The Serotonergic System and Mysticism: Could LSD and the Nondrug-Induced Mystical Experience Share Common Neural Mechanisms?

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Abstract—This article aims to explore, through established scientific research and documented accounts of personal experience, the similarities between religious mystical experiences and some effects of D-lysergic diethylamide or LSD. LSD predominantly works upon the serotonergic (serotonin-using neurons) diffuse neuromodulatory system, which projects its axons to virtually all areas of the brain including the neocortex. By its normal action it modulates awareness of the environmental surroundings and filters a high proportion of this information before it can be processed, thereby only allowing the amount of information that is necessary for survival. LSD works to open this filter, and so an increased amount of somatosensory data is processed with a corresponding increase in what is deemed important. This article describes the effects and actions of LSD, and due to the similarities with the nondrug-induced mystical experience the author proposes that the two could have common modes of action upon the brain. This could lead to avenues of research into mysticism and a wealth of knowledge on consciousness and how we perceive the universe.

Keywords—diffuse neuromodulatory system, LSD, mysticism, serotonin

The psychologist Ornstein (1972) suggested that the preoccupation with the study of such drugs as D-lysergic diethylamide (LSD) during the 1960s contributed to the reawakening of interest in particular questions of psychology such as that of consciousness. Using this drug, and its postulated theories of action, the author proposes that the system upon which LSD predominantly works is the somatosensory filter that cuts out the majority of environmental and somatic cues in order to aid survival. Furthermore, it is proposed that the LSD experience, and that of the mystical, could share a common mode of action—i.e., that these two work in similar ways upon the neural substrate.

Researchers into the brain have always valued psychotomimetic drugs because they seem to affect the core of a subject's consciousness. The molecular mechanisms that underlie such experiences need to be investigated in order to access the intangible aspects of human nature, such as beliefs, religion, and the unique state of consciousness (Snyder 1986). By studying the actions of such mind-altering drugs there is a hope of learning more about the brain processes responsible for the way that humans perceive both their selves and the outside world and the relationship between the two.

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The profound effects of the psychotomimetic drug LSD have been well documented since its synthesis in 1938, and many of these effects share similarities with the nondrug-induced mystical experience. In both cases changes in a person's perception of the "inner" and "outer" worlds are profoundly altered. Both produce a state of mind entirely unlike the normal pattern of existence. The effects experienced by a person taking a dose of LSD or another psychotomimetic (e.g. psilocybin or mescaline) can be compared quite closely to mystical experiences, as described by a number of visionaries.

Mysticism is a very difficult and complex term to define concisely. For the purposes of this article mysticism is defined as an immediate, direct, intuitive knowledge of God or of ultimate reality attained through personal religious experience (Microsoft Encarta Online Encyclopedia 2001). It does not always involve an orthodox deity, though it is found in all the major religions e.g., Christianity, Buddhism, Kabbalism in Judaism, Sufism in Islam and the bhakti movement in Hinduism. The mystical experience is often rooted in asceticism and many religious traditions prescribe strict discipline as well as meditative and contemplative techniques for achieving the mystical experience.

A phenomenological typology of the mystical state of consciousness has been defined by Pahnke (1966) after a study of the writings of mystics and of those who have tried to characterize mystical experience. These categories are:

1. Unity—experience of an undifferentiated unity, that is the subject-object dichotomy is transcended;
2. Transcendence of space and time—this category refers to the loss of the usual sense of space and time;
3. Deeply felt positive mood—the most universal elements are joy, blessedness, and peace experenced at a high level of intensity;
4. Sense of sacredness—a nonrational, intuitive response of awe and wonder in the presence of inspiring realities;
5. Objectivity and reality—that is, insightful knowledge about being or existence in general gained by direct experience and the conviction that such knowledge is ultimately real;
6. Paradoxicality—significant aspects are felt to be true in spite of the fact that they violate the laws of Aristotelian logic;
7. Alleged ineffability—language seems inadequate to contain or accurately reflect such experience;
8. Transiency—the experience is not sustained indefinitely, returning the subject to his usual state of everyday consciousness; and
9. Persistent positive changes in attitude and/or behavior—this category describes the positive, lasting effects of the experience and the resulting changes in attitude towards self, others, life and toward the mystical experience itself.

Of these nine properties, the last gives a validity to the experience. The mystical experience, if to be judged true must have this life-changing quality. All of these nine properties of the mystical experience have also been reported by the LSD user.

In order to understand the effects of LSD on perception and its postulated mechanisms of action, it will be necessary to describe a number of neurobiological systems upon which it acts. The data on these systems is vast and is beyond the scope of this article to give a comprehensive description, but sufficient detail is offered to provide an understanding of the basic mechanisms that are thought to lie behind the LSD experience.

EXPERIENCES COMMON TO BOTH THE LSD USER AND THE MYSTIC

The first person to experience the effects of LSD was Albert Hofmann, who first synthesized it and accidentally ingested some in 1943. His experiences, which he wrote down the next day, provide an insight into the nature of the effects of LSD upon the human subject. On the first occasion with unknown dosage he wrote:

> I was forced to interrupt my work in the laboratory in the middle of the afternoon and proceed home, being affected by a remarkable restlessness, combined with a slight dizziness. At home, I lay down and sank into a not unpleasant intoxicated-like condition characterized by an extremely stimulated imagination. In a dreamlike state, with eyes closed (I found the daylight to be unpleasantly glaring) I perceived an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors. After two hours this condition faded away (Hofmann 1980).

On the second occasion, he deliberately took 250 micrograms—a dose now known to be five times the effective dose. The first effects, which were recorded to have begun after 40 minutes, were a slight dizziness, unrest, difficulty in concentration, visual disturbances, and a marked desire to laugh. His laboratory notes were discontinued but he wrote after the experience that the most pronounced symptoms were: vertigo, visual disturbances; the faces of those around him appearing as grotesque, colored masks; marked motoric unrest, alternating with paralysis; an intermittent heavy feeling in the head, limbs and entire body, as if they were filled with lead; a dry, constricted sensation in the throat; and occasional out-of-body experiences. Six hours after ingestion, only disturbances to his visual and auditory perception remained. He also recorded how all acoustic perceptions (e.g. the noise of a passing car) were transformed into optical effects, every sound evoking a corresponding hallucination constantly changing in shape and color like pictures in a kaleidoscope. After a night's sleep, all these effects had worn off (Hofmann 1980).

