Biological Psychiatry: Celebrating 50 Years

# Commentary

# The Effects of Low Doses of Lysergic Acid Diethylamide in Healthy Humans: Demystifying the Microdosing of Psychedelics

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Research on the effects of psychedelics in healthy volunteers and clinical populations has seen a revival in the last decade. More recently, a practice called "psychedelic microdosing" has gained public attention, with several books and magazine and newspaper articles published on this topic within the last few years. In contrast to the pharmacological meaning of "microdosing"—administering <100 μg/1% of the pharmacologically active dose to assess the pharmacokinetics of a substance to optimize drug development and selection—microdosing psychedelics implies the use of low doses of hallucinogenic substances, primarily lysergic acid diethylamide (LSD), to increase work performance, enhance creativity, or boost energy levels. In addition to taking low doses of psychedelics as a "cognitive enhancer," microdosing has also anecdotally been described to be used for the treatment of anxiety, depression, addiction, and pain (1,2). There is no clear consensus regarding the exact dose that is considered a microdose, but it has roughly been defined as one tenth to one twentieth of a recreational psychedelic dose. These doses are suggested to be below the perceptual threshold and therefore should not induce an altered state of consciousness and are not supposed to interfere with normal functioning of an individual. Furthermore, different dosing regimens have been debated, most of them recommending repeated administrations (e.g., 5–15 μg LSD every third day). However, as Passie [commenting on Kuypers *et al.* (1)] points out, many recreational microdosers seem to be taking a low dose a few times a year and do not follow a regular dosing schedule. Despite the unabated strong public interest in psychedelic microdosing, scientific investigations regarding the effects of low doses of LSD and other hallucinogens are rare. Virtually all information on the effects of microdosing psychedelics is based on anecdotal evidence, open-label studies, or surveys and is therefore most likely biased regarding expectation and placebo effects. In this issue of *Biological Psychiatry*, this knowledge gap is diminished by Bershad *et al.* (3), who present the first double-blind, placebo-controlled, randomized, within-subject study specifically investigating the effects of low doses of LSD on mood, emotion processing, and cognition.

In their pivotal study, Bershad *et al.* (3) assess the effects of multiple single doses of LSD (0, 6.5, 13, and 26 μg). The results show that 26 μg of LSD induces clear subjective and objective effects and can therefore not be considered a subperceptual dose. In particular, after the administration of 26 μg, participants reported a significantly increased feeling of "being high"—an effect that may interfere with everyday life activities. The authors identify 13 μg of LSD as the threshold dose for minimal subjective and physiological effects, suggesting this dose for the investigation of potential beneficial effects in clinical populations.

Another strength of the study is the assessment of the impact of LSD on various cognitive and emotional functions. In contrast to anecdotal reports suggesting the use of LSD microdoses to enhance creativity and improve work performance, no beneficial effects were found in this study. None of the administered doses improved cognitive performance on the *n*-back task or the digit symbol substitution task. Rather, participants reported subjectively impaired control and cognition that increased with dose and reached significance after 26 μg of LSD. This is in line with another study investigating the effects of 5 μg to 20 μg in older adults in a between-subject design reporting a trend toward impairments in self-reported concentration (4). In addition, various studies have shown that a higher dose of LSD (100 μg) impairs performance of cognitive tasks (5,6). It is therefore not surprising that low doses of LSD did not improve cognitive performance. As pointed out by Liechti [commenting on Kuypers *et al.* (1)], there is no reason to believe that substances like LSD that impair cognition at active doses would "magically enhance concentration when used at lower doses."

The same seems to hold true for creativity. Conflicting results have been reported regarding the impact of psychoactive doses of psychedelics on creativity and cognitive flexibility (5,7). Evidence for an increase in lateral thinking after a low dose of psilocybin has been reported in an uncontrolled, open-label study with recreational users (8). However, there is no evidence for creativity-enhancing effects of low doses of psychedelics under controlled conditions [for review, see Passie (9)]. In line with this, Bershad *et al.* (3) now provide scientific evidence that low doses of LSD do not increase creativity assessed with the remote associations task when administered in a rigorously controlled study.

In addition to these cognitive measures, Bershad *et al.* (3) tested emotional and social processing. In contrast to higher doses of psychedelics (10), low doses of LSD did not induce alterations in emotional face identification, emotional ratings, or mood after social rejection, except for a slight decrease in positive ratings for International Affective Picture System images. It is therefore conceivable that higher doses—and related to this, a higher level of serotonin 2A receptor stimulation—is needed to induce measurable effects on emotional and social functions.

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While these results clearly show that low doses of LSD do not produce cognitive-enhancing effects, their impact on outcomes that are relevant for therapeutic applications is less clear. Anecdotal reports describe the use of small doses of LSD to alleviate symptoms of anxiety and depression, yet Bershad *et al.* (3) show no significant effects on mood 48 hours after the sessions in the healthy participants tested. However, only 11 questionnaires were available for the analysis of postacute effects. Acutely, 26 μg of LSD increased vigor, which could be beneficial in a therapeutic setting. However, this dose also increased anxiety. Further studies, in particular in clinical populations, are needed to evaluate the potential of low doses of LSD for therapeutic purposes in different psychiatric disorders.

This study by Bershad *et al.* (3) closes important knowledge gaps on the effects of low doses of LSD on cognition and mood. Yet, open questions remain regarding the effects of multiple repeated doses as described by Fadiman (2). It is possible that some of the effects described in anecdotal reports may emerge only after repeated administration, potentially owing to neural adaptations. However, while the administration of single doses of psychedelics is considered relatively safe, less is known about the physiological and psychological consequences of long-term intake (1). Furthermore, participants in the Bershad *et al.* study (3) had used a psychedelic substance at least once before the study. Effects in psychedelic-naïve participants still need to be evaluated. In addition, because effects of low doses are expected to be subtle, large studies may be needed to detect significant effects. Finally, because Bershad *et al.* (3) assessed healthy participants, effects on mood and emotional processing may not have been detectable. It still must be investigated whether low doses of LSD show beneficial effects in individuals suffering from mood or anxiety disorders, addiction, or pain.

In summary, Bershad *et al.* (3) present the first rigorously conducted study that assesses the effects of so-called psychedelic microdoses on cognitive and emotional processes and therefore provide a scientific investigation of a phenomenon vigorously debated in recent years. The authors identify a threshold dose (13 μg) that does not induce an altered state of consciousness and supposedly does not interfere with the normal functioning of an individual. In contrast to anecdotal reports, these low doses of LSD were not shown to have beneficial effects on cognitive or emotional measures. While these data do not support the use of low doses of LSD for the purpose of enhancing cognition, concentration, or creativity, potential beneficial effects in clinical populations still need to be investigated in future studies.

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