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Schizophrenia and LSD experiences : more similar than once thought

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ABSTRACT (100-200 WORDS): Schizophrenia and LSD have similarities not only in the neurotransmitters they activate specifically dopamine, serotonin, and glutamate; but, also, in hallucinations and psychosis. Because LSD use was criminalized in the 1960s, today limited research is being conducted on humans using LSD. If, in fact, LSD does "model psychosis", it should provide an understanding for the disorder schizophrenia; therefore, a research of existing literature was read and analyzed to see if this claim is true. Evidence found similarities in dopamine (D2) receptors, serotonin (5-HT 2A) receptors, and glutamate, but found differences in the types of hallucinations and psychosis LSD users and people with schizophrenia experience. In discussing the costs and benefits to conducting LSD research in humans, LSD should continue to be researched and further explored in animal models so one day it, again, can be used with humans.

Abstract

Schizophrenia and LSD have similarities not only in the neurotransmitters they activate specifically dopamine, serotonin, and glutamate; but, also, in hallucinations and psychosis. Because LSD use was criminalized in the 1960s, today limited research is being conducted on humans using LSD. If, in fact, LSD does "model psychosis", it should provide an understanding for the disorder schizophrenia; therefore, a research of existing literature was read and analyzed to see if this claim is true. Evidence found similarities in dopamine (D2) receptors, serotonin (5-HT 2A)receptors, and glutamate, but found differences in the types of hallucinations and psychosis LSD users and people with schizophrenia experience. In discussing the costs and benefits to conducting LSD research in humans, LSD should continue to be researched and further explored in animal models so one day it, again, can be used with humans.

Introduction

The terms schizophrenia and LSD have had much stigma attached to them by society. It is important to understand what schizophrenia, , and psychedelics, such as, LSD are before passing judgment on either. Once an understanding is established, treatment in the form of medication for schizophrenia and the use of LSD in psychotherapy should be explored. The effects on dopamine and serotonin in both schizophrenia and LSD use support further exploration and research. In addition to the neurotransmitters dopamine and serotonin, glutamate has recently been found to be affected by LSD use and people with schizophrenia. To understand how the neurotransmitters affect the brain, brain abnormalities in people with schizophrenia are examined, and physiological and psychological effects of LSD use on the brain is analyzed. Finally, the most obvious and most interesting aspects of similarities in schizophrenia and LSD use are hallucinations and psychosis. As early as the 1950s, LSD was observed to have hallucinogenic properties. It was because of these hallucinogenic properties that a comparison was made between schizophrenia and LSD. The question from that point on was, if there is some sort of connection between the effects of LSD on the brain and schizophrenia?

What Schizophrenia Is

Schizophrenia is a debilitating disorder that is usually associated with a loss in most areas of life functioning. The word schizophrenia has been called "one of the most sinister words in the language" (Torrey, 2001, p.1), the term being harsh and cruel, because of the stigma attached to it. It is a severe, chronic, and often disabling brain disease. Unlike other disorders, schizophrenia is a disorder of thought, not to be confused with multiple personality disorder (DID). Schizophrenia is a form of psychosis or loss of contact with reality. The term's literal

meaning is, "split mind." To more accurately describe schizophrenia, , it is a psychosis, an illness that causes severe mental problems that disrupt one's normal life including thought, speech, and behavior. Schizophrenia is the inability to distinguish reality from imagination; to a person with schizophrenia the voices and visions that they encounter are as real as another person.

A person with schizophrenia may think and communicate irrationally, jumping from one idea to another, repeating words or phases, jumble phrases, and create new words. People with schizophrenia tend to be suspicious and resentful believing their thoughts will be stolen, broadcast aloud, or replaced by new information from others seeking to control their behavior. It is also common for them to describe voices that speak directly to them or criticize their behavior (Torrey, 2001).

The History of Schizophrenia

Schizophrenia was first described by German psychiatrist Emil Kraepelin in the 1890s, but even today, approximately 110 years later it remains one of the most catastrophic and mysterious of all mental illnesses. Whether it brings the voices of heaven or hell, it causes what has to be the worst affliction a conscious being can suffer: the inability to tell what is real from what is imaginary (Begley, 2002). Schizophrenia is a psychotic disorder or a group of disorders that involves impaired thinking, emotions, and behavior. Schizophrenia was named by a Swiss doctor, Eugen Bleuler around 1908 to describe the splitting apart of mental functions. If untreated, schizophrenics will gradually withdraw from interaction with other people, and lose their ability to take care of personal needs and grooming ("Schizophrenia", 2000).

Different Types of Schizophrenia According to the DSM-IV-TR

According to the American Psychiatric Association's *Diagnostic and Statistical Manual 0/Mental Disorders-IV- TR* (2000) there are five subtypes of schizophrenia: paranoid;

disorganized; catatonic; undifferentiated; and residual. The main feature of paranoid schizophrenia is the combination of delusions (false beliefs), and auditory hallucinations (hearing voices). Individuals with paranoid schizophrenia have nearly normal emotions and cognitive functioning including reasoning, judgment, and memory. The delusions of people with paranoid schizophrenia typically involve delusions of persecution but may also reflect feelings of jealousy or excessive religiosity. The delusions are typically organized into a coherent framework.

Disorganized schizophrenia or hebephrenic schizophrenia is characterized by disorganized speech, thinking, and behavior combined with flat or inappropriate emotional responses to a situation. The patient may act inappropriately or withdraw socially to a profound extent.. Catatonic schizophrenia is identified by disturbances of movement that may include stiffness, trances, agitation, unusual posturing, and repetitive imitations of the movements or speech of other people.

Individuals with undifferentiated schizophrenia have both positive and negative symptoms associated with schizophrenia but do not meet the specific criteria for the paranoid, disorganized, or catatonic subtypes.

Lastly, to be labeled as a residual schizophrenic, an individual has to have at least one acute schizophrenic episode, but does not have strong positive psychotic symptoms, such as delusions and hallucinations. They may exhibit negative symptoms, such as withdrawal from others, or mild forms of positive symptoms.

