

## Altered States

### *Psychedelics and Anesthetics*

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#### ABSTRACT

The psychedelic experience has been reported since antiquity, but there is relatively little known about the underlying neural mechanisms. A recent neuroimaging study on psilocybin revealed a pattern of decreased cerebral blood flow and functional disconnections that is surprisingly similar to that caused by various anesthetics. In this article, the authors review historical examples of psychedelic experiences induced by general anesthetics and then contrast the mechanisms by which these two drug classes generate altered states of consciousness.

**T**HE psychedelic experience, rooted in spiritual traditions, has been known to humans since antiquity.<sup>1</sup> Psychedelic drugs can be defined as hallucinogenic agents that alter perceptions, thoughts, and mood, often leading to a state associated with vivid imagery, sensations of disembodiment, and the perceived ability to comprehend universal truths.<sup>2,3</sup> There are numerous historical and anecdotal reports describing this unique state of consciousness. However, despite the storied use of psychedelics and the psychedelic movement of the 1960s, little is known about the neural pathways by which these drugs produce their

so-called “mind expanding” effects. Classic psychedelic agents include lysergic acid diethylamide, psilocybin (psychoactive compound in “magic mushrooms”), mescaline (natural product of peyote cacti), and dimethyltryptamine. However, there are also psychedelic phenomena associated with low doses of clinically used general anesthetics. Here we (1) review notable psychedelic experiences reported after exposure to general anesthetics, (2) highlight recent studies of psychedelic mechanisms, and (3) contrast the mechanisms of psychedelics and anesthetics that lead to altered states of consciousness.

#### Psychedelic Anesthesia in Antiquity

One of the first reports of psychedelic phenomena comes from ancient Delphi, Greece, inside the sacred Temple of Apollo where an Oracle (also known as Pythia) presided. Ancient Greeks, from the mythic King Leonidas to ordinary citizens, would solicit the divine wisdom that emerged from the Oracle of Delphi’s mystical experiences. There are several ancient accounts of how the Oracle achieved her transcendental state. Strabo (64 B.C.–A.D. 25) wrote:

They say that the seat of the oracle is a cavern hollowed deep down in the earth, with a rather narrow mouth, from which rises a *pneuma* (vapor)...that produces divine possession. A tripod is set above this cleft, mounting which, the Pythia inhales the vapor and prophesies<sup>4</sup> (fig. 1).

The famous biographer Plutarch (A.D. 46–120) also recorded that this *pneuma* in the Temple smelled like sweet perfume. More recently, a multidisciplinary team investigating these ancient accounts found that the rare combination of crossing geologic faults, bituminous limestone, and ground water located under the Oracle’s chamber can produce volatile hydrocarbon gases, namely methane, ethane, and ethylene.<sup>5</sup> These gases were even isolated in nearby spring water, and ethylene’s sweet aroma matches Plutarch’s olfactory descriptions of the Temple. Interestingly, early experiments in the 1920s<sup>6,7</sup> with low-dose ethylene demonstrated the excitation, delirium, ataxia, and amnesia associated with the trance states of the Pythia.<sup>8</sup> Taken together, it is

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Received from the Division of Neuroanesthesiology, Department of Anesthesiology, University of Michigan Medical School, Ann Arbor, Michigan. Submitted for publication February 20, 2013. Accepted for publication August 21, 2013. This work was supported solely from institutional and/or departmental sources. The authors declare no competing interests.

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**Fig. 1.** Priestess of Delphi by John Collier (1891). Pythia is depicted in a trance state as she inhales vapors rising from the fissure underneath. This image is in the public domain.

likely that the sweet *pneuma* was ethylene, which transported the Oracle to her psychedelic states.

