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Is Microdosing a Placebo?‡

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Abstract

Some recent research and commentary have suggested that most or all the effects reported by people who microdose psychedelics may be explained by expectations or placebo effects. Here we step through all the available evidence from dose-controlled studies that have investigated the effects of low doses of LSD and psilocybin. We suggest eight reasons why current claims that microdosing is predominately a placebo are premature and possibly wrong: 1) there have been only a small number of controlled studies; 2) studies have had small sample sizes; 3) there is evidence of dose-dependent effects; 4) studies have only investigated the effects of a small number of doses; 5) the doses investigated may have been too small; 6) studies have looked only at non-clinical populations; 7) studies so far have been susceptible to selection bias; and 8) the measured impact of expectancy is small. Considering the available evidence, we conclude that it is not yet possible to determine whether microdosing is a placebo.

Keywords: microdosing; psychedelics; hallucinogen; LSD; psilocybin; low dose; placebo; expectation.

1 Introduction

Microdosing, the practice of regular ingestion of low doses of psychedelic substances, gained widespread awareness around 2015, with a barrage of positive news stories describing a wide range of potential benefits (e.g., Leonard, 2015). Information about the specific dose that constituted a microdose varied, but the common claim was that microdosers were taking doses that did not result in marked alterations to their state of consciousness. Questionnaire data indicates that microdosing quickly became a popular phenomenon, with many thousands of individuals experimenting with this novel way of using psychedelics (Winstock et al., 2020). Widespread and increasing use initially occurred against a backdrop of almost no scientific knowledge about the effects, mechanisms, or risks of regular use of psychedelic drugs at low doses.

From 2018, academic studies of microdosing began to appear in the literature (e.g., Johnstad, 2018; Prochazkova et al., 2018). Early microdosing studies were predominately self-report survey studies, qualitative interviews, or observational prospective studies. Previously, we comprehensively reviewed all microdosing research up to April 2021 and found that these early studies predominately reported positive benefits of microdosing in the domains of mental health, wellbeing, cognition, personality, changes in conscious state, and physiological changes (Polito & Liknaitzky, 2022).

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However, not all studies have indicated benefits of microdosing. One influential study used a 'self-blinded' prospective design, whereby individuals prepared their own placebo or genuine dosing materials, mixed them up so they were unaware of the contents of each specific dose, and then completed a four week microdosing regimen, providing regular reports to the investigators (Szigeti et al., 2021). That study found little difference between the placebo and active dosing conditions, and also found that participants' guesses about whether they had consumed a placebo or genuine microdose had a strong influence on outcomes. Another prospective study reported that wellbeing outcomes were predicted by microdosers' expectations (Kaertner et al., 2021).

There have also now been 16 lab-based studies of microdosing that have administered controlled doses of either LSD or psilocybin. Our earlier review included details on eight of these lab studies (i.e., eight lab studies specifically investigating microdosing, published between 2018 and 2021). Since completing that review, there have been a further eight publications reporting either controlled lab studies of microdosing or field studies that have used a measured and controlled dose (see Table 1 for all microdosing studies with controlled doses). These studies, where the quantity of psychedelic substance is known and controlled, provide a more rigorous standard of evidence than studies based on self-administration.

Overall, studies with controlled doses have provided mixed evidence about the effectiveness of microdosing. This appears to have led to a shift in sentiment in media reporting and attitudes among some scientists, with emerging claims that microdosing may be largely driven by placebo effects and expectation (Dolan, 2022; Haridy, 2022; Siebert, 2021; Smith, 2022). In this paper, we review all the microdosing studies with known and controlled doses, with a particular focus on what this body of evidence can tell us about the role of placebo in explaining the outcomes that are reported by people who microdose.

2 Method

We followed a similar search procedure to Polito and Liknaitzky (2022), aiming to identify papers with a term related to any psychedelic substance in the title, plus a term indicating low doses in the title or abstract. Notably, in this study we included only studies where microdoses were administered along with a placebo comparison control. This meant that we excluded papers where a microdose was itself used a comparator in a study investigating the effects of higher doses of psychedelics (e.g., Griffiths et al., 2018), and studies where participants reported on naturalistic microdosing experiences. We restricted our search to papers published after 2018, which is when the first controlled microdosing study was published.