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Hofmann later wrote (with Schultes) that "the familiar, daily environment appears in a new and glorious light. Forms and colors are changed or acquire a new, sometimes far-off significance. Ordinary objects lose any symbolic character, are detached, radiate their own intense entity. Colors usually become richer, transparent, radiating from the inside" (Schultes & Hofmann 1973).

People who have taken LSD or similar psychotomimetic drugs often relate experiences that are qualitatively similar to those reported in mysticism. Synesthesia is an example of this. Synesthesia is the transmutation of sensory modalities, where sound may be seen or color experienced by the sense of smell and so on. Mystics or those who study meditation as a way to attain some insight into reality report undergoing this incredible experience. BT Swami Krishnapada (1999) of the Vaishnava religious tradition related a vision wherein he visited the spiritual world:

> When we arrived there, I was totally overwhelmed by spiritual sensations. Every molecule, every cell of the body I was inhabiting started screaming out in ecstasy. Suddenly, with no effort on my part, all of my senses became interchangeable and could perform the activities of any of the others. To my joyous disbelief, I could see with my ears and hear with my nose. I even tasted with my eyes.

He goes on to say that, "the sensual stimulation I felt was a million fold greater than that which I had experienced in other environments." This is similar to the experience which subjects, under the influence of LSD, state as their own.

Another experience that is common both to the mystic and the LSD user is that of a profound sense of meaning in all things. Aldous Huxley (1954) wrote of his experiences of taking mescaline (the active ingredient of the peyote cactus) in *The Doors of Perception*. After half an hour of taking his pill he began to look at a vase of ordinary flowers, which began to take on a meaning of its own:

> At breakfast this morning I had been struck by the lively dissonance of its colors. But that was no longer the point. I was not looking now at an unusual flower arrangement. I was seeing what Adam had seen on the morning of his creation—the miracle, moment by moment, of naked existence. [This] bunch of flowers shining with their own inner light and all but quivering under the pressure of the significance with which they were charged . . . [They] signified nothing more and nothing less, than what they were— a transience that was yet eternal life, a perpetual perishing that was at the same time pure Being, a bundle of minute, unique particulars in which by some unspeakable and yet self-evident paradox was to be seen the divine source of all existence.
>
> I continued to look at the flowers . . . The Beatific Vision, Sat Chit Ananda, Being-Awareness-Bliss—for the first time I understood, not on the verbal level, not by inchoate hints or at a distance, but precisely and completely what those prodigious syllables referred to.

Although research into the effects of psychedelics can differ in its conclusions, dissolution of the sense of self has been reported as experienced by the majority of people who take a psychedelic drug. In the famous "Good Friday" double-blind experiment by Pahnke (1966), psilocybin was used as the psychedelic test substance and nicotinic acid as the placebo. Six months after the experiment, the subjects were asked to fill out a questionnaire in which the completeness with which each subject experienced each of the nine categories was measured through numerical responses to category-specific questions. Those subjects who had taken the psychedelic responded with 62% of the maximum possible score when asked whether they had experienced a sense of unity with the universe, compared to only 7% of the control subjects. It is as if the boundaries that lie between "self" and that which is "non-self" evaporate and "a sense of serene oneness with the universe occurs" (Snyder 1986). On this Huxley (1954) wrote:

> To others again is revealed a glory, the infinite value and meaningfulness of naked existence, of the given, the unconceptualised event. In the final stage of egolessness there is an obscure knowledge that All is in awe—that All is actually each. This is as near, I take it, as a finite mind can ever come to perceiving everything that is happening everywhere in the universe.

This very experience is sought after by many undergoing strict discipline in meditation. Brahman realization, as it is called in the Vedic scriptures, is the very goal of the students of the impersonalist school of Hindu philosophy who follow Sankaracarya. Students of Christian, Buddhist, and other forms of mysticism have often commented on the similarity of the psychedelic experience to the transcendental state attained through Zen or other forms of deep meditation (Snyder 1986). Great spiritual teachers have taught that all of reality is a unity and that we are one with it. Some Buddhist and Hindu religious scriptures teach that we are not separate from the other people around us or from our environment and that, on the contrary, it is the fact of our everyday living with maya, or illusion, in which we are living. These scriptures also teach that the only way to break free from this illusion is discipline in focusing the mind through meditation so that we may see things as they truly are.

Another statement made by transcendentalists (i.e., people who assert the primacy of the spiritual and transcendental over the material and empirical) is the difference in the passage of time when on the "spiritual plane" (a phrase from the Bible is a good example of this: "With God, a day is as a thousand years"). The sense of time is also markedly distorted during a hallucinogenic experience (Shanon 2001); one author wrote, "Two hours after taking the drug, I felt I had been under its influence for thousands of years" (Snyder 1986).

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We now look at LSD, a drug that has profound effects upon the brain, especially through the serotonergic neuromodulatory system.

THE EFFECTS OF LSD

The physiological effects of this powerful drug have been well documented. These effects can be grouped into five general areas of action: LSD works on the sympathetic nervous system (which is involved in regulation of heart muscle, smooth muscle and glandular organs in a response to stressful situations); the motor system (which is involved in carrying out limb movements); the affective states; thought processes; and it has profound effects upon the sensory and perceptual experience.

LSD is a semisynthetic preparation originally derived from ergot, an extract of the fungus *Claviceps purpurea*, which grows as a parasite on rye wheat. The dosage that is required to produce a moderate effect in most subjects is 1 to 3mcg per kilogram of body mass, and the effects can last from seven to 10 hours (Bowman & Rand 1980).

Stimulation of the sympathetic nervous system following LSD ingestion can lead to effects such as hypothermia with piloerection (hairs standing on end, such as can be found in reports of religious ecstasy), sweating, increased heart rate with palpitations, and elevation of blood pressure and blood glucose levels. These reactions of the autonomic nervous system are not as significant as other effects upon the body: action on the motor system can lead to increased activity of monosynaptic reflexes (such as the knee-jerk response), an increase in muscle tension, tremors, and muscular incoordination. This latter effect of muscular incoordination is also a symptom of religious ecstasy in many cultures, where the worshipper has such a profound feeling of love of God that he is said to be "intoxicated by God."