### Psychedelic Anesthesia in Modernity

There are 19th-century examples of the use of general anesthetics to achieve a psychedelic state. Benjamin Paul Blood, an American philosopher and poet, used ether and nitrous oxide as the “inspiration” for his 1874 book *The Anaesthetic Revelation and the Gist of Philosophy*. Blood discusses his use of general anesthesia to tackle deep philosophical problems:

Of this (trance) condition, although it may have been attained otherwise, I know only by the use of anaesthetic agents. After experiments ranging over nearly fourteen years I affirm...that there is an invariable and reliable condition...or “coming to,” in which the genius of being is revealed.<sup>9</sup>

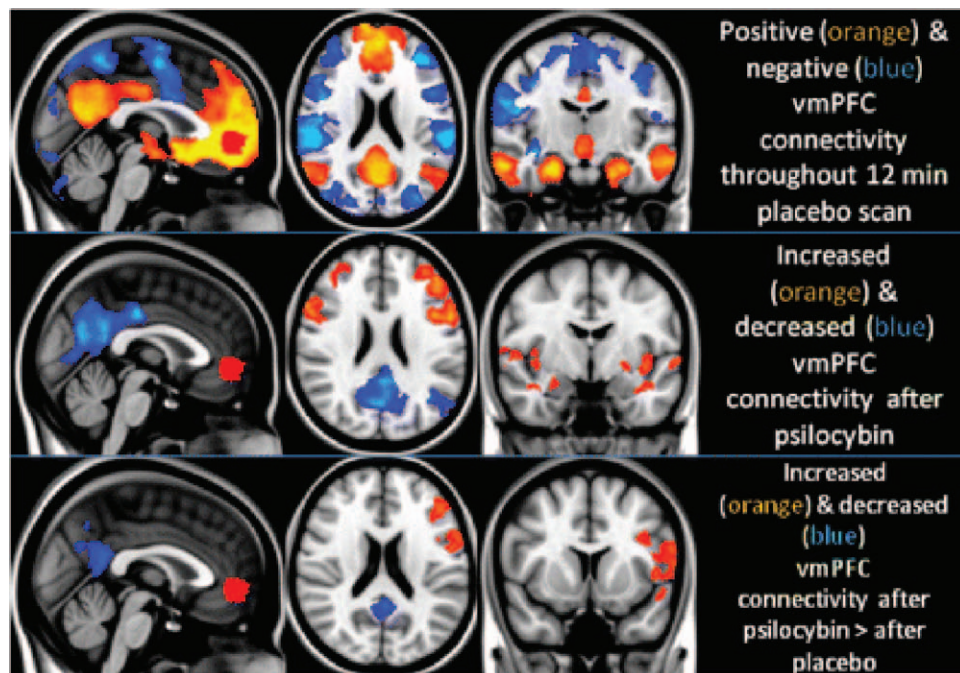
Blood’s philosophical work (and methods) also influenced prominent psychologist and philosopher William James. James experimented with nitrous oxide as a vehicle to achieve mystical states. As he describes in his essay *Subjective Effects of Nitrous Oxide*: “Truth lies open to the view in depth beneath depth of almost blinding evidence. The mind sees all the logical relations of being with an apparent subtlety and instantaneity to which its normal consciousness offers no parallel.”<sup>10</sup> James’ nitrous oxide–induced

revelations are described in the seminal work *The Varieties of Religious Experience*.<sup>11,12</sup> The psychedelic characteristics of subanesthetic concentrations of nitrous oxide described by Blood and James have also been studied in a more systematic manner by modern researchers.<sup>13</sup> By using validated surveys, inhalation of 30% nitrous oxide showed significant increases in measures of euphoria, alterations in time perception, and dream-like states, which are characteristics of the psychedelic experience.

