

PLACEBO



LSD



# LSD Revealed

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BECKLEY  
FOUNDATION

The Beckley/Imperial Research Programme

Co-directed by Amanda Feilding and David Nutt

Lead Investigator Robin Carhart-Harris

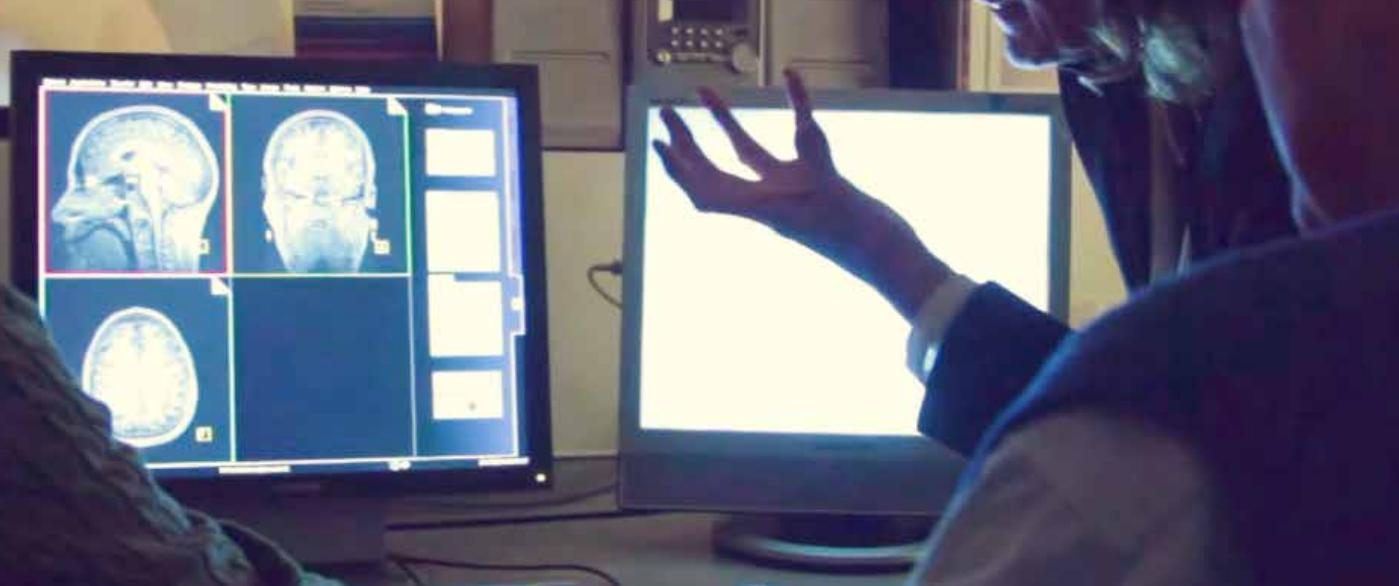


## BECKLEY FOUNDATION

The Beckley Foundation is a UK-based think tank and UN-accredited NGO founded by Amanda Feilding in 1998. We combine science and policy to further our understanding of consciousness, to effect changes in global drug policy and to improve public health. We are at the forefront of scientific research into the potential medical benefits of psychedelics, MDMA and cannabis, and are pioneering in our contribution to international drug policy reform.

**Our Scientific Programme** comprises Amanda's collaborations with leading experts and institutions to design, initiate and direct scientific research projects, including clinical trials. Together, we investigate the workings of psychoactive substances within the human brain, using the latest developments in neuroscience and brain imaging technology. Our aim is to increase the scientific understanding of consciousness and to open up new avenues of treatment for humanity's many illnesses.

**Our Policy Programme** explores new ways of reducing the harms caused by illicit psychoactive substances and the collateral damages caused by prohibition. Collaborating with a network of scientists, political leaders and drug policy analysts, Amanda was among the first to advocate drug policies based on scientific evidence in order to explore new regulatory options based on health, harm reduction, cost-effectiveness and respect for human rights.