LSD experiences seem to resemble paranoid schizophrenia. LSD experiences usually involve hallucinations, like those experienced in schizophrenia, , but whereas in LSD use, a person experiences pseudo-hallucinations, a person with schizophrenia experiences real hallucinations, as will be discussed later in the paper.

Positive and Negative Symptoms of Schizophrenia

Before a comparison of LSD experiences and schizophrenia can be discussed, it is important that one understands the symptoms of schizophrenia, as they play a role in the types of medication prescribed. The symptoms of schizophrenia are categorized into two categories: positive and negative. The positive symptoms of schizophrenia, which do not mean desirable symptoms, represent an excess or distorted version of normal functions; where as, negative symptoms, which do not mean undesirable symptoms, reflect a paucity or absence of normal functions (APA, 2000).

Positive symptoms include delusions; somatic; hallucinations, hearing voices (i.e., commenting on the patient's behavior); disorganized thought processes (e.g., thought disorders); and disorganized or catatonic behavior. A thought disorder, which is disorganized or irrational thinking, is the most important symptom of schizophrenia. Schizophrenics have difficulty arranging their thought logically. Disorganized thought processes can be seen in speech where a schizophrenic person rambles on in a way that makes no sense, combining words, and jumping from one subject to the next without any order whatsoever (APA, 2000).

Hallucinations are sensory based and can be seen in different forms such as auditory (which is the most common), perceptual, and visual. When a person hallucinates, they perceive stimuli that are not really there. A patient with schizophrenia can have more than one type of hallucination, such as, perceptual accompanied by visual, or visual accompanied by auditory. When a person has an auditory hallucination, they hear voices talking to them, telling them to do things; sometimes they scold the person, other times they just mutter meaningless things. An olfactory hallucination is often associated with the person's fear that someone is trying to kill them with poison gas (Carlson, 2002).

Delusions are thought based and are false beliefs. Like hallucinations, there are different types of delusions: such as, delusions of persecution; delusions of grandeur; and delusions of control.. Delusions of persecution are false beliefs that someone is plotting against them, the most common being the CIA and FBI. Delusions of grandeur are the false beliefs that the person is in a position of power, some believing that they are God. Delusions of control are the false beliefs that one is being controlled by others through the means of radio. In addition to delusions, of course, there is paranoia (Carlson,, 2002).

The first signs of schizophrenia usually appear as changes in behavior, but many people also show "negative" symptoms including decreased emotional arousal, mental activity, and inability to socialize (Grayson, 2001). The negative symptoms include: a lack of emotional response (affective flattening); poverty of speech or alogia; and absence of volition or will. The negative symptoms are more difficult for doctors to evaluate than the positive symptoms. Social withdrawal and social skill deficits are common negative symptoms of schizophrenia. Negative symptoms seem to be caused by brain damage where positive symptoms appear to involve excessive activity in some neural circuits that include dopamine.

What Psychedelics Are

Psychedelics are chemical compounds that alter cortical functions, including cognition, perception, and mood. The term psychedelic literally means "mind manifesting" (Grof,, 1994). They are drugs that sometimes induce hallucinations, separating people, who use them, from reality. Many terms have been used to describe these types of drugs. The term "hallucinogen" has been used because these agents can, in high doses, bring on hallucinations. The term "psychotomimetic" is another formal term used because of the alleged ability of these drugs to mimic psychoses or induce psychotic states. The term "psychedelic", invented by Humphrey

Osmond, is most commonly used to imply that these agents all have the ability to alter sensory perception, and is the term that is preferred for the focus of this paper. A psychedelic drug is defined as an agent that causes alterations in perception, cognition, and mood (Julien, 2001).

During the 1960s and 1970s, and continuing today, many people used psychedelics to enhance perception, expand reality, promote personal awareness, and stimulate or induce comprehension of the spiritual or supernatural. These drugs were used because of their ability to heighten awareness of sensory input, often accompanied by both an enhanced sense of clarity and diminished control over what is experienced (Julien, 2001).

What LSD Is

Lysergic Acid Diethylamide (LSD) was first synthesized by Albert Hofmann in 1938 and was initially developed as a circulatory and respiratory stimulant. LSD is the most potent hallucinogen known to man: it is 100 times more potent than psilocybin and psilocin; and 4,000 times more potent than mescaline (DEA, 2004). Small doses of LSD induce remarkable psychological changes in a person, enhancing self-awareness and altering internal reality, while causing few alterations in the physiology of the body. According to the DEA (2004), the dosage level that will produce a hallucinogenic effect for users of LSD is generally considered to be 25 micrograms. LSD is usually taken orally, with usual doses range from 25 micrograms to more than 300 micrograms. LSD is a classified as a Schedule I drug under the Controlled Substance Act of 1970. LSD is said to meet the three criteria of Schedule I drugs: it is considered to have a high potential for abuse; it has no legitimate medical use in treatment; and there is a lack of accepted safety for its use under medical supervision (DEA, 2004). Despite these criteria, LSD was once thought to be helpful in psychotherapy, and research continues in animal models to further understand this hallucinogenic drug.

LSD is often added to other substances, such as squares of paper, the backs of stamps, or sugar cubes, and is absorbed within about 60 minutes, reaching peak blood levels in about 3 hours. LSD diffuses easily into the brain and the largest amounts of LSD in the body can be found in the liver, where the drug is metabolized before it is excreted (Julien, 2001).

It was on April 16, 1943, when Hofmann was working with LSD, that he thinks the drug was accidentally absorbed through his skin, and found the full effects of the drug that went unnoticed for five years. Three days later, on April 19, 1943, Hofmann went on the bicycle ride that changed the world of psychedelics forever. He intentionally took LSD and experienced many great hallucinations. In the 1940s, LSD began to gain interest when it was thought to be a potential treatment for schizophrenia. It was because of LSD's structural similarity to serotonin, and its similarity, in effect, to certain aspects of psychosis that LSD was used as a research tool in studies of mental illness (DEA, 2004).