The search was conducted on PubMed on 21 April 2023 with the following syntax: ((psychedelic[Title] OR hallucinogen[Title] OR lsd[Title] OR psilocybin[Title] OR psilocin[Title] OR "Lysergic acid diethylamide"[Title] OR "Magic mushroom"[Title] OR dmt[Title] OR mescaline[Title] OR trimethoxyphenethylamine[Title] OR peyote[Title] OR "San pedro"[Title] OR dimethyltryptamine[Title] OR "2C-B"[Title] OR iboga[Title] OR ibogaine[Title]) AND (("low dose"[Title/Abstract] OR "low doses"[Title/Abstract] OR dose-related[Title/Abstract] OR microdose[Title/Abstract] OR microdosing[Title/Abstract] OR "Mini dose"[Title/Abstract] OR "Small dose"[Title/Abstract] OR "Sub-threshold"[Title/Abstract] OR "Sub-perceptual"[Title/Abstract] OR "Sub-acute"[Title/Abstract]) or "dose"[Title])) AND (("2018"[Date - Publication] : "3000"[Date - Publication])).

Inclusion criteria were: 1) use of 'classical' or serotonergic psychedelics; 2) controlled doses within a microdose range (see Table 1 in Polito & Liknaitzky, 2022); 3) inclusion of a placebo comparator condition; 4) reporting of primary empirical data; 5) use of human subjects; and 6) peer reviewed publications. The initial search resulted in 88 items, which were screened by each author independently. Any disagreements were resolved through discussion and consensus. The final sample contained 16 papers, as shown in Figure 1.

3 Results

Table 1 summarises the design and key findings of all microdosing studies with controlled doses. This summary shows a large number of variables have been investigated, with numerous findings that differentiate microdosing from placebo, and also numerous reported null effects. 11/16 (69%) of these papers reported pre-registration in clinical trials databases (Bershad et al., 2019, 2020; Cavanna et al., 2022; Holze et al., 2021; Hutten et al., 2020, 2021; Marschall et al., 2022; Ramaekers et al., 2021; Sanz et al., 2022; van Elk et al., 2022).

Table 1

Significant and null findings from microdosing studies with controlled doses

Study	Research Group	n	Doses	Target	– Significant Effects	– Null Findings
Bershad et al. (2019)	University of Chicago	20	Placebo, LSD (5, 10, 20ug)^	Acute	– DEQ: increased 'feel drug', 'feel high', 'like drug', 'dislike drug'. – ARCI: increased 'LSD effects'. – POMS: increased 'vigour'. – 11D-ASC: increased 'experience of unity', 'blissful state', 'impaired control & cognition'. – Safety/tolerability: increased blood pressure	– DEQ: no sig difference in 'wanting more'. – ARCI: no sig difference in 'amphetamine-stimulant effects', 'benzedrine-energy effects', 'morphine-benzedrine-euphoria effects', 'pentobarbital-chlorpromazine-sedative effects'. – POMS: no sig difference in 'friendliness', 'anxiety', 'elation', 'depression', 'anger', 'fatigue', 'confusion'. – 11D-ASC: no sig difference in 'changed meaning of percepts', 'spiritual experience', 'insightfulness', 'complex imagery', 'disembodiment', 'anxiety', 'elemental imagery', 'synaesthesia'. – Cognition: no sig difference in n-back accuracy or DSST digit encoding or accuracy. – Social exclusion: no sig difference in Cyberball Task. – Emotion processing: no sig difference in Emotional Images Task processing. – Creativity: no sig differences in Remote Associates Task.
Bershad et al. (2020)	University of Chicago	20	Placebo, LSD (10ug)^	Acute	– ARCI: increased 'pentobarbital-chlorpromazine-sedative effects'. – Neural connectivity: increased thalamus seed-based connectivity in cerebellum, amygdala seed-based connectivity in r angular gyrus, r middle frontal gyrus, l cerebellum; decreased amygdala seed-based connectivity in l and r post-central gyrus, superior temporal gyrus. – Correlation between LSD-induced increase in amygdala–middle frontal gyrus connectivity strength and increased in positive mood (PANAS).	– ARCI: no sig difference in 'amphetamine-stimulant effects', 'benzedrine-energy effects', 'morphine-benzedrine-euphoria effects', 'LSD-hallucinogen effects'. – Neural connectivity: No sig differences in thalamus connectivity in cortex or subcortical structures. – No correlation of changes in negative mood (PANAS) with alterations in connectivity strength. – Safety/tolerability: No sig differences on blood pressure or heart rate. – PANAS: no sig difference in positive or negative mood. – 5D-ASC: no sig difference in 'oceanic boundlessness', 'dread of ego dissolution', 'visionary restructuralisation', 'reduction of vigilance' or 'auditory hallucinations'. – DEQ: no sig difference in 'feel high', 'like drug', 'dislike drug', 'want more' or 'feel drug'