Since the 1960s, Amanda has studied the mechanisms underlying the changes in consciousness brought about by psychedelics. Her formative work with the Dutch scientist Bart Huges initiated a lifelong interest in the concept of the ‘ego’ as a conditioned-reflex mechanism that controls the distribution of blood in the brain. Her aim in setting up the Beckley Foundation was to use the latest neuroscience and brain-imaging technology to investigate the physiological changes underlying altered states of consciousness. She wished to further our understanding of brain-function and changes in cerebral circulation under the influence of various psychoactive substances. The goal of this work is to shed light on the therapeutic potential of these substances, and on how they might be used to enhance mental and physical well-being, cognitive functioning and creativity.

# The Beckley/Imperial Research Programme

The Beckley/Imperial Research Programme has been a highly productive partnership between Amanda Feilding and Prof. David Nutt, co-Founders and Directors of the Programme, Dr. Robin Carhart-Harris, the lead investigator, and associated scientists. The collaboration began in 2005, when Amanda approached David – then at the University of Bristol - to form a partnership with the objective of investigating the effects of psychedelics and cannabis on brain-function. In 2009, David moved to Imperial College London, and their collaboration became the Beckley/Imperial Research Programme.



The Beckley/Imperial Research Programme has completed the first-ever brain imaging studies, using fMRI and MEG, with psilocybin, MDMA, and now LSD. In 2012, the first results of the psilocybin brain imaging studies were published and achieved world-wide publicity. This led to a substantial grant from the Medical Research Council for the study to be extended to research the effects of psilocybin in the treatment of depression. The first study from this project has recently been completed with very positive results.

In 2014 the Beckley/Imperial Research Programme overturned a fifty-year ban on LSD research, and began their pioneering brain-imaging study with LSD. The study has revealed the enormous impact that LSD has on brain-function. It has given us unique new insights into how different brain areas regulate the nature and different forms of consciousness, as well as helping to explain the subjective psychedelic experience.

LSD is undoubtedly the most significant drug acting on the brain ever discovered. In the decades that followed its discovery, it was hailed as a powerful scientific tool for investigating consciousness and the treatment of mental illness. It was widely studied in the treatment of addiction and mood disorders, with positive outcomes. It also helped develop new insights into the nature of psychosis.

However, LSD produced significant social change in the shape of radical new approaches to art, music, spirituality, the environment, and ultimately to social control. Its impact on young people's attitude to authority and politics threatened to undermine the military-based ethos of US national and international policy. This elicited concern among the authorities and eventually led to it being made illegal and classified as a 'Schedule 1' drug in 1966. It then became extraordinarily difficult to obtain regulatory approvals and funding for legitimate scientific research. Before the scheduling, there were over a thousand published papers. Since 1966, there have been almost none until 2014.

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"This I believe is the worst censorship of research in the history of science. Overall, I think our overturning a 50 year ban on research on LSD and discovering how it works on the brain is one of the great achievements of modern science, as important to neuroscience as the Higgs boson discovery was to particle physics – both usher in new eras of research."

Prof. David Nutt

Following on the heels of our highly informative and high-impact studies with psilocybin, the LSD study confirms and expands what the psilocybin studies have shown:

