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EDITORIAL AND COMMENTARIES ON ARTICLE BY GRIFFITHS ET AL.

“Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance”

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Towards a science of spiritual experience

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People have long sought meaning and significance in their lives through a variety of spiritual practices including prayer, fasting, chanting, solitude, and meditation. Historically, some of these practices have included the use of certain psychoactive plants. A common theme of these experiences, with or without the aid of psychoactive agents, has been to free oneself of the bounds of everyday perception and thought in a search for universal truths and enlightenment. To a large extent, this type of subjective and uniquely human experience has enjoyed little credibility in the mainstream scientific world and, thus, has been given little scientific attention. However, it may be time now to recognize these extraordinary subjective experiences, even if they are, at present, not directly verifiable by objective measures and even if they sometimes involve claims about ultimate realities that lie outside the purview of science.

The article by Griffiths et al. describes one of the first attempts to study these experiences in a systematic scientific investigation of the reportedly profound and sometimes life-altering experiences induced by the powerful hallucinogen psilocybin. Their study is unique in several ways. First, it applies rigorous, modern methods of psychopharmacological research, including use of controlled, double-blind drug administration with a positive control drug and counter-balanced orders, standardized and replicable testing con-

ditions, and sensitive outcome measures. Second, the study was conducted in specially designed environment, where the drug effects could be experienced safely yet unconstrained by an unnecessarily impersonal laboratory or clinical setting. Third, this is the first modern psychopharmacology study to focus, with healthy volunteers, upon experiences of deeply meaningful insights and understanding. Finally, the study is unique in that the investigators have also begun to study the lasting, life-changing effects that have been attributed to such experiences, using systematic follow-up assessments of mood and overt behavioral changes in the participants' lives.

The Editors invited commentaries from four experts to put this study in a larger context. These commentaries by Drs. Solomon Snyder, Charles R. Schuster, Herbert Kleber, and David Nichols provide a context for the study in terms of the history, policy, psychiatry, and future research. They relate this study historically to previous studies with hallucinogens and discuss the implications for drug and drug research policy. They discuss this class of drugs in terms of potentially adverse psychiatric consequences and also in terms of potential therapeutic applications. The commentaries identify important future directions for research on the neurochemistry and neurobiology of these drugs and these experiences. Taken together, these commentaries indicate that the Griffiths et al. study will likely take an important place in the history of human psychopharmacology research.

It is time for psychopharmacologists to open their minds and their laboratories to the full domain of human drug experience. We would do well to be wary of our own preconceptions and prejudices, and to be prepared to consider the entire scope of human experience and behavior as legitimate targets for systematic and ethical scientific investigation. Griffiths et al. set an excellent example for such a venture.

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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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The article by Griffiths et al. in this issue of Psychopharmacology should make all scientists interested in human psychopharmacology sit up and take notice. It is the first well-designed, placebo-controlled, clinical study in more than four decades to examine the psychological consequences of the effects of the hallucinogenic (psychedelic) agent known as psilocybin. In fact, one would be hard-pressed to find a single study of psychedelics from any earlier era that was as well-done or as meaningful. Perhaps more importantly, despite the notion by many people that psychedelics are nothing more than troublesome drugs of abuse, the present study convincingly demonstrates that, when used appropriately, these compounds can produce remarkable, possibly beneficial, effects that certainly deserve further study.

Although many people seem to believe that “psychedelics” simply appeared during the turbulent 1960s, in fact the use of these materials spans back through many millennia of human history. Ancient substances with names such as *Soma* (India), *Kykeon* (Greece), and *Teonanacatl* (South America) served for thousands of years as psychopharmacological catalysts in a variety of sacred religious and magical rituals (Nichols 2004; Schultes and Hofmann 1979). Peyote, the ceremonial use of which is now thought by anthropologists to date back at least 5,000 years, is revered as a sacrament by the Native American Church. Ayahuasca, a decoction made from plants that grow in the Amazon basin, is a sacrament used by a syncretic church in

Brazil. This church has a small following in the US that has just received a favorable decision by the US Supreme Court allowing them continued use of this material.

The parallel between mystical states and the effects of psychedelic drugs is well-known among those familiar with the literature. Aldous Huxley, in his classic but controversial 1954 book, *The Doors of Perception*, (Huxley 1970) noted the similarity of his own mescaline-induced state to experiences described by mystics and visionaries from a variety of cultures. Perhaps it is not surprising then that the name “entheogen,” with the connotation that these materials reveal god within, is becoming increasingly popular among those who continue to use these substances for purposes that are neither medical nor “recreational.”

