



BECKLEY
FOUNDATION

BREAKING CONVENTION 2019
16TH-18TH AUGUST

MICRODOSING: BIG STEPS SMALL DOSES
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This is an exciting time for psychedelic research! We've finally reached a tipping point.

Ever more evidence from rigorously conducted research is confirming what wonderful medications of the future, psychedelics will be. They hail a paradigm shift in mental health care, with potential benefits that extend far beyond the field of psychiatry. When used in the right conditions, they may not only treat a wide range of disorders, but may also facilitate transformation and inspiration, that can leave an indelible mark, affecting us at many different levels - from our basic physiology to the depths of our souls. They can fundamentally alter our mood, perceptions and belief system. They can spark that "Aha" moment that can change our destiny.

Informed opinion is at last recognising the possibility that psychedelics may have an important part to play in addressing many of our current crises, from mental and physical health, to ecological and spiritual.

This recognition is the result of the work that we, the international Psychedelic research community, have accomplished over the past decade, carrying out pioneering research that demonstrates the beneficial effects of psychedelic-assisted therapy, particularly when compared with the currently available conventional therapies.

In the UK, our *Beckley/Imperial Research Programme* has produced some ground-breaking studies, from the first neuro-imaging study of LSD, to the first study looking into the potential of psilocybin-assisted psychotherapy to overcome treatment-resistant depression, both of which have done much to raise the profile of this field of research.

In the US, *Johns Hopkins University*, (with whom I collaborated on the first trial investigating psilocybin-assisted-therapy for the treatment of nicotine addiction), has been the most prominent research team in America. As the research expands, the misplaced taboo around these compounds begins to dissipate.

But another mini-wave has been capturing the media attention for the past few years: the increasingly popular trend of Microdosing. This growing public interest increases the

obvious need for rigorous scientific studies to inform us about its potential benefits and drawbacks.

However, the use of low/medium doses of LSD is not really a new phenomenon. I have long been attracted by the experience of regular dosing to reach a level where one's consciousness is enhanced, but one remains in control. This was an experience I learned to value greatly back in the 1960s.

I was introduced to LSD in 1965. In the years that followed, other than the mystical, or peak experience, my aim was to hit that "sweet spot", where vitality and creativity are enhanced, while leaving me in control of my concentration. I grew to love this state. It was, in a way, comparable to what people are doing today with microdosing.

From my own experience, before LSD was criminalised, the mini/median-dose approach was a very interesting complementary way of making use of the potential benefits of LSD. I found that having the full pallet of alternative doses available to enhance cognitive functioning, mood, focus, and increased awareness was a *great advantage*.

My interest in the science underlying the effects of LSD began 1966, when I met and started working with Bart Huges, who had developed 2 game-changing hypotheses:

- 1) Linking changes in consciousness to changes in cerebral circulation;
- 2) Providing a mechanistic description of the ego.

I found these explanations *life changing* as they enabled me to live and work on LSD, and in my opinion, to see much *further* and deeper than I would have been able to without them.

In those days, we took high doses, but by using them regularly, and with a methodical use of vitamin C and glucose, we became able to better navigate this elevated state of consciousness, so the experience was more like a strong microdose, or, as I used to call it, a "psychovitamin", which enhanced work, creativity, self-discovery and enjoyment and provided a new and more profound insight into psychology, physiology and the science of consciousness.

For relaxation in the evenings, we played endless games of Go, an ancient Chinese game. I found that playing Go was a perfect test of increased cognition. It enabled one to explore the particular changes in cognitive functioning that occur with medium doses of LSD, a mode of thinking that is much more fluid and intuitive and is conducive to that Aha! moment which comes with intuitive pattern-recognition, due to a looser, less restrained state of consciousness.

This period of my life fundamentally influenced my future endeavours. From the early 1970s, I realised that the only way to break through the barricades of repression built up by prohibition, was with the very best science.

I decided to devote my life to understanding more about the brain and how to improve its functioning, and to undertake scientific research in an attempt to unravel some of the mysteries underlying consciousness and its altered states. Ultimately this led me to set up the Beckley Foundation 30 years later.

My aim was, and still is, to *re-integrate* these valuable compounds into the fabric of modern medicine and society, and to make their benefits available to those in need. Through the Beckley Foundation, I established collaborations with leading scientists around the world.

The most fruitful of these collaborations has been with Professor Dave Nutt, with whom I set up the *Beckley/Bristol Programme* in 2005, which in 2008 became the *Beckley/Imperial Research Programme*. We were later joined by Robin Carhart-Harris as Principal Investigator.

Instead of starting our programme with investigating LSD, as I had hoped, we started with psilocybin, as it is less taboo, no one knowing how to spell it, or what it means! Only later were we finally able to conduct the first brain imaging study of LSD in humans I had been dreaming about for so long.

