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Dark Classics in Chemical Neuroscience: Lysergic Acid Diethylamide (LSD)

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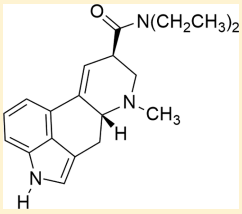
ABSTRACT: Lysergic acid diethylamide (LSD) is one of the most potent psychoactive agents known, producing dramatic alterations of consciousness after submilligram (≥20 μg) oral doses. Following the accidental discovery of its potent psychoactive effects in 1943, it was supplied by Sandoz Laboratories as an experimental drug that might be useful as an adjunct for psychotherapy, or to give psychiatrists insight into the mental processes in their patients. The finding of serotonin in the mammalian brain in 1953, and its structural resemblance to LSD, quickly led to ideas that serotonin in the brain might be involved in mental disorders, initiating rapid research interest in the neurochemistry of serotonin. LSD proved to be physiologically very safe and nonaddictive, with a very low incidence of adverse events when used in controlled experiments. Widely hailed by psychiatry as a breakthrough in the 1950s and early 1960s, clinical research with LSD ended by about 1970, when it was formally placed into Schedule 1 of the Controlled Substances Act of 1970 following its growing popularity as a recreational drug. Within the past 5 years, clinical research with LSD has begun in Europe, but there has been none in the United States. LSD is proving to be a powerful tool to help understand brain dynamics when combined with modern brain imaging methods. It remains to be seen whether therapeutic value for LSD can be confirmed in controlled clinical trials, but promising results have been obtained in small pilot trials of depression, anxiety, and addictions using psilocybin, a related psychedelic molecule.



KEYWORDS: *LSD, lysergic acid diethylamide, Albert Hofmann, hallucinogen, psychedelic, psychotherapy, consciousness, brain dynamics, mystical experiences, 5-HT$_{2A}$ receptor*

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INTRODUCTION

LSD is the acronym for Lysergsäure Diäthylamid, the German name for lysergic acid diethylamide. LSD is a unique molecule and has a continuing and rather remarkable history. It was first synthesized in 1938 by Swiss natural products chemist Dr. Albert Hofmann, working in the Sandoz laboratories in Basle, Switzerland. He synthesized it as the twenty-fifth substance in a series of lysergic acid derivatives designed to explore possible therapeutic uses of ergot derivatives.[1]

Hofmann reports that he had planned the synthesis of LSD with the intention of obtaining a circulatory and respiratory stimulant because of its structural similarity to nicotinic acid diethylamide (Coramine), a known analeptic agent. He apparently reasoned that an ergot derivative that incorporated a diethylamide function might be a potent analeptic agent. Testing of LSD-25 in the pharmacological department of Sandoz revealed that it had a strong contractile effect on the uterus. The research report also noted, in passing, that the mice became restless after administration of the new drug. Nevertheless, the new substance aroused no special interest in the Sandoz pharmacologists and physicians so there was no further testing. There things remained until April 16, 1943. As Hofmann has reported:[1,2]

The following description of this incident comes from the report that Hofmann sent on April 22, 1943 to the Head of the Pharmaceutical Department at that time, Professor Arthur Stoll:

> *"A peculiar presentiment—the feeling that this substance could possess properties other than those established in the first investigations—induced me, five years after the first synthesis, to produce LSD-25 once again so that a sample could be given to the pharmacological department for further tests. This was quite unusual; experimental substances, as a rule, were definitely stricken from the research program if once found to be lacking in pharmacological interest. In the final step of the synthesis, during the purification and crystallization of lysergic acid diethylamide in the form of a tartrate (tartaric acid salt), I was interrupted in my work by unusual sensations."*
>
> *"Last Friday, April 16, 1943 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 some two hours this condition faded away."*

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The extraordinary nature of this mental disturbance led Hofmann to suspect that some exogenous compound might be responsible. He had been using column chromatography to separate the lysergic acid diethylamide from the epimeric isolysergic acid diethylamide that resulted from the synthesis and had prepared the crystalline water-soluble tartrate salt of lysergic acid diethylamide. He concluded that perhaps the lysergic acid diethylamide that he had been working with that afternoon somehow could have been responsible.

To test that hypothesis, he decided to conduct a self-experiment with the LSD tartrate. He started with the lowest dose that might have been expected to have any effect, i.e., 0.25 mg. The notes in his laboratory journal read as follows:[2]

"April 19, 1943: Preparation of an 0.5% aqueous solution of D-lysergic acid diethylamide tartrate.

4:20 P.M.: 0.5 cc (0.25 mg LSD) ingested orally. The solution is tasteless.

4:50 P.M.: no trace of any effect.

5:00 P.M.: slight dizziness, unrest, difficulty in concentration, visual disturbances, marked desire to laugh..."

The laboratory notes discontinue at that point, and he reports that the last words were written only with great difficulty.[2] He asked his laboratory assistant to accompany him home, as he believed that he might suffer a repetition of the disturbance of the previous Friday. While cycling home, however, he experienced much stronger symptoms than the first time. He reports he had great difficulty speaking coherently, his field of vision swayed before him, and objects appeared distorted, like images in curved mirrors. He had the impression of being unable to move from the spot, although afterward his assistant told him that they had cycled at a good pace. Once at home, his physician was called.

By the time the doctor arrived the peak of the crisis had passed. Hofmann recalls[1] that the most outstanding symptoms included: vertigo, visual disturbances; the faces of those around him appeared as grotesque, colored masks; marked motoric unrest, alternating with paralysis; an intermittent heavy feeling in the head, limbs and the entire body, as if they were filled with lead; a dry, constricted sensation in the throat; and a feeling of choking. He had a clear recognition of his condition, in which state he sometimes observed, in the manner of an independent, neutral observer, that he shouted half insanely or babbled incoherent words. Occasionally, he says he felt as if he was out of his body.

This self-experiment showed that LSD-25 behaved as an extraordinarily potent psychoactive substance. It also seemed very significant to Hofmann that he could remember the LSD experience in great detail. That meant to him that his "conscious recording function" was not interrupted, even at the peak of the LSD experience. For the entire duration of the experiment, Hofmann says he had even been aware of participating in an experiment. "Everything was experienced as completely real, as alarming reality; alarming, because the picture of the other, familiar everyday reality was still fully preserved in the memory for comparison."[1]

When Hofmann wrote the report to Professor Stoll about his extraordinary experience with LSD-25, he also sent a copy to the director of the pharmacology department, Professor Ernst Rothlin. Not surprisingly, their first reaction was rather incredulous. A telephone call quickly came; Professor Stoll asked him: "Are you certain you made no mistake in the weighing? Is the stated dose really correct?" Professor Rothlin also called, asking the same question. Hofmann was certain of that point; he had carried out the weighing and dosage himself. They could be excused for their doubt because at that time no other substance was known that could exert a psychoactive effect after a submilligram dose.

Professor Rothlin and two of his colleagues then repeated Hofmann's experiment, albeit with only one-third of the dose. The effects were still extremely impressive, and validated Hofmann's observations. Subsequent experiments on volunteer colleagues at the Sandoz research laboratories confirmed the extraordinary potency of LSD and showed that an oral dose of 0.03−0.05 mg of LSD tartrate was effective in humans.

Hofmann pondered how this substance could have gotten into his body; I personally asked him that question at a meeting more than 20 years ago. He honestly did not know. He was certainly well aware of the toxic nature of ergot alkaloids, and has reported that he always maintained very neat work habits. The question still lacks a good answer, however, as LSD tartrate would not be expected to penetrate the skin. It does seem possible, however, that his skin might have contacted a solution of the free base during column chromatography, a process he had just completed for the purification of the LSD, and the free base could have been absorbed through his skin. Swiss chemists of that era, although meticulously neat, rarely, if ever, wore protective gloves.

