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Review article

The emerging science of microdosing: A systematic review of research on low dose psychedelics (1955–2021) and recommendations for the field☆

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ABSTRACT

The use of low doses of psychedelic substances (microdosing) is attracting increasing interest. This systematic review summarises all empirical microdosing research to date, including a set of infrequently cited studies that took place prior to prohibition. Specifically, we reviewed 44 studies published between 1955 and 2021, and summarised reported effects across six categories: mood and mental health; wellbeing and attitude; cognition and creativity; personality; changes in conscious state; and neurobiology and physiology. Studies showed a wide range in risk of bias, depending on design, age, and other study characteristics. Laboratory studies found changes in pain perception, time perception, conscious state, and neurophysiology. Self-report studies found changes in cognitive processing and mental health. We review data related to expectation and placebo effects, but argue that claims that microdosing effects are largely due to expectancy are premature and possibly wrong. In addition, we attempt to clarify definitional inconsistencies in the microdosing literature by providing suggested dose ranges across different substances. Finally, we provide specific design suggestions to facilitate more rigorous future research.

1. Introduction

Microdosing is the practice of regularly ingesting very low doses of psychedelic substances, usually for the purpose of improving wellbeing, cognition, mood, or interpersonal processes (Kuypers et al., 2019). Over the past five years, the popularity of microdosing has increased rapidly in Western societies (Cameron et al., 2020; Winstock et al., 2020). Whereas illicit drug use of all kinds has often been considered a taboo topic, microdosing is now positively discussed in mainstream news stories (Leonard, 2015), documentaries (Gleiberman and Gleiberman, 2020), books (Waldman, 2017), movies (Schroeder, 2019) and entertainment television (Nicholson, 2018). After describing what microdosing entails and providing context for the sudden popularity of this practice, this review outlines and summarises scientific findings on the effects of microdosing from both the first and current waves of psychedelic research. We draw out the most robust findings to date, examine the methodological quality of the included studies, and discuss patterns across the literature that may shed light on the possible actions and effects of microdosing. We conclude with several open questions for the field, and provide a list of recommendations for a robust science of microdosing.

1.1. What is microdosing?

Microdosing can refer to the ingestion of a wide range of psychedelic substances at very low doses: lysergic acid diethylamide (LSD) and psilocybin are the most common, but people also report microdosing with mescaline, dimethyltryptamine (DMT), amphetamines, Salvia divinorum and other research chemicals (Polito and Stevenson, 2019; Rosenbaum et al., 2020). Critically, unlike other forms of psychedelic use, microdosers usually consume these substances regularly or semi-regularly for prolonged periods of time (for example, a common

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schedule is to dose every 3 days; Rosenbaum et al., 2020).

1.2. How much is a microdose?

The precise quantity that constitutes a microdose is difficult to define, and to date there have been no consistently accepted criteria amongst researchers. The most commonly reported definition is that a microdose is a dose between approximately one tenth and one twentieth of a typical recreational dose, although this range is uncomfortably imprecise for scientific purposes. There are perhaps three key reasons for uncertainty in defining dosing criteria. First, as microdosing typically involves taking unregulated substances, users cannot be confident about the identity of their drugs, or quantities of the active constituents they contain.

Second, there is considerable variation in pharmacological and subjective effects within and across substances, and also across individual responses to a given substance. That is, it is difficult to establish equivalent dose ranges for different classes of drug (e.g., LSD vs. psilocybin), for variants of a given class (e.g., different species of psilocybin-containing mushrooms), for different methods of preparation (e.g., identical mushrooms dried or fresh), or for different people (e.g., individual differences in subjective effects to an identical dose and substance can vary widely).

Third, there is no consensus regarding the subjective effects (or lack of effects) that should be associated with microdosing. In popular reports and guides, microdosing is often referred to as 'sub-perceptual', meaning that users should take a dose so low that they cannot identify any drug effects (e.g., Leonard, 2015). Many microdosers claim anecdotally that this is the case (i.e., that they notice no effects of microdosing). Yet, in qualitative studies, participants often describe alterations of consciousness (Andersson and Kjellgren, 2019) and in lab-based studies, participants frequently report some acute effects following ingestion of microdoses (see 3.3.5). This suggests that individuals who are microdosing often have insight into subtle subjective changes. Considering this, it may be that the effects of microdosing are not truly sub-perceptual, and instead may better be described as *sub-hallucinogenic* (e.g., Anderson et al., 2019a; Cameron et al., 2020; Petranker et al., 2020; Rosenbaum et al., 2020).

