relationships with the world.[1]

Psychedelic substances have the potential to show mind-manifesting properties under appropriate internally and externally supported conditions. They can offer lucid insights into one's psychological make-up and functioning. They are also capable of inducing a spectrum of inner experiences, sometimes referred to as 'religious' or 'mystical'.[2,3] Another commonly used term for these substances is 'hallucinogens', although this synonym is viewed as controversial because of the implication that they somehow cause hallucinations, which they do very rarely. Most psychedelic substances produce visual alterations of perceived objects and pseudohallucinations which are understood by the subject to be 'illusionary' in character.

A somewhat separate and newer group of psychedelic substances are the entactogens; for example, MDMA, MDE, MBDB (i.e. 3,4-methylenedioxy-*N*-methylamphetamine, 3,4-methylenedioxy-*N*-ethylamphetamine and 2-methylamino-1-(3,4-methylenedioxyphenyl)butane). These usually do not induce any major alterations in perception of outer reality, although they may be considered mind-manifesting in terms of significant alterations/expansions of conscious awareness of self and others.

When thinking about psychedelic substances, two general subgroups are typically considered. One core group of psychedelics is represented by the hallucinogenic tryptamines (e.g. *d*-lysergic acid diethylamide (LSD), psilocybin, *N,N*-dimethyltryptamine (DMT) and phenethylamines (e.g. 3,4,5-trimethoxyphenethylamine (mescaline), 2,5-dimethoxy-4-bromophenethylamine (2C-B), 2,5-dimethoxy-4-bromoamphetamine (DOB)) and most of the entactogens (e.g. MDMA, MDE, MBDB, and possibly some cathinones). In a broader sense, the second group of psychedelic substances might include cannabis, ketamine, nitrous oxide, and some anti-cholinergics. These substances, however, typically produce a slight to severe reduction of vigilance, affectivity, and cognitive performance as well as memory impairment. These constitute a quite different pattern of effects when compared to the core group. Major LSD researcher Hanscarl Leuner introduced the terms hallucinogens of the first and second order when referring to these two groups.[4]

From a clinical point of view, one may be tempted to further divide the core group into a range of substances that shows a more interindividually stable and predictable pattern of effects (MDMA, MDE, cannabis) in contrast to substances which produce less interindividually stable and predictable effects (e.g. LSD, mescaline, DOB, DMT). The first group may display a broader spectrum of pharmacological effects and may therefore induce a more stable and predictable matrix of effects, i.e. their psychoactive effects are less dependent on interpersonal and extrapharmacological variables. The second group has less stable and predictable outcomes. It can render the subject more sensitive to a broader spectrum of psychological effects and perceptual alterations which can be influenced much more by individual set and setting.

Some historical aspects

From a historical perspective, one cannot help but notice a variety of changes in how psychedelics have been perceived and approached by science and society. Naturally occurring psychedelics have been explored for millennia and scientific interest began to deepen at the turn of the twentieth century with mescaline. This initial research into mescaline appeared to tail off until bolstered by the discovery of LSD and with it neurotransmitter research and the search for therapeutic applications. Nearly 10 000 publications appeared on LSD alone between the 1950s and the 1970s,[5] at which point research endeavours virtually stopped as a consequence of the compound adopting a counter-cultural popularity beyond research settings of the 1960s.

Following the abandonment of clinical research of psychedelic substances, it is interesting to remember that pharmacological research focused on neurotransmitter antagonists (e.g. neuroleptics) and the development of tranquilizers (e.g. benzodiazepines). Arguably, the thrust of research into antagonists and tranquilizers somewhat disregarded the field of psychedelic substances. That said, LSD does appear to have played a major role in the development of new medications during the 1980s, in the form of the so-called second-generation neuroleptics (risperidone and others). In this particular context, LSD was administered to rats under long-term dosage regimens in the attempt to make them schizophrenic and potentially new neuroleptics were applied with the aim of curing these drug-induced conditions. This research was initially kept secret because of rivalry between pharmaceutical companies but findings were published later.[6]

The 1990s witnessed a cautious resurgence of academic research with psychedelic substances, especially towards the neurobiological and clinical effects of psilocybin, ketamine, DMT, and the entactogens. During this phase, it was confirmed that the major psychedelic substances belong to a class of their own and that they could be divided into classical hallucinogens and entactogens, which reflected their own distinct neurobiological profiles.[7]

Development of psychedelic substances as treatment options

While psychedelic substances are seen by some to play a marginal role, others point to the stimulation of (psycho)pharmacological research following the discovery of LSD in the 1940s[8,9] and the fact that their potential was not appropriately evaluated because of the harsh interruption of research catalyzed by sociopolitical developments in the 1960s.[10]

Preclinical and clinical research indicates that many psychedelic substances act as complex receptor agonists which points towards the potential for a valuable reservoir of therapeutically useful substances. These interact in a complex and versatile fashion with

the major neurotransmitter systems; their activating psychopharmacological effects may offer a complementary perspective in addition to the deactivating and tonic/chronic actions of neuroleptics, tranquilizers and conventional psychostimulants.

