**Microdosing LSD & Psilocybin: The Future of Psychiatry or Placebo?**

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# Why talk about microdosing?

The idea of using psychedelics to treat psychiatric symptoms has been approaching mainstream popularity thanks to podcasters like Joe Rogan, Tim Ferris, and Sam Harris. As interest in these substances continues to grow, so does the size of the online communities centered around this topic. One such community is the microdosing community. On Reddit alone there are nearly 240 thousand members of the microdosing subreddit, where you can find thousands of anecdotes about how microdosing is helpful for treating depression, anxiety, PTSD, ADHD, etc., along with microdosing guides, harm reduction resources, links to participate in microdosing studies, and reviews of scientific articles. While there is undoubtedly value in recognizing some of the claims being made about microdosing, it's important to recognize where the literature currently stands and to identify where there are gaps in understanding.

# Quotes on microdosing:

Joe Rogan:

- "People are using psilocybin these days in what they call 'microdosing,' taking very small doses and seeing these profound benefits ya know. One of the things that I'm aware of is that kickboxers are using it. A good buddy of mine using it says that he can see things happen before they happen" (Joe Rogan Experience #946 - Dennis Mckenna).
- "Microdosing for just daily life makes things really fun."
- "I have done it many times and I have taken a gram a day for 30 days in a row. I enjoy it a lot. It gives you a silly, carefree consciousness that is unperturbed, meaning that it doesn't affect my judgment, it doesn't affect my ability to have a conversation with someone, it doesn't affect my ability to do my job."
- "It just puts me in this very appreciative, thankful, low anxiety state" (Joe Rogan Experience #1958 - Andrew Huberman).

Ayelet Waldman, from her book, *A Really Good Day: How Microdosing Made a Mega Difference in My Mood, My Marriage, and My Life*:

- "For the first time in so long, I feel happy. Not giddy or out of control, just at ease with myself and the world. When I think about my husband and my children, I feel a gentle sense of love and security. I am not anxious for them or annoyed with them. When I think of my work, I feel optimistic, brimming with ideas, yet not spilling over."

Paul Stamets:

- "Coders in Silicon Valley from the biggest computer companies that we all know [do it]. This is a not only a fashion, but a tool that they're seeing an increased ability for coming up with codes and it's a competitive advantage in the capitalistic system" (Joe Rogan Experience #1035 - Paul Stamets).

# What is Microdosing?

Microdosing was first popularized by Dr. James Fadiman in his book, *The Psychedelic Explorer's Guide*, in which he coined the term microdosing and described a microdosing regimen. Dr. Fadiman studied LSD at Stanford during the 1960s, and in the early 2000s his curiosity in microdosing was supposedly sparked after hearing that Albert Hoffman, the first person to synthesize LSD, had microdosed LSD well into his 90s.

From his book:

> *Microdosing involves taking small amounts of a psychedelic substance (usually one-tenth to one-fifth of a recreational dose) with the intention of enhancing cognitive, emotional, or spiritual functioning. The goal is not to experience a full-blown psychedelic trip, but rather to tap into the subtle, yet powerful, effects of these substances in a more controlled and sustainable way (Fadiman, 2011, p. 29).*

The microdosing protocol Dr. Fadiman created is known as "The Fadiman Protocol," and is the most popularly followed microdosing regimen. The Fadiman Protocol involves taking a low dose of a psychedelic every three days for a period of around 4-6 weeks. The other commonly used protocol is The Stamets Protocol (named after Paul Stamets). It involves taking a microdose for 4-5 days in a row followed by 2-3 days off for 4-6 weeks. Supplements like Niacin and Lion's Mane mushroom are often "stacked" with the Stamets Protocol.

In regard to the doses used, LSD is commonly taken at 10-26ug, compared to recreational doses of 100-300ug. For psilocybin mushrooms, recreational doses typically range from 3-5g of dried mushrooms, while microdoses are in the range of 0.1-0.7g.

# History/background

(covered in more detail in Episode 104)

Psychedelics have historically been used around the world by indigenous tribes in ritualistic practices for the purpose of enhancing religious experiences or rites of passage.

Some examples include:

- Mazatecs in Mexico and psilocybin mushrooms (Maria Subina)
- Shipibo in the Amazon and Ayahuasca
- Ebene and the Yanomami in the Amazon and 5 Meo-DMT
- Bwiti people in Western Africa and Ibogaine
- Ainu people in Japan and mushrooms
- North American Indians and Peyote

LSD was the first psychedelic to become popularized in America after its discovery in 1938 by Swiss Scientist and employee of Sandoz, Albert Hoffman. It was largely limited to researchers up until the 1950s.

Psilocybin mushrooms were later brought to America in the 1950s by Americans who visited the Mazatec people in Mexico.