In 1947, the first scientific study was published on the effects of LSD.[3] (Unless stated otherwise, all references to LSD in this review are to the tartrate of LSD.) In this extensive clinical report, LSD was administered a total of 49 times; 29 times to 16 normal subjects, and 20 times to six treatment-resistant schizophrenics. Most doses given to normals were 30 μg, but doses varied for the schizophrenics, ranging from 20 to 130 μg. The treatment protocol was the same for schizophrenics as for normals. The report included an extensive table with demographics for the normal subjects, along with their responses to LSD. There was a comprehensive analysis of effects, with very detailed descriptions for five of the normal subjects. In general, the effects started around 30 min after oral drug administration, reaching a peak about 1.5 h later, maintaining that level of effect for about 2 h, with the earliest return to normal at about 8 h.

In normal subjects, LSD generally produced feelings of euphoria, visual patterns, feeling young, beautiful, and reborn. Subjects also reported being more sensitive to music. There was less of an effect in schizophrenics than in normals and the authors noted that none of the schizophrenics were made worse by the LSD. They also made the first observation of rapid tolerance to the effects of LSD when they administered 100 μg to one subject, and then gave the same dose the next day, which had no effect. Considering all the doses they administered, they concluded that 30 μg was effective, although some subjects received 100 or 130 μg. The investigators drew parallels to the similarity of effects produced by mescaline, but emphasized that the very high potency was unique to LSD. They could draw no conclusions about the therapeutic effectiveness of LSD, but strongly encouraged further clinical research. They also suggested that a radioactive form of LSD might be useful in animal experiments, possibly to determine where in the brain the LSD effects originated.

Gion Condrau, working at the same hospital, reported observations from LSD treatment of seven additional normal subjects and 30 treatment-resistant psychiatric patients, with similar results.[4] Again, psychiatric patients proved more resistant than normals to the psychological effects of LSD, even at doses of 100 μg. They suggested that LSD might eventually find use for experimental induction of psychotic states. In a 1949 summary that included both clinical reports, Stoll reported[5] that LSD had by then been administered a total of 240 times; 40 administrations to 20 healthy volunteers and 200 administrations to

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36 patients with psychiatric illness, mostly schizophrenia. In 40 administrations of LSD to the healthy volunteers, euphoria and visual effects were noted. Psychological effects of LSD in psychiatric patients were subtle, and not pronounced.

The first Sandoz LSD was brought to the United States for testing in 1949 by Boston psychiatrist Max Rinkel and Los Angeles psychiatrist Nick Bercel.[6,7] Subsequently, Sandoz made LSD-25 available to research institutes and physicians as an experimental drug, giving it the trade name Delysid (D-Lysergsäure-Diäthylamid), a name that Hofmann had proposed.

It is instructive to read the drug label that accompanied investigational samples of Sandoz LSD:[8]

Indications and dosage

(a) Analytical psychotherapy, to elicit release of repressed material and provide mental relaxation, particularly in anxiety states and obsessional neuroses. The initial dose is 25 μg (1/4 of an ampule or 1 tablet). This dose is increased at each treatment by 25 μg until the optimum dose (usually between 50 and 200 μg) is found. The individual treatments are best given at intervals of 1 week.

(b) Experimental studies on the nature of psychoses: By taking Delysid himself, the psychiatrist is able to gain an insight into the world of ideas and sensations of mental patients. Delysid can also be used to induce model psychoses of short duration in normal subjects, thus facilitating studies on the pathogenesis of mental disease. In normal subjects, doses of 25 to 75 μg are generally sufficient to produce a hallucinatory psychosis (on an average 1 μg/kg body weight). In certain forms of psychosis and in chronic alcoholism, higher doses are necessary (2 to 4 μg/kg body weight).

There were two different approaches to psychotherapy with LSD: "psycholytic" and "psychedelic".[9,10] The psycholytic approach was more commonly employed in Europe, whereas psychedelic therapy had its origin in Canada. Psycholytic therapy involved administering 50−200 μg of LSD to patients once or twice a week just prior to psychotherapy. The dosage was individually adjusted so that the patient remained oriented and in communication with the therapist, and able to realize the therapeutic character of the situation. The patient lay on a couch in a darkened room with one attendant (usually a specially trained nurse) and was occasionally visited by the physician. The drug-induced experience played only a supporting role in a primarily conventional psychoanalytical treatment, because low dose LSD was believed to facilitate the recall of unconscious material. Typically, treatment continued for months to years, with between 10 and 50 psycholytic sessions being conducted.[10]

A second treatment approach was known as psychedelic therapy, and was originally developed primarily for the treatment of alcoholics, addicts, and those with personality problems.[11] This procedure made induction of mystic/religious experiences the basis of its therapeutic action. It used a quasi-religious preparation of the patient, higher doses, specific surroundings, and music to favor evocation of deep-reaching insights and religious experiences. With this approach, patients underwent daily psychotherapy for weeks prior to a single high dose administration of LSD, typically 400 μg or more, to ensure an overwhelming transcendental experience. The drug session might typically last from 12 to 16 h.

One other type of therapy from that era also should be mentioned. In 1962, Eric Kast, an Assistant Professor of Medicine and Psychiatry in Chicago, compared the analgesic action of dihydromorphinone and meperidine (Demerol) with LSD in a double-blind study with 50 gravely ill patients.[12,13] When compared with LSD, both opioid drugs were inferior in their analgesic action. In addition to pain relief, however, it was noted that the patients given LSD displayed a peculiar disregard for the gravity of their situations, and talked freely about their impending death with an affect considered inappropriate in Western culture, but most beneficial to their own psychic states. This perspective on their disease often persisted for periods longer than the analgesic action.

This early finding served as the impetus for the use of psychedelic therapy in cancer patients at The Maryland Psychiatric Research Center in Baltimore, MD from 1963 until 1976, where 700 patients were treated, mostly with LSD, to relieve their anxiety and depression. Their results were generally considered encouraging. This institution was the last to stop its clinical research with LSD and related drugs.[14]

Early on, LSD was widely hailed as a new breakthrough for psychiatry. By 1963, more than 1000 papers had been published on the effects of LSD in approximately 40,000 humans.[15] In 1965 there were more than 200 research projects in the United States using LSD or other psychedelics in human subjects. Unfortunately, despite such high enthusiasm, the relatively rudimentary clinical instruments, lack of controls, and poor follow-up used in those early clinical studies often led to inconclusive results, and it was difficult to assess whether LSD had any real therapeutic value. For example, one popular treatment of the time was the use of LSD in a program of therapy for alcoholism. Until very recently, it had been widely assumed that this therapy was ineffective. Yet in a recent meta-analysis in a pooled analysis of six early randomized controlled clinical trials, Krebs and Johansen found that a single dose of LSD had a significant beneficial effect on alcohol misuse at the first reported follow-up assessment, which ranged from 1 to 12 months after discharge from each treatment program.[16] They report that the treatment effect of LSD on alcohol misuse was seen at 2 to 3 months and at 6 months, but was not statistically significant at 12 months post-treatment. They note that the effectiveness of a single dose of LSD compared well with the effectiveness of daily naltrexone, acamprosate, or disulfiram.

With the passage of the Controlled Substances Act (CSA) of 1970, LSD was placed in the most restrictive category of drugs, Schedule 1, where it was classified to have a high potential for abuse, no recognized medical use, and no safety when used by a physician. There were other factors that contributed to the end of clinical research with LSD, but 1970 is considered the date when LSD research essentially stopped. Bonson[17] has written a fascinating regulatory history of LSD that goes into some detail regarding the end of approved LSD research. With that, clinical research with LSD stopped for nearly four decades.