There are alterations in the affective state of the subject. Often alternating mood swings occurr, ranging from depression, anxiety or dread to euphoria, elation or exaltation, all exhibiting with corresponding displays of behavior. LSD has an effect on thought processes causing objective, logical processes to be slow; ideas without obvious connection are associated, and the subject is indecisive, easily distracted and given to introspection. Depersonalization (dissolution of the ego) may occur but generally the subject remains in contact with at least a vestige of reality and is aware that the experiences are drug-induced.

The thresholds for both auditory and visual stimuli are reduced under the influence of LSD so that colors and sounds have more of a presence and seem more significant. Synaesthesia occurs. Perspective, vision and perception of movement are distorted. Proprioception (a sense of where the limbs are in space) is disturbed, which may give rise to dizziness. The threshold for pain increases. Tactile illusions may occur where the subject may feel like he can't feel anything but can feel things too much at the same time. The subject's body image is distorted, as is the relationship to the surrounding environment. Time sense is impaired. Disturbances of perception and their consequences for the emotional state of the subject occur; these have been likened to those arising from sensory deprivation (Bowman & Rand 1980). Many of these alterations in perceptual awareness have also been noted as resulting from a nondrug-induced mystical experience.

DIFFUSE NEUROMODULATORY SYSTEMS

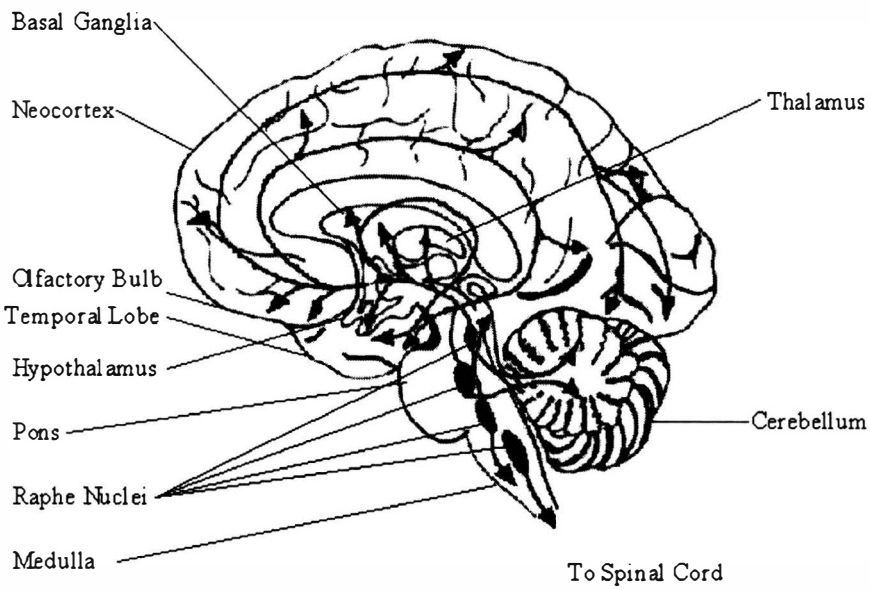
In order to understand how LSD may work in the body to bring about these effects it will be necessary to first look at those systems upon which it acts. Looking at the normal functioning of these systems will give an indication of how a drug, acting upon it, may alter such functions.

There exists within the brain, along with discrete centers for visual, auditory and other processing centers, a number of diffuse neuromodulatory systems. These consist of several collections of neurons regulating vast assemblies of postsynaptic neurons within, for example, the cerebral cortex, thalamus and spinal cord. Systems such as sensory perception and motor coordination are not independent processes, but are modulated and regulated by these systems to ensure efficiency. These become more or less excitable and synchronously active under certain physiological, or environmental, conditions.

Different modulatory systems are essential for the regulation of different aspects of motor control, memory, mood (affect), motivation and metabolic state. These systems involve neurons utilizing noradrenaline, dopamine, acetylcholine, or serotonin as their neurotransmitter substance. In general terms, the diffuse modulatory systems of the brain have a number of aspects in common. First, the core of each system has a relatively small set of neurons consisting of just several thousand. Each set of neurons arises from the central region of the brain, mostly from the brain stem, and each individual neuron is capable of influencing a large number of others. This action is due to the design of the synapses of many of these systems, which allows the transmitter to be released into the extracellular fluid and so diffuse to many neurons instead of being confined to the synaptic cleft and influencing just one.

The two systems that will be examined here are those that utilize noradrenaline and serotonin. LSD is thought to work upon the serotonergic system directly, but also uses the connections that this system makes to produce other effects leading to the psychedelic experience. LSD is thought to act in such a way on the noradrenergic system. Those noradrenergic neurons that have serotonin receptors will be stimulated, leading to a modulation of the action of the noradrenergic system.

FIGURE 1
The Serotonergic Diffuse Neuromodulatory System



The nine raphe nuclei, clustered along the midline of the brain stem, project axons that extensively innervate all levels of the CNS. Based on Bear, Connors & Paradiso (1996).

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The Noradrenergic Diffuse Modulatory System

Noradrenaline plays a large role as a neurotransmitter in the peripheral autonomic nervous system and as neuromodulator in the neurons of the small areas of the brain called the locus coeruleus. In the human each locus coeruleus has about 12,000 neurons. These axons leave the nucleus running in discrete noradrenergic bundles and give rise to many millions of nerve terminals (Rang, Dale & Ritter 1995). The axons fan out to enervate almost every part of the brain, including the cerebral cortex, midbrain, hypothalamus, thalamus, olfactory bulb, cerebellum and the spinal cord.

The locus coeruleus makes some of the most diffuse connections in the brain, with each neuron making more than 250,000 synapses. These synaptic contacts are not close and discrete, but rather the neurotransmitter is released at some distance from the target cells. This has given rise to the term "neural aerosol" for the noradrenergic system, with the locus coeruleus being the push-button (Rang, Dale & Ritter 1995).