During the Cold War, LSD was a prevailing symbol of the 1960s counterculture, and a tool used by the CIA to conduct clandestine experiments for the purpose of creating mind-control techniques. This project was termed MK-Ultra and often involved dosing Americans (mainly prostitutes and their clients, prisoners, and CIA agents) against their will and trying to get information from them or control them.

The book, *Chaos: Charles Manson, the CIA, and the Secret History of the Sixties,* discusses the idea that Charles Manson used psychological techniques along with LSD on his followers, potentially progressively brainwashing them. It seemed that LSD may have contributed to the absolute loyalty of Manson's followers, but meth was likely used during the murders. Despite the CIA's failure to discover mind-control practices, there's speculation that they backed Manson's cult and helped keep him out of prison.

# Psychedelic research today

Psychedelics are overcoming their dark history in America, as we are in the midst of the third wave of interest thanks to the resurgence in macrodosing research and the enthusiasm of social media personalities. However, the research has largely been limited to macrodoses (see: Carhart-Harris et al., 2021; Griffiths et al., 2016; Ross et al., 2016; Grob et al., 2011; Davis et al., 2021).

Considering the limited number of studies on microdosing, there has been a "citizen science" movement by online communities where members are encouraged to collect personal data and share it with forums and online researchers.

With the massive influx of anecdotal reports Dr. Fadiman received in response to his book, he decided to create one of the first online platforms through which microdosers could share their anecdotal experiences and complete mood tracking with the PANAS checklist. In 2019, he published a paper reporting their findings (Fadiman and Korb, 2019).

In this paper and in numerous talks, he has described how microdosers report improvements in general anxiety, academic anxiety, party anxiety, social anxiety, Asperger's, mood during bipolar depressive episodes, focus, learning, habit formation, headaches, PMS, concussions, trauma, procrastination, stuttering, writer's block, flow, libido, pain, and more.

# Microdosing and Mood/Mental Health

Multiple online surveys and qualitative studies have corroborated Dr. Fadiman's results, showing decreased depression and anxiety and improved mood in microdosers (Anderson et al., 2019; Fadiman and Korb, 2019; Johnstad, 2018; Polito and Stevenson, 2019; Lea et al., 2020; Cameron et al., 2020), with many microdosers perceiving the practice to be more effective than conventional treatments for psychiatric symptoms (Hutten et al., 2019; Lea et al., 2020). Despite the fact many of these studies often lacked a control group entirely and selected participants from online forums, their statistically significant findings further propelled the microdosing movement (for review of these studies and other microdosing studies up to 2021, see Polito and Liknaitzky, 2022).

Only recently have there been any randomized-control trials of microdosing, and all but two have been in healthy populations. Both of these studies used the microdose group as the active control and later crossed over to the macrodose group, so this limits the ability to make conclusions about long-term effects. Nevertheless, they are worth looking into.

The first study conducted in a clinical population was by Gasser et al., 2014:
Safety and Efficacy of Lysergic Acid Diethylamide-Assisted Psychotherapy for Anxiety Associated With Life-threatening Diseases (2014)

- Participants/methods
  - RCT where 11 cancer patients who scored > 40 on the STAI (State Trait Anxiety Inventory) were randomized to two psychotherapy sessions in which received either 200ug (n=8) or 20ug (n=3) of LSD, with 2-3 weeks between experimental sessions. After 2 months, the 20ug group crossed over to the high dose condition.
  - Half of participants met diagnostic criteria for GAD based on DSM-IV criteria, and all but one participant was hallucinogen naïve.

        - Participants received two preparatory sessions prior to the 8-hour treatment sessions and three 60-90 minute psychotherapy sessions after each experimental session.
    - Results
        - Two months after the first block of sessions, the high dose group showed significantly lower scores of STAI state and trait anxiety compared to the low dose group (d=1.2 and 1.1 respectively). 3 out of the 8 participants in the high dose group dropped below the threshold of 40 for both state and trait anxiety, while all 3 participants in the low dose group had higher trait anxiety scores and 2 had higher state anxiety scores.
        - On secondary outcome measures related to quality of life (QLQ-30), psychiatric symptoms (SCL-90-R), and anxiety/depression (HADS), participants only improved in these metrics after receiving the high dose, and these effects were maintained at 12-month follow-up. But there were no statistical analyses performed on these data due to the authors' concerns of multiplicity.

Griffiths et al., 2016: Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

- Participants/methods
    - Double blind crossover RCT where 51 cancer patients in various stages of cancer with comorbid DSM-IV diagnosis of depression and/or anxiety disorder were randomized to first receive either a low (1-3 mg) or high (22-30 mg) dose of oral psilocybin followed by the opposite dose 5 weeks later.
    - Participants also met with monitors before, after, and between sessions for a mean total of about 15 hours.
- Results
    - 5 weeks after the first dosing session, only the high dose group showed significant decreases in clinical questionnaires scores (HAM-D, HAM-A); however, there was a trend in the low dose group.
    - There was a 32% response rate ( ⩾50% decrease relative to baseline) and 16% remission on the HAM-D in the low dose 1st group, compared to 92% response rate and 60% remission rate in the high dose group. For the HAM-A and 24% response rate and 12% remission in the low dose group compared to 76% response rate and 52% remission in the high dose group.

