LSD and the Importance of Changes in the Cerebral Blood Supply:

from Expanded States of Consciousness to New Therapeutic Interventions

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I have long been fascinated by the mechanisms underlying the profound shift in consciousness that can be achieved using psychedelics.

In 1966 my meeting and love affair with Bart Huges, a scientist of exceptional insight, marked a turning point in my life, inspiring me to research psychedelics and their impact on consciousness as my life's mission. Bart had two important new hypotheses about the mechanisms underlying consciousness and its changing states: the first proposed that *the level of consciousness is dependent on the volume of blood in the capillaries of the brain;* and the second described the *'ego'* as a *conditioned reflex mechanism*, which controls the distribution of blood in the brain, and thereby controls what enters consciousness and what does not.

These hypotheses, which I will further develop later in my talk, changed my life for the better, and for the next 30 years, or so, I worked with Bart and Joey Mellen exploring consciousness, and developing our understanding of the mechanisms underlying its changing states, and how through this knowledge, one can both live and work at a higher level. Our passion was exploring how LSD can *enhance cognitive functioning*, as well as enable one to reach the hidden depth of the psyche, which can then become hyperflexible, and more able to adapt to a more positive pattern of behaviour. But in those days, the field of neuroscience was non-existent, or still in its infancy, and it was not possible to put these hypotheses to the test of rigorous science, so they were ignored.

The development of neuroimaging tools in the 1990s, such as PET and functional MRI offered the opportunity to finally test our hypotheses. However, even then, I typically met with considerable resistance from the scientific community: the vascular system was out of vogue, and all eyes were on the neuronal system.

Indeed, in most neuroimaging studies, a change in blood flow is only treated as a consequence of a change in neuronal activation, but we proposed an alternative

mechanism, where a change in blood capillary volume and its distribution would be at the *origin* of the expanded states of consciousness brought about by psychedelics.

In 1998, I set-up the Beckley Foundation, in order to further the integration of psychedelics into society by developing the best possible research using the newly developed brain imaging technologies to address this fascinating domain of inquiry. Over the last 24 years, we have helped propel psychedelics from the taboo terrain in which they had been imprisoned since the late 1960s, to being the most promising emerging therapy in psychiatry.

However, there are still a lot of unanswered questions remaining to be addressed in order to better harvest the unique potential of these compounds. I remain particularly interested in LSD, a compound I consider to be the 'Queen' of psychedelics, whose unique qualities have perhaps got lost in the false and hysterical propaganda of the War on Drugs.

When I met Albert Hofmann, the father of LSD, I thought he was the happiest man I had ever met, and I could see why. It must be truly joyful to know that you have given such a wonderful gift to humanity.

I first met him in the 1990s at a conference in Amsterdam. I asked him if he'd ever thought that LSD might increase the overall capillary volume of blood in the brain, as our hypothesis postulated. He answered in his humble way, that he was 'just a little Swiss chemist, not a physiologist', but that he and Anita hung from their feet every day 'to get more blood in their brain'.

I told him that since 1966 I had dedicated my life to gaining a better understanding of how LSD works, and I promised him that, by his 100th birthday, I would obtain the first official permissions to carry out scientific research with LSD, thereby breaking the spell which had excluded his 'wonderchild' from its natural role as an invaluable tool for neuroscience, psychotherapy, and the transformation of the human soul.

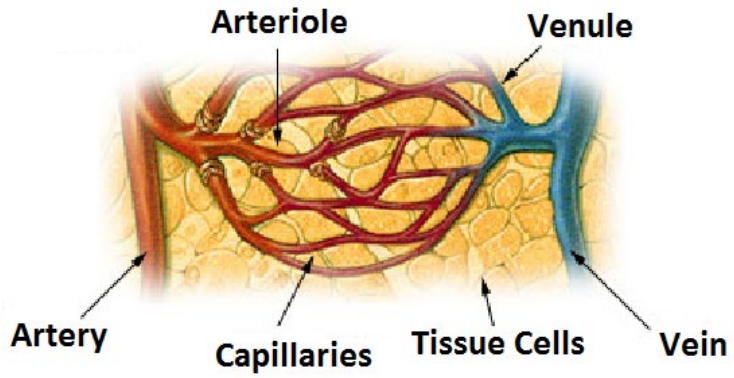
I obtained the necessary approvals and funding in 2005, at Berkley University, but sadly I underestimated the power of the Taboo, and the research was aborted. It took me almost another decade before I accomplished my promise and, finally, we undertook in 2014 the first brain-imaging study of LSD in human subjects, as part of the *Beckley/Imperial Psychedelic Research Programme* which I had set up with Dave Nutt in 2008.