Study	Research Group	n	Doses	Target	– Significant Effects	– Null Findings
Cavanna et al. (2022)	Universidad de Buenos Aires	34	Placebo, Psilocybin (.5 truffles = .8mg)	Cumulative 2 doses	– VAS: increased subjective intensity – EEG measures: reduced eyes closed resting state theta band power	– EEG measures: No sig difference in auditory oddball ERPs – Cognition: no sig difference in TECA, CFS, TAS, FSS, MWQ, Stroop test, go/no go, backward masking. – Perception: no sig difference in binocular rivalry, backward masking. – BIEPS: no sig difference in wellbeing rating. – Physical activity: no sig difference in Fitbit record. – Creativity: no sig difference in CPS, RAT, AUT, W-KT scores. – BFI: no sig difference in personality assessment. – Mood: no sig difference in STAI, SSS, PANAS scores.
Sanz et al. (2022)					– NLP: Increased verbosity (sig differences found for answers related to perception, mood and alertness) and sentiment (positivity).	– NLP: No sig difference in semantic variability.
De Wit et al. (2022)	University of Chicago	56 (19 per condition)	Placebo, LSD (10, 20ug)^	Cumulative: 4 doses	– DEQ: increase in 'feel drug', 'feel high'. – POMS: increase in 'vigour'. – ARCI: increase 'amphetamine-stimulant effects', 'morphine-benzedrine-euphoria effects', 'LSD-hallucinogen effects'. – Social exclusion: reduced negative mood ratings during cyberball task. – 11D-ASC: increases in 'experience of unity', 'blissful state', 'insightfulness' and 'complex imagery'	– DEQ: no sig difference in 'like drug', 'dislike drug', 'want more'. – POMS: no sig difference in 'anger', 'depression', 'confusion', 'fatigue', 'friendliness', 'anxiety', 'elation'. – ARCI: no sig difference in 'pentobarbital-chlorpromazine-sedative effects', 'benzedrine-energy effects'. – Social exclusion: no sig difference in negative mood ratings at 3 or 4 day follow up. – 11D-ASC: no sig difference in 'spiritual experience', 'elementary imagery', 'audio-visual synaesthesia', 'changed meaning of percepts', 'disembodiment', 'impaired control and cognition' and 'anxiety'. – Safety/tolerability: No sig differences on heart rate or blood pressure. – Emotion-reading: no sig difference in performance on emotional faces or emotional images task. – Cognition: no sig difference in n-back or digit symbol substitution task performance.

Study	Research Group	n	Doses	Target	– Significant Effects	– Null Findings
Glazer et al. (2022)	University of Chicago	18/22	Placebo, LSD (10, 20ug)^	Acute	– EEG: increased RewP and LPP amplitudes for reward (vs. neutral) feedback, and increased FB-P3 amplitudes for positive (vs. negative) feedback	– None.
Murray et al. (2022)					– DEQ: increases in 'feel drug', 'feel high', 'like drug', 'want more'. – POMS: increase in 'elation', 'anxiety', 'positive mood'. – ARCI: increase 'amphetamine-stimulant effects', 'benzedrine-energy effects', 'morphine-benzedrine-euphoria effects', 'LSD-hallucinogen effects'. – Safety/tolerability: increased heart rate and blood pressure. – EEG measures: reduced resting state activity in DMN and temporoparietal cortices; reduced oddball error rates and attenuated potentials associated with P300 and N170 ERPs.	– DEQ: no sig difference in 'dislike drug'. – POMS: no sig difference in 'anger', 'depression', 'confusion', 'fatigue', 'friendliness', 'arousal', or 'vigour'. – ARCI: no sig difference in 'pentobarbital-chlorpromazine-sedative effects'.
Hutten et al. (2020)	Maastricht University	23/24	Placebo, LSD (5, 10, 20ug)	Acute	– Psychomotor Vigilance Test: fewer attentional lapses. – DSST: reduced number of digits correctly encoded – POMS: changes across all items, specifically increased 'anxiety', 'confusion', 'elation', 'fatigue', 'friendliness', 'vigour'; decreased 'anger', 'depression'. – VAS: increases in 'under the influence', 'high', 'good drug effect', 'bad drug effect', 'liking' 'concentration', 'happy' and 'productive'. – 5D-ASC: increased 'oceanic boundlessness', 'dread of ego dissolution', 'visionary restructuralisation', 'reduction of vigilance'. – 11D-ASC: increased 'insightfulness', 'impaired control & cognition', 'changed meaning of percepts'.	– Psychomotor vigilance test: No sig difference in reaction time. – DSST: no sig difference in accuracy. – Cognitive Control Task: no sig difference in cognitive control – 5D-ASC: no sig difference in 'auditory alterations'. – 11D-ASC: no sig difference in 'experience of unity', 'spiritual experience', 'blissful state', 'disembodiment', 'anxiety', 'complex imagery', 'elemental imagery', 'synaesthesia'. – Ego Dissolution Inventory: no sig difference in ego dissolution. – Groninger Sleep Scale: no sig difference in sleep quality.
Holze et al. (2021)					– VAS: increase in 'under the influence', 'good drug effect'.	– VAS: No sig difference in 'bad drug effect'. – Pharmacokinetics: No LSD accumulation with repeated doses. – Pharmacodynamics: No acute tolerance.
Hutten et al. (2021)					– Increased BDNF following 5µg and 20µg LSD. – Cold pressor test: increased pain tolerance, reduced	– No sig difference in BDNF following 10 µg LSD.