Notes/limitations of these studies

- No control to compare outcomes with microdose
- Support from monitors could confound results
- All subjects received a high dose at some point, so can't discern the long-term effects of a low dose
- Highly educated and predominantly white sample with favorable attitudes towards psychedelics in the Griffiths study

# Effects on mood, anxiety, and depression

## Acute studies

In the following years, eight lab-based controlled trials of microdosing have addressed mood or symptoms of anxiety/depression as one of their outcome measures. All lab-based studies have been in healthy volunteers, with most volunteers having prior experience with psychedelics. The basic design of most of these lab studies is as follows: participants were randomized to receive one to four microdoses of LSD or psilocybin with a washout of at least 5 days between doses. Most of the studies were within-subjects design where participants may have been given, for example, either a placebo, 5ug, 10ug, or 20ug in random order, or they were allocated to receive a placebo or a microdose for multiple sessions and then crossed over to the other treatment condition. Sample sizes ranged from 20 to 56.

Contrary to what is reported in Dr. Fadiman's work (Fadiman and Korb, 2019), PANAS (Positive and Negative Affect Schedule) was insignificant in two of these lab studies (Bershad et al., 2020 (LSD) and Cavanna et al., 2022 (Psilocybin)).

Four studies measured the acute effects of a microdose of LSD on anxiety, depression, and mood using the POMS. (Profile of Mood States measures six different dimensions of mood swings over a period of time. These include: Tension or Anxiety, Anger or Hostility, Vigor or Activity, Fatigue or Inertia, Depression or Dejection, Confusion or Bewilderment.) Two studies observed a significant increase in the anxiety subscale of POMS during the acute effects of the highest dose (Bershad et al., 2019; Murray et al., 2022), while the other two studies (Hutten et al., 2020a; De wit et al., 2022) found no effect on any subscales of the POMS. One of these studies (Hutten et al., 2020a) found a dose-dependent increase in an anxiety subscale of another questionnaire, the 5D-ASC (5-Dimensional altered states of consciousness rating scale). One of the studies that observed an increase in anxiety also found an increase in elation and positive mood in the highest dose group (26ug-Murray et al., 2022).

Another study (Ramaekers et al., 2021) used the BSI-18 (a symptom scale with subscales of somatization, anxiety, and depression). Compared to baseline, 6h after dosing, the highest dose group showed increases in average anxiety and somatization subscale scores. No changes in the depression subscale were observed.

## Repeated dosing studies

Cavanna et al., 2022 studied the effect of microdosing .5g of psilocybin and found no change in acute anxiety using the STAI (State Trait Anxiety Inventory) during the effects of a microdose. This study had 34 participants take two doses total, once Wednesday and once Friday. On Sunday, they measured trait anxiety using the STAI and found no difference compared to the week they took placebo doses.

De Wit et al. (2022) conducted a similar study in which 56 participants were randomized to take four doses of either a placebo (n=18), 13ug (n=19), or 26ug (n=19) of LSD, with doses separated by 3-4 day intervals. Three to four days after completing the 4 doses, all groups showed significant reductions in DASS (Depression, Anxiety and Stress Scale) scores (depression, anxiety, stress, total), but no group differences were observed.

Marschall et al. (2022) conducted a double-blind crossover trial with 52 participants, where participants were randomized to first take capsules containing either .7g (equated to about 1.5mg psilocybin) of truffles or non psychedelic mushrooms. The researchers had participants follow the Fadiman protocol, where they took a microdose every 3 days. After 3 weeks, they stopped dosing, waited another 2 weeks and then crossed over to the other group. Depression and stress scores on the DASS were significantly lower after the first block of doses, but this effect was observed in both the microdose group and placebo group.

## Takeaways/Limitations of these studies

- Participants in these studies were most often recruited from online forums or at psychedelic conferences and had prior experience with psychedelics. They also reported favorable attitudes towards psychedelics.
- There was a high rate of breaking blind in all of these studies (about 70% on average), where most participants were able to guess correctly if they had taken either the highest dose or a placebo.
- It's possible that these studies were too short to see any antidepressant effects, with the longest lab study being 3 weeks long.
- Considering these studies were completed in healthy volunteers, baseline scores of depression and anxiety were low. Without a clinical population, the magnitude of antidepressant/anxiolytic effects of microdosing cannot be measured adequately.