Following this ground-breaking study, and other studies investigating microdosing LSD, I have recently developed a very exciting research programme entirely dedicated to the study of LSD, from full, hallucinogenic doses, investigating the nature of the mystical experience, to low doses, investigating their therapeutic potential, particularly in aging, mood and cognition.

As part as this new research programme, one key project I am developing in collaboration with researchers from Yale and Cornell universities will directly put to the test the blood capillary hypothesis, by assessing, for the first time, the impact of LSD on the capillary volume and vasoconstriction in the brain.

According to our hypothesis, the agonism of serotonin receptors by classic psychedelics at the level of the vascular system, cause an expansion of capillary

volume via a dual effect, whereby large arteries[1] are constricted (mainly via 5-HT1b receptor agonism), and arterioles[2] are dilated (mainly via 5-HT7 receptor agonism). The net effect of this is the *increase in blood volume in capillaries*, making available a greater supply of *glucose and oxygen* to regions that are normally not that well supplied, and *removing the previous hard limit on the brain's available energy reserve*.



We are planning to directly measure how cerebral blood flow changes following administration of LSD, using advanced optical imaging to record the diameter and flow rate of capillaries[3], arterioles, arteries, venules[4] and veins, in mice. The second phase of the experiment involves studying how psychedelics influence neurovascular coupling – that is, the mechanism that links neural activity to changes in cerebral blood flow. This is an important subject for investigation, as understanding precisely how psychedelics alter neurovascular coupling will allow for a more accurate interpretation of how psychedelics alter blood flow and brain activity, and could indeed cause the need to reinterpret much of the prior literature.

To me, a farmer's daughter, to increase the 'irrigation' is an obvious way to increase productivity, and it would therefore seem obvious that this increase in capillary brain volume, and associated increase in energetic resources, result in an expanded field of simultaneous activity across the whole brain. This leads to a global expansion of connectivity, which manifests as the expanded state of consciousness characteristic of the psychedelic and mystical experience. One can see this increase in connectivity in our wonderful Beckley/Imperial images of 2016, with its dramatically increased connectivity in the post-LSD brain.

However, some regions benefit more from this redistribution than others, particularly those neocortical regions which developed more recently in our evolutionary history, and that in part owe their highly plastic function to their development outpacing the brain's metabolic budget. In keeping with that, PET studies have shown *increased* glucose metabolism in many cortical regions under psychedelics. This would explain

[1] With the exception of pulmonary blood vessels, arteries carry oxygenated blood and veins carry deoxygenated blood. Arteries have thick walls with muscle tissue. Veins have thinner walls and use valves to keep blood flowing.

[2] An arteriole is a small diameter blood vessel in the microcirculation system that branches out from an artery and leads to capillaries.

[3] A capillary bed can consist of two types of vessels: true capillaries, which branch mainly from arterioles and provide exchange between cells and the circulation, and vascular shunts, short vessels that directly connect arterioles and venules at opposite ends of the bed, allowing for bypass.

[4] Veins carry blood toward the heart. After blood passes through the capillaries, it enters the smallest veins, called venules. From the venules, it flows into progressively larger and larger veins until it reaches the heart.

why, as I have experienced consistently while on LSD, extra glucose intake is essential if one wants to maintain a state of high-functioning, particularly when using regions of the neocortex involved in higher order cognition. As the daughter of a diabetic father, I learned from early childhood the importance to supply my father with regular glucose in order to maintain a normal level of consciousness (and prevent him from falling into a ditch or driving over the centre of a roundabout!).

But other regions of the brain do not benefit from this new high energy supply: *Regions of the default mode network*, for instance, receive their energy supply via large blood vessels that constrict under the effect of psychedelics , resulting in a *reduction* in the activity of this normally hyper-active network, which has been attributed with the acute psychedelic experience of ego loss following psychedelics.

Until now, modern neuroscience has been almost exclusively focused on the impact of psychedelics on neural mechanisms, largely ignoring the fact that the serotonin system is *deeply* involved in many other important *physiological* mechanisms, in particular the regulation of the *vascular tone*, and therefore the distribution of blood and energetic resources in both the body and brain. Since the most widely used neuroimaging technique, fMRI, is based on fluctuations of the vascular signal, this lack of interest seems hard to conceive. In our new double headed programme of research, my hope is to address this 'blind spot' of current neuroscience, and investigate in much greater depth the hypothesis that I have followed and helped develop since 1966. The change in capillary volume hypothesis I have just introduced has, I think, never been investigated before with modern brain imaging technology, and, if proven to be correct, could radically alter the way we interpret and understand the underlying physiology of expanded states of consciousness, and how best we can manage them, in order to optimise their potential benefits.