As a consequence of these difficulties, not all microdosing studies have specified explicit dose ranges. Based on doses and associated subjective effects that have been reported, we summarise plausible ranges for microdosing various substances in Table 1.

1.3. Why has microdosing become popular?

The current wave of interest in microdosing can be traced back to 'The Psychedelic Explorers Guide', a book by James Fadiman (2011), which popularised the term and led to a subsequent boom in anecdotal reports of psychedelic microdosing, media stories, and scientific research. This interest in microdosing coincides with a broader positive shift in attitudes to psychedelics over the past few years, evidenced by dramatic increases in reported lifetime use of hallucinogens (Yockey et al., 2020), the easing of legal restrictions around personal use (Aday et al., 2019), and the establishment of high-profile psychedelic research centres (Aday et al., 2020).

These changes have been largely driven by a reinvigoration of scientific interest in the therapeutic potential of psychedelics (Nutt et al., 2020). However, whereas the bulk of research involving 'high dose' psychedelics has focused on their clinical potential (Carhart-Harris and Goodwin, 2017), an additional theme in microdosing research has been the capacity of these substances to enhance cognition and wellbeing in healthy individuals. With a wide range of benefits ascribed to microdosing (Fadiman and Korb, 2019), a considerable uptake of the practice in the community (Andersson and Kjellgren, 2019; Lea et al., 2020a), the recent emergence of commercial interests (Rosner, 2020), and almost no controlled science until a few years ago, microdosing is a curious phenomenon. Given this level of public, scientific, and industry interest in microdosing, it is important to establish what has been empirically demonstrated, and separate scientific data from anecdote and hype.

Table 1
Plausible dose ranges for microdoses of various substances.

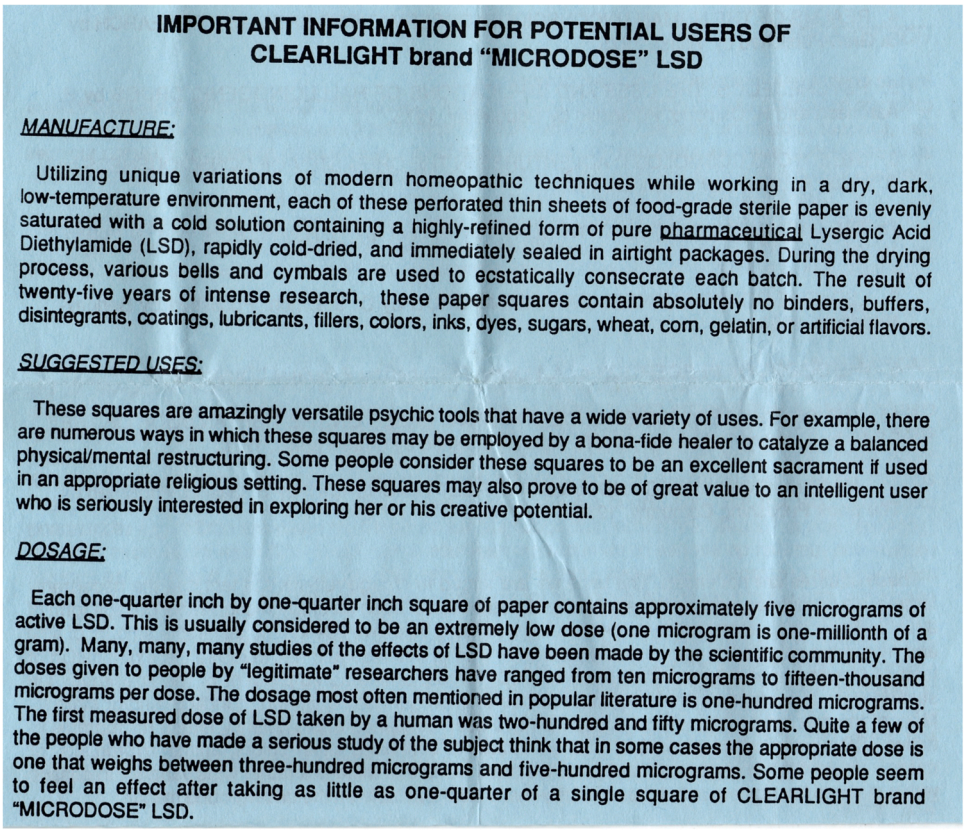
Compound	Typical recreational or therapeutic dose range	Intoxication threshold dose range	Plausible microdose dose range
Psilocybe cubensis dried mushroom: PO	3–5 g	0.5–1.5 g	0.1–0.5 g
Psilocybin synthetic: PO	17–30 mg[a]	3–8 mg[b]	0.8–5 mg[c]
Psilocybin synthetic: IV[#]	2 mg/70 kg – moderate dose[d]	1 mg[e]	0.5 mg[e]
LSD: PO	100–200 μg	20–25 μg[f]	6–20 μg[g]
DMT: IV[#]	14–28 mg/70 kg[h]	3.5 mg/70 kg	0.7–3.5 mg/70 kg
DMT: smoked	25 mg[i]		8–9 mg[j]
DMT: IM[#]	50–70 mg/70 kg	30 mg/70 kg[k]	6–25 mg/70 kg
Ibogaine synthetic: IV[#]	1000–2000 mg/70 kg (possibly starting at 200 mg/70 kg)	100–210 mg/70 kg[l]	20 mg/70 kg[m]