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There are also some interesting results from the largest placebo controlled study to date, by Szigeti et al, 2021: Self-blinding citizen science to explore psychedelic microdosing (2021)

- Participants/methods
  - This is actually a naturalistic study in which 191 participants learned a self-blinding procedure to use with their own microdoses. There were three groups:
    - 1) 4 weeks of microdosing twice weekly with two weekly placebo doses
    - 2) 2 weeks of microdosing twice weekly along with 2 weeks of placebo
    - 3) 4 weeks placebo
  - 84% of subjects microdosed with LSD, compared to 14% psilocybin, and 2% using another psychedelic
- Results
  - After 5 weeks, all self-reported psychological outcomes improved significantly in the MD group: well-being (RPWB) increased with 4.2 ± 3.9 (adjusted mean estimate ±95% CI; p=0.04*), mindfulness (CAMS) increased with 2.4 ± 1.1 (p<0.001***), life satisfaction (SWL) increased with 1.2 ± 1.2 (p=0.04*), and paranoia (GPTS) decreased with 5.0 ± 1.7 (p<0.001***).
  - Big 5 showed reduced neuroticism trait score (1.3 ± 0.9, p<0.01**) and increased openness (0.9 ± 0.8, p=0.03*).
  - Placebo group and half/half group also improved in mindfulness (PL: 1.6 ± 1.1, p<0.01**; HH: 1.3 ± 1.2, p=0.02*) and paranoia (PL: 3.4 ± 1.7 p<0.001***; HH: 4.9 ± 1.9 p<0.001***), but not for well-being or life satisfaction.
  - Neuroticism also decreased in the PL group (1.0 ± 1.0, p=0.04*), but only the microdose group showed sustained decreases at 9-week follow-up.
  - On days they took a microdose, participants reported significantly higher scores on the VAS subscales of mood, energy, creativity, and drug effects and higher PANAS positive mood (with small effect sizes < 0.3) on all scales, with the exception of the drug intensity VAS (d=0.58).
  - STAIT-anxiety was also significantly decreased in the microdose group, while other outcomes of depression (QIDS), mental well-being (WEMWB), social connection (SCS) were insignificant.

    - **However, when accounting for belief effects, by including the number of times the participant guessed they had taken a microdose as a covariate, there was no difference between the dosing groups on any long-term measure or short-term measure other than self-reported drug effects (VAS subscale).**
    - The number of times that a participant guessed they had taken a microdose significantly correlated with Big 5 agreeableness, openness, and well-being and mindfulness.

Kaertner et al., 2021: Positive expectations predict improved mental-health outcomes linked to psychedelic microdosing

- Participants/Methods
    - It was a naturalistic online survey study with 253 participants who were planning to begin microdosing.
    - 46% of the participants reported having been diagnosed with one or more psychiatric disorders in the past, with MDD and an anxiety disorder being the most common.
    - Participants were not instructed on a microdosing regimen and were free to choose the substance and the dosing schedule.
    - 48% chose to microdose with psilocybin, 42% LSD, and the remaining 10% chose another psychedelic or a mix of the two.
    - Over 4 weeks, participants took an average of 9 doses (SD=2.31), with most participants following the Fadiman protocol.
- Results
    - After 4 weeks, participants showed significant improvements in self-reported well-being, symptoms of depression and anxiety, emotional stability, with the greatest difference being observed after the first week.
    - However, when controlling for baseline expectations of the long-term benefits of psychedelics, there were significant correlations with well-being ($r=0.275$, $p=0.007$), depressive symptoms ($r= -0.263$, $p=0.009$), and anxiety ($r= -0.220$, $p=0.025$).
    - Participants also saw significant increases in openness, agreeableness, and improvements in Social Connectedness (SCS), Nature-Relatedness (NR-6), Resilience (BRS), Avoidance (BEAQ).
- Notes/limitations
    - 68% dropout rate
    - The authors suggest that, given the context sensitivity (of set and setting) for psychedelic experiences, microdosing could serve as “active placebos,

> amplifying the expectations due to the plasticity-promoting nature of the drug effects."

# Theoretic mechanism of action

## Are microdoses exerting a neurobiological effect, are they just a placebo, or are they amplifiers of the placebo effect?

The self-blinding study supports the idea for a placebo effect, while the authors of the study we just covered suggest microdoses could amplify "expectations due to the plasticity-promoting nature of the drug effect."

The idea of psychedelics interacting with the placebo effect is intriguing, especially considering the placebo effect is a neurobiological mechanism in and of itself. In a paper discussed recently in the social anxiety episode (Hjorth et al., 2021), two groups received SSRIs, where one group was told they would be receiving an SSRI. Participants who believed they were taking an SSRI showed greater improvements and also increased striatal dopamine activity. In fact, the increase in striatal dopamine from the placebo effect has been shown to correlate with clinical improvement in parkinson symptoms (de la Fuente-Fernández and Stoessl, 2002). The placebo effect is also thought to modulate orbitofrontal and ventromedial prefrontal cortical connectivity with the nucleus accumbens and other reward-related circuitry (Wager and Atlas, 2015). Psychedelics are thought to preferentially increase plasticity in the cortex, particularly in the PFC (de Vos et al., 2021). Therefore, although it's somewhat of a stretch, psychedelics might potentiate the placebo effect.