The 1960s saw the development of a controversial counterculture and an associated psychedelic movement. Many artists, writers, and academics such as neuroscientist John Lilly and psychologist Timothy Leary supported the psychedelic movement and the study of psychedelic drugs. Drugs such as lysergic acid diethylamide (known as LSD) were explored initially as potential clinical therapies in psychiatry. Lilly self-experimented with ketamine, a phencyclidine analog. As Lilly describes in one of his autobiographies (curiously written in the third person), “With his adjusted awareness through the drug K, John [Lilly] felt and understood the currents of information traveling through the galaxy by means unknown at present. He felt the tremendous variety of intelligences which exist in the galaxy.”<sup>14</sup> The psychoactive effects of both subanesthetic and anesthetic doses of ketamine are often noted in emergence reactions and have been quantified in the scientific literature.<sup>15–17</sup> More recently, research aimed at developing objective measures of altered states of consciousness has shown related psychometric profiles of ketamine, psilocybin, and 3,4-methylenedioxy-methamphetamine (known colloquially as Ecstasy).<sup>18</sup> Ketamine and psilocybin evoked quantitatively similar degrees of “spiritual experience,” “insightfulness,” “altered state of consciousness,” and “oceanic boundlessness.” Beyond nitrous oxide and ketamine, the psychoactive properties and abuse potential of both inhaled<sup>19</sup> and intravenous<sup>20</sup> anesthetics are well known.

### Anesthetics and Psychedelics: Contrasting Mechanisms

The foregoing examples of psychedelic experiences with subclinical doses of ethylene, ethers, nitrous oxide, and ketamine are of cultural interest, but they also prompt the question of whether anesthetics and psychedelics share some mechanistic interface. This hardly seems possible, as most anesthetics depress the central nervous system and lead to functional disconnections in the cortex, whereas the effects of psychedelic drugs must surely activate the brain and facilitate novel connections that are inaccessible in the normal waking state. Or do they? A groundbreaking study recently published by Carhart-Harris *et al.*<sup>21</sup> used functional magnetic resonance imaging (fMRI) to assess the brain’s transition from normal consciousness to a psychedelic state induced by intravenous psilocybin. Psilocybin is a 5-hydroxytryptamine<sub>2A</sub> (serotonin) agonist known to induce states of vivid imagination, altered sense of time, and unusual bodily sensations. These



**Fig. 2.** Psilocybin decreases functional connectivity of posterior cingulate and ventromedial prefrontal cortex. (Top) Positive (orange) and negative (blue) connectivity with the ventromedial prefrontal cortex during saline placebo infusion. (Middle) Psilocybin induces significant increases (orange) and decreases (blue) in connectivity to ventromedial prefrontal cortex. (Bottom) Shows areas where psilocybin-induced increases (orange) and decreases (blue) in connectivity were significantly greater compared with placebo. Overall, the findings suggest that psilocybin induced a significant decrease in positive coupling between the posterior cingulate cortex and the ventromedial prefrontal cortex. Reproduced with permission from Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, Tyacke RJ, Leech R, Malizia AL, Murphy K, Hobden P, Evans J, Feilding A, Wise RG, Nutt DJ: Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A* 2012; 109:2138–43.<sup>21</sup>

healthy volunteers reported a psychedelic experience as fMRI revealed significant *decreases* in cerebral blood flow in the medial prefrontal cortex, posterior cingulate cortex, anterior cingulate cortex, and thalamus. The intensity of psychedelic effects varied directly with reductions in cerebral blood flow. Importantly, further analysis revealed that functional connectivity between the anterior and posterior regions of the cortex was also significantly *decreased* (fig. 2). Suppression of the thalamus and association cortices, as well as decreased anterior-posterior connectivity, during psilocybin exposure is remarkably similar to uncoupling patterns of brain regions during general anesthesia.<sup>22</sup> The following sections consider how anesthetics can lead to altered states of consciousness, with a focus on cortical excitation.

#### ***γ*-Aminobutyric Acid Anesthetics and Altered States**

The  $\gamma$ -aminobutyric acid (GABA) receptor A agonist propofol is known to increase GABAergic activity in interneurons of the cortex, thalamus, midbrain, and pons.<sup>23</sup> This is of relevance to the neurochemical mechanisms of psilocybin, because multiple preclinical studies have shown that 5-hydroxytryptamine<sub>2A</sub> receptor activation increases GABAergic transmission.<sup>24–26</sup> Investigations using positron emission tomography while volunteers were administered propofol demonstrated dose-dependent reductions