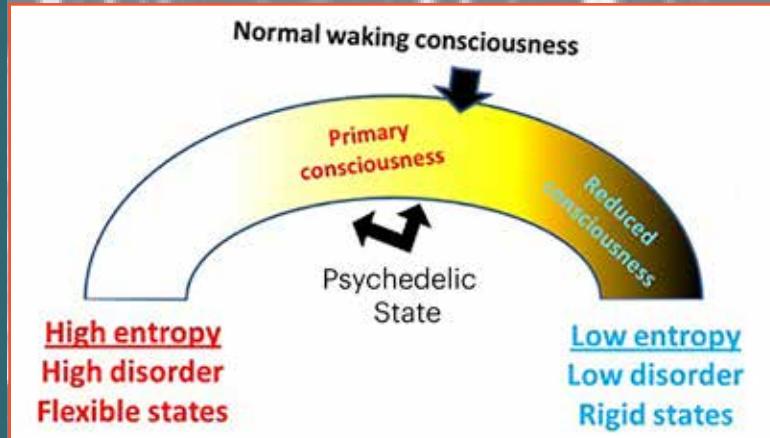
1. Under psychedelics, consciousness becomes less constrained, more fluid and dynamic.
2. Brain networks become less integrated under psychedelics (called ‘network disintegration’), but the brain in general becomes more integrated.
3. Psychedelics reduce the differentiation between brain networks, increasing whole-brain integrity. That is, networks that normally function separately from one another become less independent, losing their ‘separateness’ and communicating more with each other. This is also called ‘network desegregation’.
4. Network desegregation means that the individual identities of brain networks are compromised as they “blend” with each other, potentially explaining phenomena such as synesthesia.
5. The phenomenon of ‘ego-dissolution’ correlates with decreased default mode network (DMN) integrity; increased whole-brain integrity; and decreased neural synchrony within a particular region of the DMN - the posterior cingulate cortex (PCC). This supports the view that normal activity in the PCC is important for maintaining the sense of self and of ego-boundaries.

Under both psilocybin and LSD, we found increased functional connectivity between regions that are not structurally linked (i.e., that have no direct white-matter pathways - axons) and belong to different brain-systems. This enables brain regions that are not wired to each other to communicate [Tagliazucchi *et al.*, in press]. This effect correlated with ratings of ‘ego-dissolution,’ suggesting that it contributes to the changes in consciousness experienced under LSD, and may also contribute to the reported propensity of LSD to increase creativity and facilitate new insights.

The findings from our psychedelic research prompted the so-called ‘entropic brain theory’ (where ‘entropy’ refers to ‘chaotic’ or ‘erratic’ brain activity). According to this model, during normal waking consciousness, the brain operates between a highly ordered, low-entropy state and a highly disordered, high-entropy state. This optimal position between perfect order and complete disorder allows the brain to operate in a well-defined and organised, yet flexible manner.

Our work shows that psychedelic drugs increase the entropy of the brain and generate a more disordered, fluid state of consciousness. This state is more flexible and less rigid; it makes people more open to new concepts and ideas. This may lead to the breaking of rigid thought-patterns such as those found in depression, addiction, and OCD.

## THE ENTROPIC BRAIN



## NEW INFORMATION ABOUT THE NEUROBIOLOGICAL BASIS OF THE PSYCHEDELIC STATE GAINED FROM THE LSD STUDY:

Brain-imaging data has improved our understanding of **how psychedelics produce visual hallucinations**. Visual areas of the brain were the only regions to show increased blood flow after LSD during eyes-closed resting-state. All the imaging measures showed changes that are normally associated with visual stimulation – even though participants had their eyes closed. These changes correlated with self-reported visual hallucinations, suggesting a ‘seeing with eyes-shut,’ consistent with previous ayahuasca research. Moreover, the visual areas were more connected with the rest of the brain under LSD. Additional analyses, looking at the connectivity between the early visual areas (V1 and V3) confirm this result, providing further clues on how psychedelics modulate the activity in the visual cortex [Roseman *et al.*, in press].

Using a new statistical approach, we showed **increased ‘sample entropy’** in the imaging data [Lebedev *et al.*, in press] – another measure to quantify the ‘chaos’ in the brain. This increase correlated with the self-reported personality trait ‘openness’ two weeks later, which may relate to how psychedelics and the entropic brain-state they induce, could be therapeutically useful.

We also explored the interaction of LSD with music. Music is an effective tool for evoking emotions. Increased access to emotions have been shown to have therapeutic advantages. We found that LSD enhances the emotional response to music, creating a deeper and stronger experience than placebo [Kaelen *et al.*, 2015]. Brain imaging showed that LSD-induced changes in network connectivity differed in the presence vs. absence of music, i.e. regions involved in emotional memories (‘parahippocampus’) affected the visual

regions more. Perceiving complex scenes in the absence of visual input may therefore result from a “flip” in the normal direction of information flow within the visual system, such that higher-level components of the system, responsible for processing high-level features, take precedence over incoming sensory information. This effect correlated with self-reported ‘visual imagery’ and ‘visions of one’s past,’ suggesting that memories are influencing visions. This is the first study that reveals some of the brain-mechanisms via which LSD and music work in synergy. The results provide tentative empirical support for the use of music in psychedelic-assisted psychotherapy to evoke personal memory and enhance mental imagery [Kaelen *et al.*, in press].