Psychoplastogens, such as ketamine and psychedelics, are seeing recent interest for their ability to rapidly improve psychiatric symptoms, and it's possible that this could be a mechanism of microdosing. The downstream effects of 5-HT2A activation likely includes an increase in neurotrophic factors (Carhart-Harris and Nutt, 2017; Vargas et al., 2021), and microdoses can increase plasma BDNF (Hutten et al., 2020b). Neurotrophic factors like BDNF are thought to be lower in patients with MDD (Dwivedi Y. et al., 2009).

## The Psychedelic Experience, Suggestibility, and the Role of the Therapist

While the mechanism of psychedelics is unclear, it's known that the valence of the psychedelic experience and the psychological engagement in the experience play a considerable role in dictating the improvements in mental health symptoms. For instance, there is an example

described by Daniel Schmachtenburger, where, if someone sees a demon and is told by their trip-sitter that the demon is a threat to their soul and that the only means of avoiding the demon is by turning from it and by wearing a feather, this person can develop delusional thoughts about being chased and adopt avoidant behaviors and an emotional dependency for the feather that can persist long after the trip. Meanwhile, if the trip-sitter had instead told them that the demon is only a figment of their mind and that they should turn towards it, the demon can become an abstract representation of their negative thoughts and emotions. As the tripper turns to face the demon and is encouraged by their monitor, they can be encouraged to face it with curiosity and facilitate deep psychological insight. The demon can morph into their father screaming at them and then their grandfather screaming at their father, where they now come to the insight of generational trauma and can forgive their father for how he treated them as a child, allowing for the cultivation of self-acceptance and empathy.

It's important to recognize that all of the clinical studies to date have been guided in a way that promotes relaxation and introspection, as participants are briefed on what to expect during a psychedelic experience and are told to confront the challenging aspects they may encounter with a sense of curiosity. They also wear a blindfold and listen to comforting music. Without standardized practices in place, there is a concern that therapists can significantly influence the beliefs of patients who take psychedelics.

The psychological insights and beliefs gained from the psychedelic experience could be the driving factor in directing the increased plasticity for precipitating behavioral change. There are also studies suggesting the positive psychological effects of psychedelics are mediated by the feelings of mysticism experienced during a trip (Yaden and Griffiths, 2021; McCulloch et al., 2022**)**, where the psychedelic ("mind-revealing") effect is only seen with high enough doses.

Microdoses might not be powerful enough to elicit these insights for feelings of mysticism, which begs the question: is the psychedelic experience necessary for the antidepressant effects?

# Acute Effects on Creativity

Increased creativity is one of the most heavily touted benefits of microdosing in the community and is observed in subjective reports within observational studies (Fadiman and Korb, 2019; Johnstad, 2018; Lea et al., 2020; Anderson et al., 2019a).

Up until 2019, only a few studies had compared how microdosing changes one's objective performance of creativity, which is most often measured by performance on divergent and convergent thinking tasks.

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One of the first studies exploring objective measures of creativity in response to microdoses was by Prochazkova et al. in 2018 in a study titled, "Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting." This study was an open-label study at a psychedelic conference, where 38 participants completed divergent and convergent thinking tasks early in the day and then later that same day after taking a microdose of psychedelic truffles (.22-.44g).

In the second session when participants had taken the microdose, they showed significantly higher scores in divergent and convergent thinking tasks (Picture Concept Task for convergent thinking and the Alternative Uses Task for divergent thinking) compared to earlier in the day. They had higher scores in fluency (the number of ideas generated) and originality with small to moderate effect sizes. But the study was open-label and all participants first completed the tasks sober and then later in the day after taking a microdose of psilocybin, so we can't discern whether practice effects are at play here or whether there was an increased motivation to perform better on these tasks (Prochazkova et al., 2018).

In 2019, as part of an online survey study, Anderson et al. had microdosers and non-microdosers complete an online version of the Unusual Use Task (UUT) for divergent thinking, in which participants generate creative uses for mundane objects. On average, responses made by microdosers were rated to be more clever ($b=0.57$, $SE=0.13$, $z(423)= 4.25$, $p < 0.001$, $r=0.15$), more uncommon ($b=0.50$, $SE=0.15$, $z(427) =3.42$, $p < 0.001$, $r= 0.14$), and more remote ($b=0.74$, $SE=0.16$, $z(425)=4.49$, $p < 0.001$, $r=0.20$) than those made by non microdoses.