Renewed Clinical Research Interest in LSD. Liechti[18] has reviewed all of the clinical studies that employed LSD in the last 25 years. He has summarized the general findings of those studies, but the most recent results will be briefly highlighted in this review. Generally, in a controlled setting, LSD acutely induces bliss, audiovisual synesthesia, altered meaning of perceptions, derealization, depersonalization, and mystical experiences. In several studies, blockade of the subjective effects of LSD following oral administration of the 5-HT_{2A}-selective antagonist ketanserin demonstrated that the subjective effects of LSD were mediated by the 5-HT_{2A} receptor. LSD also increased feelings of closeness to others, openness, trust, and suggestibility, impaired the recognition of sad and fearful faces, reduced left amygdala reactivity to fearful faces, and enhanced emotional empathy. Interestingly, LSD increased the emotional response to music and the meaning of music, providing a scientific basis for the widespread subjective impression that psychedelics improve appreciation of music.

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Resting-state functional magnetic resonance imaging studies have shown that LSD acutely reduces the integrity of functional brain networks and increases connectivity between networks that normally are more dissociated. LSD increases functional thalamocortical connectivity and functional connectivity of the primary visual cortex with other brain areas, an effect that is correlated with subjective hallucinations. Acutely, LSD-induced global increases in brain entropy were associated with greater trait openness 14 days later. In patients with anxiety associated with life-threatening disease, anxiety was reduced for two months after two doses of LSD.

There has been only one recent clinical trial of LSD where a potential therapeutic outcome was the goal. Gasser et al.[19] reported on a double-blind, randomized, active placebo-controlled pilot study to examine safety and efficacy of LSD-assisted psychotherapy in 12 patients with anxiety associated with life-threatening diseases. The participants received either 200 μg of LSD (free base) (n = 8) or 20 μg of LSD as an active placebo, with an open-label crossover to 200 μg of LSD after the initial blinded treatment was unmasked (n = 4). At 2 month follow-up, positive trends were found on the State-Trait Anxiety Inventory (STAI) in reductions in trait anxiety (p = 0.033) with an effect size of 1.1, and state anxiety was significantly reduced (p = 0.021), with an effect size of 1.2. No acute or chronic adverse effects persisted beyond the day after treatment. They conclude that LSD can reduce anxiety when administered in a methodologically rigorous medically supervised psychotherapeutic setting.

In a one year follow up to their study, Gasser et al.[20] reported that the significant benefits measured with the STAI were sustained over a 12 month period. From a Qualitative Content Analysis (QCA), participants consistently reported insightful, cathartic, and interpersonal experiences, accompanied by a reduction in anxiety (77.8%) and an increase in quality of life (66.7%). Evaluations of subjective experiences suggested facilitated access to emotions, confrontation of previously unknown anxieties, worries, resources, and intense emotional peak experiences as major psychological working mechanisms. The experiences led to a restructuring of the person's emotional trust, situational understanding, habits, and worldview.

Although there has been only one recent therapeutic trial of LSD, the drug now has been used in a variety of clinical research studies designed to understand how LSD affects emotion or affect, or to understand the basic brain pharmacology/physiology that leads to its unique effects. For example, clinical applications of psychedelics usually include listening to music during the acute drug effects. Indeed, music is thought to be an important element in psychedelic-assisted psychotherapy, yet no one had provided a scientific basis for this belief. In the past few years, however, research has been carried out to study the effect of music on the altered state of consciousness produced by LSD or other psychedelics. In the first of these studies, Kaelen et al.[21] sought to test the hypothesis that music-evoked emotions are enhanced under LSD. Ten healthy volunteers were recruited who listened to five different tracks of instrumental music during each of two study days, a placebo day followed by an LSD day, separated by 5−7 days. The dosage of LSD (free base) varied among participants: one received 40 μg, two 50 μg, six 70 μg, and one 80 μg. Subjective ratings completed after each music track included a visual analogue scale (VAS) and the nine-item Geneva Emotional Music Scale (GEMS-9). Based on results using these instruments, the authors were able to demonstrate that LSD enhances the emotional response to music, especially the emotions "wonder," "transcendence," "power," and "tenderness." The authors conclude that their "findings reinforce the long-held belief that psychedelics enhance music-evoked emotion, and provide tentative and indirect support for the notion that this effect can be harnessed in the context of psychedelic-assisted psychotherapy."

In a second study, Kaelen et al.[22] investigated the interaction between LSD and music-listening on eyes-closed imagery using a placebo-controlled, functional magnetic resonance imaging (fMRI) approach. Twelve healthy volunteers received 75 μg of intravenously administered LSD free base, and on a separate occasion, placebo, before being scanned under eyes-closed resting conditions with and without music-listening. The parahippocampal cortex (PHC) had previously been linked with music-evoked emotion, the action of psychedelics, and mental imagery. Their imaging analyses thus focused on changes in the connectivity profile of the PHC. Results revealed increased functional connectivity between the PHC-visual cortex (VC) and PHC to VC information flow in the interaction between music and LSD. This latter result positively correlated with ratings of enhanced eyes-closed visual imagery, including imagery of an autobiographical nature. Their findings suggest a possible mechanism by which LSD works in combination with music to enhance certain subjective experiences that may be useful in a therapeutic context.

Barrett et al.[23] analyzed the blood oxygen level-dependent (BOLD) signal during music listening in 25 healthy adults after administration of placebo, LSD (100 μg free base), and LSD following pretreatment with the $5HT_{2A}$ antagonist ketanserin. They carried out a secondary analysis of data published by Preller et al.[24] Tonality-tracking analysis of BOLD data revealed that $5HT_{2A}$ receptor signaling alters the neural response to music in brain regions supporting basic and higher-level musical and auditory processing, and areas involved in memory, emotion, and self-referential processing. Their finding suggests a critical role of $5HT_{2A}$ receptor signaling in the neural tracking of dynamic tonal structure in music, as well as in supporting the associated increases in emotionality, connectedness, and meaningfulness in response to music that are commonly observed after LSD.

The effect of LSD on suggestibility also has recently been studied. Carhart-Harris et al.[25] administered intravenous LSD (40−80 μg; free base) to 10 healthy volunteers in a within-subject placebo-controlled design. The investigators assessed suggestibility and cued mental imagery using the Creative Imagination Scale (CIS) and a mental imagery test (MIT). CIS and MIT items were split into two versions (A and B), balanced for "efficacy" (i.e., A ≈ B), and counterbalanced across conditions (i.e., 50% completed version "A" under LSD). The MIT and CIS were given at 110 and 140 min, respectively, postinfusion, corresponding to the peak drug effects. Volunteers gave significantly higher ratings for the CIS (p = 0.018), but not the MIT (p = 0.11), after LSD, compared to placebo. The magnitude of suggestibility enhancement under LSD was positively correlated with baseline trait conscientiousness (p = 0.0005). Their findings imply that LSD enhances the influence of suggestion. The ability of LSD to enhance suggestibility may have implications for its use as an adjunct to psychotherapy, where suggestibility plays a major role. The inability of LSD to affect cued imagery implies that suggestions must be of a sufficient duration and level of detail to be enhanced by the drug.

Although LSD is well-known to induce perceptual alterations, it was not known whether LSD could alter emotional processing in ways that would support psychotherapy. Dolder et al.[26]

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investigated the acute effects of LSD on emotional processing using the Face Emotion Recognition Task (FERT) and Multifaceted Empathy Test (MET). The Social Value Orientation (SVO) test was used to test the effects of LSD on social behavior. Two similar placebo-controlled, double-blind, randomized, crossover studies were conducted using 100 μg of oral LSD in 24 subjects and 200 μg of oral LSD (free base) in 16 subjects. All of the subjects were healthy and most were hallucinogen-naive 25−65 year old volunteers (20 men, 20 women). LSD produced feelings of happiness, trust, closeness to others, enhanced explicit and implicit emotional empathy on the MET, and impaired the recognition of sad and fearful faces on the FERT. LSD enhanced participants' desire to be with other people and increased their prosocial behavior on the SVO test. The investigators suggest that these effects of LSD on emotion processing and sociality may be useful for LSD-assisted psychotherapy.