Interestingly, this hypothesis may explain the similarity between the psychedelic experience and *non-ordinary states of consciousness* that can be attained endogenously, and through various techniques, such as breathwork. It could therefore provide a *unifying theory* to explain the commonality between diverse techniques that can lead to expanded states of consciousness, by placing *increases in energy resource, at the very core of the shift in consciousness.*

Alongside this ground-breaking exploration of the effects of psychedelics on cerebral blood volume, I am continuing to follow the exciting tradition of neuroimaging research which I started to use in 1998. A study I am particularly excited about, which I have been developing in collaboration with leading neuroimaging experts from King's College London and UCL, will investigate, in much more depth than ever done before, the physiological and subjective effects of LSD during the peak, or mystical experience. It has long been my goal to better understand the neurophysiology underlying consciousness and its expanded states, so that we might more easily integrate their advantages into our individual lives, and into the web of society, and I believe that this cutting-edge study will considerably advance our understanding of the ways psychedelics can bring about such profound shifts in consciousness, which are at the core of their healing and transformative potential. We will employ, for the first time in psychedelic research, a new approach to collecting brain imaging data, called

'*precision fMRI',* building upon our previous pioneering neuroimaging research with an *enhanced* and *individualised approach* to imaging participants brains. This will allow the neural correlates of the psychedelic experience to be recorded with unprecedented detail.

Our previous work has demonstrated the therapeutic relevance of the psychedelic-induced mystical experience for treatment-resistant depression and addiction. The mystical experience may manifest as a sense of unity, bliss, insightfulness and disembodiment, imbued with profound meaning. Importantly, we found the greatest success and efficacy of psychedelic therapy correlated with the intensity of mystical experience. We've also shown that these deeply meaningful experiences can prompt lasting changes in perspective and positive traits such as mindfulness, openness and connectedness. This is a state of hyper-plasticity in which the brain, like when heating metal, can reshape itself along more positive patterns.

However, the physiological mechanisms associated with the occurrence of mystical experiences are still poorly understood. What differs between someone undergoing a mystical experience and someone experiencing a 'bad trip'? Can we learn to predict and guide physiological states and psychological traits that are more conducive of positive experiences? What are the physiological counterparts of the profound insights that may be generated during a psychedelic experience? Can their occurrence be promoted? Is there a common mechanism underlying the type of experience induced by psychedelics, and other ways of attaining expanded states of consciousness?

To answer these questions, it is essential to develop a better understanding of the neurophenomenology of these experiences, which, by nature, are highly personal, varying significantly between users. It is therefore of particular interest here to adopt a *'precision medicine'* approach, in which the intertwining influences within subjects are thoroughly characterised, in contrast to group-level analyses, which usually do not afford the same level of nuance.

By combining this approach with the use of the highest resolution MRI scanner (7 Tesla instead of the commonly used 3 Tesla), we will be able to measure with unmatched precision, the involvement of small subcortical brain structures (such as the caudate, putamen, thalamus, and claustrum) and the way they interact with the rest of the brain, including the cerebellum.

The Caudate is a small region nested deep within the brain that I am particularly interested in, as it has been linked, among many other functions, to intuition, expert cognition, advanced meditation practice, and has also been implicated in anomalous experiences, where it has been suggested that it may act as an 'antenna' for receiving anomalous information from unconventional sources. After having on several occasions undergone anomalous experiences while under the effects of LSD, from enhanced intuitive pattern recognition while playing Go, to telepathic communication, particularly with my Beloved pigeon, Birdie, I believe a greater focus on this region can uncover fascinating underexplored anomalous elements of the psychedelic experience, which are frequently considered taboo within the scientific community.

In order to go deeper in our understanding of the brain mechanisms involved during the peak experiences induced by LSD, we will also use MEG, an invaluable

neuroimaging tool with high spatial and temporal resolution, as a complementary technique to study the dynamics and connectivity of large-scale brain activity.

On the day following the dosing session, participants interviews will be conducted, in order to collect a deeply detailed account of their psychedelic experience, at a much finer level than previously obtained using questionnaires. This will allow us to carefully map, for each participant individually, the content of their experience onto fluctuations in brain activity, thereby gaining a unique evaluation and insight of the neurophysiological correlates of the peak experience.

This study will thus bring another important novel element to previously conducted research. Unlike other neuroimaging studies, which have been entirely focused on the changes in neuronal function occurring as a result of psychedelics, we will also be looking at other physiological mechanisms that could play a critical part in the profound consciousness altering effect of psychedelics, such as how changes in blood distribution and energy metabolism in the brain may drive changes in neural activity, rather than, or as well as, the other way around; and how changes in the glucose level of the blood can also effect awareness and concentration.