Our work so far has primarily been focusing on larger doses of psychedelics, demonstrating the *key role* that the peak experience plays in the long-term therapeutic effects. I find it a *fascinating* fact that the ‘mystical’ experience is closely correlated with the positive therapeutic outcomes.

However, I believe that microdosing will also have a *valuable* role to play in the psychedelic spectrum of therapy, and as a *tool* to improve cognition and well-being - It can act as a *nootropic* - or as a “psychovitamin” – improving mood and cognitive functioning, among many other potential attributes. In order to test this hypothesis, I am developing an *exciting* multi-armed microdosing research programme with a number of collaborators around the world.

As part of the *Beckley/Imperial Research Programme*, we are conducting the first placebo controlled naturalistic study of microdosing led by Balázs Szígeti, which David Erritzoe has already spoken about this morning. This research is unique in the sense that it is the first to introduce a self-blinding procedure, where the participants set up their own placebo control. We are still recruiting participants for the study, so do apply if interested.

Although much valuable information can be gained through naturalistic studies, lab-based studies are essential in order to investigate the underlying changes in brain-function and gather other important physiological measures.

It will be particularly interesting to compare the changes in neural activity, functional connectivity, blood-flow, and if possible, capillary volume, to what happens with larger doses. However, prior to diving into an expensive brain-imaging study of microdosing, the first step was to conduct a dose-finding study to identify the different characteristics of various low doses.

Most people do not know for sure what LSD dose they are microdosing with, as it can only be sourced illegally, and it is still not clear what is the ideal dose, particularly as different doses suit different people.

To investigate this, in 2017, I set up a collaboration with Jan Raemakers at the University of Maastricht. In our recently completed dose-finding microdosing study, we tested the effect of a placebo and 3 different doses of LSD (5, 10, 20 micrograms) on mood and cognitive performance.

Although data are still being analysed, a few interesting findings have already emerged:

- 1) Microdosing, at the doses typically used, i.e. between 10 and 20 mics, is definitely **not** sub-perceptual. Participants could tell the difference between placebo and doses of 10 and 20 mics.
- 2) Looking at the effects on mood, the 20 mics dose was associated with *elevated* mood, and *more* energy. It is somewhat surprising that positive effects on mood were not picked up at 10 mics, as that is the dose that is likely the closest to what most people typically microdose with, and reports of positive effects on mood are among the most *consistent* effects noticed across most observational studies.

One possible explanation for this is that the effect of microdosing on mood is closely linked to the type of activities people are engaged in. In our study, participants spent most of their time filling questionnaires and performing tasks, which is not an ideal setting to generate positive feelings.

- 3) Moving on to cognitive effects, significant improvements in the ability to maintain focused attention over an extended period of time, termed vigilance, were observed with 20 mics, but not with the other 2 doses and placebo. However, this dose was *also* associated with diminished performance on another task measuring a different set of cognitive functions, including working memory.

There is still a lot of data waiting to be analysed, looking into cognitive flexibility, creativity, empathy and resilience to pain.

However, these preliminary results *reinforced* my previous feeling that probably the best dose for our repeated-dosing study would be 15 mics, with 20 mics being too noticeable for some people, and 10 mics maybe not being sufficient to evoke significant improvement in mood and cognition.

Before I talk about our next microdosing study, let me briefly discuss a rather fascinating property of psychedelics, that is: their ability to promote the growth of nerve cells and the connections between them, in a process called *neuroplasticity*. All learning and adaptation is based on neuroplasticity.

Last year, an exciting study published in *Cell*, reported that the classical psychedelics are capable of robustly increasing the growth of neurites and synapses both *in vitro* and *in vivo*. Researchers from the University of California found that LSD, DMT, and DOI significantly increased the growth and complexity of neurones, with LSD showing the most *striking* effects.

This property of enhancing neuroplasticity (i.e. forming new connections between neurons) is likely to play an important part in the therapeutic benefit of psychedelic compounds, helping to *consolidate* the changes and insights that can be brought about by psychedelic therapy.

In the studies we have carried out as part of the *Beckley/Imperial Research Programme* with psilocybin and LSD, we have shown the *dramatic* increase in communication between normally distinct areas of the brain, which appeared to correlate with the subjective reports of ego-dissolution.

The peak psychedelic experience is a richer state of consciousness, characterised by a more complex, less predictable, and more 'entropic' (less organised, or constrained) neural activity. These shifts in brain-function can *facilitate* personality changes, by temporally rendering our neuronal circuitry *less constrained* and *more plastic*, thereby allowing the overcoming of rigid, maladaptive patterns of thought, which underlie most mental illnesses such as depression, addiction and post-traumatic stress disorder. In this state of increased plasticity, a new imprint can be laid down, which is better adapted to the individual's healthy functioning and development.