We must, therefore, take note of what has come to be known as the “Good Friday Experiment,” carried out by Walter Pahnke for his Ph.D. studies at a small private chapel in Boston. His 1963 Ph.D. dissertation was titled *Drugs and Mysticism. An analysis of the relationship between psychedelic drugs and the mystical consciousness*. He described in an experiment with 20 student volunteers from a local Christian theological seminary. Subjects were given either 30 mg of psilocybin or 200 mg of nicotinic acid as a “placebo.” The experiment was carried out in a religious setting during a Good Friday service. Pahnke concluded, “Under the conditions of this experiment, those subjects who received psilocybin experienced phenomena which were indistinguishable from, if not identical with, certain categories defined by our typology of mysticism.”

Clearly, these substances have profound effects on human consciousness, and in the 1950s and 1960s, the drug known as LSD was hailed as a revolutionary new technology for psychiatry. LSD was intensively investigated for its medical potential and for possible use as an adjunct to psychotherapy until clinical research was

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abruptly halted by laws passed in response to concerns over widespread recreational use. Despite studies that involved tens of thousands of patients, using “therapeutic” approaches that employed LSD in a variety of ways, little of clear significance resulted, at least partly due to faulty experimental design and data analysis. As a consequence, a conventional wisdom seems to have developed that psychedelic drugs are generally pretty worthless. But medical technology has advanced in the past four decades; we know quite a bit more about the brain now than we did then, and human experimental methods are certainly much better.

All that being said, there was one indication for the use of psychedelics, particularly LSD, that was reasonably well-documented. Chicago internist Eric Kast first reported in 1964 that some “gravely ill” patients treated with LSD obtained mood elevation and reductions in the need for pain medication that lasted for nearly 2 weeks after the drug, and that some patients “displayed a peculiar disregard for the gravity of their situations” (Kast and Collins 1964). In a subsequent study, he further noted that, “Patients who had been listless and depressed were touched to tears by the discovery of a depth of feeling they had not thought themselves capable” (Kast 1966).

Kast’s findings served as the foundation for a series of groundbreaking studies into the value of LSD in the treatment of terminal cancer patients. That work was carried out at the Maryland Psychiatric Research Center in Baltimore, Maryland by Drs. Stanislav Grof, Al Kurland, Walter Pahnke, Sanford Unger, and their colleagues (Grof et al. 1973; Pahnke et al. 1969, 1970a,b). Significantly reduced need for analgesics and improved mood and quality of life were observed in 60–70% of patients treated with LSD. The treatment response appeared to be correlated with the extent to which the patients experienced a mystical or transcendental state. That is, those who experienced the most profound LSD-induced states seemed to gain the most improvement. The basis for this benefit appeared to be related to a reduced or abolished fear of death, with an attendant reduction in anxiety, which we know affects subjective pain.

What Griffiths et al. have done in their present work represents an important extension of Pahnke’s “Good Friday” experiment. They have used proper controls, better experimental design, and have provided a better analysis of the experience using more modern instruments. The experiments were not conducted in a church, or in a venue that would lead to a strong expectation of some sort of religious experience. The subjects in the Griffiths et al. study were not theology students, but were simply ordinary people with an interest in spiritual things. The work by Griffiths et al. demonstrates that, under appropriate experimental conditions, psilocybin occasioned experiences similar to

spontaneously occurring mystical states. Most importantly, some of the persisting positive changes in attitudes and behavior reported by subjects were confirmed by independent ratings from community observers such as family members or friends.

The prospects for far-ranging scientific advancement are exciting. We know that psychedelics have powerful effects in many areas of the brain that are critically important for cognition and awareness. Our present understanding is that they act principally by activating serotonin 5-HT_{2A} receptors, especially those densely expressed on the apical dendrites of cortical pyramidal cells, the quintessential computational units within the cortex of the brain. In that respect, psychedelics depolarize these cortical cells, leading one to speculate that they may become more sensitive to low-level signals. That is, perhaps they can do more with less, potentially amplifying processes that are normally running, but which are not generally apparent in everyday awareness.

The science of pharmacology involves perturbing biological systems with chemical modulators (i.e., drugs), the results of which have had profound effects on our understanding of both normal and disease state physiology. Rigorous research with psychedelics may hold the key to understanding the very nature of consciousness, self-awareness, the ability to introspect, and the properties of mind that set us apart from other species.