It has been proposed that, with eyes-closed under psychedelics, the brain may function as if there is visual input when there is none. Roseman et al.[27] tested this hypothesis, analyzing resting-state functional connectivity (RSFC) data from 10 healthy subjects under the influence of LSD and, separately, placebo. The investigators suspected that eyes-closed psychedelic imagery might involve transient local retinotopic activation, of the sort typically associated with visual stimulation. It was hypothesized that, under LSD, patches of the visual cortex with congruent retinotopic representations would show greater RSFC than incongruent patches. During the nondrug baseline condition, a retinotopic localizer was used to identify nonadjacent patches of visual cortex V1 and V3 that represent the vertical or the horizontal meridians of the visual field. Subsequently, RSFC between V1 and V3 was measured with respect to these a priori identified patches. Consistent with the investigators' hypothesis, the difference between RSFC of patches with congruent retinotopic specificity (horizontal−horizontal and vertical−vertical) and those with incongruent specificity (horizontal−vertical and vertical−horizontal) increased significantly under LSD relative to placebo. Their finding suggests that activity within the visual cortex becomes more dependent on its intrinsic retinotopic organization in the drug condition. This result may indicate that under LSD, with eyes-closed, the early visual system behaves as if it were seeing spatially localized visual inputs.

Terhune et al.[28] investigated the impact of LSD on color experiences in response to standardized graphemes and sounds and the consistency and specificity of grapheme- and sound-color associations. The design was within-groups and placebo-controlled. Participants reported more spontaneous synesthesia-like experiences under LSD, relative to placebo, but did not differ across conditions in color experiences in response to inducers, consistency of stimulus-color associations, or inducer specificity. Further analyses suggested that individual differences in a number of these effects were associated with the propensity to experience states of absorption in one's daily life. Their preliminary results suggest that LSD-induced synesthesia-like experiences do not exhibit consistency or inducer-specificity and thus do not meet two widely established criteria for genuine synesthesia.

Kraehenmann et al.[29] tested the hypotheses that LSD produces dreamlike waking imagery that depends on 5-HT$_{2A}$ receptor activation, and is related to subjective drug effects. Twenty-five healthy subjects performed an audio recorded guided mental imagery task 7 h after drug administration during three drug conditions: placebo, LSD (100 μg of free base orally), and LSD together with the 5-HT$_{2A}$ receptor antagonist ketanserin (40 mg orally). A standardized formal measure of dream mentation was used to quantitate cognitive bizarreness of guided mental imagery reports. The state of consciousness was evaluated using the Altered State of Consciousness (5D-ASC) questionnaire. Compared with placebo, LSD significantly increased cognitive bizarreness ($p < 0.001$). The LSD-induced increase in cognitive bizarreness was positively correlated with the LSD-induced loss of self-boundaries and cognitive control ($p < 0.05$). Ketanserin fully blocked both LSD-induced increases in cognitive bizarreness and changes in state of consciousness. Thus, LSD produced mental imagery similar to dreaming, primarily through activation of the 5-HT$_{2A}$ receptor and in relation to loss of self-boundaries and cognitive control.

Kraehenmann et al.[30] tested the hypotheses that LSD increases primary process thinking and that primary process thinking depends on 5-HT$_{2A}$ receptor activation and is related to subjective drug effects. Twenty-five healthy subjects performed an audio-recorded mental imagery task 7 h after drug administration during three drug conditions: placebo, LSD (100 μg orally) and LSD together with the 5-HT$_{2A}$ receptor antagonist ketanserin (40 mg orally). The main outcome variable in this study was primary index (PI), a formal measure of primary process thinking in the imagery reports. State of consciousness was evaluated using the 5D-ASC rating scale. LSD, compared with placebo, significantly increased primary index. The LSD-induced increase in primary index was positively correlated with LSD-induced disembodiment, and blissful state on the 5D-ASC. Ketanserin fully blocked both LSD-induced increases in primary index and changes in state of consciousness. Thus, LSD induces primary process thinking through activation of 5-HT$_{2A}$ receptors and in relation to disembodiment and blissful state. Primary process thinking appears to organize inner experiences crucially during both dreams and psychedelic states of consciousness.

To study LSD-induced mystical experiences, Liechti et al.[31] conducted two placebo-controlled, double-blind, crossover studies using oral administration of 100 and 200 μgof LSD free base in 24 and 16 subjects, respectively. Acute effects of LSD were assessed using the 5D-ASC scale after both doses, and the Mystical Experience Questionnaire (MEQ) only after 200 μg. On the MEQ, 200 μg of LSD induced mystical experiences that were comparable to those in patients who underwent LSD-assisted psychotherapy. On the 5D-ASC scale, LSD produced higher ratings of blissful state, insightfulness, and changed meaning of percepts after 200 μg compared with 100 μg. Plasma levels of LSD were not positively correlated with its effects, with the exception of ego dissolution at 100 μg. LSD may produce greater or different alterations of consciousness at 200 μg (i.e., a dose that is currently used in psychotherapy in Switzerland) compared with 100 μg (i.e., a dose used in imaging studies). Ego dissolution may reflect plasma levels of LSD, whereas more robustly induced effects of LSD may not result in such associations.

Recent studies of psychedelics have incorporated modern brain imaging techniques to reveal important information about brain dynamics and functional connectivity. The use of psychedelics as tools to study brain function has proven to be particularly important. Tagliazucchi et al.[32] studied the effects of LSD on intrinsic functional connectivity within the human brain using fMRI. High-level association cortices (partially overlapping with the default-mode, salience, and frontoparietal attention networks) and the thalamus showed increased global connectivity under LSD. The cortical areas showing increased global connectivity overlapped significantly with a map of 5-HT$_{2A}$ receptor

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densities. LSD also increased global integration by increasing the level of communication between normally distinct brain networks. The increase in global connectivity observed with LSD correlated with subjective reports of "ego dissolution." These results provided the first evidence that LSD selectively expands global connectivity in the brain, compromising the brain's modular organization and, simultaneously, the perceptual boundaries between the self-and the environment.

Carhart-Harris et al.[33] employed three complementary neuroimaging techniques: arterial spin labeling (ASL), BOLD measures, and magnetoencephalography (MEG), implemented during resting state conditions. These studies revealed marked changes in brain activity after LSD that correlated strongly with its psychological effects. Visual cortex cerebral blood flow (CBF) was increased, with decreased visual cortex alpha power, and a greatly expanded primary visual cortex (V1) functional connectivity profile, all of which correlated strongly with ratings of visual hallucinations, indicating that intrinsic brain activity exerts greater influence on visual processing in the psychedelic state. Surprisingly, the marked effects of LSD on the visual cortex did not significantly correlate with the drug's other characteristic effects on consciousness. Instead, decreased connectivity between the parahippocampus and retrosplenial cortex (RSC) correlated strongly with ratings of "ego-dissolution" and "altered meaning," suggesting the importance of this particular circuit for the maintenance of "self" or "ego" and its processing of "meaning." Strong relationships also were found between the different imaging metrics, enabling firmer inferences to be made about their functional significance.

Timmermann et al.[34] presented an auditory oddball paradigm to 20 healthy participants (16 males, 4 female) under LSD and placebo conditions, and recorded brain activity using MEG. Scalp level Event Related Fields (ERF) revealed reduced neural adaptation to familiar stimuli, and a blunted neural "surprise" response to novel stimuli in the LSD condition. Dynamic causal modeling revealed that both the presentation of novel stimuli and LSD modulate backward extrinsic connectivity within a task-activated fronto-temporal network, as well as intrinsic connectivity in the primary auditory cortex. These findings suggest that, rather than being a marker of conscious level per se, backward connectivity may index modulations of perceptual learning common to a variety of altered states of consciousness, perhaps united by a shared altered sensitivity to environmental stimuli.