Psychedelic substances stimulate receptors in a much more diverse and often quite non-selective fashion leading to the concept of 'dirty drugs' or 'dirty ligands' based on pharmacological grounds. On the other hand, there appears to be a slight shift in perception towards these substances. What was seen as pharmacologically promiscuous is beginning to be considered as pharmacologically rich, in cases where substances act as agonists, partial agonists, or even antagonists and this may even be different with the range of neurotransmitter systems and receptor subtypes. Their interactions with receptors may lead to specific synergistic effects as well as opposing effects and/or both at the same time, in addition to the phenomena of functional selectivity. Psychedelic substances appear to induce an altered state of mind by influencing the whole brain's information flow, conceptual cognition, affectivity, and sensory processing. Potentially some of these actions might induce a specific matrix of brain alterations that could give rise to neurobiological configurations of brain activity which may then be able to help with the treatment of some serious disorders.[11,12]

Their specific value may lie in the short-term rearrangement of brain activity rather than in tonic long-term action as it is known from antidepressants, neuroleptics, or typical psychostimulants, possibly reflecting the complex and diverse receptor interactions that may correlate with a complex pattern or matrix of altered mental functioning that might also prove useful for some therapeutic interventions (MDMA-assisted therapy, psycholytic and psychedelic therapy). Nevertheless, one has to be aware that these complex effects are very sensitive to extrapharmacological variables. One major difference between psychedelic substances and their neuroleptic, antidepressive, tranquilizer, and psychostimulant counterparts may be seen in their ability to result in an opening of the psyche which can, under appropriate circumstances, lead to an enhancement of psychotherapeutic processing. These effects may also be seen in traditional religious and ritualistic healing contexts (e.g. peyote rituals of the Native American Church, ayahuasca churches). In successful cases, these substances do not primarily appear to help in compensating or suppressing symptoms, but rather precipitate forms of healing in a more direct and causal manner.

The notion that some of these substances might hold significant potential for medical and psychological treatments has emerged over the last decade.[13] More recently, it was established that some psychedelic substances (e.g. MDMA, psilocybin) can also be used as effective treatments for some grave and prevalent conditions such as posttraumatic stress disorder (PTSD) and end-of-life anxiety.[14–16]

This specific activating pattern of effects is not seen with the cannabis-driven mitigation of symptoms of PTSD or with the treatment of cluster headaches with LSD, psilocybin, and 2-bromo-LSD. These treatment strategies follow a more conventional pattern in which symptoms are alleviated, but not causally healed.[17–20] Another important field of research involving these substances is the temporary experimental alteration of brain activity designed to understand the aetiology of psychotic and depressive states.[21,22]

Research on psychedelic substances in this issue

In this issue, three representative examples of psychedelic substances are presented: phenethylamines, tryptamines and cannabinoids. The introductory contribution is provided by Bogenschutz and Pommy who are concerned with approaches to the treatment of addictions and the idea that recovery from substance abuse could potentially benefit from therapeutic uses of psychedelics.[23] The authors review some pharmacological principles and a range of testable hypotheses that could lead to reduced craving, enhanced self-efficacy, increased motivation, and possibly abstinence.

Phenethylamines

Phenethylamines and amphetamines that carry the 2,4,5-trisubstitution pattern belong to what might now be referred to as a classic group of potent psychoactive/psychedelic substances. (*R*)-(−)-2,5-Dimethoxy-4-iodoamphetamine (DOI) is probably one of the most potent primary amine representatives that has also found its place as an important pharmacological agent and receptor probe. Canal and Morgan not only give an extensive review of its pharmacology, they also provide a thorough assessment of the head-twitch response (HTR) in rodents, a key animal model commonly employed for the determination of 5-HT_{2A} activity. However, one has to be mindful that HTR can also be elicited by other compound classes and that 5-HT_{2A} activation may be necessary but not sufficient for the full range of effects of DOI and other psychedelics.[24]

Fluorine plays an important role in the area of medicinal chemistry, reflected by the availability of many fluorinated medicinal products. As such it seems prudent to consider the impact of fluorine chemistry on the properties of psychedelic substances. A comprehensive review is provided by Daniel Trachsel who explores the phenethylamine/amphetamine pharmacophore and, in addition to previously unreported data, includes an assessment of the fluorinated trisubstituted 2,4,5-, 2,4,6-, 3,4,5- and 3,4-methylenedioxy series.[25]

Another potent and long-lasting phenethylamine is the classic DOB. The ability to unambiguously identify any substance is often hampered by the absence of suitable reference materials, especially when it is considered that more than one positional isomer might exist. Maher *et al*. close this gap by offering an analytical characterization of six regioisomeric brominated dimethoxyamphetamines. Procedures include the implementation of gas chromatography mass spectrometry (including derivatization) and the ability to obtain differentiating data based on gas chromatography vapour-phase infrared detection.[26]