This system seems to be involved in the regulation of blood pressure, attention, and the state of arousal. Activation of noradrenergic pathways can lead to an increased behavioral arousal, as well as affecting the sleep-wake cycle, learning and memory, anxiety, mood and pain perception.

The neurons of the locus coeruleus are most active when subjected to novel, unexpected and nonpainful sensory stimuli, and least active when a person is not vigilant or moving, just digesting a meal sedentarily. Therefore this system may participate in a general arousal of the brain during interesting events in the environment and function to increase brain responsiveness in the relay between sensory and motor systems and so make them more efficient. Psychology has a place in this part of the system's functioning: by influencing a subject's level of awareness, the locus coeruleus may play an important role in defining the ego, that is, the awareness of being a distinct person separate from all others (Snyder 1986).

The Serotonergic Diffuse Modulatory System

This system utilizes serotonin (5-hydroxytryptamine, or 5-HT) as its neuromodulator. Serotonin remains historically the most intimately involved with neuropsychopharmacology, and the system that utilizes it is the most extensive monoaminergic system in the brain stem (see Figure 1). These neurons outnumber both the noradrenergic and dopaminergic cells of the brain stem (Role & Kelly 1991) and are the first to differentiate during the development of the mammalian central nervous system (CNS).

The cell bodies lie within the nine large clusters in the pons and upper medulla, often called the raphe nuclei, which lie to either side of the midline. Each nucleus projects to different regions within the CNS; those rostrally situated

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project, via the median forebrain bundle, in a diffuse way to many parts of the cortex, hippocampus, limbic system and hypothalamus (although relatively few serotonergic fibers enervate the cerebellum). This arrangement is very similar to that of the noradrenergic neurons of the locus coeruleus.

Both the locus coeruleus and the raphe nuclei are part of the reticular activating formation. Many different functions are assigned to the serotonergic system of the reticular activating formation. Firstly, it is implicated in the modulation of segmental stretch reflexes and muscle tone, thereby providing information on proprioception. It is also involved in cardiorespiratory function by regulating the activity of the motor neurons that enervate the inspiratory and expiratory intercostal muscles. Also, by regulating the output of preganglionic neurons associated with vagus nerve enervation of the heart it can control both the acceleration and depression of the heart rate in response to appropriate stimuli.

The serotonergic system (that is, those of the more caudally situated raphe nuclei) are involved in the modulation of the sense of pain by influencing the flow of information through the dorsal horn of the spinal cord. Serotonin may also function to control the amount of food eaten, play a role in certain autonomic and endocrine functions such as the regulation of body temperature and blood pressure as well as sexual function (Rang, Dale & Ritter 1995). Finally, and perhaps most importantly for the subject of this essay, it is involved in controlling the level of brain, and therefore behavioral, arousal and different levels of awareness.

Jacobs and Trulson (1979) reported that the blockade of serotonin neurotransmission by either inhibition of its synthesis or receptors, or destruction of its neurons "consistently produces an animal that is hypersensitive to virtually all environmental stimuli and hyperactive in all situations." These animals are startled easily and quickly develop an avoidance response to stimuli that would normally not elicit this effect. An increase in the tonic activity of serotonergic neurons during waking arousal would serve to enhance motor neuron excitability via descending projections to the ventral horn of the spinal cord. A suppression of sensory input, conversely, would serve to screen out distracting sensory cues. It would thus appear that the normal organism's ability to disregard, or screen, irrelevant forms of sensory input requires an intact, fully functional, serotonergic system. Therefore it can be implied that the serotonergic system, through a general inhibitory action, serves to modulate an organism's awareness of its surroundings and thus its behavior, and so restrict its behavior within specific limits.

Serotonin is released in a wide variety of situations with an extreme regularity. In view of the extraordinarily widespread projections of the serotonergic system and the characteristically highly regulated pacemaker pattern of activity, a broad homeostatic function has been suggested. By exerting simultaneous modulatory effects on neuronal excitability in varied regions of the brain and spinal cord, the serotonergic system is in a strategic position to orchestrate complex sensory and motor patterns during varied behavioral states (Cooper, Bloom & Roth 1996).

The characteristically slow regularity of discharge (one or two action potentials, i.e., nerve signals, per second) leads to tonic neuronal function. An overall increase in the level of arousal and/or motor activity corresponds with the increase in activity of these cells, and vice versa. This regularity of serotonin release becomes increasingly less frequent as the organism sleeps until, during REM sleep (a state in which the mind is active with dreaming but in which tonic muscle activity is abolished) the cells stop firing completely. Lesions of the raphe nuclei or enforced depletion of serotonin prevents sleep in experimental animals, whereas micro-injection of serotonin at certain points of the brain stem induces sleep (Rang, Dale & Ritter 1995). This is thus the activity of serotonin during the sleep-wake cycle, although its mechanisms of action are not yet fully elucidated.

Serotonin Receptors

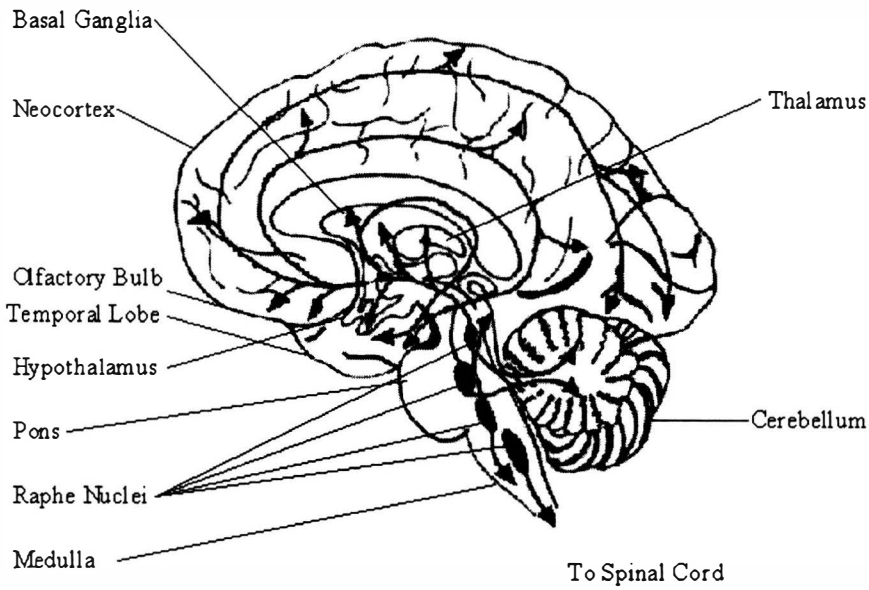
After release from the presynaptic serotonergic nerve terminal, the neuromodulator diffuses to a number of different receptors on the postsynaptic neuron. These receptors respond to the presence of serotonin by setting a cascade of events into motion inside the cell and so the signal is passed on between cells. Each receptor causes a slightly different cascade. The number of different receptor subtypes exists to allow the diverse cellular effects of serotonin. At least fifteen distinct types of serotonin receptor have been cloned from mammalian tissue, and at least six of these have been found in the brain. These have been named receptor 5-HT1A, 1C, 1D, 2A, 2C and 5-HT 3 respectively.

