

This Is Your Brain on Drugs

To the great surprise of many, psilocybin, a potent psychedelic, reduces brain activity

BY CHRISTOF KOCH



IN THE 1954 foundational text of the Age of Aquarius, *The Doors of Perception*, Aldous Huxley describes his encounters with mescaline, a psychoactive substance derived from the peyote cactus and traditionally used by Native Americans for religious purposes. Huxley's experiences include profound changes in the visual world, colors that induce sound, the telescoping of time and space, the loss of the notion of self, and feelings of oneness, peacefulness and bliss more commonly associated with religious visions or an exultant state: "A moment later a clump of Red Hot Pokers, in full bloom, had exploded into my field of vision. So passionately alive that they seemed to be standing on the very brink of utterance, the flowers strained upwards into the blue.... I looked down at the leaves and discovered a cavernous intricacy of the most delicate green lights and shadows, pulsing with undecipherable mystery." Yet remarkably these enhanced percepts are not grounded in larger but in reduced brain activity, as a recent experiment reports. More on that in a moment.

Mescaline, together with psilocybin, another natural psychoactive compound produced by "magic" mushrooms, and lysergic acid diethylamide (LSD or, simply, acid), a potent synthetic psychedelic drug, became widely popular in the 1960s counterculture. The striking similarities between the reports of LSD users and symptoms of acute psychosis led researchers to postulate

that serotonin, a chemical-signaling compound or neurotransmitter released by certain groups of neurons in the brain stem, helped to mediate both types of experiences. Indeed, it is now



quite certain that the characteristic subjective and behavioral effects of psychedelics are initiated via stimulation of serotonin 2A receptors (known as 5-HT_{2A}) on cortical neurons.

All these hallucinogens were declared controlled drugs in the late 1960s and early 1970s for a variety of medical, political and cultural reasons. Their use moved underground, and research on their psychological, physiological and neuronal effects all but ceased. With the

realization of possible therapeutic benefits of psychedelics to reduce anxiety and chronic pain, however, the societal taboos against scientific research on their neurobiology have somewhat relaxed. A number of well-controlled European studies have carefully explored the action of hallucinogens on the brains of normal volunteers [see "Psychedelic Healing?" by David Jay Brown; *SCIENTIFIC AMERICAN MIND*, December 2007/January 2008].

Functional brain-imaging experiments done at the end of the past century using positron-emission tomography (PET) found marked activation in the frontal lobe of volunteers who had taken hallucinogens, in particular in the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and the insula cortex. This was in line with the expectation that the intensification of ordinary experiences and the consciousness-expanding aspects that are so widely associated with psychedelics would be reflected in higher than usual brain activity. Now comes a study from David Nutt, a psychopharmacologist at Imperial College London, and his colleagues that completely upends this view.

Turn On, Tune In and Drop Out

The British scientists injected either a harmless saltwater concoction (a placebo) or two milligrams of psilocybin directly into the veins of 30 volunteers while they were lying inside a magnetic scanner. As expected, the subjects expe-

CHRISTOF KOCH (Koch); PAUL SALE VERN HOFFMAN Aurora Photos (background); ISTOCKPHOTO (head)

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rienced within a minute or two the effects of the drug. During their short "trip," their brains were scanned with one of two different functional MRI techniques. Both gave consistent but very surprising results.

Brain activity was widely reduced! That is, these mind-altering drugs de-

neuronal activity. A standard reading of Nutt's fMRI data seems to imply that expanding your mind by taking magic mushrooms turns many brain circuits down rather than up. Suddenly, Timothy Leary's famous admonition to hippies to "turn on, tune in and drop out" acquires a whole new meaning.

tions of neurons that carries the specific information, the messages, that are represented in consciousness.