Enhancing the supply of blood, increasing plasticity, and inducing a transformative peak experience have obvious therapeutic benefits. Much has been said of this already, most particularly in connection with treatment-resistant depression and overcoming existential anxiety. However, I am excited to announce a cutting-edge new research programme which I have been working on over the last years, exploring the use of psychedelics as therapeutic agents in palliative care settings and for different types of cognitive decline. Typically, in psychedelic-assisted therapy, the hallucinogenic effects of psychedelics have been directly linked to their therapeutic action, largely through the mystical experience. However, in older people, or patients suffering from neurodegenerative disorders, these intense experiences may be too demanding. Beyond their use to induce expanded states of consciousness, I have long been convinced that the use of lower doses of psychedelics, also have an important *role to play*, both therapeutically, and as wellbeing-enhancing *'psychovitamins'*. Lately, I have been particularly interested in exploring how microdosing has the potential to play an invaluable role in 'healthy longevity', as a tool to boost neuroplasticity, neurogenesis and reduce inflammation, and thereby improve cognition, vitality and the sense of 'self'.

Over the last years, I have been working in collaboration with many different researchers and institutions around the world, such as Maastricht University, where, in collaboration with Jan Ramaekers and Kim Kuypers, we set up an LSD microdosing research programme. Our first study demonstrated the potential of low doses of LSD to enhance mood, vigilance and tolerance to pain. Importantly, our microdosing research has also shown that even a sub-hallucinogenic dose of LSD increases the level of Brain-derived Neurotrophic Factor (BDNF), a key protein involved in neuroplasticity, which decreases in production in patients with Mild Cognitive Impairment and Alzheimer's.

Building on these and other initial results, I have for the past year been developing an exciting research programme combining several complementary projects aiming to investigate the potential benefits of LSD and psilocybin microdosing in cognitive

decline, Alzheimer's Disease and palliative care. This programme, which had been in my mind for some time, became a top priority after, last year, I observed the most astonishing changes within a wonderful 97-year-old lady, who had been suffering from advanced Alzheimer's and vascular dementia since 2011. At 97, her condition deteriorated substantially, to the point where her caregiver, with the agreement of her family, decided to try whether microdoses of LSD might help spark her out of a deep apathetic (almost vegetative) state. According to her caregiver and her children, the effects were nothing short of '*remarkable'*, restoring her to a full state of awareness, with presence of mind, wit, and personality. What had previously manifested as despair, hopelessness and distress, was transformed now into a fully awake condition of being able to talk, read, and relate to those around her.

This case confirmed my intuition regarding the efficacy of LSD microdosing for those suffering from Alzheimer's and related conditions. Her case was so a striking that I felt compelled to develop a research programme in order to investigate the potential benefits of LSD for Alzheimer's and other forms of dementia, and further investigate what might be the underlying mechanisms of recovery.

Today, it is my great pleasure to announce that I have started a collaboration with a team of experts, including the head of the Geriatrics department at Basel University, in order to conduct the first proof-of-concept study into LSD microdosing for Alzheimer's disease. This ground-breaking study will allow us to assess the various ways in which microdoses of LSD may benefit people suffering from Alzheimer's, and pave the way to develop new treatments strategies for neurodegenerative illnesses. Although this study will focus on patients with relatively mild dementia, who can still provide informed consent, I am convinced of the incredible potential of this intervention in much more advanced forms of dementia, where low doses of psychedelics may trigger something close to what has been termed "Paradoxical Lucidity", a rare and fascinating phenomenon where individuals in deep states of apathy, or vegetative states, can spontaneously regain the use of their faculties, recalling lost memories, thinking and conversing without difficulty, and – most profoundly – *regaining their old sense of 'self'*.

I am also working on the development of a new concept for a Care Home, which will deliver this treatment in the most supportive setting.

I hope I've given you a preliminary overview of the work we have been doing this past year, and where the Beckley Foundation is heading. Before ending my talk, I would like to thank the generous contributors who have made all this possible. To continue advancing our exploratory research into psychedelics and their therapeutic potential, and ensure that governments, and indeed the public and private sectors, are properly informed, it is essential that non-profit organisations, like ours, continue to receive the necessary support to carry out further research.

I fear because of time limitations, I have only been able to give a brief overview of the work I started in the late 1960s and now, with the advance of brain imaging technologies, I can hopefully bring this work to an exciting apex, that may give to the world a new insight into what these sacred compounds are capable of providing for humanity, at this time of crisis and change.

As a child, my dream was to “water the desert”, then I realized that “the desert is the human brain!”
Thank you.