Sandoz Laboratories, LSD's sole producer, originally marketed LSD as a psychiatric "cure-all" curing everything from schizophrenia to alcoholism (DEA, 2004). Six years after Albert Hofmann's accidental discovery of the effects of LSD, in 1949, the first North American study of LSD on humans took place. In the 1950s, LSD was distributed to scientists for research purposes. It found that the effects of LSD constituted a model for psychosis, which would give insight into the biochemical and physiological processes of schizophrenia Sandoz Laboratories even suggested that psychiatrists take LSD themselves in order to gain insight into what their patients were experiencing and to see first hand what it is like to have schizophrenia (DEA, 2004).

An LSD induced psychedelic experience usually occurs in three stages:

1. The somatic phase occurs after absorption of the drug and consists of CNS stimulation and autonomic changes that are predominantly sympathomimetic in

nature.

2. The sensory (or perceptual) phase is characterized by sensory distortions and pseudo-hallucinations, which are the effects desired by the drug user.
3. The psychic phase signals a maximum drug effect, which changes mood, disruption of thought processes, altered perception of time, depersonalization, true hallucinations, and psychotic episodes. Experiencing this phase is considered a 'bad trip'. (Julien, 2001, p. 347).

In the 1960s and 1970s, LSD was the drug of choice until negative publicity surfaced on "bad trips". "Bad trips" can be characterized as psychotic psychological trauma that is associated with the use of LSD. In addition to "bad trips", flashbacks, uncontrolled recurrences of LSD experiences, had negative publicity attached to it as well (DEA, 2004). However, in addition to "bad trips", a user of LSD can experience a good trip in which clarity and understand of one's self can be reached. When using LSD, in order to avoid experiencing a bad trip, the setting should be one in which there is comfort and no danger. Experiencing good trips may be the reason why a person would continue to use LSD. In order to understand how LSD use and schizophrenia are related, the medical treatment of schizophrenia will be discussed.

Medical Treatment for Schizophrenia

The medical treatment of schizophrenia is discussed because certain medications target specific neurotransmitters that are activated in people with schizophrenia and people who use LSD. By understanding what these medications do to these neurotransmitters, an understanding of what schizophrenia and LSD use does to these neurotransmitters can be established as well. Discovered in the 1950s neuroleptic medications provided a significant advance in the treatment for persons suffering from schizophrenia. Neuroleptics work by affecting positive symptoms, presumably through their effects on neurotransmitters involving dopamine and serotonin. Antipsychotic medications fall into two classes: the older dopamine receptor antagonists, or DAs, and the newer serotonin-dopamine antagonists, or atypical antipsychotics. Traditional

antipsychotic drugs are highly correlated with the ability to completely block dopamine receptors. In addition to blocking dopamine D2 receptors, the phenothiazines (traditional antipsychotics) also block a number other receptors, among them serotonin. (Julien, 2001).

Atypical antipsychotics, on the other hand, block dopamine and act on serotonin and glutamate neurons. The atypical antipsychotics include: molindone (Moban), which is a structurally unique medication that resembles the neurotransmitter serotonin; lozapine (Loxitane), which binds to both dopamine (D2 and D4) receptors and serotoninergic (5-HT2) receptors; primozide (Orap) which also blocks dopamine receptors; risperidone (Risperdal), which acts as a potent inhibitor of both D2 and 5-HT 2; olanzapine (Zyprexa), in vivo, completely blocks 5-HT 2 receptors at low doses and D2 blockade is increased with increasing doses; sertindole (Serlect), which is primarily a 5-HT2 antagonist, binding to serotonin 5-HT2 and dopamine D2 receptors and has a unique dual action of blocking both D2 and 5-HT 2; quetiapine (Seroquel), which blocks both D2 and 5-HT_2 receptors, but has a greater affinity for 5-HT2 receptors than for D2 receptors and reduces the expression of glutamate receptor mRNA; ziprasidone (Zeldox), which blocks both D2 and 5-HT 2 receptors and is an agonist at 5-HT 1A receptors, but is unclear what contribution the 5-HT 1A action contributes to its pharmacologic actions at the present time; and amisulpride, which is highly selective for blocking both D2 and both D3 receptors in the limbic system, but not the basal ganglia. There is increased dopamine activity in the mesolimbic system, which both LSD use and schizophrenia affect, at low doses of amisulpride and antipsychotic actions at high doses (Julien,, 2001).

Unlike all the other atypical antipsychotics, amisulpride does not bind to serotonin 5-HT_2 receptors. Finally, the most well known atypical antipsychotic, clozapine (Clozaril) has a high binding affinity for dopamine D4, serotonin, 5-HTIC, and serotonin, 5-HT2' and has a low rate of

binding to D2 receptors and has a greater blockade of 5-HT 2. Clozapine specifically causes 5HT receptor blockage in the meso limbic and nucleus accumbens which are sites that schizophrenia and LSD both affect; both causing a decrease in serotonin levels (Julien, 2001).

LSD Psychotherapy

Much of the early LSD research in the 1950s was influenced by the "model-psychosis" approach (Grof, 1994). During the 1950s, LSD was used for treatment in addiction; giving a patient a dose of LSD and having them talk about their experiences and thoughts. Two types of psychotherapy could be conducted using LSD; psychedelic or psycholytic. Psychedelic psychotherapy is categorized as giving a person an overwhelming positive experience using LSD in one session. Psycholytic LSD psychotherapy resembles traditional psychotherapy in which doses of LSD are taken over a number of months or years. In the 1950s, LSD psychotherapy was a useful method to stop addiction, so why not use LSD on Schizophrenia? According to Nichols (2004), it is possible that LSD use can be helpful in treating alcoholism, substance abuse, and some psychiatric disorders, such as schizophrenia. In the 1940s through the 1970s, extensive research was done on LSD. From 1950 to approximately 1965, research on LSD and other hallucinogens produced over 1,000 papers, dozen of books, half a dozen international conferences, and LSD was prescribed as a treatment for more than 40,000 patients (DEA, 2004).