Under normal physiological conditions, serotonin does not preferentially act at any one of these receptor subtypes because the endogenous neurotransmitter is active at all. The effects produced by serotonin on a specific cell are dependent on the type of receptor present.

5-HT1A receptor activation leads to inhibition of the postsynaptic neuron, as does 5-HT1D and 5-HT3. 5-HT1C and 5-HT2 subtypes produce postsynaptic excitation (Egan et al. 1998; Fiorella, Rabin & Winter 1995; Gothert & Schlicker 1990). The cellular response of the postsynaptic neuron, that is an increase or decrease in frequency of action potential production, is determined by the sum of all the inputs (including those from other neurotransmitters acting on different receptors).

Serotonin receptor subtype 1D differs from the others in respect to its location. This receptor is found on the presynaptic serotonergic nerve terminal and functions as an autoreceptor—that is, it regulates the release of serotonin and so provides an automatic negative feedback. Release of serotonin will result in the activation of the 1D receptor

FIGURE 1
The Serotonergic Diffuse Neuromodulatory System



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5-HT1A receptor activation leads to inhibition of the postsynaptic neuron, as does 5-HT1D and 5-HT3. 5-HT1C and 5-HT2 subtypes produce postsynaptic excitation (Egan et al. 1998; Fiorella, Rabin & Winter 1995; Gothert & Schlicker 1990). The cellular response of the postsynaptic neuron, that is an increase or decrease in frequency of action potential production, is determined by the sum of all the inputs (including those from other neurotransmitters acting on different receptors).

Serotonin receptor subtype 1D differs from the others in respect to its location. This receptor is found on the presynaptic serotonergic nerve terminal and functions as an autoreceptor—that is, it regulates the release of serotonin and so provides an automatic negative feedback. Release of serotonin will result in the activation of the 1D receptor

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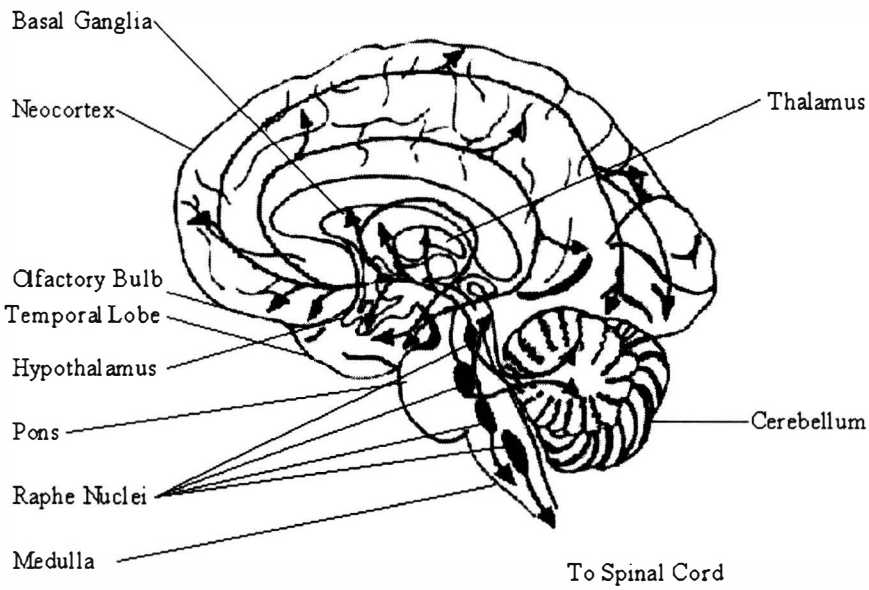
FIGURE 1
The Serotonergic Diffuse Neuromodulatory System



The nine raphe nuclei, clustered along the midline of the brain stem, project axons that extensively innervate all levels of the CNS. Based on Bear, Connors & Paradiso (1996).

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The Noradrenergic Diffuse Modulatory System

Noradrenaline plays a large role as a neurotransmitter in the peripheral autonomic nervous system and as neuromodulator in the neurons of the small areas of the brain called the locus coeruleus. In the human each locus coeruleus has about 12,000 neurons. These axons leave the nucleus running in discrete noradrenergic bundles and give rise to many millions of nerve terminals (Rang, Dale & Ritter 1995). The axons fan out to enervate almost every part of the brain, including the cerebral cortex, midbrain, hypothalamus, thalamus, olfactory bulb, cerebellum and the spinal cord.

The locus coeruleus makes some of the most diffuse connections in the brain, with each neuron making more than 250,000 synapses. These synaptic contacts are not close and discrete, but rather the neurotransmitter is released at some distance from the target cells. This has given rise to the term "neural aerosol" for the noradrenergic system, with the locus coeruleus being the push-button (Rang, Dale & Ritter 1995).

This system seems to be involved in the regulation of blood pressure, attention, and the state of arousal. Activation of noradrenergic pathways can lead to an increased behavioral arousal, as well as affecting the sleep-wake cycle, learning and memory, anxiety, mood and pain perception.