Behavioural measures showed that LSD – even with a relatively low dose in a laboratory environment – altered consciousness and induced hallucinations and synesthesia. Subjects reported some psychosis-like symptoms but, in contrast to actual psychosis, the overall mood was positive and anxiety was low [Carhart-Harris *et al.*, 2016]. Two weeks later, subjects reported increased ‘optimism’ and ‘openness’. This is consistent with findings from Beckley collaborator Prof. Roland Griffiths, whose subjects reported increased well-being and life satisfaction after psilocybin (Griffiths *et al.*, 2008). In our pilot LSD study, we also showed that LSD enhances ‘suggestibility,’ which is a major factor in determining the success of psychotherapy [Carhart-Harris *et al.*, 2015].

**To conclude:** The findings from the Beckley/Imperial Research Programme have important **therapeutic implications**: Certain mental disorders (e.g., depression, anxiety, addiction, OCD) can be conceptualised as resting on ‘inflexible’ and ‘excessively-organised’ patterns of thought and brain activity, and psychedelics may work by breaking down or ‘loosening’ these patterns.

Our research suggests that psilocybin and LSD loosen patterns of thought and entrenched behaviour by creating ‘entropy’ in the brain. As brain activity becomes more chaotic and loose, the personality trait of ‘openness’ increases. This trait is linked to imagination, aesthetic appreciation, non-conformity and creativity. Subjects who demonstrated the most marked increases in ‘openness’ were also those who reported the greatest amount of ‘ego-dissolution’. Research suggests that ‘openness’ and an experience of ‘ego-dissolution’ may be desirable in a therapeutic context.

We have been able to study the therapeutic potential of psychedelics in greater detail in a study on **the effects of psilocybin in the treatment of depression**. Preliminary results show highly promising effects in substantially reducing depressive symptoms. [Carhart-Harris *et al.*, in press *Lancet Psychiatry*].

**Our next projects will:** 1) compare the effects of LSD to those of DMT, and determine the similarities and differences between these two psychedelics; 2) further elucidate the mechanisms of visual hallucinations; and 3) investigate the propensity of LSD to enhance creativity and problem-solving.

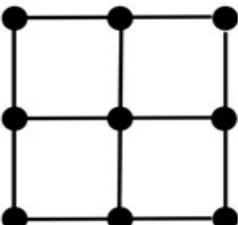
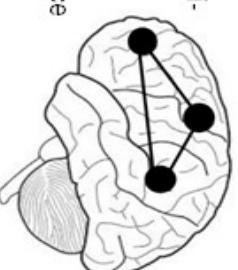
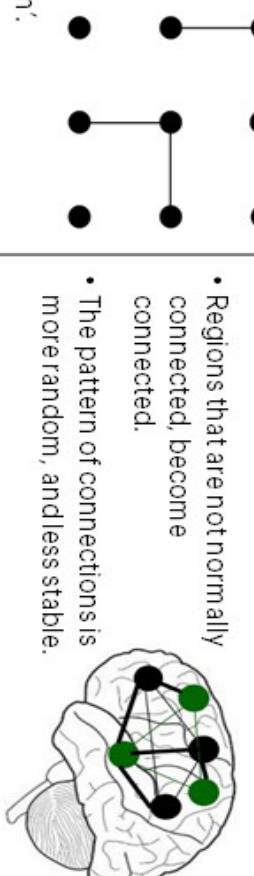
The studies described here are just the beginning – many exciting research possibilities lie ahead.