in cerebral blood flow in the thalamus, occipitotemporal, and orbitofrontal regions in transition from awake states to sedation to unconsciousness.<sup>27</sup> Studies using fMRI to assess the brain in transition to propofol-induced unconsciousness have demonstrated decreased cerebral blood flow and decreased connectivity across frontoparietal and thalamocortical networks.<sup>28–30</sup> Of course, the psychoactive or hallucinatory properties of propofol are only observed at lower (*i.e.*, subanesthetic) doses of the drug, in which paradoxical excitation of the cortex is observed.<sup>31</sup> Previous studies have explored both cortical and corticostriatal mechanisms for the paradoxical excitation observed with low doses of propofol. McCarthy *et al.*<sup>31</sup> conducted a modeling study suggesting that the shift from synchronous to asynchronous activity of GABAergic inhibitory interneurons in the cortex accounts for the appearance of electroencephalographic activation. Brown *et al.*<sup>32</sup> proposed a role for the basal ganglia in the paradoxical excitation observed with both propofol and zolpidem. Zolpidem has been demonstrated (in some instances) to cause behavioral improvement in patients suffering from disorders of consciousness due to brain injury.<sup>33</sup> These GABAergic drugs may act through the globus pallidus interna to disinhibit the thalamus and activate the cortex. It is important to note, however, that altered states of consciousness attributable to paradoxical cortical excitation by

propofol do not share the same subjective phenomenology as psilocybin or other psychedelic drugs.

### **Non-GABAergic Anesthetics and Altered States**

There has been a recent resurgence of interest in ketamine and related glutamatergic *N*-methyl-D-aspartate antagonists as potential therapies for pain management and depression, as well as tools for modeling psychosis.<sup>34</sup> At low doses of ketamine (0.2 mg/kg bolus over 1 min, followed by 0.58 mg/kg infused over 1 h), fMRI reveals *increased* global brain connectivity.<sup>35</sup> Other fMRI studies on ketamine (0.26 mg/kg bolus over 1 min, followed by 0.25 mg kg<sup>-1</sup> h<sup>-1</sup> infusion) found paradoxical *hypo*activation in the ventromedial frontal cortex and subgenual cingulate,<sup>36</sup> the same area modulated by intravenous psilocybin. Low-dose ketamine has also been associated with increased connectivity in cerebellum and visual cortex as well as a decrease in connectivity in amygdala, insula, and anterior cingulate cortex.<sup>37</sup> In addition, fMRI investigations of pain found significant ketamine-induced reductions in activity in the thalamus and insula.<sup>38</sup> The patterns of these findings suggest that although ketamine causes widespread activation and increased metabolic rate, specific networks undergoing altered connectivity may be relevant to ketamine's unique dissociative state. At the neuronal level, ketamine preferentially blocks *N*-methyl-D-aspartate receptors on GABAergic interneurons, which decreases their inhibitory influence on pyramidal neurons and therefore permits aberrant activation of cortical and subcortical structures.<sup>32</sup> This dysregulated activation may lead to alterations of spatiotemporal information processing and synthesis, resulting in hallucinatory experiences. At anesthetic doses of ketamine (2 mg/kg), cortical activation is seen in association with significant disruptions of corticocortical connectivity.<sup>39</sup> More recently, hyperpolarization-activated cyclic nucleotide-gated 1 channels have become a focus for the molecular mechanism of the hypnotic actions of ketamine.<sup>40,41</sup>

Nitrous oxide is also thought to act at the molecular level through antagonism of *N*-methyl-D-aspartate receptors.<sup>42</sup> Like ketamine, nitrous oxide causes an increase in high-frequency electroencephalographic activity and increased cerebral metabolic rate. However, a recent study using electroencephalography during 20, 40, and 60% nitrous oxide administration revealed significant decreases of functional connectivity in frontal and parietal networks.<sup>43</sup> It is important to note that most of the subjects in this study did not lose consciousness. Furthermore, this study suggests that cortical excitation and decreased functional connectivity are not mutually exclusive.