Study	Research Group	n	Doses	Target	– Significant Effects	– Null Findings
Ramaekers et al. (2021)					ratings of 'unpleasantness' and 'painfulness'. – CADSS: increased 'amnesia', 'depersonalization', 'derealization', 'dissociation'. – Safety/tolerability: increased diastolic and systolic blood pressure.	– Cold pressor test: No sig difference in ratings of 'stress'. – Safety/tolerability: no sig difference in heart rate.
Marschall et al. (2022)	Leiden University	52/30	Placebo, Psilocybin (.7g truffles = 1.5mg)	Cumulative 5-7 doses	– None.	– Emotional go/no go: no sig difference in emotion processing. – DASS-21: no sig difference in depression, anxiety or stress ratings
van Elk et al. (2022)					– Awe video task: Increased ratings of awe; higher expectations produced stronger feelings of awe	– MAIA: no sig difference in interoceptive awareness. – Art rating task: no sig difference in aesthetic experience rating. – Self-appraisal: No sig difference in ratings of body size.
Murphy et al. (2023)	University of Auckland	80 (40 per condition)	Placebo, LSD (10ug)	Cumulative 14 doses	– VAS: dosing day increases for 'connected', 'creative', 'energy'*, 'happy', 'well'*; decreases of 'angry', irritable. – Expectancy/Experience: Self-reported changes post intervention exceeded expectancies for 'energy', 'happy', connected'.	– VAS: no sig. differences in 'calm', 'focused', 'motivated', 'anxious', craving', 'jittery', 'sad', 'stressed', 'tired'. – Expectancy/Experience: No sig. differences between self-reported changes post intervention and baseline expectancies for 'angry', 'anxious', 'calm', 'cog functioning', 'craving', 'creative', 'focused', 'guilty', 'meditative', 'motivated', 'open', 'sad', 'self efficacy', 'stressed', 'well'. – Trait: no sig differences on BFI, DFlex, FFMQ, MODTAS. – Emotion: do sig differences on NIH Emotion Battery, DASS, PSS. – Cognition: No sig. differences on NIH Cognitive Battery. – Safety/tolerability: No sig. differences in AEs, blood pressure, heart rate.

Study	Research Group	n	Doses	Target	– Significant Effects	– Null Findings
Yanakieva et al. (2019)	Eleusis Benefit Corporation / Goldsmiths, University of London	48 (12 per condition)	Placebo, LSD (4, 8, 15ug)	Cumulative: 4 doses	– VAS: increase in 'feel drug'. – Temporal Reproduction Task: Longer reproduction times for intervals > 2000ms.	– VAS: No significant differences on 'feel high', 'perceptual distortion', 'unusual thoughts', 'concentration'.
Family et al. (2020)				Cumulative: 6 doses	– VAS: Increased 'feeling dizzy', 'body changes'. – 5D-ASC: Increased 'vigilance reduction'. – Safety & Tolerability: Mild-moderate headaches.	– VAS: No sig differences in 'liking drug', 'disliking drug', 'wanting more'. – 5D-ASC: No sig differences in 'oceanic boundlessness', 'dread of ego dissolution', 'visionary restructuralisation', 'auditory alterations'. Safety & Tolerability: No sig. differences in blood pressure, pulse, haematology, blood chemistry, urinalysis, ECG. – CANTAB: No sig. difference on any task (reaction time, paired associates, vis info processing, spatial working memory). – BTrackS: No sig difference in balance or proprioception.