Schmidt et al.[35] explored the effect of 5-HT_{2A} receptor activation on response inhibition neural networks in healthy subjects given LSD, and further tested whether brain activation during response inhibition under LSD exposure was related to LSD-induced visual hallucinations. In a double-blind, randomized, placebo-controlled, crossover study, LSD (100 μg of free base) and placebo were administered to 18 healthy subjects. Functional magnetic resonance imaging was used to assess response inhibition in a Go/No-Go task. Relative to placebo, LSD administration impaired inhibitory performance and reduced brain activation in the right middle temporal gyrus, superior/middle/inferior frontal gyrus and anterior cingulate cortex and in the left superior frontal and postcentral gyrus and cerebellum. Parahippocampal activation during response inhibition was differently related to inhibitory performance after placebo and LSD administration. Finally, activation in the left superior frontal gyrus under LSD was negatively related to LSD-induced cognitive impairments and visual imagery. Their findings show that 5-HT_{2A} receptor activation by LSD leads to a hippocampal-prefrontal cortex-mediated breakdown of inhibitory processing, which might subsequently promote the formation of LSD-induced visual images.

It has been proposed that the thalamocortical system is an important site of action for hallucinogenic drugs and an essential component of the neural correlates of consciousness. Muller et al.[36] orally administrated 100 μg of LSD free base to 20 healthy participants prior to fMRI assessment. Whole brain thalamic functional connectivity was measured using ROI-to-ROI and ROI-to-voxel approaches. Relationships between thalamic connectivity to regions involved in auditory and visual hallucinations and subjective ratings on auditory and visual drug effects were explored using correlation analyses. LSD caused significant alterations in all dimensions of the 5D-ASC scale and significantly increased thalamic functional connectivity to various cortical regions. In addition, LSD-induced functional connectivity measures between the thalamus and the right fusiform gyrus and insula correlated significantly with subjective auditory and visual drug effects. Hallucinogenic drug effects thus might be induced by facilitations of cortical excitability via thalamocortical interactions.

Mueller et al.[37] used functional magnetic resonance imaging (fMRI) to investigate the acute effects of LSD on the neural substrate of emotional processing in humans. Using a double-blind, randomized, crossover study design, placebo or 100 μg of LSD free base was orally administered to 20 healthy subjects before the fMRI scan, taking into account the subjective and pharmacological peak effects of LSD. The plasma levels of LSD were determined immediately before and after the scan. The administration of LSD significantly reduced reactivity of the left amygdala and the right medial prefrontal cortex relative to placebo during the presentation of fearful faces. The investigators noted a significant negative correlation between LSD-induced amygdala response to fearful stimuli and the LSD-induced subjective drug effects. Their data suggest that acute administration of LSD modulates the engagement of brain regions that mediate emotional processing.

Despite their clinical relevance, the neurochemical and anatomical substrates enabling meaningful experiences are largely unknown. Therefore, Preller et al.[24] investigated the neuropharmacology of personal relevance processing in humans by combining fMRI and the administration of LSD, well-known to alter the subjective meaning of percepts, with and without pretreatment with the 5-HT_{2A}-selective receptor antagonist ketanserin. Ketanserin fully blocked general subjective LSD effects. Further, ketanserin inhibited the LSD-induced attribution of personal relevance to previously meaningless stimuli and modulated the processing of meaningful stimuli in cortical midline structures. These findings point to the essential role of the 5-HT_{2A} receptor subtype and cortical midline regions in the generation and attribution of personal relevance.

Personality is known to be relatively stable throughout adulthood. Nonetheless, it has been shown that major life events with high personal significance, *including experiences engendered by psychedelic drugs*, can have an enduring impact on some core facets of personality. Using a balanced-order, placebo-controlled study, Lebedev et al.[38] investigated biological predictors of post-LSD changes in personality. Nineteen healthy adults were administered resting state fMRI scans under LSD (75 μg, I.V.) and placebo (saline I.V.). Participants completed the Revised NEO Personality Inventory at screening and 2 weeks after LSD/placebo. Scanning sessions consisted of three 7.5 min eyes-closed resting-state scans, one of which involved music listening. Measures of sample entropy were extracted using a standardized

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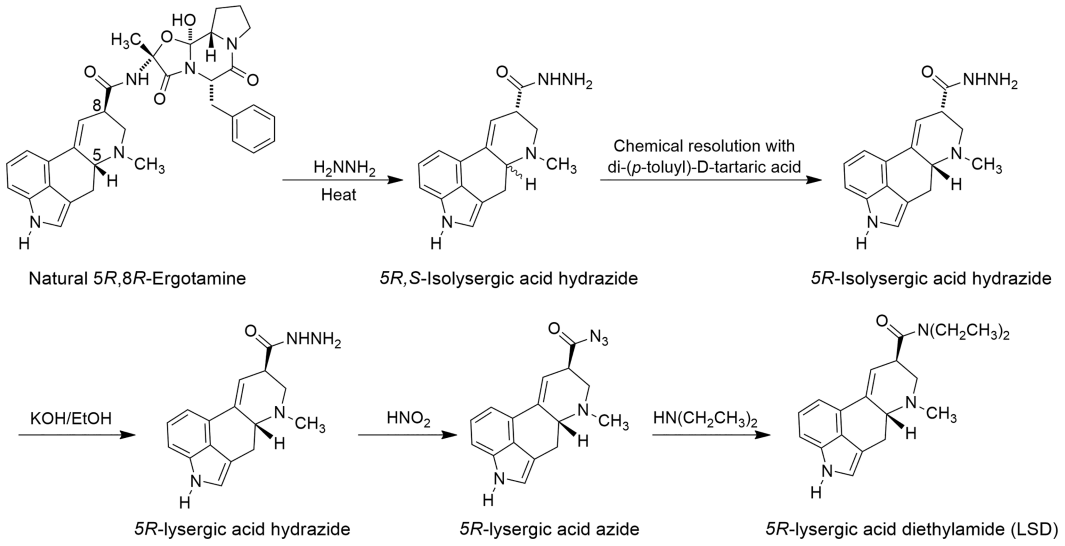
Scheme 1. First Synthesis of LSD, reported by Stoll and Hofmann in 1943[40]



preprocessing pipeline, which characterizes the predictability of an fMRI time-series. Mixed-effects models were used to evaluate drug-induced shifts in brain entropy and their relationship with the observed increases in the personality trait openness at the two-week follow-up. Globally, LSD had a pronounced effect on brain entropy, increasing it in both sensory and hierarchically higher networks across multiple time scales. These shifts predicted enduring increases in trait openness. In addition, the predictive power of the entropy increases was greatest for the music-listening scans and when "ego-dissolution" was reported during the acute experience. These results shed new light on how LSD-induced shifts in brain dynamics and concomitant subjective experience might be predictive of lasting changes in personality. It also seems likely that increased openness would be very useful for psychotherapeutic interventions.