Tryptamines

A variety of DMT-containing plant products, for example, ayahuasca and jurema vine, are used in indigenous communities and syncretic churches in several parts of South America and other parts of the world. The psychoactive and pharmacological properties associated with these brews began to instigate a wide range of research projects in the early 1990s and it seems fair to say that the knowledge and awareness of ayahuasca has become more prevalent throughout some parts of the western world. Recent years have seen an increasing attempt to study these effects over a period of time going beyond acute effects. A total of 15 studies were identified by Barbosa *et al*. who examine what is currently known in terms of health of ayahuasca users. Some of the studies reviewed point to possible positive effects of the use of these substances in ritual settings.[27]

A 24 h metabolism study in urine following an oral dose of encapsulated freeze-dried ayahuasca is presented by Riba *et al*., who determined the extensive metabolic fate of DMT and

the associated β-carbolines.[28] A range of interesting findings are reported. For example, an 80:20 ratio for indole-3-acetic acid: DMT-*N*-oxide was observed after ayahuasca administration and tetrahydroharmol, the *O*-demethylation product of tetrahydroharmine, was also formed.

The idea that endogenous *N*-methylated tryptamines might play a physiologically relevant role started to develop in the 1950s following their detection in urine which was subsequently related to the suggestion that biochemical features might be relevant for schizophrenic conditions.[29] Over the last few decades, the presence of psychedelic substances in humans triggered a range of speculations and controversies regarding their functions and implications of these findings. Thankfully, Barker *et al*. provide a long-awaited critical review and discussion on the topic carefully examining a total of 69 studies on endogenous tryptamines.[30] While technical considerations placed significant limitations on the ability to unambiguously identify these derivatives, especially when examining earlier work, advances in mass spectrometry began to open the door for the opportunity to apply more robust and sensitive methodologies.

The increased interest in ayahuasca and other related plant products and mixtures, which may be obtained from traditional sources or the Internet, serves as a reminder that there is a need to establish appropriate quality control procedures. Gaujac *et al*. review the literature on analytical methodologies employed for the characterization of these plant products and highlight the need for the implementation of fully validated analytical methods.[31]

Cannabis

Passie *et al*. offer an overview of accumulating clinical and preclinical evidence that cannabinoids may mitigate some major symptoms associated with PTSD. A case report is presented of a patient with severe PTSD symptoms, who learned to smoke Cannabis resin in order to cope with grave PTSD symptoms. Recent evidence demonstrates that the endocannabinoid system is involved in different neurobiological systems critical for the complex pathogenesis of PTSD.[20] Therefore, it is not astonishing that cannabinoids may modulate or alleviate some major symptoms of PTSD.

As is the case with any natural product, a large range of variations exists between Cannabis cultivars and their impact on psychopharmacological properties and distribution of chemical entities needs to be understood more clearly. Hazekamp and Fischedick describe a fascinating study in which the authors characterized the analytical profile of some major Cannabis cultivars that represented both coffee shop products and varieties of pharmaceutical-grade.[32] The quantitative determination of 28 different constituents (GC-FID and GC-MS) is followed by principal component analysis which allows the ability to distinguish between chemovar groups. This study also draws attention to the fact that the presence of the key cannabinoids alone might not be sufficient to characterize the overall psychoactive differences between cultivars and that other constituents, for example terpenoids, might play an important role as well.

Subsequently, the article from Bylda *et al*. discusses the development of a sensitive and reliable liquid chromatography-tandem mass spectrometry procedure for the detection of Δ^9-tetrahydrocannabinol (THC) and 11-nor-9-carboxy-THC in oral fluid. This method was equally robust when a number of possible exogenous and endogenous interferences were added to oral fluid samples.[33] There is always a need to develop and evaluate novel detection methods and applications. Holland *et al*. show that it is possible to detect a range of dihydroxybenzene isomers when using chemiluminescence detection. This method is based on the reaction with acidic potassium permanganate and includes an application to the determination of cannabidiol (CBD) in industrial-grade hemp which highlights the opportunity to extend this approach to other cannabinoids.[34]

This multidisciplinary Special Issue follows on from two issues previously published in *Drug Testing and Analysis* dedicated to the topic of psychoactive substances: New Psychoactive Substances (July/August 2011) and Illicit Drugs (September 2011). The editors are grateful to Prof. Mario Thevis and Paul Trevorrow for their kind help and support and are indebted to the contributing authors for their submission and to the reviewers for scrutiny. It is hoped that the topic described in this issue will be of interest to a wide readership.

Simon D. Brandt[a]* and Torsten Passie[b,c]

[a]School of Pharmacy and Biomolecular Sciences,
Liverpool John Moores University
Byrom Street
L3 3AF
United Kingdom
E-mail: s.brandt@ljmu.ac.uk

[b]Laboratory for Integrative Psychiatry, McLean Hospital,
Harvard Medical School
Belmont, MA 02478
USA

[c]Department of Psychiatry, Social Psychiatry and Psychotherapy,
Hannover Medical School
D-30625 Hannover
Germany
E-mail: dr.passie@gmx.de

Both authors contributed equally to this editorial.

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