Note: Papers reporting on the same data are displayed in a single row. Table is ordered alphabetically, based on the first published paper for each dataset.
^ Some LSD studies used LSD tartrate. Doses reported in this table show the equivalent dose in LSD base.
* In Murphy et al. (2023), measures marked with '*' remained significant when only analysing participants who were unsure of which condition they were in.
ARCI = Addiction Research Centre Inventory; ASC = Altered States of Consciousness Scale; AUT = Alternative Uses Test; BFI = Big Five Inventory; BIEPS = Psychological Well-being Scale; BTrack = Balance Management System; CANTAB = Cambridge Neuropsychological Test Automated Battery; CFS = Cognitive Flexibility Scale; CPS = Creative Personality Scale; DASS = Depression Anxiety Stress Scale; DEQ = Drug Effects Questionnaire; Dflex = Detail and Flexibility Questionnaire; DSST = Digit Symbol Substitution Test; FFMQ = Five Facets of Mindfulness Questionnaire; FSS = Flow State Scale; MAIA = Multidimensional Assessment of Interoceptive Awareness; MEG = magnetoencephalography; MODTAS = Modified Tellegen Absorption Scale; MWQ = Mind Wandering Questionnaire; NLP = Natural Language Processing; PANAS = Positive and Negative Affect Scale; POMS = Profile of Mood States; PSS = Perceived Stress Scale; RAT = Remote Associates Test; SSS = Short Susceptibility Scale; STAI = State-Trait Anxiety Inventory; TAS = Tellegen Absorption Scale; TECA = Cognitive and Affective Empathy Test; VAS = Visual Analog Scales (exact items vary across studies); W-KT = Wallach-Kogan Test.

Neurobiological: There have been four neuroimaging studies to date, showing consistent evidence of neural changes related to microdosing. In an fMRI study, Bershad et al. (2020) showed that microdosing LSD led to increased neural connectivity across the amygdala and cerebellum. In an EEG study, Murray et al. (2022) showed reduced resting state activity in the default mode network and reduced error rates in an oddball paradigm. Cavanna et al. (2022) similarly showed reduced EEG resting state power, but did not find differences in oddball ERP responses. Finally, in an ERP study, Glazer et al. (2022) showed increased neural responses to reward processing in a microdosing condition compared to placebo.

Physiological: Studies also showed microdosing impacts other physiological and biological processes. In particular, microdosing appears to increase pain tolerance (Ramaekers et al., 2021) and levels of brain derived neurotrophic factor (BDNF; Hutten et al., 2021). However, there was no evidence that microdosing impacts sleep (Hutten et al., 2020), general levels of physical activity measured by an app-based fitness tracker (Cavanna et al., 2022), or balance (Family et al., 2020).

Phenomenological: There is consistent evidence showing that microdosing changes individuals' acute conscious state. In particular VAS ratings of feeling 'under the influence', 'good drug effects' 'subjective intensity', 'happy' and 'productive' were reliably increased following microdosing (Cavanna et al., 2022; Holze et al., 2021; Hutten et al., 2020; Murphy et al., 2023; Yanakieva et al., 2019). Ratings using standardised measures of consciousness alteration (the 5D-ASC, 11D-ASC or Ego Dissolution Inventory) were less clear. There were indications that microdosing impacted scores on 'oceanic boundlessness', 'dread of ego dissolution', 'visionary restructuralization', 'vigilance reduction', 'experience of unity', 'blissful state', 'changed meanings of percepts', 'insightfulness', 'complex imagery' and 'impaired cognition and control', but these findings were not consistent across all of the studies that used the ASC scales (Bershad et al., 2019, 2020; de Wit et al., 2022; Family et al., 2020; Hutten et al., 2020). None of the studies found evidence that microdosing increased altered state dimensions related to 'ego dissolution', 'spiritual experience', 'disembodiment', 'anxiety', 'elemental imagery', or 'synaesthesia'. Similarly, studies using the Addiction Research Centre Inventory (ARCI; Haertzen et al., 1963) all showed that microdosing was scored higher than placebo, but across different subscales in different studies (A. Bershad et al., 2020; A. K. Bershad et al., 2019; de Wit et al., 2022; Murray et al., 2022).