As can be seen from the above discussion, recent studies have begun to elucidate the effects of LSD on the human brain, but the underlying dynamics certainly are not yet completely understood. Atasoy et al.[39] very recently used "connectome-harmonic decomposition," a novel method to investigate dynamical changes in brain states after LSD. They found that LSD alters the energy and the power of individual harmonic brain states in a frequency-selective manner. Remarkably, that led to an expansion of the repertoire of active brain states, indicating a general reorganization of brain dynamics given the nonrandom increase in coactivation across frequencies. Interestingly, they observed that the frequency distribution of the active repertoire of brain states under LSD closely follows power-laws, indicating a reorganization of the dynamics at the edge of criticality. A natural functional consequence of tuning brain dynamics toward criticality, as was observed under LSD, is an increased sensitivity to both internal intrinsic activity, as well as external stimuli, which in turn leads to greater sensitivity to both the internal milieu and the external environment, referred to as "set" and "setting," respectively, in relation to psychedelics. The expanded repertoire of brain states and increase in cross-frequency correlations under LSD demonstrate that more brain states contribute to neural activity under LSD, leading to a richer, more flexible repertoire of dynamics. The fact that their coactivation patterns also are highly correlated over time indicates a preserved stability in brain dynamics, albeit a "stability" of a different kind with more complex dynamics.

It now should be evident that earlier ideas that psychedelics "expanded consciousness" were not far from the mark. Further, the class name psychedelics, which essentially means "mind manifesting," is probably the best name for this class, despite the fact that "hallucinogen" continues to be the legal classification for these substances.

Properties and Chemical Synthesis. (5*R*,8*R*)-9,10-Didehydro-*N*,*N*-diethyl-6-methylergoline-8β-carboxamide (*N*,*N*-diethyl lysergamide; *d*-lysergic acid diethylamide; Lysergide; LSD-25; Delysid) $C_{20}H_{25}N_3$ (323.42). The free base has mp 83 °C after recrystallization from benzene and $[\alpha]_D$ +30 (c = 0.44, pyridine).[40] Two molecules of LSD base form a crystalline salt with one molecule of D-tartaric acid that includes two molecules of MeOH and has mp 198−200 °C and $[\alpha]_D$ +30 (c = 1, H_2O).[41] The pK_a of LSD is reported as 7.8.[42]

The first synthesis of lysergic acid *N*,*N*-diethylamide (LSD, LSD-25) was reported by Stoll and Hofmann in 1943,[40] and is illustrated in Scheme 1. Ergotamine, or another peptide ergot alkaloid, was heated with anhydrous hydrazine to produce racemic isolysergic acid hydrazide. This process racemizes the lysergic acid nucleus at C(5) and also epimerizes the carboxylic acid moiety at C(8). The *d*-and *l*-isolysergic acid hydrazides thus obtained were then chemically resolved using *d*- or *l*-di(*p*-toluyl)-tartaric acids. The resolved *d*-isolysergic acid hydrazide was then treated with ethanolic KOH to epimerize the C(8) position and afford *d*-lysergic acid hydrazide. This hydrazide was then treated with nitrous acid to afford the corresponding lysergic acid azide, which was layered over with a cold diethyl ether solution of diethylamine, whereupon the diethyl group attacked and replaced the azide. The *d*-lysergic acid *N*,*N*-diethylamide thus obtained was then crystallized as the natural tartrate salt.

In 1966, U.S. patent 3,239,530 was awarded to Hofmann and his Sandoz co-workers for an improved method of preparing optically active isolysergic acid hydrazides that avoided racemization at carbon 5.[43] Adding 1 equiv of a strong acid for each equivalent of ergot alkaloid, followed by heating with anhydrous hydrazine, resulted predominantly in the formation of (+)-(5*R*)-isolysergic acid hydrazide, with no racemization at C(5). This hydrazide was then carried forward as indicated in Scheme 1.

More efficient methods were subsequently developed using lysergic acid that had been obtained by alkaline hydrolysis of ergot alkaloids, e.g. ergotamine. These methods largely

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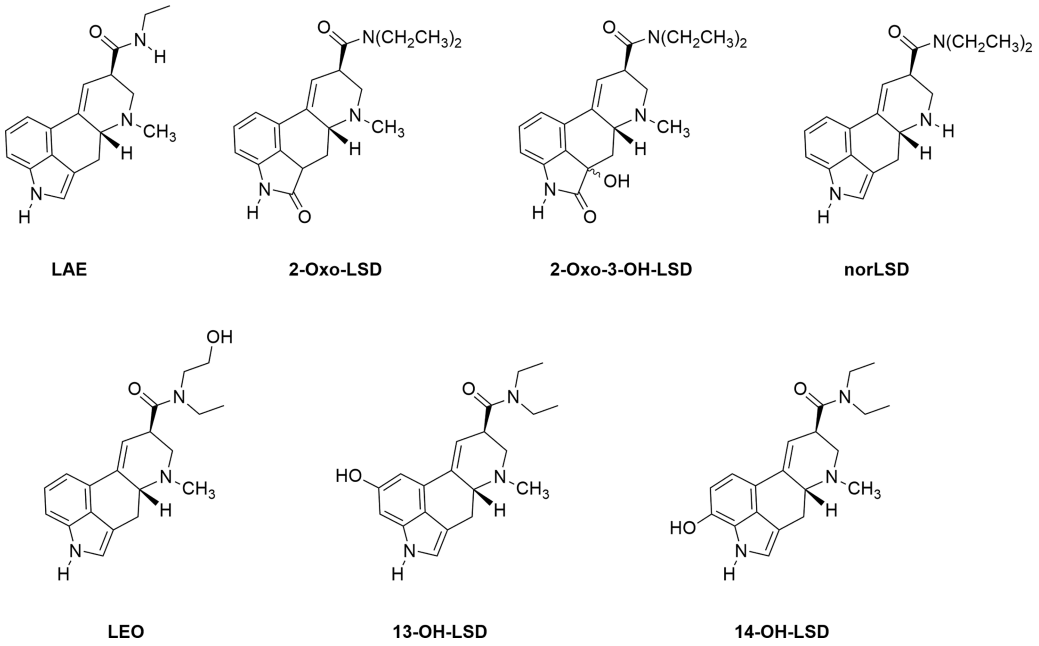

Figure 1. Structures of identified LSD metabolites.

minimized epimerization at C8. Typically, the carboxylic acid function of lysergic acid was activated for nucleophilic attack. A very early example includes activation of the carboxylic acid function with carbonyl diimidazole, followed by treatment with diethylamine.[44] Formation of the mixed anhydride with trifluoroacetic acid also has been reported, followed by reaction with diethylamine.[45] These methods gave good yields but required the use of anhydrous lysergic acid, which demanded vacuum drying. Another method that gave excellent yields involved treatment of the lithium salt of lysergic acid with a solution of SO_3 in DMF, followed by treatment with diethylamine.[46] This synthesis was the one used to make large quantities of "black market" LSD during the 1960s.[47] Obviously, great care has to be taken when using a solution of SO_3. One of the simplest syntheses was reported by Johnson et al.[48] This method was applicable to preparation of a variety of lysergamides using lysergic acid hydrate when the appropriate primary or secondary amine was readily available.[49] The reaction is rapid and is carried out in $CHCl_3$ at reflux with $POCl_3$ as the condensing agent. All syntheses of LSD typically required a final purification by column chromatography over alumina, where the normal lysergic acid diethylamide elutes from the column first as a bright blue fluorescent band under long wave UV.

A recent very useful synthesis employs (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP),[50] a crystalline and stable peptide condensing agent that readily couples lysergic acid with amines. It can be especially useful when the amine is the limiting reagent.[51,52] This synthesis is carried out at room temperature in CH_2Cl_2 and proceeds very rapidly with no epimerization at C8. This method also is scalable, but as in other preparations, the crude amide requires chromatography to obtain pure product.

Drug Metabolism. LSD is rapidly absorbed from the gut after oral administration and is almost completely metabolized, primarily by the liver. It was first established by Axelrod in 1957, using in vitro studies, that LSD is metabolized by NADH-dependent microsomal liver enzymes from the guinea pig to the inactive 2-oxo-LSD and 2-oxo-3-hydroxy LSD (Figure 1).[53,54] In Rhesus monkeys given 0.2 mg/kg LSD i.v., urine was collected for 24 h and feces for 48 h. Axelrod et al.[53] found less than 1% of the administered LSD in urine or feces, and concluded that LSD underwent almost complete metabolic transformation in monkeys. In later studies using rat liver microsomes, Niwaguchi et al.[55,56] identified lysergic acid monoethylamide (LAE) (which originates from enzymatic *N*-dealkylation of the diethylamide moiety), and nor-LSD, by *N*(6)-demethylation of LSD.