With such a huge potential impact, is there any good reason why a well-done study like the one reported here by Griffiths et al. should appear only once in half a century? Until a related compound, DMT, was studied by Rick Strassman at the University of New Mexico in the mid-1990s (Strassman and Qualls 1994; Strassman et al. 1994; Strassman 1996), no significant work on the clinical effects of psychedelics had appeared in the scientific literature for more than a generation. Perhaps the time has now come to reinvestigate the psychopharmacological properties of psychedelics. Thus, the study by Griffiths et al. in this issue could be a watershed event.

Finally, Griffiths et al. conclude, “The ability to occasion such experiences prospectively will allow rigorous scientific investigations of their causes and consequences.” Indeed.

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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.

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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The study by Griffiths et al. is noteworthy both for the rigorousness of its design and execution, as well as the clarity of its results. It demonstrates that psilocybin can be safely studied in normal human beings who do not have a history of hallucinogenic drug use. As would be expected, during the psilocybin session participants showed perceptual changes and labile mood. It is striking that majority of the participants reported 2 months later that the psilocybin-induced experience was personally very meaningful and spiritually significant. Indeed, most of them rated the psilocybin-induced experience as one of the top five most important experiences in their life. It is especially notable that participants reported that the drug produced positive changes in attitudes and behaviors well after the sessions, and these self-observations were consistent with ratings by friends and relatives. These participants were well-prepared for the psilocybin experience by an experienced monitor, who expressly stated that psilocybin might produce increased personal awareness and insight. However, it is clear that the effects of psilocybin were more than expectancy effects because the active drug control condition (40 mg of methylphenidate) did not produce similar effects on ratings of significance or on measures of spirituality, positive attitude, or behavior.

The term psychedelic, when applied to drugs, implies that the drug experience is “mind-expanding.” The paper by Griffiths et al. illustrates the accuracy of this description for psilocybin, and I hope that this landmark paper will also be “field-expanding.” The report clearly demonstrates that we can objectively study the experiences reported by many to

be profoundly spiritual and meaningful, and that we can investigate the long-term positive consequences for the individual’s attitudes and behavior. It will open the way to study the neural mechanisms responsible for these drug-altered states of consciousness. It is entirely conceivable that psychotropic agents that produce these experiences may have a role in the treatment of addictive states. Spirituality has long been a major component of the 12-step approach to the treatment of alcoholism and other forms of drug addiction. Although the investigations of LSD for the treatment of alcoholism failed to show any clear-cut significant beneficial effects, the possibility that a spiritual experience, such as that reported in the present study, might be useful cannot be discounted. The set and setting in which the drug is administered may dramatically alter the drug experience. In the present study by Griffiths et al., the set was well-established for a positive experience by the preparatory sessions with the monitor, and the setting was one that was designed to produce an introspective state. This may be an important determinant of the experience and could well alter any possible therapeutic efficacy. The possibility of easing the ennui and anguish of impending death with agents such as psilocybin is also suggested in the study by Kast (1966) and those that are reviewed in the commentary of Professor Nichols. It is likely that psilocybin might have the same salutary effects. This is not an insignificant issue especially considering the large numbers of aging individuals in our society who may be in need of hospice care.

In summary, I hope that this paper by Griffiths et al. renews interest in a fascinating and potentially useful class of psychotropic agents. The misuse of these substances that led to their control in Schedule I of the Controlled Substances Act cannot be allowed to continue to curtail their use as tools for understanding the neurobiology of

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human consciousness, self-awareness, and their potential as therapeutic agents. Personally, I also believe that these drugs have a role in discovering the brain mechanisms underlying feelings of spirituality and that such understanding may lead to our investigation of nonpharmacological means of engendering such states. Ultimately, human consciousness in its ever-changing state is a function of the ebb and flow of neural impulses interacting in the various regions of the brain—the very substrate that drugs such as psilocybin act upon. Understanding the brain

mechanisms mediating these effects is clearly within the realm of neuroscience and deserves further intensive investigation. Griffiths et al. are to be highly commended for reinvigorating this important area of research.

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The decade of the 1960s began the current era of heavy drug use in America, beginning perhaps with Timothy Leary's Pied Piper invitation to, "Turn On, Tune In, Drop Out" (with psychedelic drugs). While fortunately most youths who experimented did not suffer lasting damage, those of us on the mental health front lines at the time saw a number of casualties (Kleber 1967). Eventually, the hippies and the LSD-fueled "Summer of Love" in San Francisco were replaced by motorcycle gangs, amphetamines, and gratuitous violence. Psychedelic drugs receded into a permanent background of US drug use, never going away altogether, but not reaching the same penetration.