Affective: Microdosing was consistently shown to increase mood states related to feeling of vigour (Bershad et al., 2019; de Wit et al., 2022; Hutten et al., 2020; Murphy et al., 2023). There were also indications of increases in mood state scores related to 'friendliness', 'anxiety', 'elation', 'depression', 'anger', 'fatigue' and 'confusion', but these were not found across all studies (Hutten et al., 2020; Murphy et al., 2023; Murray et al., 2022). Murphy et al. (2023) found some evidence of acute increased positive mood states and decreased negative mood states only on the days that participants took a microdose, but little evidence of persisting mood changes after a period of six weeks microdosing. Microdosing did lead to increased perception of awe but not lead to changes in aesthetic experience (van Elk et al., 2022). Individuals who microdosed, also did not differ from placebo on the Positive and Negative Affect Scale (Bershad et al., 2019; Cavanna et al., 2022), Emotional Images Task (Bershad et al., 2019; de Wit et al., 2022) or an emotion based go/no go task (Marschall et al., 2022).

Cognitive: There have been some intriguing indications that microdosing may impact cognitive functioning, in particular leading to changes in time perception (Yanakieva et al., 2019) and reduced attentional lapses (Hutten et al., 2020). There were also mixed findings related to social cognition with one study showing reduced negative social processing during a cyberball task (de Wit et al., 2022) and one showing no changes (Bershad et al., 2019). Finally, microdosing did lead to changes in language production, characterised by increased verbosity and sentiment scores (Sanz et al., 2022). However, these findings must be interpreted cautiously as several studies failed to find any evidence that microdosing impacts performance on standard cognitive batteries (Bershad et al., 2019; Cavanna et al., 2022; de Wit et al., 2022; Family et al., 2020; Murphy et al., 2023), creativity tasks (Bershad et al., 2019; Cavanna et al., 2022), suggestibility (Cavanna et al., 2022), or self-representation (van Elk et al., 2022).

Mental health: Only two studies investigated measures related to wellbeing or mental health. Cavanna et al. (2022) did not find evidence of wellbeing improvements or any change in state or trait

anxiety in microdosers. Marschall et al. (2022) similarly did not find any changes in depression, anxiety, or stress in their microdosing condition. However, it is worth noting that these studies both recruited healthy samples (see Section 4.6).

4 Discussion

This review highlights a range of neurobiological, physiological, phenomenological, cognitive, and affective changes associated with microdosing psychedelics in placebo-controlled studies (see Table 1). On the one hand, this set of findings appears to indicate that microdosing is having some effects. The most compelling or reliable effects include: changes in acute conscious state, increased feelings of vigour, and increased pain tolerance.

Table 1 also shows that there are several variables that do not appear to differ between microdosing and placebo conditions. These results indicate that microdosing may not have beneficial effects on creativity or cognition, despite these being the main benefits reported in anecdotes and media stories.

However, a methodological challenge for many microdosing studies is that the success of blinding methods is largely unknown, making any distinction between drug and expectancy effects difficult. Only seven studies assessed participants' ability to guess their experimental condition, and these, indicated only partial success of the blind in the drug condition (see Polito and Liknaitzky, 2022 for further discussion of blinding issues in microdosing research). No microdosing studies to date have used an active placebo. As the majority of studies reviewed here indicated significant subjective effects in the microdosing condition only, it is likely that a substantial proportion of participants in these studies were able to identify whether they had taken a microdose. Relatedly, Szigeti et al., (2021) reported that participants' beliefs about what they had taken had a stronger influence on outcomes than their actual experimental condition.

Given the null findings reviewed above, difficulty blinding, and a small number of studies that suggest a larger role for expectancy than drug effects with microdosing, it is understandable that scepticism has tampered some of the early enthusiasm for the effects and potential usefulness of microdosing, at least within the scientific community. However, in our view there is currently insufficient evidence to be confident that the effects attributed to microdosing are drug or placebo effects, or some combination of both. Instead, the field is nascent, with good reasons for both scepticism and enthusiasm, with considerable need for more research. Below, we present eight reasons that one ought to be cautious about jumping to conclusions regarding the mechanisms driving current findings.