In animals, metabolism of LSD is highly species dependent, but generally seems to follow several pathways. Aromatic hydroxylation leads to 13- and 14-hydroxy LSD, which are primarily excreted as glucuronides.[57] Metabolites are secreted in the bile and excreted via the gut, with negligible amounts of unchanged drug found in feces or urine.

[^{14}C]-LSD is almost completely metabolized by rats, guinea pigs, and rhesus monkeys,[58] with only very little of the unchanged drug excreted. The elimination of [^{14}C]-LSD in the rat, guinea pig, and rhesus monkey over a 96 h period was investigated by Siddik et al.[58] Rats (1 mg/kg i.p.) excreted 73% of the ^{14}C in feces, 16% in urine, and 3.4% in the expired air as $^{14}CO_2$. Guinea pigs (1 mg/kg i.p.) excreted 40% in feces, 28% in urine, and 18% as expired $^{14}CO_2$. Rhesus monkeys (0.15 mg/kg i.m.) eliminated 23% in the feces and 39% in the urine.

The major metabolites in rats and guinea pigs (urine and bile) were glucuronic acid conjugates of 13- and 14-hydroxy-LSD. guinea pigs excreted significant amounts of 2-oxo-LSD in urine and bile. Lysergic acid ethylamide (LAE) was a minor urinary metabolite in both species. In rat livers perfused with [^{14}C]-LSD, Siddik et al.[59] identified the glucuronides of 13- and 14-hydroxy-LSD, as well as 2-oxo-LSD, LAE, and nor-LSD.

LSD had a unique metabolic profile in rhesus monkeys. Their urine contained at least nine metabolites. Four of them were identified as 13- and 14-hydroxy-LSD (as glucuronic acid conjugates), LAE, and a naphthostyril derivative. Glucuronic acid conjugates of 13- and 14-hydroxy-LSD were present in only small amounts in rhesus monkeys, setting them apart from rats and guinea pigs.

Klette et al.[60] have reported that in 144 human urine specimens of subjects who had taken LSD, 2-oxo-3-OH-LSD was found in every specimen studied (n = 144) at a mean concentration 16−43 times higher than the parent LSD.

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These investigators studied Phase I drug metabolism of LSD by incubating human liver microsomes and cryopreserved human hepatocytes with LSD. They positively identified 2-oxo-3-OH-LSD in all human liver microsomal and human hepatocyte fractions incubated with LSD. In a later in vitro study that used human liver microsomes, LAE was determined to be the major metabolite.[61] Faed and McLeod[62] reported the elimination half-life for LSD in man as 3.6 h. LSD and its metabolites were reported to be detectable in the urine for as long as 4 days after ingestion.

Canezin et al.[63] found the following LSD metabolites in human urine: nor-LSD, LAE, 2-oxo-LSD, 2-oxy-3-hydroxy-LSD, 13- and 14-hydroxy-LSD as glucuronides, lysergic acid ethyl-2-hydroxyethylamide (LEO), and "trioxylated LSD." The major metabolite in urine is 2-oxy-3-OH-LSD, which could not be detected in blood plasma.

In order to characterize and quantify better the human metabolites of LSD, Dolder et al.[64] recently developed and validated a liquid chromatography triple quadrupole tandem mass spectrometry (LC-MS/MS) method for the quantification of LSD, iso-LSD, 2-oxo-3-OH-LSD, and nor-LSD in plasma samples from 24 healthy subjects after administration of 100 μg (free base) LSD in a clinical trial. In addition, recently described in vitro metabolites, including LAE, lysergic acid LEO, 2-oxo-LSD, trioxylated-LSD, and 13- and 14-hydroxy-LSD, could be identified. A reversed phase chromatography column after turbulent-flow online extraction was used to separate LSD and its metabolites. A triple quadrupole LC-MS/MS instrument was employed for identification and quantification of metabolites. The limit of quantification was 0.05 ng/mL for LSD, iso-LSD, and nor-LSD, and 0.1 ng/mL for 2-oxo-3-OH-LSD. The limit of detection was 0.01 ng/mL for all compounds. The method was described as accurate, precise, and the calibration range within the range of expected plasma concentrations. LSD was quantified in the plasma samples of the 24 subjects of the clinical trial. Iso-LSD, 2-oxo-3-OH-LSD, nor-LSD, LAE, LEO, 13/14-hydroxy-LSD, and 2-oxo-LSD could be detected only sporadically, and concentrations were too low for quantification.

Dolder et al.[65] characterized the pharmacokinetic profile, pharmacokinetic-pharmacodynamic relationship, and urine recovery of LSD and its main metabolite after administration of a single oral dose of lysergic acid diethylamide (200 μg of free base) in 8 male and 8 female healthy subjects. Only 1% of the orally administered LSD was eliminated in urine as unchanged drug, with 13% eliminated as 2-oxo-3-OH-lysergic acid diethylamide within 24 h. No sex differences were observed in the pharmacokinetic profiles of lysergic acid diethylamide. The acute subjective and sympathomimetic responses to lysergic acid diethylamide lasted up to 12 h and were closely associated with the concentrations in plasma over time.

Dolder et al.[66] analyzed pharmacokinetic data from two published placebo-controlled, double-blind, crossover studies using orally administered LSD 100 and 200 μg (free base) in 24 and 16 subjects, respectively. The pharmacokinetics of the 100 μg dose was presented for the first time, and data for an earlier study of a 200 μg dose[65] were reanalyzed. Plasma concentrations of LSD, subjective effects, and vital signs were assessed repeatedly. Concentration-effect relationships were described using pharmacokinetic-pharmacodynamic modeling. Geometric mean (95% confidence interval) maximum plasma concentration values of 1.3 (1.2−1.9) and 3.1 (2.6−4.0) ng/mL were reached 1.4 and 1.5 h after administration of 100 and 200 μg of LSD, respectively. The plasma half-life was determined as 2.6 h (2.2−3.4 h). The subjective effects lasted (mean ± SD) 8.2 ± 2.1 and 11.6 ± 1.7 h for the 100 and 200 μg LSD doses, respectively. Subjective peak effects were reached 2.8 and 2.5 h after administration of LSD 100 and 200 μg, respectively. There was a close relationship between the plasma LSD concentration and subjective response within subjects. Half-maximal effective concentration values were in the range of 1 ng/mL. Oral LSD presented dose-proportional pharmacokinetics and first-order elimination up to 12 h. The effects of LSD were related to changes in plasma concentrations over time, with no evidence of acute tolerance.