At this point, there was a lot of excitement about the potential for microdosing to increase creativity, but since then, there have been two lab-based RCTs that have shown no change in convergent thinking as assessed by the remote associations test (Bershad et al., 2019 N=20, LSD at 3 different doses vs placebo; Cavanna et al., 2022; N=34, psilocybin vs placebo), or on divergent thinking as assessed by the Alternative Uses Task (Cavanna et al., 2022), or the Wallach-Kogan test (Cavanna et al., 2022). The naturalistic placebo-controlled study I had mentioned earlier, in which participants blinded themselves (Szigeti et al, 2021), showed increased perceived creativity on days when participants took a microdose. Again, a majority of participants broke blind here.

Unlike the literature on depression, there is limited evidence of the effect of macrodoses on creativity, especially on divergent and convergent thinking. A 2021 placebo-controlled study by Mason et al., in which moderate macrodose of psilocybin (0.17 mg/kg or 12 mg/70 kg) showed acute deficits in both convergent thinking ($d=0.85$) and measures of DT, including fluency (the number of ideas generated; $d=0.84$) and originality (the number of unusual or unique ideas; $d=0.65$) compared to placebo, but participants reported an increase in the perceived quality of

their creative insights**.** At the 7-day follow-up, CT was still significantly decreased compared to placebo (d=0.60) while novel responses for the divergent thinking task (responses they had never thought of before or seen elsewhere) were increased compared to placebo (d=0.52).

- Limitations/takeaways
    - Divergent and convergent thinking are not perfect tools for assessing one's creativity, as most tasks used to quantify these measures rely heavily on semantic knowledge and processing speed, which both are likely disrupted in a psychedelic experience.
    - Because of the ability for psychedelics to alter self-referential processing, aspects of creativity related to personally-relevant problem solving could be a future direction of study. It's possible the increased between-network connectivity among cortical regions that do not normally influence each other could allow for the emergence of latent insights or "eureka moments."
    - "They are not at a higher level of creativity, but they can be creative longer - kind of steady, more in flow" (The Tim Ferriss Show Ep 66: The Psychedelic Explorer's Guide - Risks, Micro-Dosing, Ibogaine, and More).
        - It's possible that the anecdotes and observational studies in which participants report increased feelings of creativity could be due to psychedelics allowing people to access a creative mindset more often, or being forced into creative thinking, even though they are not objectively more creative. Otherwise, the placebo effect is likely the driving factor.

# Acute Effects on Cognitive Performance

Improving cognitive performance is the most common motive given by people who choose to microdose, according to an online survey study (Hutten et al., 2019), and qualitative and observational studies report increased self-rated focus and productivity with microdosing. (Fadiman and Korb, 2019; Anderson et al., 2019b).

However, the majority of laboratory studies (a total of 7) show no changes while subjects were under the effects of a microdose. Three studies showed no changes in general cognitive function (assessed by digital span substitution task; Hutten et al., 2020a, N=24, LSD; Family et al., 2019, N=48, LSD; De wit et al., 2022, N=56, LSD), two showed no change in working memory (n-back task; Bershad et al., 2019, N=20, LSD; De wit et al., 2022), one for reaction time (psychomotor vigilance task; Hutten et al., 2020a), one for visuospatial processing (Bershad et al., 2019), one showed slight but nonsignificant deficits for attention using the attentional blink task and for the stroop task (Cavanna et al., 2022, N=34, psilocybin vs. placebo), and this same study showed no differences for mind wandering, flow, or cognitive flexibility (Cavanna et al., 2022).

Two studies actually showed impairments in control and cognition based on 5 Dimensions of Altered States of Consciousness Questionnaire (5D-ASC), a 94-item self-report scale with subscales consisting of Oceanic Boundlessness (OB), Anxious Ego Dissolution (AED), Visionary Restructuralization (VR), Auditory Alterations (AA), and Reduction of Vigilance (RV) scales. Both studies showed the highest ratings of impairment in the highest dose group (Bershad et al., 2019; Hutten et al., 2020a), but Hutten et al. showed no effect on a cognitive control task.

Some of these lab-based studies of LSD show slight increases in vigor on the POMS in the highest dosing group relative to placebo (Bershad et al., 2019; De wit et al., 2022) and mild stimulatory/amphetamine-like effects on the Addiction Research Center Inventory (ARCI) (De wit et al., 2022; Murray et al., 2022), but others show sedating effects (Bershad et al., 2020; Family et al., 2019) and others show no difference (Hutten et al., 2020a).

There have yet to be any studies assessing microdosing's potential effects on learning.

- Limitations/takeaways
    - It seems like participants may feel as if they are impaired, but their performance is not significantly changed.
    - However, this goes against the notion that microdosing increases focus, as there weren't any studies that showed clear and consistent increases in performance on any of these tasks.