4.1 Only a small number of studies

First, there is a relatively small amount of empirical data to draw conclusions from. Although there have been 16 papers reporting dose-controlled microdosing studies, several of these papers have come from the same datasets. There have been just nine independent dose-controlled microdosing experiments, conducted by just six different labs (see Table 1). Furthermore, the substance, doses, measures, and methods used have varied considerably across these studies, meaning that there have not been a many directly replicated findings across this literature.

4.2 Studies have small sample sizes

Second, sample sizes in these controlled studies have been small. The average number of participants in microdosing conditions across all nine experiments was 26. If there are true pharmacological effects of microdosing, these are likely to be relatively small (certainly smaller than the effect sizes found in high dose psychedelic studies). To detect such effects, larger samples are likely to be needed.

4.3 Evidence of dose-dependent effects

Third, these studies have reported a range of outcomes that differ between microdosing and placebo conditions. For example, there is consistent evidence that microdosing leads to changes in neurophysiology and subjective effects. Of particular note, studies that included multiple doses within the microdosing range consistently showed dose dependent effects. This was the case for both psychological (e.g., Hutten et al., 2020) and neurophysiological variables (e.g., Murray et al., 2022). This suggests pharmacology is impacting certain outcomes, distinct from any expectancy effects.

4.4 Studies have only investigated a small number of doses

Fourth, most of these dose-controlled studies have investigated the acute effects of a single microdose. Only two psilocybin studies have investigated the effects of cumulative dosing: Marschall et al. (2022) and van Elk et al. (2022) reported on the cumulative effects of 5-7 doses of psilocybin taken over three weeks; and Cavanna et al. (2022) and Sanz et al. (2022) reported on the cumulative effects of 2 doses of psilocybin taken over a single week. Three LSD studies have looked at cumulative dosing: de Wit et al. (2022) reported on the cumulative effects of four doses of LSD taken over three weeks; and Yanakieva et al. (2019) and Family et al. (2020) reported on the effects of 4 or 6 doses of LSD taken over two weeks. Only Murphy et al. (2023) have investigated the effects of microdosing for a period longer than a month. They reported on the cumulative effects of 14 doses of LSD taken over six weeks. Although it is scientifically interesting to explore the effects of a single dose or a small number of doses, findings from studies focused on short term microdosing may have limited generalisability to the reported benefits of microdosing in naturalistic settings, which are generally associated with recurrent dosing for many weeks or months. Like pharmaceutical serotonergic medications, microdoses may have long term cumulative effects. Studies to date have not investigated this possibility. As a comparison, if we were to assess changes to an individual's mood after administration of a single dose of a traditional antidepressant medication we would be unlikely to find any effect, even though long term use of that medication may lead to significant improvement. This may explain the apparent lack of mood and mental health benefits in these studies, despite common reports of such effects in 'the wild'.

4.5 Doses investigated may be too small

Fifth, studies of psilocybin may have investigated doses that are too low for therapeutic or cognitive enhancement effects. Determining the appropriate doses for microdosing research is complex: the appropriate dose range is likely to be quite narrow, being high enough to produce meaningful changes but low enough to be sub-hallucinogenic and without functional impairment. However, people appear to show wide variability in dose-response to psychedelics, implying that optimal microdoses, and any associated benefits, may depend on precise individual tailoring. Consequently, it is possible that many microdosing studies have used inadequately small doses to produce meaningful changes (see Polito & Liknaitzky, 2022 for related discussion on bidirectional effects). In particular, only two psilocybin experiments were included, one of which used psilocybin truffles with the equivalent of .8mg synthetic psilocybin (Cavanna et al., 2022; Sanz et al., 2022), the other used truffles with the equivalent of 1.5mg synthetic psilocybin (Marschall et al., 2022; van Elk et al., 2022). Madsen et al. (2019) reported pharmacokinetic analyses of low doses of psilocybin, showing that the peak plasma psilocin concentration following ingestion of 3mg synthetic psilocybin was just 2 µg/L. Inferring from these results, it seems likely that the doses investigated in the psilocybin microdosing studies (.8 and 1.5mg psilocybin) would lead to psilocin concentration levels of approximately 1 µg/L or less. This may not be sufficient for meaningful psychopharmacological effects.

4.6 Studies have only looked at non-clinical populations

Sixth, all of the microdosing studies reviewed here investigated non-clinical volunteers. Findings across these samples were mostly not supportive of microdosing improving mental or physical health variables. However, such findings may be explained by ceiling effects at the group level (e.g., the limited ability for any intervention to improve levels of depression in a non-depressed sample). Indeed, self-

report data on microdosing indicates significant clinical benefits (e.g., Hutten et al., 2019b; Lea et al., 2020c). These claims can only be validly tested in controlled clinical samples, and this research has not yet been done.