Unfortunately, one of the lasting casualties of the street use of these agents was research. Sandoz, the manufacturer of LSD, discontinued supplying it to researchers around 1965, concerned that the company's reputation was being tainted by the illicit use. Even though street chemists supplied the vast majority of the illicit use, the licit supply for research more or less disappeared and so did research funding. Prior to the cessation, research with LSD and other psychedelics was active in a variety of areas: as a potential producer of a model psychosis (it has significant limitations); the nature of hallucinations (it produces more illusions); as a therapeutic agent for trauma and the dying (inadequate data); and as a way to study altered reality states, e.g., Huxley's *The Doors of Perception*, Pahnke's

Good Friday Experiment, and Blum's *Utopiates: The Use and Users of LSD-25*. Some of the research was carefully done; in most, the researchers seem to be carried away by the effects of the agents.

This category of agents has many names, each reflecting a different point of view as noted above: psychotomimetics (mimicking psychosis), hallucinogens (producing hallucinations), entheogens (revealing the God within), and psychedelics (mind-manifesting). It is in these last two domains that the findings of the study of Griffiths et al. belong to even though they did not use either term.

The authors should be commended for the way they designed and carried out the double-blind project. The design involved using 30 mg/70 kg of psilocybin as the active experimental agent and 40 mg/70 kg of methylphenidate as an active control. All subjects received at least one session with each agent in a counterbalanced method. Great care was taken both to minimize risk to subjects, who were all naïve to this category of drugs, and to be able to separate drug effects from expectancy and possible suggestion bias by the monitors. The blinding was done so carefully that even the experienced monitors misidentified the administered agent approximately one quarter of the time. The extensive time with the monitors both before and after the sessions kept adverse effects such as fear and panic to a minimum although 8 of the 36 subjects described all or most of the psilocybin sessions to be dominated by anxiety or dysphoria. These effects did not persist beyond the session, were handled by reassurance, and apparently were of no lasting negative consequence. None of the methylphenidate subjects reported this response. As far as positive effects were concerned, psilocybin increased measures relating to mystical experiences: 22 of the 36 volunteers had a "complete" mystical experience after psilocybin compared to only 4 of the 36 after methylphenidate. At

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the 2-month follow-up, 67% rated the psilocybin experience to be either “The single most meaningful experience” of their lives or among the top five most meaningful “experiences.” After methylphenidate, 8% of the volunteers rated the experience to be “among the top five most meaningful experiences,” with none rating it as the single most meaningful experience. Thus, psilocybin significantly increased subjective reports of such experiences while methylphenidate was associated with them only occasionally and to a much lesser effect.

As far as future research is concerned, this study suggests a number of possibilities, both basic and translational, that should merit NIH support. More information is needed on dose effects, subject differences, and the actions of various selective antagonists. Neuroimaging may shed light on sites and mechanisms of action. It would be interesting to see whether the positive responders to methylphenidate activated similar brain sites as the positive psilocybin responders or different ones, as well as what was happening in the brains of the psilocybin nonresponders. From a translational perspective, experienced clinicians are well aware of the profound role that spiritual reawakening experiences, whether achieved through Alcoholics Anonymous, traditional religious venues, or some life experience, can have on successful outcomes from addictive disorders. Increased knowledge about the neuroscience underpinnings of such transformational events could improve drug abuse treatment. It is necessary to keep in mind, however, that drug-induced states are unlikely to have lasting effects in inadequately prepared individuals, as LSD studies on alcoholism in the 1960s suggested.

The positive findings of the study cannot help but raise concern in some that it will lead to increased experimenting with these substances by youth in the kind of uncontrolled and unmonitored fashion that produced casualties over the past three decades. Such a concern, in view of history, is

not unwarranted. Even a proponent of such research, Humphry Osmond, who coined the term “psychedelic,” noted, “Psychedelics are instruments and like most of our artifacts are capable of being used well or ill. Unluckily, misuse is at least as likely as good use...”

Any study reporting a positive or useful effect of a drug of abuse raises these same concerns. In this Internet age, however, where youth are deluged with glowing personal reports in chat rooms and web sites as well as detailed information about the various agents and how to use them, it is less likely that a scientific study would move the needle much. Psychedelic drug use has remained in a relatively constant range over the past three decades as various fads have come and gone and enthusiastic personal accounts are balanced by negative reports about casualties. Discovering how these mystical and altered consciousness type states arise in the brain could have major therapeutic possibilities, e.g., treatment of intolerable pain, treatment of refractory depression, amelioration of pain and suffering of the terminally ill, to name but a few, as well as the already noted and needed improvement in treatment of substance abuse and dependence states so that it would be scientifically shortsighted not to pursue them.

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