PHARMACOLOGY, MEDICINAL CHEMISTRY, AND STRUCTURE−ACTIVITY RELATIONSHIPS

Passie has presented a comprehensive review on the pharmacology of LSD,[67] and the present author also has provided a recent review that includes aspects of the pharmacology of LSD.[68] Although LSD has high affinity for a variety of G protein coupled receptors,[67] the potent psychoactive effects of LSD can be attributed to its partial agonist activity at the brain serotonin 5-HT_{2A} receptor.[68] In behavioral studies in rats, however, there is a time-dependent change in pharmacology, from initial 5-HT_{2A} receptor activation to dopamine D2-like pharmacology at later times.[69−72]

Although early research from numerous in vitro and animal behavioral models had clearly shown the key importance of the 5-HT_{2A} receptor,[68,73] validation in human clinical studies was provided by research from the Vollenweider laboratory, in Zürich, Switzerland. It was first shown in 1998 that ketanserin, a selective 5-HT_{2A} antagonist, could block the psychedelic effects of psilocybin, a naturally occurring tryptamine with psychoactive effects similar to LSD.[74] In the past year, however, several clinical studies have appeared from the same laboratory demonstrating that the psychoactive properties of LSD also can be blocked by pretreatment with ketanserin.[23,24,29,30]

The structure−activity relationships of lysergic acid amides are unique, in that virtually any structural change leads to marked attenuation in potency and altered qualitative human psychopharmacology.[75] No other amide that has been studied, other than the *N*,*N*-diethyl, appears to have potency or psychopharmacology comparable to that of LSD, although some other amides do have in vitro or uterotonic activities similar to LSD.[76] The one exception may be a rigid analogue of LSD, where the two diethyl groups of the diethylamide moiety are tethered into a 2,4-dimethylazetidine ring with the 2*S*,4*S* stereochemistry in the azetidine moiety (Figure 2).[52] In general, however, there is a paucity of human data for other LSD congeners. *N*(1)-acetyl or -propionyl derivatives of LSD appear to be prodrugs, and are converted into LSD in the body.[77] Some of these have been sold on the "recreational chemicals" market, and their psychopharmacology is given in anecdotal reports https://erowid.org/experiences/subs/exp_1PLSD.shtml.

One analogue of LSD modified in the amide moiety has been reported to have human activity approximately equipotent to LSD. The lysergamide of 2*S*,4*S*-dimethylazetidine[52] has been sold as "LSZ" and anecdotal reports of its human activity have appeared. Interestingly, the crystal structure of LSD bound within the human serotonin 5-HT_{2B} receptor was recently reported.[78] The conformation of the LSD molecule within the crystal structure was essentially superimposable on the structure of the lysergamide of 2*S*,4*S*-dimethylazetidine.[52]

The only other LSD analogues reported to have significant human activity are *N*(6)-ethyl-norLSD ("ethlad")[79−81] and *N*(6)-allyl norLSD ("Al-lad").[79,81,82]

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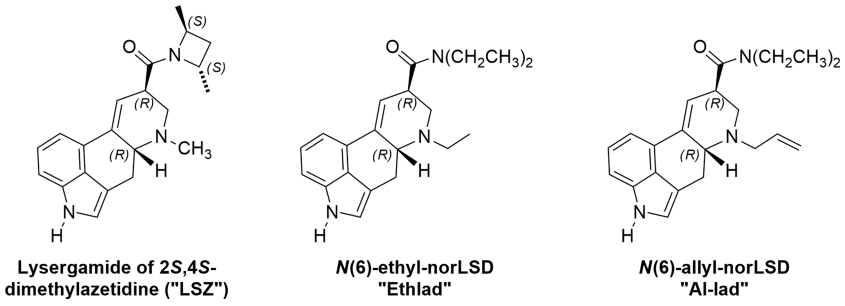

Figure 2. LSD analogues reported to have significant human activity.

■ ADVERSE EFFECTS AND DOSAGE

Comprehensive reviews of clinical outcomes of experimental LSD studies conducted in the United States and the United Kingdom during the 1950s and 1960s identified very low rates of adverse effects.[83−85] Although United States Food and Drug Administration approved clinical studies of LSD ended with the passage of the controlled substances act (CSA) of 1970, controlled clinical studies have recently resumed in Europe, although not as yet in the United States.[18,24,25,33,86−89]

Although LSD is classified as a Schedule 1 drug with no safe or recognized therapeutic use, its use by the public has continued over the past 45 years.[90,91] Interestingly, reports of psychological adverse events outside of formal and approved research settings have declined over the past several decades. That may be due to general availability of lower doses, access to better and more accurate information about LSD, improved psychological preparation, and greater attention given to supportive environmental conditions.

Experts generally recognize that LSD is an extremely physiologically safe substance, when moderate dosages are used (50−200 μg) in controlled settings, with only modest elevations of blood pressure, heart rate, and body temperature.[26,87,92] LSD does not show any dependence liability. It is estimated that 10.2% of the current United States population has ever taken LSD,[93] indicating that approximately 31 million people have ever used LSD, with not a single documented death due to LSD at recreational doses.[93−95]

Although fatalities after LSD use can occur when the intoxication leads the user to carry out dangerous activities such as walking across a busy highway, attempting to swim, rock climbing, etc., there are only two documented cases where LSD presumably directly led to fatality. In both cases, post-mortem analysis indicated that the decedents had ingested massive doses of LSD.[96]

■ HISTORY AND IMPORTANCE IN NEUROSCIENCE

Although the high potency and unique psychopharmacology of LSD are widely recognized, often overlooked is one very important scientific consequence of the discovery of LSD. As noted earlier, the powerful psychological effect of LSD was accidently discovered in 1943. Only a decade later, in 1953, serotonin was detected in mammalian brain.[97] Scientists quickly noticed the tryptamine moiety embedded within LSD to be the same scaffold as in the chemical structure of serotonin (Figure 3).

Thus, only one year later, Woolley and Shaw[98] proposed that "mental disturbances caused by lysergic acid diethylamide were to be attributed to an interference with the action of serotonin in the brain." To put that finding into context, in the 1940s, and earlier, psychiatry was primarily focused on the use of psychoanalytical methods; there was no general recognition that mental disturbances could be attributed to neurochemistry. When a child was diagnosed with a mental disorder, the parents,

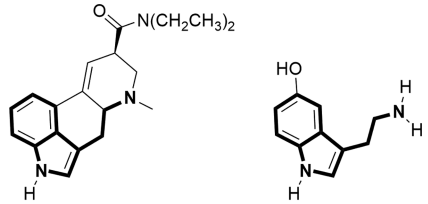

Figure 3. Comparison of the structure of LSD with that of serotonin.

especially the mother, were most often blamed for not providing emotional nourishment to the child, and being "bad parents." The connection between the potent psychoactive effects of LSD, its structural relationship to serotonin, and the detection of serotonin in the brain was a sort of "ah ha" moment. One can thus reasonably argue that the discovery of LSD catalyzed the beginning of the entire field of serotonin neuroscience, and especially the role of serotonin in brain function. By way of illustration, in 1952, there were only 10 publications in the National Library of Medicine concerning serotonin, nearly all of them dealing with some aspect of its action in the periphery, e.g., its ability to constrict blood vessels. Only 8 years later, in 1960, there were 300 publications on serotonin, 35 of which involved studies of serotonin in the brain. Green[99] has provided an interesting overview of the 1950−1970 period of intense research activity following the detection of serotonin in the brain.

As of today, it is clear that the combination of modern brain imaging methods with LSD and other psychedelics offers an extremely powerful approach to understanding brain dynamics. These approaches are providing insight into the way that different brain regions communicate with each other, and how those communications affect behavior, perception, and consciousness itself. The name "psychedelic," which essentially means "mind manifesting" appears today to be an apt description for this class of psychoactive agents. This knowledge will no doubt inform future approaches to mental health treatments, irrespective of whether or not psychedelics themselves become useful therapeutic agents.

The final chapter on the importance of LSD to neuroscience and medicine is yet to be written. Although the early enthusiasm for the therapeutic value of LSD has faded, recent studies, especially with the related molecule psilocybin, have provided positive results in small pilot studies suggesting that psychedelics may be useful in treating depression, anxiety, and a variety of addictions.[100] The major pharmaceutical companies have reduced or eliminated their research efforts toward development of psychiatric drugs. Most psychiatrists bemoan the lack of improved drugs for treatment of psychiatric illnesses, with no hope on the horizon for new more efficacious medicines anytime

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soon. It seems possible that LSD, and other psychedelics, may offer a new therapeutic approach,[100,101] perhaps fulfilling the promise that they seemed to offer more than half a century ago.

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Notes

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