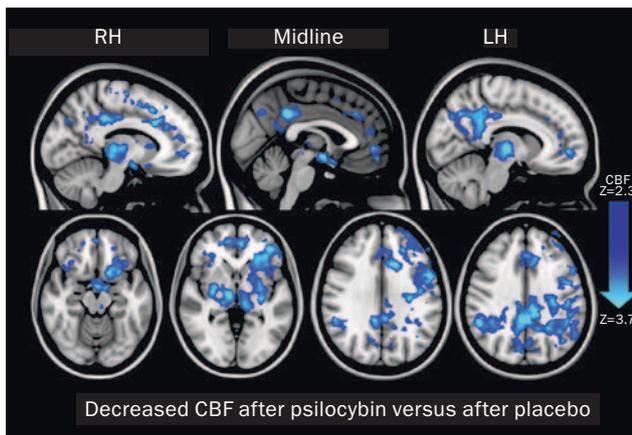
At this point, this is all pure speculation because the detailed biophysical mechanisms and the effects of psilocybin on different neurons remain to be worked out.

Any such remarkable finding needs to be replicated by other groups before it becomes part of textbook knowledge. Moreover, the discrepancy with the earlier PET experiments needs to be explained. Two major differences are the mode of taking the drug (intravenously versus orally) and the time of measurement (immediately versus an hour later).

What is intriguing is that the regions that show the strongest reduction in activity are among the most heavily interconnected in the brain. They act like traffic circles or hubs that link disparate regions. Thus, the brain on psilocybin becomes more disconnected, more fragmented, which might explain some of the dissociative aspects of acid trips. Yet why this state should cause the mind-expanding effects that are the prime reason these drugs are treasured is utterly unclear. The study once again highlights how elusive our knowledge of the mind-brain hinge remains. **M**

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Blue areas show where there has been decreased cerebral blood flow (CBF) after psilocybin as compared with after saline (placebo). Remarkably, no significant increase in blood flow was detected in either the left hemisphere (LH) or the right hemisphere (RH).



creased hemodynamic activity, including blood flow, in selected regions, such as the thalamus, the medial prefrontal cortex (mPFC), the ACC and the posterior cingulate cortex (PCC). Activity in these regions dropped by up to 20 percent, relative to before the injection. Even more striking, the deeper the reduction in activity in the ACC and mPFC, the stronger the subject felt the effects of the hallucinogen. Nowhere did activity show an increase. Furthermore, the communication between the PFC and cortical regions in the back of the brain was also disrupted. The surprise is not that reduction of hemodynamic activity in specific sectors of the brain is unheard of. Nor was the activity completely turned off—that would lead within minutes to permanent damage and brain death.

Hemodynamic activity as registered by fMRI scanners is tightly linked to

The ACC and parts of the mPFC inhibit limbic and other structures. Thus, their downregulation, or reduction in response, would allow the content of the limbic systems that process emotion and perhaps sensory cortices to play a relatively more dominant role. It is not that enhanced hemodynamic, or even neuronal, activity by itself gives rise to perception and thought. After all, epileptic seizures are hypersynchronized discharges that engulf the entire cortex in massive rhythmic activity that renders the patient unconscious. It is the pattern of spiking across heterogeneous popula-

(Further Reading)

- ◆ **The Neurobiology of Psychedelic Drugs: Implications for the Treatment of Mood Disorders.** Franz X. Vollenweider and Michael Kometer in *Nature Reviews Neuroscience*, Vol. 11, pages 642–651; September 2010.
- ◆ **Neural Correlates of the Psychedelic State as Determined by fMRI Studies with Psilocybin.** Robin L. Carhart-Harris et al. in *Proceedings of the National Academy of Sciences USA*, Vol. 109, No. 6, pages 2138–2143; February 7, 2012.

FROM "NEURAL CORRELATES OF THE PSYCHEDELIC STATE AS DETERMINED BY fMRI STUDIES WITH PSILOCYBIN," BY ROBIN L. CARHART-HARRIS ET AL., IN PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES USA, VOL. 109, NO. 6, FEBRUARY 7, 2012