

Commentary on: *Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance* by Griffiths et al.

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Psychedelic drugs such as psilocybin, lysergic acid diethylamide (LSD), mescaline, dimethyltryptamine (DMT), and many others include synthetic chemicals and the active ingredients in psychoactive extracts of plants that have been used since time immemorial for their mind-altering properties. These agents were first employed for religious purposes, evidently to facilitate contact with the supernatural. After the discovery of LSD by Albert Hofmann in the early 1940's, much attention was devoted to the perceptual distortions elicited by LSD and related substances, as well as to the similarity of the drug-induced state to transcendental states reported by mystics of varied religious persuasions.

The different effects elicited by these drugs have led to different names. They are designated "psychotomimetics" because one can reasonably argue that individuals taking the drugs have lost contact with reality and are, hence, psychotic. They are called "hallucinogens" because of the perceptual distortions. However, frank hallucinations—seeing or hearing something that doesn't exist at all in the environment—are rare. Rather, visual and auditory perceptions are notably intensified and altered. Subjects report

synesthesia, a seeming transmutation of the senses, e.g., visualizing sound waves upon hearing a loud noise. Humphrey Osmond coined the term "psychedelic" meaning "mind-manifesting" to emphasize the extraordinary change in the sense of self, a feeling of communion with the infinite, a dissolution of ego boundaries with the self, seeming to merge with environment. These are arguably the most remarkable of all the drug effects and may teach us much about neurochemical systems that mediate our sense of consciousness. Hence, I prefer the term psychedelic despite this term's possibly connoting the irresponsible use of these drugs by some in the late 1960s. In the interests of full disclosure, I myself had single sessions each with LSD and DMT well over 40 years ago and experienced the effects described here. Numerous clinical studies with psychedelic drugs were conducted in the 1950s and 1960s. One of the few controlled investigations of the relationship of psychedelic drugs and mystical consciousness was carried out by Walter Pahnke as his doctoral dissertation at Harvard University. He utilized psilocybin, the psychoactive ingredient in the mushroom psilocybe, which for logistic reasons, has been the most widely employed psychedelic drug in clinical research. Psychedelic drugs vary in chemical structure with mescaline, (DOM), and 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy), being phenethylamines that resemble neurotransmitters such as norepinephrine and dopamine. Others, such as psilocybin, LSD, and DMT, contain indole moieties and more closely resemble serotonin. Extensive pharmacologic studies have established that all the drugs, phenethylamines and indoles, exert their actions primarily by mimicking serotonin at one of its receptor subtypes, 5-HT_{2A,C}. In the Pahnke "Good Friday" study, groups of ten theological seminary students were administered either 30 mg psilocybin or 200 mg nicotinic acid in a group setting as part of a

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religious service. Psilocybin consistently elicited a mystical experience not evident with nicotinic acid.

The rampant abuse of psychedelic drugs in the late 1960s led to strict controls with such severe restrictions that clinical and even laboratory research virtually vanished. Griffiths et al. now report a rigorous, blinded study of mystical experiences associated with psilocybin. Exquisite care was devoted to the design of the trial to minimize risk to subjects and to discriminate drug effects from the influences of suggestion. Participants were emotionally stable, generally middle-aged college graduates. They received either 30 mg of psilocybin or 40 mg of methylphenidate (Ritalin) per 70 kg, with each subject receiving the two drugs in separate sessions. Most important was the careful preparation with study monitors meeting with subjects on multiple occasions before and after each drug session. Such a setup was designed to diminish the likelihood of panic and to facilitate each subject's acceptance of major changes in consciousness. Subjects were administered an extensive array of questionnaires evaluating potential mystical experiences and they were followed up in depth 2 months later. One striking result was the effectiveness of the blinding procedure, which is often virtually impossible for psychoactive agents. Surprisingly, even the sophisticated monitors mistook one of the drugs for the other in about 25% of the sessions. Thus, the study results are not likely to be contaminated by expectant attitudes and biases of experimenters and/or subjects.

Psilocybin elicited what one would expect, perceptual distortions including visual distortions, feelings of transcendence, and a high incidence of mystical experiences, substantially greater than in the Pahnke study. Particularly impressive was the persistence of influences of psilocybin upon subjects' sense of their selves. When interviewed 2 months after the drug session, subjects reported that psilocybin enhanced their attitudes about life in general, their mood and relationships with others. Most remarkable was the sentiment of two-thirds of the subjects that the

psilocybin experience was either the "single most meaningful experience of his/her life or among the top five most meaningful experiences of his/her life."

What are the major take-home messages of the Griffiths et al. investigation? The ability of these researchers to conduct a double-blind, well-controlled study tells us that clinical research with psychedelic drugs need not be so risky as to be off-limits to most investigators. Indeed, there were very few adverse events acutely and none at the 2-month and 1-year follow-ups.

The observation that psilocybin reliably elicits a transcendent, mystical state tells us that investigations of these drugs may help us understand molecular alterations in the brain that underlie mystical religious experiences. Religious sensibilities are increasingly prominent throughout the world and often involve "born again" ineffable experiences analogous to psychedelic drug effects. Thus, seeking the "locus of religion" in the brain is by no means fanciful. We already have a hint in evidence that psychedelic drugs act by mimicking serotonin at 5HT_{2A,C} receptors. The major serotonin neuronal projections in the brain have their cell bodies in midline brainstem structures called the raphe nuclei, which receive input from neuronal input for the major senses. Accordingly, it is not far-fetched to ascribe to altered serotonin neurotransmission the subjective interconversion of senses that occurs with synesthesia. As the boundaries of our sense of self, our ego, are determined by the integration of sensory perception, it is conceivable that changes in serotonin systems mediate the diffusion of ego boundaries that underlies the transcendent merger of "self with universe" that is reported consistently by mystics of all religious persuasions and occurs often under the influence of psychedelic drugs.

By showing that one can responsibly conduct clinical research with psychedelic drugs and by confirming the mystical influences of these agents, Griffiths et al. may help resurrect psychedelic drugs as major tools in probing the molecular bases of consciousness.