As an illustration of this richer state of connectivity, our brain-imaging study with 75 mics of LSD demonstrated the increased level of connectivity in the visual cortex, which extends its connectivity to over twenty extra brain regions, including those involved in memory and emotional processing, thereby creating a much richer sensory and emotional experience.

What the new findings are now showing, at the cellular level, is that this fluid state brought about by psychedelics within the whole brain, is also reflected in the neural cells themselves, through an increased ability to create new connections with other cells.

I find it really fascinating how psychedelics appear to open up our own connection and growth potential at so many levels, from cells, to brain networks, to our relation to others and to nature.

This ability of psychedelics to promote neuroplasticity in the brain opens-up a *wide* range of potential therapeutic applications beyond the field of psychiatry, such as neurodegenerative disorders, and even rehabilitation following brain trauma, and may also explain the long-term positive personality changes brought about by these compounds.

With our collaborators in Brazil, we are carrying out a series of very exciting studies in this area. With Prof Sidarta Ribeiro and his colleagues, we are looking into the effects of LSD on cognition, and cognitive rescue at all ages.

Prof Stevens Rehen, another of our colleagues in the Beckley/Brazil collaboration, is also conducting some fascinating work. He will be speaking at 12:00 tomorrow in the Hofmann Hall. Stevens and his colleagues at the D'Or Institute have developed a new approach of cultivating laboratory-made 'mini-brains' grown from human stem cells in order to study neurological diseases and the effects of new drugs on the nervous system.

This cutting-edge approach allows us to investigate the effects of LSD on the brain in greater detail, and further, to explore new applications, with a particular focus on **neuroplasticity**, **neurogenesis** and **inflammation**, 3 areas where the psychedelics can play a prominent role.

As part of this translational research programme, we are currently looking into the effects of LSD on cognitive functions, moving between mini-brains, animals and humans.

Moving back to microdosing, one of the hypotheses I am most interested in testing is whether the regular use of low doses of LSD may be able to *increase neuroplasticity*, which may produce long-term beneficial changes in behaviour.

The effect of microdosing on brain function and neuroplasticity has never been investigated in humans, and could considerably enhance our understanding of the possible therapeutic value of low doses of LSD.

Microdosing could be an alternative way of benefitting from some of the extremely valuable therapeutic properties of psychedelics, in a way that is more manageable than the larger doses, both for patients and therapists.

In our lab-based microdosing study, taking place as part of the *Beckley/ Maastricht Research Programme*, we are comparing the acute and long-term effects of LSD microdosing on brain-network-connectivity and on neuroplasticity, using EEG, and relating those changes to the effects observed on mood and cognitive functions.

What I have presented here today is only the beginning of an ambitious LSD research programme, which is covering multi-centres worldwide, and will explore a wide range of doses and possible therapeutic applications.

Our future microdosing studies will explore a range of specific conditions from pain to mood, to cognitive decline and various other applications, including studies to investigate improvement in well-being, through, for instance, the enhancement of mindfulness and openness, and enjoyment of nature.

Albert Hofmann once told me his greatest joy was when an inner-city youth would tell him how a small dose of LSD had opened his or her eyes to the beauty of nature...

Much more exciting results from our work will soon become available on the LSD front, and we are also continuing our research into psilocybin and DMT, with three recently completed studies, using *cutting edge* neuroimaging tools, to gain a better understanding of the mechanisms of action of these compounds, as part of the Beckley/Imperial and the Beckley/Maastricht research programmes.

Sadly, because of lack of time, I cannot develop on this further. However, I invite you to visit our website for more information on these.

Before ending my talk, I would like to bring up our great need of funding. To investigate the full benefits of LSD has been my *particular passion* ever since the late 1960s, where I grew to *love* and know the *great benefits* of this compound. I made it my *life work* to dedicate myself to the study of the human condition, and what makes us *such an exceptional* animal, but at the same time an animal with a *serious* problem at the *core* of our being. The introduction of the ego-mechanism, which became a *unique* characteristic of *Homo-sapiens*, was at the core of my new understanding of the problem.

The brain-imaging studies we did as part of the *Beckley/Imperial Research Programme* appear to confirm our original hypothesis: Psychedelics reduce the blood supply to the Default Mode Network (the likely physiological basis of the ego), thereby reducing its repressive function of controlling what enters consciousness, and what does not.

By loosening its censorship, the brain becomes much more interconnected, neuroplastic, and capable of changing embedded patterns.

Now, fifty years later, with the world waking up to the great potential of these psychedelic compounds to improve our approach to healing human sickness, it has become possible for us to *expand* the work of the Beckley Foundation, by setting up collaborations with a *much wider* network of scientists and institutions around the world, and to build up a *greater* understanding of the *numerous* benefits that these compounds can engender with intelligent use.

Great breakthroughs are in sight, the only thing limiting the full blossoming of this potential is the lack of the necessary funding to carry out this much-needed research.

Thanks a lot for your attention.