## DETAILS OF THE LSD STUDY

*The study involved 2 scan sessions – one after LSD (75 $\mu$ g intravenous) and one after placebo (saline) – and used 3 different brain-imaging techniques: 1) Arterial spin labelling (ASL) to measure blood flow to the brain; 2) functional MRI (fMRI/BOLD) to assess functional connectivity of brain networks; and 3) magnetoencephalography (MEG) to detect synchronised neuronal firing patterns (oscillations, or ‘brain waves’). We also administered self-report questionnaires. 20 healthy volunteers (4 females) participated in the study.*

# General Principles of How Psychedelics Work

● Nodes/Regions  
– Connectivity

	Within Network	Between Networks	Effects on Cognition
<b>Psychedelics</b>	<p><b>Normal functioning</b></p> <p><b>High integrity</b></p> <ul style="list-style-type: none"> <li>Different networks serve distinct functions, e.g. Default Mode Network is active during introspection, Task Positive Networks are active during various tasks.</li> <li>Very little variance in the network activity, the activity is consistent.</li> </ul> 	<p><b>Segregation</b></p> <ul style="list-style-type: none"> <li>Different networks are distinct and show an 'anti-correlation'; when the Default Mode Network is active, Task Positive Networks are not, and vice versa.</li> </ul> 	<p><b>'Organised' brain</b></p> <ul style="list-style-type: none"> <li>Efficient information processing.</li> <li>Well-defined and ordered manner of functioning, while still maintaining flexibility and adaptability.</li> </ul> 
	<p><b>Disintegration = Low integrity</b></p> <ul style="list-style-type: none"> <li>Functional connectivity decreases within many brain networks.</li> <li>But only within the <b>Default Mode Network</b>, disintegration correlated with 'ego-dissolution'.</li> </ul> 	<p><b>Desegregation</b></p> <ul style="list-style-type: none"> <li>Individual networks become less distinct, they 'blend'.</li> <li>Regions that are not normally connected, become connected.</li> <li>The pattern of connections is more random, and less stable.</li> </ul> 	<p><b>'Disorganised' or 'entropic' brain</b></p> <ul style="list-style-type: none"> <li>Increased 'cognitive flexibility', fluid cognition</li> <li>New connections facilitate new concepts: creativity, imagination</li> <li>Break from 'entrenched' patterns of thinking and behaviour.</li> </ul> 

# LIST OF BECKLEY/IMPERIAL LSD SCIENTIFIC PAPERS

1. **LSD enhances suggestibility in healthy volunteers.** Carhart-Harris RL, Kaelen M, Whalley MG, Bolstridge M, Feilding A, Nutt DJ (2015). *Psychopharmacology* 232, 785-94.
2. **LSD enhances the emotional response to music.** Kaelen M, Barrett F, Roseman L, Family N, Bolstridge M, Curran HV, Feilding A, Nutt DJ, Carhart-Harris RL (2015). *Psychopharmacology* 232, 3607-14.
3. **The paradoxical psychological effects of LSD.** Carhart-Harris RL, Kaelen M, Bolstridge M, Williams TM, Williams LT, Feilding A, Nutt DJ (2016). *Psychological Medicine* 5, 1-12.
4. **Neural correlates of the LSD experience revealed by multimodal neuroimaging.** Carhart-Harris RL, Roseman L, Kaelen M, Muthukumaraswamy SD, Droog W, Murphy K, Tagliazucchi E, Schenberg E, Nest T, Orban C, Leech R, Williams LTJ, Williams TM, Bolstridge M, Sessa B, McGonigle J, Sereno M, Nichols D, Hellyer P, Hobden P, Evans J, Singh KD, Wise R, Curran VH, Feilding A, Nutt DJ. Accepted to *PNAS*
5. **LSD modulates music-induced imagery via changes in parahippocampal connectivity.** Kaelen M, Roseman L, Kahan J, Ribeiro AS, Orban C, Lorenz R, Barrett F, Bolstridge M, Williams T, Wall M, McGonigle J, Leech R, Feilding A, Muthukumaraswamy S, Nutt DJ, Carhart-Harris R. Accepted to *European Neuropsychopharmacology*
6. **LSD-induced entropic brain activity predicts subsequent personality change.** Lebedev AV, Kaelen M, Lövdén M, Nilsson J, Feilding A, Nutt DJ, Carhart-Harris RL. Under review in *Human Brain Mapping*
7. **Increased global cross-talk in the brain correlates with reports of ego-dissolution under LSD.** Tagliazucchi E, Roseman L, Kaelen M, Orban C, Muthukumaraswamy S, Murphy K, Laufs H, Crossley N, Bullmore E, Williams T, Bolstridge M, Feilding A, Nutt DJ, Carhart-Harris R Accepted to *Current Biology*.
8. **LSD alters eyes-closed functional connectivity within the early visual cortex in a retinotopic fashion.** Roseman L, Sereno MI, Leech R, Kaelen M, Orban C, McGonigle J, Feilding A, Nutt DJ, Carhart-Harris R. Under review in *Human Brain Mapping*
9. **Decreased mental time travel to the past correlates with default-mode network disintegration under lysergic acid diethylamide.** Speth J, Speth C, Kaelen M, Schloerscheidt AM, Feilding A, Nutt DJ, Carhart-Harris RL (2016). *Journal of Psychopharmacology* 30(4),344.