LSD used in psychotherapy was discontinued for a variety of reasons, but mainly due to the media. LSD psychotherapy was no longer looked at through the existing scientific research, but rather through the media's claims of unsupervised self-experimentation, , and the spread of unscientific rumors about LSD causing chromosome damage (Grof, 1994).

LSD psychotherapy has already been used with adult who suffered from schizophrenia. According to Masters and Houston (1970), psychedelics have been used with adults with

schizophrenia to help condense the psychosis temporarily and help predict the course of schizophrenia. Though used in psychotherapy, the use of LSD was a risk in the 1960s and 1970s, and was considered too great for paranoids, outpatient psychotics and prepsychotics; those predisposed to schizophrenia. According to Grof (1994), because of the potency of LSD and the fact that effects were seen in such small doses, speculations surfaced about the biochemical nature of endogenous psychoses, particularly schizophrenia. LSD use produced changes in perception, emotion, ideation, and behavior that closely resembled those effects seen in a person with schizophrenia. It was because of this similarity in the effects of LSD on a person and the symptoms seen in schizophrenia, that researchers in the 1950s believed if the metabolism of the body could create small quantities of abnormal substances identical with or similar to LSD, then schizophrenia would not primarily be a mental disorder, rather, just "autointoxications" of the organism caused by shifts in body chemistry.

The possibility of simulating schizophrenic symptoms in normal patients, to model psychosis, looked promising to finally understand schizophrenia, but when criminalization of LSD use was passed, research in humans using LSD became a challenge, one that still exists today. In the years following 1957, after the term "psychedelic" was coined, effort was directed to giving an accurate description of LSD experiences and the assessment of similarities and differences between the psychedelic state induced by LSD and schizophrenia. Through research it was found that LSD-induced states had many specific characteristics separating it from schizophrenia, such as the pseudo hallucinations that LSD use creates.

LSD was often regarded as a psychotomimetic, because of its ability to mimic psychosis. For a therapist, the use of psychedelics gave the therapist an idea of what it was like to be psychotic. The problem using animals in LSD research is they can't verbalize the distortions of

perception, alterations in affective state, and overt visual hallucinations induced by LSD. It makes it harder for humans to understand exactly what these animals are going through making assessment of these effects nearly impossible (Winter, Eckler, & Rabin, 2004).

The benefits of using LSD in psychotherapy may include a better understanding of schizophrenia. As discussed later, schizophrenia and LSD have similarities in serotonin and dopamine receptors that are affected by the use of LSD and the disorder of schizophrenia. With such similarities, it is possible that LSD would help the world understand one of the most confusing disorders that exists.

The problems that arise with the use of LSD, first and foremost, is the legal status of the drug. LSD use was criminalized in the 1960s because of the move from the laboratories to the streets, however, LSD used in studies with animal models today are approved by the government. Secondly: is the ethical issue that arises; is it ethical to administer LSD to people with schizophrenia? To make a good experiment, a control group would be needed; and if a control participant ends up with a disposition for schizophrenia, , the use of LSD could onset the disorder. According to Torrey (2001), there is no evidence that LSD use causes schizophrenia in patients that are not already in the process of developing the disorder. Therefore, a person who is predisposed for developing schizophrenia or has the disorder, but has yet to show symptoms, can be affected by LSD use in which the drug use can initiate the disorder. With all these considerations, it seems that the use of LSD in order to help understand schizophrenia is a long way off.

Information About Dopamine

Considering dopamine is affected in both the brains of people with schizophrenia and those who choose to use LSD, it is helpful to understand what dopamine is and where in the

brain it can be found. Dopamine is considered a catecholamine and is a neurotransmitter produced from the amino acid tyrosine that can be found in some peripheral nerve fibers and many of the CNS (central nervous system) neurons, particularly in the substantia nigra,, midbrain, and hypothalamus (perrine, 1996). The substantia nigra is a region of the tegmentum; ventral part of the midbrain that includes gray matter and the substantia nigra,, which contain. neurons that communicate with the caudate nucleus in the basal ganglia. The midbrain, is the central of portion of the brain that contains the tectum and the tegmentum. The hypothalamus is a group of nuclei of the diencephalon located underneath the thalamus (Carlson, 2002).

Dopamine is generally excitatory, but may be inhibitory at some sights. D_4, a subtype of dopamine, is highly localized in both the meso limbic system; a system of dopaminergic neurons beginning in the tegmental area and ending in the prefrontal cortex, and prefrontal cortex; a region of the frontal lobe involved in formulating plans and strategies, which are found primarily in the structures of the basal ganglia (a group of subcortical nuclei in the telencephalon and caudate nucleus). Schizophrenia and LSD use are thought to affect D2 receptors in the mesolimbic pathway which will be discussed in more detail in the following paragraphs (Carlson, 2002; Julien, 2001). Many theories of why schizophrenia occurs have been proposed among the most famous is the dopamine hypothesis.

What Causes Schizophrenia?

The Dopamine Hypothesis

The dopamine hypothesis is probably the most well known hypothesis related to schizophrenia. It basically says there is too much dopamine (DA) in the brain, particularly the mesolimbic system (Chemist & Druggist,, 2002) thus the goal is to decrease DA neurotransmission. Evidence to support this theory is that with the use of amphetamines and

LSD, a person who does not have schizophrenia can experience hallucinations and delusions as seen with drug use. Drugs that act on dopamine agonists, produce the positive symptoms of schizophrenia and block the reuptake of dopamine, and L-Dopa; the antecedent of the catecholamines and dopamine agonist,, which stimulates the synthesis of dopamine (Carlson, 2002).