# Acute effects on perception

Within the microdosing community, microdoses are traditionally regarded as being sub perceptual or barely noticeable, but a large proportion of the lab studies and even qualitative studies report significant, dose-dependent increases in subjective drug effects (Anderson and Kjellgren, 2019; Bershad et al., 2019; Family et al., 2019; Holze et al., 2021; Hutten et al., 2020a).

On a similar note, Ramaekers et al. studied the effects of microdosing on pain and perception using a cold water submersion task in their study titled, "A low dose of lysergic acid diethylamide decreases pain perception in healthy volunteers." They randomized 24 participants to receive 5ug, 10ug, 20ug, or placebo and observed that 20 µg of LSD increased subjective ratings of pain tolerance ($p=0.006$) and decreased ratings of painfulness ($p=0.012$) and unpleasantness ($p=0.008$). They also found that, compared to placebo, the 10ug increased symptoms of

derealization (p=0.027) and dissociation (p=0.032) and 20ug of LSD increased symptoms of derealization (p=0.002), depersonalization (p=0.001), dissociation (p<0.001), and amnesia (p=0.002) according to a questionnaire (Brief Symptom Inventory-BSI18, which was mentioned for anxiety and depression earlier) (Ramaekers et al., 2021).

There are plenty of anecdotes on online forums of people using microdosing to support mindfulness practices and to increase mental clarity and emotional processing. Two lab studies showed that microdosing does not significantly influence acute responses to emotional faces or interoceptive awareness (Marschall et al., 2022; Bershad et al., 2019). The self-blinding study showed that all subjects improved on the cognitive and affective mindfulness scale (CAMS).

- Limitations/takeaways
    - At the doses used in these studies, participants in the higher dose groups tend to feel the effects. It seems the threshold for feeling the subjective effects tends to be around 10-13ug for most people (Bershad et al., 2019; Szigeti et al, 2021; Holze et al., 2021).
    - Microdosing may be useful for pain, but more evidence is needed.
    - It seems microdosing can increase feelings of dissociation and derealization, so more studies need to be conducted in patient populations that experience these symptoms and to determine what percent of the population experiences these effects.
    - No placebo-controlled studies have studied visual acuity.

# Neurophysiology

There has only been one imaging study of microdosing's effects on the brain, conducted by Bershad et al., 2020, in which they found connectivity changes in the amygdala and thalamus. Although mood changes were inconsistent, the increase in amygdala-middle frontal gyrus connectivity strength was positively correlated with positive mood after the drug (r=0.49, p<0.03).

Bershad et al., 2020: Preliminary report on the effects of a low dose of LSD on resting state amygdalar functional connectivity

- Participants/methods
    - Double-blind crossover study (N=20) comparing brain connectivity changes of healthy adults in response to a single dose of 13ug LSD or placebo
    - Measured resting-state connectivity via seed-based fMRI
- Results

    - LSD microdose increased amygdala connectivity with right angular gyrus, right middle frontal gyrus, and the cerebellum, and decreased amygdala connectivity with the left and right postcentral gyrus and the superior temporal gyrus.
    - Although mood changes were inconsistent, the increase in amygdala-middle frontal gyrus connectivity strength was positively correlated with positive mood after the drug ($r=0.49$, $p<0.03$).
    - No change in thalamocortical connectivity.
- Notes/limitations
    - Changes in resting state amygdala activity and connectivity have been inconsistent in macrodosing studies (Barrett et al., 2020). However, in response to emotional stimuli, increased amygdala activity has been observed (Roseman et al., 2018), as opposed to attenuated responses seen in patients taking SSRIs (Ma et al., 2015).
    - Alterations to thalamocortical connectivity are supposedly what leads to increases in brain entropy and altered perception (two parameters considered by some researchers to be driving factors for therapeutic effects), and the fact there was no change in this connectivity might suggest 13ug isn't enough to lead to changes in sensory processing or perception of oneself.

EEG was also used as part of two microdosing studies:

- Decreased theta band power with eyes closed (Cavanna et al., 2022; Murray et al., 2022)
- Decreased broadband power in major areas of DMN with eyes closed and in the PCC with eyes open (Murray et al., 2022), which are findings observed with larger doses.

# Safety

Psychedelics are considered to be benign substances with limited physiological effects.

However, according to a 2020 online survey study by Hutten et al., approximately 6% of microdosers report experiencing side effects, with headache, fatigue, dizziness, nausea, and trouble sleeping being the most commonly reported effects (Polito and Liknaitzky, 2021).

Multiple studies of macrodoses show mildly increased heart rate and blood pressure in a dose-dependent manner, while microdoses of LSD increase systolic/diastolic blood pressure by less than 10mmHg and do not significantly influence heart rate (Bershad et al., 2019; Bershad et al., 2020; Ramaekers et al., 2021).