4.7 Selection bias

Seventh, the studies reviewed involve considerable levels of selection bias. Specifically, all bar one of these studies either recruited volunteers with prior experience of psychedelics or recruited from community events organised by psychedelic education organisations. This means that it is likely that participants across all of these studies had well-formed expectations and beliefs about the efficacy of psychedelics that may differ from psychedelic-naïve individuals. These expectations may have influenced results in several ways. For example, experienced psychedelic users may have been more able to distinguish when they were in a placebo condition, and therefore more disappointed. Studies in more representative samples would provide a clearer test of potential pharmacological effects with less confounding by effects related to beliefs and expectations.

4.8 Measured impact of expectancy is small

Eighth, although several papers have suggested that the effects of microdosing may be largely due to placebo and expectation effects (Cavanna et al., 2022; Kaertner et al., 2021; Szigeti et al., 2021; van Elk et al., 2022), when these effects are measured directly, findings are at best mixed. The strongest evidence for the claim that expectations drive the reported effects of microdosers comes from: a) Cavanna et al. (2022), who showed that participants who broke blind reported greater microdosing effects compared to those that remained blinded; and b) Szigeti et al. (2021), who showed that participants' guess as to whether they had taken a microdose or placebo had a much greater impact on outcomes than whether or not they had actually consumed a microdose. These results are compelling, however it is notable that Cavanna et al. may have used insufficient doses for pharmacological effects (.8mg psilocybin; see section 4.5) and Szigeti et al. was an observational study with unknown dosing. Additional evidence for expectancy effects comes from Kaertner et al. (2021), who found that baseline expectations predicted mood and wellbeing outcomes in an observational, prospective microdosing study. However, the proportion of variance explained by expectations was only 5 - 8%, suggesting that this is not a primary mechanism for explaining the outcomes of microdosing. Similarly, the other studies reviewed here do not provide strong evidence for expectation effects. In the study out of Leiden University (reported in Marschall et al., 2022 and; van Elk et al., 2022), the role of expectation was inconsistent: expectation did predict feelings of awe but did not predict mood or interoception. Finally, Hutten et al. (2020) reported a clear disconnect between expectations and outcomes on a cognitive vigilance task, with the majority of participants increasing accuracy in the microdosing condition but reporting expectations that their performance had deteriorated. Overall, based on the current data, it seems that although expectations likely have an influence on at least some microdosing outcomes, there is not compelling evidence to suggest that this is the primary mechanism for the majority of reported effects in these studies or in the wild.

4.9 Conclusion

So, is microdosing a placebo? This is a question that seems to evoke strong opinions amongst psychedelic researchers. A microdosing sceptic will look at the results in Table 1 and argue that all or most of the effects that have been reported are due to expectation and placebo effects. Ultimately, that may turn out to be correct. However, we argue that based on current data, there is not strong evidence for a placebo interpretation of the effects of microdosing. Specifically, there have only been a small number (Section 4.1) of low powered studies (Section 4.2), with methodological concerns including selection bias (Section 4.7) and problematically small doses (Section 4.5). Additionally, most research has looked only into the acute effects of microdosing in healthy populations – almost nothing is known about the sustained impacts of a course of microdoses in a controlled setting (Section 4.4), and we have no data at all on

potential clinical effects (Section 4.6). These issues mean that research to date may not have been sensitive enough to detect subtle pharmacological effects of low doses. Nevertheless, even within this restricted set of data there is considerable evidence of dose-dependent changes that do suggest microdosing drug effects (Section 4.3). Finally, studies that have directly investigated the role of expectation have not found consistent evidence that participants' beliefs are the primary driver of outcomes (Section 4.8), undermining the case for a placebo interpretation.

Overall, in light of consistent reports of benefits from self-report studies (e.g., Anderson et al., 2019; Cameron et al., 2020; Hutten et al., 2019b; Lea et al., 2020c; Polito & Stevenson, 2019; Rootman et al., 2021, 2022) and lack of clear evidence on the role placebo in controlled studies to date, further microdosing research is warranted. To definitively determine what is driving the positive effects reported by microdosers, we need well-powered, longitudinal studies across both healthy and clinical populations.

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