Evidence to support this theory is that antipsychotic drugs, neuroleptics, which are effective in the treatment of schizophrenia, , interfere with the release of dopamine, thus they are dopamine antagonists (inhibits or blocks the effects of dopamine), and partially block the brain's use of dopamine. Also the drugs that increase dopamine transmission, dopamine agonists (facilitates the effects of dopamine) such as L-dopa,, may produce schizophrenic symptoms in some people. Support for this theory comes from the fact that stimulating dopamine release produces symptoms of psychosis and all antipsychotic drugs block dopamine receptors. LSD is thought to act as an agonist on D2 receptors in the mesolimbic pathway, affecting the nucleus accumbens and amygdala. It is thought that schizophrenia is caused by "over-activity of dopamine synapses, probably those in the mesolimbic pathway, which projects from the ventral tegmental area to the nucleus accumbens and amygdala" (Carlson, 2002, p. 452). The nucleus accumbens is a nucleus of the basal forebrain that receives dopamine-secreting terminal buttons from neurons in the ventral tegmental area. The amygdala is part of the limbic system and is located in the interior of the temporal lobe (Carlson, 2002). However, antipsychotics block up to 95 per cent of dopamine receptors but do not completely remove symptoms. It is because other receptor systems are involved, such as serotonin and glutamate, that one medication will not "cure" the disorder (Schizophrenia, , 2002). Because of the hypersensitivity to dopamine, treatment includes chemicals that block the receptors for the dopamine signals decreasing the

amounts of dopamine in the brain. However, when dopamine is decreased, symptoms of Parkinson's disease occur, since there is less dopamine.

The most important systems of dopaminergic neurons begin in the midbrain nuclei: in the substantia nigra and the ventral tegmental area. It is believed that the mesolimbic pathway, which begins in the ventral tegmental area and ends in the nucleus accumbens and amygdala, is involved in the symptoms of schizophrenia. Drugs that act as agonists in the dopaminergic synapses in the nucleus accumbens, such as LSD, reinforce behavior, and if large doses are taken, they produce positive symptoms of schizophrenia. It is assumed the euphoria that most schizophrenics' experience at the beginning of a schizophrenic episode is caused by the hyperactivity of dopaminergic neurons involved in reinforcement. The disorganized thinking that a schizophrenic experiences may be caused by disorganized attentional processes; the indiscriminate activity of the dopaminergic synapses in the nucleus accumbens makes it hard for the patient to follow an orderly, rational thought pattern. Paranoid delusions may be caused by increased activity of the dopaminergic input to the amygdale. It is thought that the nucleus accumbens and the amygdala which are involved in the functions might be related to the positive symptoms of schizophrenia (Carlson, 2002). Similar findings in the hippocampus suggest that there may be a larger development defect that leads to both positive (limbic system) and negative (prefrontal cortex) symptoms in schizophrenia (Julien, 1998).

Dopamine's Role in the Brains of LSD Users

Research has suggested there is a complex interaction between the serotoninergic system and the dopaminergic system, with LSD acting as a partial agonist, (facilitates the effects of dopamine), at dopaminergic receptors specifically D2 receptors (Julien, 2001; Nichols, & Sanders-Bush,2002). As stated before, drugs that act as dopamine agonist, create the positive

symptoms of schizophrenia. LSD has a high attraction for dopamine receptors and has been shown to act as an agonist at these receptors. The effects LSD has on dopamine are similar to those effects that schizophrenia has on dopamine. In order to produce hallucinations, which are a positive symptom of schizophrenia, , there is an excess of dopamine in the brain. LSD, which acts as an agonist, also creates an excess of dopamine in the brains of LSD users, just as schizophrenia does. LSD acts as an agonist,, specifically at D2 receptors, like in schizophrenia. Based on this information, antipsychotics that act as antagonists in schizophrenia; block dopaminergic receptors and lower the amount of dopamine in the brain. Since LSD increases levels of dopamine in the meso limbic system, as in schizophrenia, , antipsychotic medication, , if used, would block the dopaminergic receptors and low the levels of dopamine in the brain. (Carlson, 2002).

Information About Serotonin

Again, considering that serotonin levels are affected in both the brains of people with schizophrenia and those who choose to use LSD, it is helpful to understand what serotonin is, where serotonin is located in the brain, and understanding the different subtypes of serotonin. Serotonin is a neurotransmitter generally found in the central nervous system (CNS), and is generally inhibitory, which means serotonin decreases activities of motor neurons. Serotonin plays a role in the regulation of mood, eating, sleeping, arousal, and in pain. The cell bodies of serotonergic neurons are found in nine clusters, with the most important clusters of serotonin found in the dorsal and medial raphe nuclei.. Raphe literally means "seam" or "crease", and most of the raphe nuclei are found at or near the midline of the brain stem. The dorsal and medial raphe nuclei have axons that propel to the cerebral cortex, which covers the cerebral hemispheres that make up the cerebrum and contain the limbic system and basal ganglion. Neurons found in

the dorsal raphe innervate the basal ganglion, which is a group of subcortical nuclei found in the caudate nucleus among other neural structures. Serotonin is found to playa role in activating behavior. When the raphe nucleus, the site of most of the brains serotonergic neurons, is stimulated, , it causes locomotion and cortical arousal (Carlson, 2002).

There are four 5-HT receptor subtypes: 5-HTt,, 5-HT2, 5-HT3, and 5-HT4 receptors. These four receptors are further broken down into subtypes of each receptor. 5-HT 2aare postsynaptic receptors mainly located in the frontal cortex, the frontal lobe, and caudate nucleus, the part of the basal ganglion, and are likely to be related to psychotic phenomena in schizophrenia and possibly in LSD use (Iqbal, & Praag, 1995).

The Role of Serotonin in the Brains of People with Schizophrenia

The concept of a 5HT deficit in the brains of people with schizophrenia was offered as one of the first explanations for the causes of schizophrenia. It was through the discovery of 2-bromo-LSD, a 5HT antagonist, not having hallucinogenic properties, that the initial serotonin hypothesis of schizophrenia was disconfirmed. It was around this time as well that LSD was found to have some agonistic properties, in addition to its antagonist properties. In addition to these setbacks, LSD was soon after banned from human experimentation and antipsychotics were discovered showing these medications blocked dopaminergic transmission, placing the dopamine hypothesis as the most well known cause of schizophrenia. It is in recent years that the relationship between schizophrenia and serotonin has again been looked at to explain what role serotonin has in schizophrenia (Iqbal, & Praag, 1995).