The neurons of the locus coeruleus are most active when subjected to novel, unexpected and nonpainful sensory stimuli, and least active when a person is not vigilant or moving, just digesting a meal sedentarily. Therefore this system may participate in a general arousal of the brain during interesting events in the environment and function to increase brain responsiveness in the relay between sensory and motor systems and so make them more efficient. Psychology has a place in this part of the system's functioning: by influencing a subject's level of awareness, the locus coeruleus may play an important role in defining the ego, that is, the awareness of being a distinct person separate from all others (Snyder 1986).

The Serotonergic Diffuse Modulatory System

This system utilizes serotonin (5-hydroxytryptamine, or 5-HT) as its neuromodulator. Serotonin remains historically the most intimately involved with neuropsychopharmacology, and the system that utilizes it is the most extensive monoaminergic system in the brain stem (see Figure 1). These neurons outnumber both the noradrenergic and dopaminergic cells of the brain stem (Role & Kelly 1991) and are the first to differentiate during the development of the mammalian central nervous system (CNS).

The cell bodies lie within the nine large clusters in the pons and upper medulla, often called the raphe nuclei, which lie to either side of the midline. Each nucleus projects to different regions within the CNS; those rostrally situated

project, via the median forebrain bundle, in a diffuse way to many parts of the cortex, hippocampus, limbic system and hypothalamus (although relatively few serotonergic fibers enervate the cerebellum). This arrangement is very similar to that of the noradrenergic neurons of the locus coeruleus.

Both the locus coeruleus and the raphe nuclei are part of the reticular activating formation. Many different functions are assigned to the serotonergic system of the reticular activating formation. Firstly, it is implicated in the modulation of segmental stretch reflexes and muscle tone, thereby providing information on proprioception. It is also involved in cardiorespiratory function by regulating the activity of the motor neurons that enervate the inspiratory and expiratory intercostal muscles. Also, by regulating the output of preganglionic neurons associated with vagus nerve enervation of the heart it can control both the acceleration and depression of the heart rate in response to appropriate stimuli.

The serotonergic system (that is, those of the more caudally situated raphe nuclei) are involved in the modulation of the sense of pain by influencing the flow of information through the dorsal horn of the spinal cord. Serotonin may also function to control the amount of food eaten, play a role in certain autonomic and endocrine functions such as the regulation of body temperature and blood pressure as well as sexual function (Rang, Dale & Ritter 1995). Finally, and perhaps most importantly for the subject of this essay, it is involved in controlling the level of brain, and therefore behavioral, arousal and different levels of awareness.

Jacobs and Trulson (1979) reported that the blockade of serotonin neurotransmission by either inhibition of its synthesis or receptors, or destruction of its neurons "consistently produces an animal that is hypersensitive to virtually all environmental stimuli and hyperactive in all situations." These animals are startled easily and quickly develop an avoidance response to stimuli that would normally not elicit this effect. An increase in the tonic activity of serotonergic neurons during waking arousal would serve to enhance motor neuron excitability via descending projections to the ventral horn of the spinal cord. A suppression of sensory input, conversely, would serve to screen out distracting sensory cues. It would thus appear that the normal organism's ability to disregard, or screen, irrelevant forms of sensory input requires an intact, fully functional, serotonergic system. Therefore it can be implied that the serotonergic system, through a general inhibitory action, serves to modulate an organism's awareness of its surroundings and thus its behavior, and so restrict its behavior within specific limits.

Serotonin is released in a wide variety of situations with an extreme regularity. In view of the extraordinarily widespread projections of the serotonergic system and the characteristically highly regulated pacemaker pattern of activity, a broad homeostatic function has been suggested. By exerting simultaneous modulatory effects on neuronal excitability in varied regions of the brain and spinal cord, the serotonergic system is in a strategic position to orchestrate complex sensory and motor patterns during varied behavioral states (Cooper, Bloom & Roth 1996).

The characteristically slow regularity of discharge (one or two action potentials, i.e., nerve signals, per second) leads to tonic neuronal function. An overall increase in the level of arousal and/or motor activity corresponds with the increase in activity of these cells, and vice versa. This regularity of serotonin release becomes increasingly less frequent as the organism sleeps until, during REM sleep (a state in which the mind is active with dreaming but in which tonic muscle activity is abolished) the cells stop firing completely. Lesions of the raphe nuclei or enforced depletion of serotonin prevents sleep in experimental animals, whereas micro-injection of serotonin at certain points of the brain stem induces sleep (Rang, Dale & Ritter 1995). This is thus the activity of serotonin during the sleep-wake cycle, although its mechanisms of action are not yet fully elucidated.

Serotonin Receptors

After release from the presynaptic serotonergic nerve terminal, the neuromodulator diffuses to a number of different receptors on the postsynaptic neuron. These receptors respond to the presence of serotonin by setting a cascade of events into motion inside the cell and so the signal is passed on between cells. Each receptor causes a slightly different cascade. The number of different receptor subtypes exists to allow the diverse cellular effects of serotonin. At least fifteen distinct types of serotonin receptor have been cloned from mammalian tissue, and at least six of these have been found in the brain. These have been named receptor 5-HT1A, 1C, 1D, 2A, 2C and 5-HT 3 respectively.

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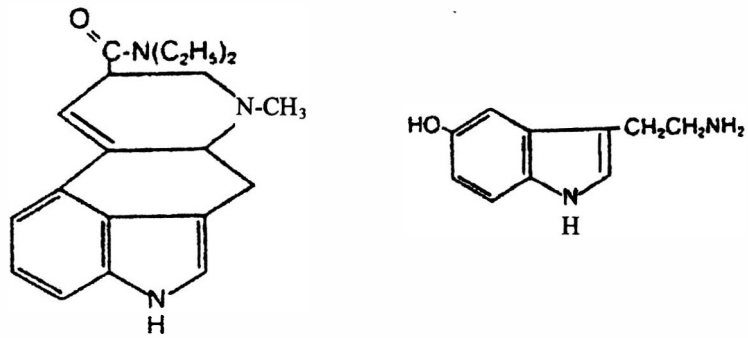
FIGURE 2
The Structures of Both LSD (Left) and the Neurotransmitter Serotonin (Right)



and so prevent an overaccumulation of serotonin at the synaptic cleft (Gothert & Schlicker 1990). Agonists of these receptors produce an inhibition of aggressive behavior and food intake in rodents. After the serotonin has performed its function it is disposed of in a number of ways.