In summary, altered states associated with low doses of general anesthetics are likely driven by cortical activation involving modulation of GABAergic interneurons, rather than the serotonergic mechanisms associated with most classic psychedelic drugs. Clearly, some anesthetics—specifically, ketamine and nitrous oxide—have more potent psychedelic

effects than others,<sup>44</sup> which may relate to altered spatiotemporal information processing associated with dysregulated activation of the cortex. Future research will be required to clarify why activation due to drugs such as ketamine or nitrous oxide is associated with a significantly different subjective experience compared with the paradoxical excitation induced by propofol.

### **Caveats**

The studies reviewed, and interpretations based on them, have notable limitations. Only one psychedelic drug—psilocybin—was discussed because this is the only classic psychedelic drug that has been studied with neuroimaging in humans. The neuroimaging methods (electroencephalography, positron emission tomography, and fMRI) used to explore the actions of anesthetic or psychedelic drugs each has their own limitations, compromising the ability to map neural circuits accurately and with appropriate temporal resolution; functional and effective connectivity analyses are also laden with assumptions. Furthermore, some of the evidence reviewed was gathered using different imaging models and analytic techniques, which hinders a complete synthesis of the findings.

### **Potential Impact of Future Study**

Despite the limitations of this initial synthesis, the study of psychedelic or other altered states of consciousness induced by general anesthetics could be impactful in a number of ways. First, the ability of some anesthetics to induce psychedelic experiences with intact explicit recall challenges our current understanding of anesthetic dose–response relationships. It also stimulates investigation into which mechanisms give some anesthetic drugs the ability to produce a psychedelic state. By comparing psychedelic and anesthetic pathways that can alter or even “heighten” consciousness, we may be able to identify key brain areas and networks that mediate conscious experience. Second, understanding the neurophysiological basis for disrupted cortical processing and distorted perceptual experience by low doses of general anesthetics could have clinical impact. For example, delirium is a common neurologic complication that occurs in both the perioperative and critical care settings.<sup>45</sup> Identifying the mechanisms by which anesthetics and sedatives perturb perceptual processing—or create conditions for abnormalities of perceptual processing beyond the drug exposure itself—has translational relevance to the operating room, postanesthesia care unit, and intensive care unit. Finally, it is important to consider the possibility of a social impact related to the understanding of how anesthetics modulate the mind. It could be argued that the scientific investigation of general anesthetics as psychoactive drugs might encourage their use. However, abuse of anesthetic drugs such as ketamine is already prevalent, and it seems unlikely that systematic study within the field of anesthesiology

would reach, let alone encourage, illicit users. Furthermore, although volatile anesthetics were not discussed extensively in this article, the use of volatile inhalants for psychoactive purposes is already common, with approximately 22.5 million Americans having used an inhalant for recreational use at least once.<sup>46</sup> Inhalant abuse has been referred to as the “hidden” or “forgotten” epidemic, and systematic research agendas are actively being discussed in the literature.<sup>47,48</sup> As with the case of Michael Jackson and propofol abuse,<sup>49</sup> anesthesiologists have a role to play in understanding why people are motivated to experiment with anesthetic drugs and in educating the public as to the potentially devastating consequences of nonmedical use.

## Conclusion

Psychedelic and anesthetic drugs are potent modulators of consciousness and have the potential to induce altered states. It is important to emphasize that we are not advocating the use of general anesthetics as psychedelic drugs. Rather, we are suggesting that the current description of cognitive effects of commonly used anesthetics is likely incomplete. Characterizing the phenomenology, mechanisms, and social implications of anesthetic-induced altered states will require an integrated study involving anesthesiology, neuroscience, and psychology in order to understand the fascinating transformation from the waking state, to altered consciousness, to oblivion. A collaborative effort using anesthetics as a vehicle might help unravel some secrets of the mind, as Beat poet Allen Ginsberg suggested toward the end of his poem *Laughing Gas*:<sup>50</sup>

The universe is a void  
in which there is a dreamhole  
The dream disappears  
the hole closes  
It's the instant of going  
into or coming out of  
existence that is  
important—to catch on  
to the secret of the magic  
box

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