In research conducted by Iqbal and Praag (1995), the authors critically discussed the evidence for and against a link between serotonergic defects and schizophrenia. They reached three conclusions about the link between serotonin and schizophrenia.

> (1) Interruption of certain serotonergic circuits represents an antipsychotic principle. (2) Tentative evidence suggests the involvement of serotonergic dysfunctions in the pathogenesis of schizophrenic psychoses. (3) It is not yet known whether serotonergic lesions contribute directly to the occurrence of schizophrenic psychopathology or via alterations in the dopaminergic system. (Iqbal, & Praag, 1995, p. 11).

The role of serotonin in schizophrenia can be seen by the therapeutic effects that atypical antipsychotics have on controlling symptoms of schizophrenia Atypical antipsychotics have inhibiting effects on 5-HT receptor subtypes, specifically 5-HT 2A,thus increasing the low levels of serotonin. LSD acts as an agonist and lowers the levels of serotonin, creating symptoms that resemble those of schizophrenia. Atypical antipsychotics that block 5-HT 2Areceptors have antipsychotic effects, which control the psychotic symptoms in schizophrenia, , meaning there is a connection between 5-HT$_{2A}$and schizophrenia (Iqbal, & Praag, 1995).

Serotonin's Role in the Brains of LSD Users

Most psychedelic drugs structurally resemble one of four neurotransmitters: acetylcholine, two catecholamines (norepinephrine and dopamine), and serotonin. These structural similarities lead to three classes for categorizing psychedelic drugs: anticholingeric; catecholamine-like; and serotonin-like. LSD is categorized as a serotonin-like psychedelic drug. LSD is considered a serotonin-like psychedelic drug, because it has structural resemblances to serotonin. LSD exerts its psychedelic actions through alterations of serotonin synapses in the brain, although it is structurally much more complex than serotonin, however, the basic similarity of the two molecules is apparent (Julien, 2001).

As early as the 1960s, LSD use marked alterations in serotonin levels in the brain (Halpern, 1996). During the 1980s, it was noted that LSD promoted marked alterations in brain serotonin. Psychedelic actions are probably full agonists at postsynaptic serotonin 5-HT2A receptors, which would account for their LSD-like effects. During the 1990s, it became clear that

LSD was a serotonin receptor agonist; the dopamine-like psychedelics functioned ultimately as indirectly acting serotonin agonists. Today the focus of attention is on a subgroup of the 5-HT2 receptors, specifically the 5-HT 2Areceptor. LSD can therefore be safely classified as mixed dopamine and serotonin agonists, with 5-HT2Areceptors involved. There have been a number of claims about how LSD affects serotonin, the most common being a binding site for LSD on the 5-HT2Areceptor and that LSD has an agonist action at 5-HT2Areceptor (Julien, 2001).

Because there is evidence that LSD lowers serotonin levels in the brain, a question could be asked: why does serotonin not induce psychotomimetic effects? Also, psychotomimetic effects are not seen after any treatment that increases serotonin availability at its postsynaptic receptors. One speculation is the process by which LSD manifests alterations of mood, perception, and thought is through the pontine (dorsal) raphe; neurons that innervate the basal ganglion, a group of subcortical nuclei found in the caudate nucleus, a major center of serotonin activity. This site serves as a filtering station for incoming sensory stimuli, thus, does not cause schizophrenia-like symptoms when not on LSD or any other drug that would lower serotonin levels (Carlson, 2002; Julien, 2001). Nichols and Sanders-Bush (2002), found that 5-HT2A receptor levels were about three times higher in the prefrontal cortex than in either the hippocampus or midbrain (Nichols, & Sanders-Bush, 2002). It is this researcher's understanding that if serotonin 5-HT 2Areceptor levels are higher in the prefrontal cortex after administration of LSD, that LSD affects serotonin levels in the prefrontal cortex more so than in other serotonergic site regions in the brain.

Serotonin Similarities Between Schizophrenia and LSD Use

In the 1950s, a hypothesis stated LSD psychosis and schizophrenic psychoses are related to dysfunction in the central serotonergic systems (Nichols, 2004). Based on research since this

time, similarities have been found between some subtypes of 5-HT in people with schizophrenia and LSD users. Research has shown LSD use and schizophrenia have similarities especially in 5-HT 2A levels. In LSD use, LSD can act as both an agonist and antagonist for 5-HT 2A; whereas antipsychotics are used to block agonize serotonin in the brains of people with schizophrenia. Yet the question remains: if LSD affects serotonin, then why does serotonin itself not produce "psychotic-like" states?

Glutamate in LSD and Schizophrenia

According to Svenningsson et al. (2003), dopaminergic agonists, serotonergic agonists (such as LSD), and glutamatergic antagonists all induce psychotomimetic states in experimental animals that resemble symptoms of schizophrenia as seen in humans. Glutamate, an amino acid, is the most important excitatory neurotransmitter in the brain, and is found in the CNS (Carlson, 2002). Stimulation of 5-HT 2A receptors by drugs, such as LSD, result in the release of glutamate. According to Winter, Eckler, and Rabin (2004), by using a stimulus control model of the hallucinogenic effects of LSD, it provides support for the hypothesis that glutamate release is a factor in hallucinogenesis by both 5-HT2A agonists and NMDA (a neurotransmitter) antagonists. They also found that *mGlu2/3* (glutamate) agonists act on presynaptic autoreceptors on glutamatergic neurons to suppress glutamate release and that glutamate release is an essential component of the actions of LSD. Glutamate receptors control sodium and calcium channels in the brain, and have both excitatory and inhibitory affects in the brain. Because glutamate has five different binding sites depending on where it binds and how little or much of the glutamate binds, it can produce a number of different behaviors and experiences. If glutamate levels get too high at one site, they can cause convulsions. In another site, high doses of glutamate can cause difficulty in walking and talking, unconsciousness, coma, and even death (Carlson, 2002).