Considering the functions of the noradrenergic and the serotonergic diffuse neuromodulatory systems seen here and the known effects of LSD, it would seem logical to assume that LSD works upon these systems. The next section discusses the present state of research into investigating the mechanism of LSD action.

THE ROLES OF THE NEUROMODULATORY SYSTEMS IN THE LSD EXPERIENCE

How can the large variety of distortions upon the mind and its perceptual awareness, taking place during an LSD session, be mediated through the neuromodulatory systems? The answer lies in the aforementioned fact that once a drug acts upon the extensive serotonergic diffuse neuromodulatory system it sets into motion a cascade of effects, each regulated by the serotonergic target neurons, with some of these themselves being part of a modulatory system.

Aghajanian and colleagues (1990) reported an indirect facilitatory effect mediated via the 5-HT receptors on neurons of the noradrenergic locus coeruleus. Systemic phenethylamine and indoleamine hallucinogens caused a decrease in the spontaneous activity but, paradoxically, a facilitation of activation by somatosensory stimulation of these neurons. Another way of saying this would be to say that LSD makes people hyperalert to their environment and their own body. Users have reported that the changes in perception and cognition may reflect more reality than they are normally attuned to in everyday consciousness.

The indirect effect on the locus coeruleus neurons is an enhancement of the acceleration of action potential firing under sensory stimulation such as sight, sound, smell, taste and tactile sensation (Aghajanian et al. 1990) although the drug does not cause the neurons to fire spontaneously in the absence of such stimulation. LSD may therefore be better described not as a hallucinogenic drug (an agent that causes a perception that takes place in the absence of an environmental stimulus) but as a psychedelic, i.e., mind-enhancing (although this word now has been used so much that it has secondary, if not tertiary meanings attached to it (Schultes & Hofmann 1973)).

The distortion of time may also be due to the indirect action of the serotonergic system upon the substantia nigra neural loop, which has been described recently as an "internal reference clock" (Wearden et al. 1997). This controversial theory implicates dopamine as playing a role in the sense of time; when the frontal cortex is flooded with an abnormal amount of sensory stimulation, it fails to acknowledge time's passage, and so the subject feels as if time has stopped or that each moment lasts for a much longer period than normal.

The alterations in sensory perception, sense of time and space, and sense of self are so different from everyday experience that they shed new light on the mechanism of normal functioning. Research into the actions of psychotomimetic drugs has already enriched our understanding of how the brain regulates behavior, although there is so much that is yet unknown.

MECHANISMS FOR THE ACTION OF LSD

Postulated Mechanisms

It is extremely difficult to track all of the individual cellular actions of an extremely potent drug like LSD and fit these effects together into a jigsaw-like puzzle to solve the question of how LSD works. Similar jigsaw puzzles lie just below the surface of every simple attempt to attribute the effects of a drug or a complex behavioral task to a single family of chemicals like serotonin. But a great deal of research has been carried out, and an outline of the mechanisms is beginning to show through the clouds of conflicting data.

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Much of the research into hallucinogenic drugs, including LSD, has focused on brain serotonin. Initial research found that LSD structurally resembled this neuromodulator (see Figure 2), which, as was shown previously, is implicated in the regulation of many systems known to be affected by LSD. Furthermore, the only reliable and consistent change common to all LSD-like hallucinogens (and the first to be noticed by researchers) was seen in the levels of serotonin in the brain, manifesting itself as changes in synthesis, release, catabolism, or receptor action (Jacobs 1983).

The major primary site of action of LSD is upon the serotonergic system, which sets into motion many of the brain's neuromodulatory systems. Thus the serotonergic system initiates a number of changes, whose elaboration generates the psychedelic experience (Jacobs 1987). The theory that LSD acts as an agonist of certain serotonin receptors seems the most likely from data already gathered.

The Presynaptic Hypothesis of LSD Action

The presynaptic hypothesis states that LSD and related hallucinogens act by directly suppressing the activity of serotonin neurons themselves, possibly by activating the serotonergic autoreceptors. Evidence that supports this includes the finding that the administration of the drug to animals increased the level of serotonin and decreased the level of its metabolites (Trulson & Jacobs 1979). Both LSD-type and mescaline-type hallucinogens administered intravenously depress the rate of firing of serotonergic neurons in the raphe nuclei (Trulson & Jacobs 1979). LSD desynchronizes the cortical EEG, producing an arousal pattern with an effect similar to that of electrical stimulation of the reticular formation. This EEG arousal effect of LSD is absent in *encéphé isolé* preparations where the cerebrum is isolated from the rest of the brain, suggesting that it facilitates the effect of sensory input on the reticular formation (Bowman & Rand 1980).

However there are also a number of experimental findings which cannot be explained by this theory. For example, the behavioral effects of LSD continue long after the suppression of neuronal activity. Also there is a build up of tolerance, resulting in no behavioral effects although the action potential frequency is still dramatically decreased (Trulson & Jacobs 1979). Furthermore, the prior destruction of the serotonergic neurons enhances, rather than diminishes, the effects of LSD.

Postsynaptic Hypothesis of LSD Action

This hypothesis proposes that LSD acts at postsynaptic receptors on the target neurons of the serotonergic system and not on the serotonin-containing neurons themselves. A large body of evidence supports this theory (Snyder 1986) and studies have shown that repeated administration of LSD decreases the availability of the 5-HT2 receptor subtype. Also, the correlation between the binding affinity of the phenethylamine (e.g., mescaline) and indoleamine (which includes LSD) hallucinogens at the 5-HT2 receptor and its human hallucinogenic potency is almost perfect (Glennon, Teitler & McKenny 1984). Evidence from studies with phenylisopropylamine hallucinogens indicates that the 5HT2A receptor is the likely target for the initiation of events leading to hallucinogenic activity associated with LSD and related drugs (Burris, Breeding & Sanders-Bush 1991). Another study showed that although 5HT2A agonist activity may be required, it is not in itself sufficient for LSD-like compounds to elicit hallucinations in humans (Penington & Fox 1994).