# LIST OF BECKLEY/IMPERIAL PSILOCYBIN SCIENTIFIC PAPERS

1. **The administration of psilocybin to healthy, hallucinogen-experienced volunteers in a mock-functional magnetic resonance imaging environment: a preliminary investigation of tolerability.** Carhart-Harris RL, Williams TM, Sessa B, Tyacke R J, Rich AS, Feilding A, & Nutt DJ (2011). *Journal of Psychopharmacology*, 25(11), 1562-1567.
2. **Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin.** Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiolas, T, Feilding A, ... Nutt DJ (2012). *The British Journal of Psychiatry*, 200(3), 238-244.
3. **Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin.** Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, ..., Feilding A, ..., Nutt DJ (2012). *Proceedings of the National Academy of Sciences*, 109(6), 02138-2143.
4. **Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis.** Carhart-Harris RL, Leech R, Erritzoe D, Williams TM, Stone JM, Evans J, Feilding A, ... Nutt DJ (2013). *Schizophrenia Bulletin*, 39(6), 1343-1351.
5. **Broadband cortical desynchronization underlies the human psychedelic state.** Muthukumaraswamy SD, Carhart-Harris RL, Moran RJ, Brookes MJ, Williams TM, Erritzoe D, Feilding A, ... Nutt DJ (2013). *Journal of Neuroscience*, 33(38), 15171-15183.
6. **The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs.** Carhart-Harris RL, Leech R, Hellyer PJ, Shanahan M, Feilding A, Tagliazucchi E, ... Nutt DJ (2014). *Frontiers in Human Neuroscience*, 8(20), 1-22
7. **Enhanced repertoire of brain dynamical states during the psychedelic experience.** Tagliazucchi E, Carhart-Harris RL, Leech R, Nutt D, Chialvo DR (2014). *Human Brain Mapping*, 35(11), 5442-5456.
8. **The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers.** Roseman L, Leech R, Feilding A, Nutt DJ, Carhart-Harris RL (2014). *Frontiers in Human Neuroscience*, 8.
9. **Homological scaffolds of brain functional networks.** Petri G, Expert P, Turkheimer F, Carhart-Harris R, Nutt D, Hellyer PJ, Vaccarino F (2014). *Journal of The Royal Society Interface*, 11(101).
10. **A Qualitative Report on the Subjective Experience of Intravenous Psilocybin Administered in an fMRI Environment.** Turton S, Nutt DJ, Carhart-Harris RL (2014). *Current Drug Abuse Reviews*, 7(2), 117-27.
11. **Finding the self by losing the self: neural correlates of ego-dissolution under psilocybin.** Lebedev AV, Lövdén M, Rosenthal G, Feilding A, Nutt DJ, Carhart-Harris R (2015). *Human Brain Mapping*, in press.
12. **Psilocybin for treatment-resistant depression: a feasibility study.** Carhart-Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe DE, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran HV, Nutt DJ, submitted to *Lancet Psychiatry*.



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