Glutamate is not only affected by LSD use, but it also plays a role in schizophrenia. Another hypothesis for schizophrenia has to do with glutamate hypofunction. This hypothesis states: there is an excessive release of glutamate (excitatory neurotransmitter) in the frontal cortex, which damages cortical neurons and triggers the deterioration of the mind of a person with schizophrenia experiences. Where excessive dopamine in the brain can explain the positive symptoms of schizophrenia, a deficiency of glutamate can explain the cognitive dysfunction and negative symptoms of schizophrenia (Julien, 2001).

As more studies begin to look at glutamate'S role in LSD use and schizophrenia, it is possible glutamate may help us understand more about schizophrenia and the psychological effects that take place in the minds of people on LSD. Since glutamate release is a factor is hallucinations by 5·HT2A agonists, this would suggest a possible connection with schizophrenia and, perhaps, glutamate's role in LSD use similar to the role it plays in schizophrenia, if any.

Brain Abnormalities in the Brains of People with Schizophrenia

There is deterioration of several parts of the brain for people with schizophrenia, however, to date, there have been no observed brain abnormalities in the brains of LSD users. Abnormalities are seen in the medial temporal lobes affecting the hippocampus, amygdala, the parahippocampal gyrus, the lateral temporal cortex, prefrontal cortex, and medial diencephalons for people with schizophrenia. The severity of the brain abnormalities are correlated with the severity of the schizophrenic's negative symptoms (Carlson, 2001). There are also abnormalities of the eye; attention is drawn to the rapid eye movement. In recent years, findings show the left side of the brain is primarily affected in schizophrenia more often than the right side (Torrey, 2001). Based on monozygotic twin studies, MRI scans showed schizophrenics have larger third

and lateral ventricles, smaller anterior hippocampi, and reduced total volume of gray matter in the left temporal lobe (Carlson, 2002).

Despite no brain alterations, there are physiological and psychological effects seen in LSD users. Subtle physiological changes occur in LSD users. A person who takes LSD may experience a slight increase in body temperature; dilation of the pupils; slightly increased heart rate and blood pressure; increased levels of glucose in the blood; and dizziness, drowsiness, nausea; and other effects that rarely interfere with the psychedelic experience of the drug. LSD is known to possess a low level of toxicity; the effective dose is only 50 micrograms while the lethal does is about 14,000 microgram, which makes the drug a remarkable non-lethal compound. This calculation does not, however, include any fatal accidents or suicides that occur when a person is intoxicated by LSD (Julien, 2001).

In schizophrenia, there are brain abnormalities that prove this disorder is not only a mystery but is also a true disorder. One difference seen in the brain of a person with schizophrenia is the ventricles are enlarged, meaning that more CSF (cerebral spinal fluid) can flow through the ventricles leading to a decrease in the volume of the brain. There is less gray matter in the brain of a people with schizophrenia. The ventricles are asymmetrical, and in some brains of people with schizophrenia, the brain is smaller than the brain of a person who does not have schizophrenia. There are also differences in the frontal cortex. The hypothesis is that there are fewer connections between the frontal cortex and other brain regions.

Three areas may be particularly important in schizophrenia: the prefrontal cortex, the cerebellum, and the thalamus. The dysfunctions that occur in schizophrenia are almost certainly not limited to these three areas; other cortical regions that are connected with the thalamus and cerebellum are also important like the hippocampus and temporal lobes (Andreasen, 1999). The

frontal lobe may be less active in people with schizophrenia. This may account for the negative symptoms of schizophrenia and may produce effects in other areas of the brain that are responsible for the positive symptoms.

> The thalamus is of great theoretical importance for schizophrenia because of its crucial central placement, its dense interconnectivity, and its potential role as a "filter" or "gate." Postmortem studies provided the earliest empirical evidence for thalamic abnormalities in schizophrenia. Magnetic resonance imaging studies have given additional support, as have PET studies (Andreasen, 1999).

Evidence shows during hallucinations, structures involved in memory, (e.g., hippocampus), in emotions, (e.g., amygdale), and in consciousness, (e.g., thalamus), all become active.

Users of LSD in high enough doses, should expect to experience alterations in perception, thinking, emotion, arousal, and self-image. To users, time may appear to be slowed or distorted and sensory input intensifies. Visual alterations are the most characteristic phenomenon of LSD use and include seeing colored lights, distorted images, and vivid images and shapes. To someone on LSD, colors may be heard and sounds may even be seen (Julien, 2001).

Suicide, Schizophrenia, and LSD

Neither schizophrenia nor LSD use itself is life-threatening, but the effects of both are what can cause someone to take their own life. Sometimes, especially with chronic schizophrenia, a person becomes so tormented by their hallucinations and their inability to distinguish reality from fantasy, that suicide seems like the only choice (Torrey, 2001). With LSD use, even if the user knows the hallucinations they are experiencing are temporary, the effects are so great they feel the only way to escape the psychosis is to take their own life.

In paranoid schizophrenia, according to the DSM-IV -TR (2000), although paranoid schizophrenics can function at a higher level than other subtypes of schizophrenia, they are at

risk for suicidal or violent behavior due to their delusions. A person with schizophrenia may begin to believe that others want him or her dead and therefore commit suicide to fulfill the supposed wishes of others.

Hallucinations and Psychosis in LSD and Schizophrenia

The hallucinogenic properties of LSD have especially been examined through research, which discloses the hallucinations experienced both by LSD users and people with schizophrenia. Hallucinogenic drugs, such as LSD, have profound effects on humans including hallucinations and detachment from reality. These remarkable behavioral effects have many similarities to the debilitating symptoms of neuropsychiatric disorders, such as schizophrenia (Nichols, & Sanders-Bush, 2002).

It was in 1954, LSD was first observed to have hallucinogenic properties, and a comparison was made to the psychotic symptoms of schizophrenia (Iqbal, & Praag, 1995). Certain aspects of the behavior elicited by acute doses of LSD closely resemble symptoms of mental disorders, such as schizophrenia (Nichols, & Sanders-Bush, 2002). In the mind of someone with schizophrenia, , all reality becomes distorted.