However, one of the greatest areas of concern is the potential effect of microdosing on heart valves. "Fen-phen" (fenfluramine), also a 5-HT2B agonist, was withdrawn from the market due

to its role in causing valvulopathies similar to those seen in carcinoid syndrome (Roth, 2007) and there have been reports of valvulopathies in people who have taken MDMA chronically (Droogmans et al., 2007), as well as in people taking antiparkinsonian drugs with 5-HT2B agonist properties like cabergoline and pergolide (Zanettini et al, 2007). LSD is particularly potent in its activation of 5-HT2B, as well as psilocybin (Wacker et al., 2017). It's also a possibility that the metabolites of these drugs have a high affinity for 5-HT2B.

It's not clear yet how psychedelics interact with other drugs. Fadiman and Korb attempted to address this in their online study, and found limited interactions with a wide range of medications, but more research is needed (Fadiman and Korb, 2019).

It seems that people taking SSRIs need higher doses to feel effects of psychedelics compared to most people (Bonson et al., 1996), but it's not yet clear if this is due to some antagonistic interaction or whether the global downregulation of 5-HT receptors with SSRIs is at play here.

Serotonin syndrome is an obvious concern with psychedelics due to their serotonergic activity and has been observed in a few cases of patients taking MAOIs (Malcom and Thomas, 2021), but not specifically in patients taking SSRIs. However, ayahuasca, which contains DMT and MAOIs, may be more likely to lead to serotonin syndrome with concurrent use of SSRIs.

A recent study was conducted where participants took Escitalopram (10-20 mg) or placebo for 14 days before two high dose psilocybin treatment sessions (Becker et al., 2022). Escitalopram did not reduce the positive mood effects of psilocybin, level of circulating BDNF, SCL6A4 (SERT gene), or 5-HT2AR expression, and actually decreased negative mood effects and cardiovascular response. There were no significant changes in the QT interval or in pharmacokinetics.

# Conclusions and future directions

Ongoing trials:

- Murphy et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8062934/
    - "Eighty healthy male participants will receive 14 doses of placebo or 10 µg lysergic acid diethylamide orally every 3rd day over a 6-week treatment protocol. A battery of personality, creativity, mood, cognition, and EEG plasticity measures, as well as resting-state fMRI imaging, will be administered at baseline and at the end of the protocol. Creativity, mood, and plasticity measures will additionally be assessed in the acute phase of the first dose. Daily functioning will be monitored with questionnaires and a wearable sleep and activity tracker."
- Petranker et al. https://clinicaltrials.gov/ct2/show/NCT05259943

- "This protocol is for a University of Toronto sponsored, randomized, placebo-controlled crossover phase 2 study of the safety and efficacy of low doses of psilocybin in subjects with depressive symptoms who meet Diagnostic and Statistical Manual 5 (DSM-5) criteria for diagnosis of a persistent depressive disorder (PDD) with pure dysthymic syndrome and who are either unwilling to pursue standard treatment (psychotherapy and/or pharmacotherapy) or have previously been non responsive to standard treatment. This feasibility study will assess whether microdosing has a short-term impact on participant ratings of depressive symptoms. Participants will be administered one dose of either placebo or psilocybin once weekly for four weeks, and then all participants will be administered a dose of psilocybin once weekly for four additional weeks. Short surveys will be collected once weekly three days after the administration of psilocybin/placebo, and follow-ups will occur for up to two years following the beginning of the trial. Using this design will maximize the experimental power to detect an effect if one exists and would inform future research on microdosing in terms of duration, effect size, and expectancy bias."

# Concluding Thoughts:

- Placebo and confirmatory effects are a huge concern for the psychedelics field as a whole, and are likely to explain many of the beneficial effects observed in observational studies and in online anecdotes.
- Microdosing needs to be studied in clinical populations before conclusions can be made about its effectiveness in treating patients with psychiatric disorders.
- Likewise, more tests and applications of creativity are needed to discern whether microdosing can influence creative output.
- It seems relatively clear that cognitive performance is not enhanced.
- More research is needed to study the effects of microdosing on addiction.
- Is the psychedelic experience necessary for therapeutic effects? (Olson, 2020; Yaden and Griffiths, 2020)
- Would non psychedelic agonism of the 5HT2A receptor lead to clinical improvement? There's been a large push by pharmaceutical companies in designing non-hallucinogenic 5HR2AR agonists, but they have yet to be studied in humans.
- It might be the case that an individual's baseline functional connectivity or level of 5HT2A receptors influences the subjective and physiological response to psychedelics (Stenbæk et al., 2021; Preller et al., 2020), so even if the evidence continues to blow everyone away, it's likely that these substances won't be beneficial for everyone.

# Microdosing LSD & Psilocybin: The Future of Psychiatry or Placebo?

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