Although relatively few details of the action of LSD have been elucidated, the overall picture has been discovered. LSD causes a decrease in the inhibitory action of the serotonergic diffuse neuromodulatory system, but moreover uses the serotonin receptors to make its effects.

The Serotonergic System as a Somatosensory Filter

Aldous Huxley (1954) believed that over the course of evolution, the brain has been trained to screen out all those perceptions that do not directly aid our everyday survival. In his book, *The Doors of Perception*, he cites the theory of Bergson, who suggested that the function of the central nervous system and the sensory organs is mainly eliminative and not productive.

> Each person is at each moment capable of remembering all that has ever happened to him and of perceiving everything that is happening everywhere in the universe. The function of the brain and nervous system is to protect us from being overwhelmed and confused by this mass of largely useless and irrelevant knowledge, by shutting out most of what we should otherwise perceive or remember at any moment, and leaving only that very small and special selection which is likely to be practically useful (Huxley 1954).

To make biological survival possible, he goes on to say, the full consciousness has to be "funneled through the reducing valve of the brain and nervous system. What comes out at the other end is a measly trickle of the kind of consciousness which will help us to stay alive on the surface of this particular planet" (Huxley 1954).

It would seem, from the research discussed in this essay, that the serotonergic system acts as the filter which Huxley and Bergson describe. During an LSD experience this filter appears to be weakened and prevented from working to its normal, full capacity so that the brain is bombarded with an abnormal amount of somatosensory information.

Due to the similarities between the experience an LSD user may have and that of a trained mystic, the above statement may also be true for a nondrug-induced mystical experience. It could be the case that the mystic also opens the "reducing valve of the brain and nervous system." It could be shown experimentally that during a nondrug-induced mystical experience, the action of the serotonergic

system is modified such that its inhibitory action is reduced. This lack of inhibitory action would then certainly lead to increased activity in other areas of the brain (such as the cortex, basal ganglia and temporolimbic systems) that create the perceptual, sensory, cognitive and emotional distortions.

THE SEROTONERGIC SYSTEM AND THE NONDRUG-INDUCED MYSTICAL EXPERIENCE

Because of the close similarities between the experiences of the LSD user and that of the mystic, could the two share common mechanisms of action? Could it be the case that the nondrug-induced mystical experience works in the same way on the neural substrate? The mystics themselves would surely be loathe to hear that their experiences can be explained in purely materialistic ways, but this need not be the case. It is like understanding the way the eye receives and the brain processes visual information, which does not take away from the experience and importance of seeing.

Josephson (1988) thought that a mystic, or someone trying to follow a path of enlightenment, was following a special training program (like meditation) which enabled him to have closer contact with the Absolute. He likened this to an athlete undertaking special training programs to enable him to carry out greater physical feats; but whereas the athlete is training the muscles etc., the mystic is training the central nervous system. Could it be the case that the neural systems of a mystic, especially the diffuse neuromodulatory systems, are trained to be quantitatively different from those of a person who has never undergone such training?

Research could indeed be focused on seeing if these neurological differences between the mystic and nonmystic are different. The possibility exists that the filter of the serotonergic system is opened a little wider in the case of the mystic, perhaps by the production of endogenous hallucinogens that have been discovered such as the endogenous cannabinoid anandamide (Devane 1994), or by changes in other chemical metabolism (caused by strict training). The information gained from research into the experiences of the LSD user could be transferred and used as a model to investigate the mind of the mystic.

Although it is accepted by science that religious experience is based in the brain, the investigation of the neural ground of religious experience is hampered by the absence of a widely accepted animal correlate that would allow laboratory experimentation (Saver & Rabin 1997). However, recent research by Newberg, d'Aquila & Rause (2001) utilizing modern methods of brain imaging has captured the moment a person undergoing meditation achieves the sense of oneness and loss of self. Using Single Photon Emission Computed Tomography (SPECT) the researchers were able to determine increased attention, due to deep concentration of the mediator, but more importantly they found a significant lack of activity in the part of the parietal lobe that determines the self's body image and that which is self and nonself. These researchers have also shown that the limbic system is active during religious feelings of awe and deep significance.

In concert with d'Aquila and Newberg (1993), this article is intended as a call for research into the genesis of mystical experiences in terms of information that is already possessed and for empirical testing of theories and models of mysticism using modern, noninvasive techniques on the human subject. In this way research could answer the question that has stood for many years: do drug-induced experiences relate to the same state of reality as those induced by strict religious training? Many cultures that used, and still use, psychotomimetic substances in religious rituals would certainly think they do. But research along this avenue would certainly unearth a number of tentative truths that could be used in many fields and disciplines and especially help in the study of consciousness.

CONCLUSION

Clearly there are many similarities between the drug-induced mystical experience and the nondrug-induced experience. These similarities have been known for a long time. It is now time to discover how close this similarity really is and why they are similar. Intense research into the former has led to a wealth of knowledge about the mechanisms of such an experience. Although all of the details have certainly not yet been elucidated, a broad picture of how the drug works upon the diffuse neuromodulatory systems has been drawn. By its action upon the serotonergic receptors (both the pre- and postsynaptic nerve terminals) a long chain of events is set in motion to alter the perception of the individual. It is thought that the simultaneous inhibition of the serotonergic system itself and also the activation of serotonin receptors on postsynaptic terminals lead to the LSD experience.

However, although a wealth of first-hand experiences have been written over the millennia, little research has been conducted into the underlying mechanisms of the nondrug-induced, mystical experience. The mystical experience is important in itself not only because it can be considered as life changing, but also because it could lead to new knowledge about the consciousness and perception of an individual.

In this article the author has proposed that the two experiences detailed above could have similar mechanisms of action. Such a hypothesis could be tested using techniques similar to those used on human subjects in LSD experiments. Investigations into the state of the brain in general, and also the serotonergic system in particular, before, during, and after a mystical experience could be carried out, including measurements of related metabolites etc. It

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may be the case that the diffuse neuromodulatory systems of an experienced and advanced mystic are quantitatively different from those of the novice or pure beginner.

I also agree with previous proposals that the serotonergic system acts as the somatosensory "filter," working to eliminate all information not essential to survival. Further research is necessary to investigate the validity of this proposal, although many details point towards such an action for this system.

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