Where people with schizophrenia usually experience hallucinations and psychosis; people using LSD may experience hallucinations and psychosis. During hallucinations, structures involved in memory, (e.g., hippocampus); in emotions, (e.g., amygdale); and in consciousness, (e.g., thalamus) all become active. There are differences, though, in the types of hallucinations and the duration of the psychosis that LSD users and people with schizophrenia experience. Many reactions of LSD resemble the symptoms of the psychosis experienced by people with schizophrenia. "The relationship between drug induced states, schizophrenia, and other unusual forms of consciousness is still an open question and an important one, but even

those who continue to use the term psychotomimetic now agree that the drug effect is not the same as schizophrenia or any other naturally occurring psychosis" (Grinspoon, , & Bakalar, 1997).

Auditory hallucinations are the most common type of hallucinations experienced by people with schizophrenia. Visual alterations can be experienced more by LSD users. Psychosis is a mental disorder so severe it involves a loss of contact with reality (perrine, 1996). Like schizophrenia, , LSD can produce a psychotic state or loss of contact with reality. A person using LSD experiences illusory phenomena and perceptual distortions, similar to what a person with schizophrenia experiences with hallucinations.

LSD users may experience post-hallucinogenic perceptual disorder. This is when a LSD user has flashbacks of persistent flashbacks, which may occur weeks, months, or even years after the last use of the drug. Post-hallucinogenic perceptual disorder is characterized by the periodic hallucinogenic imagery months or even years after the immediate effect of LSD has worn off (Julien,2001). There is controversy surrounding post-hallucinogenic perceptual disorder whether or not, such a disorder does exist.. Because LSD reduces a person's normal ability to control emotional reactions, drug-induced alterations in perception can become so intense that they overwhelm one's ability to cope. A person with schizophrenia experiences real hallucinations in which the images or voices are always there. With LSD use, the user knows they took a drug and the hallucinations they experience are temporary, or what can be called pseudo-hallucinations.

Unpleasant experiences with LSD are relatively frequent and may involve an uncontrollable drift into confusion, dissociative reactions, acute panic reactions, a reliving of earlier traumatic experiences, or an acute psychotic hospitalization. This is not the same as in the

case of schizophrenia, , in which psychosis is persistent and ongoing (Julien,, 2001). Despite these negative effects of LSD use, if LSD is done in the right setting and in the right state of mind, the user will experience a favorable outcome. LSD can be used for self..discovery; being able to look within oneself and experience a "rebirth" of oneself (Orof, 1994).

There is the idea that psychosis that occurs in LSD users happens only to those who are predisposed for schizophrenia; in this case, the psychosis may never go away. In a study conducted by Frosch, et al. (1965, cited in Grinspoon, & Bakalar, 1997), 12 of27 patients were admitted to a hospital with LSD reactions. Of the 12, there were seven panic reactions, three flashbacks,, and three with psychosis. Of the 12 patients,, at least five were judged to have been psychotic before LSD use and the three patients, that needed prolonged hospitalization, all had chronic schizophrenia before taking the LSD (Grinspoon, & Bakalar, 1997). Frosch later examined another sample, this time with 27 patients, admitted with LSD reactions and found that eleven had panic reactions, eight had flashbacks, and eight experienced psychosis. Of the eight who experienced psychosis, five had been psychotic before they took the drug, the other three had been seriously disturbed, but probably not psychotic (Grinspoon, & Bakalar, 1997).

In 1972, Dewhurst and Hatrick (cited in Grinspoon, & Bakalar, 1997) conducted a study that shed light on the idea of prolonged adverse psychedelic reactions. The authors studied 16 hospitalized patients, that were experiencing: philosophical, delusions, visual hallucinations, and affective and neurotic symptoms. The symptoms experienced, though resembling classical psychosis, were more likely a prolonged and intensified bad trip if not a flashback.. It is because of the presence of insight or the ability to test reality and the predominance of visual hallucinations, they are not characterized by psychosis: therefore showing LSD psychosis and

psychosis experienced by people with schizophrenia are in fact different (Grinspoon, & Bakalar, 1997).

In experiments conducted by Barr and Langs (cited in Grinspoon, & Bakalar, 1997), the authors concluded the most likely candidates for adverse reactions to LSD are those who are schizoid and are predisposed for having schizophrenia. Even though most psychosis experienced after drug use is a result of a predisposition for schizophrenia, , some studies in the 1970s suggested that psychedelic drugs occasionally produce psychosis in a person with little previous mental disturbance. Bowers (1972, cited in Grinspoon, & Bakalar, 1997) found LSD can cause prolonged psychotic reactions even in people not vulnerable to psychosis (Grinspoon, & Bakalar, 1997). Based on these conflicts, more research needs to be conducted to determine if LSD use can potentially create psychosis in all users or if psychosis only occurs in those already predisposed to schizophrenia.

Conclusion

Despite the criminalization of LSD in the 60s, research still continues to look for a connection between LSD and schizophrenia. Research has shown activation of both dopamine and serotonin, specifically D2 and 5-HT 2A, in both people with schizophrenia and people who use LSD. More recently, within the last five years, research is looking at glutamate which is thought to be affected by LSD use and schizophrenia. LSD is found to stimulate 5-HT 2Aand increase glutamate levels.

Other than neurotransmitters, medications, such as antipsychotics and atypical antipsychotics, work mainly as agonists on D2 and 5-HT2Areceptors. Activation of these receptors, beyond normal activation levels, are thought to create the positive symptoms of schizophrenia (e.g., hallucinations, delusions), and create the hallucinations experienced by LSD

users. In addition to medication, LSD psychotherapy can help to understand how schizophrenia works, due to the fact LSD causes symptoms, in part, that resemble those seen in people with schizophrenia. Though there are differences between schizophrenia and LSD use on the brain, similarities, no matter how small, can lead to a better understanding of each.

To date, there are no brain abnormalities as a result of LSD use, yet, it is important to know this to understand how LSD use differs from someone with schizophrenia, , where abnormalities in many regions of the brain can be seen. Finally, the reason that most people link schizophrenia and LSD together is because of the hallucinations and psychosis a person with schizophrenia experiences; and the hallucinations and psychosis that an LSD user may experience.

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