Note: PO, per oral; IV, intravenous; IM = intramuscular; LSD, lysergic acid diethylamide; # = depends on infusion rate.
[a] Griffiths et al., (2016, 2018); Wackermann et al. (2008).
[b] Abramson and Rolo (1965); Griffiths et al. (2011).
[c] Fanciullacci et al.(1974); Griffiths et al., (2016, 2018); Hasler et al. (2004); Madsen et al. (2019); Moreno et al. (2006); Wackermann et al. (2008).
[d] Hasler et al. (1997); Turton et al. (2015).
[e] Hasler et al. (1997).
[f] Abramson and Rolo (1965); Fanciullacci et al. (1974); Gasser et al. (2014); Greiner et al. (1958); Holze et al. (2021); Isbell Ramaekers et al., (1956, 2021); Yanakieva et al. (2019).
[g] Abramson and Rolo (1965); Bershad et al., (2019, 2020); Preller (2019); Family et al. (2020); Greiner et al. (1958); Holze et al. (2021); Isbell et al. (1956).
[h] Strassman et al. (1994).
[i] Riba et al. (2015).
[j] Lea (2020b).
[k] Shulgin (1976).
[l] Goutarel et al. (1993).
[m] Forsyth et al. (2016); Glue et al. (2015).

1.4. The scope of this review

This study reviews all scientific research to date on the effects of microdoses of psychedelics (referred to as "very low dose" in some reports; Kuypers et al., 2019). Most research on microdosing has been published recently (i.e., since 2018); however, there exists an additional under-reported set of relevant scientific publications from before the prohibition of psychedelic use in 1970. Although the contemporary practice of microdosing was not the specific focus of any pre-prohibition scientific studies, a subset of early studies administered doses that would today be considered microdoses, either within dose escalation studies or as control conditions in high-dose psychedelic studies. The results of many of these studies were summarised in a book, 'The science of microdosing psychedelics' by Torsten Passie (2019). Passie also reports popular experimentation with microdosing in earlier decades, and in one intriguing example describes the availability of pre-packaged microdoses of LSD – branded 'Clearlight' – in Berkeley in the 1980s (see Fig. 1). However, despite these records, few contemporary microdosing studies refer to any research or popular use of very low dose psychedelics prior to the 2010s (although see Kuypers, 2020, 2021).

Three previous reviews have investigated evidence for the effects of microdosing. Two of these reviews focused on recent research: Bornemann (2020) reviewed 21 studies from 2014 to 2019; and Ona and Bouso (2020) reviewed 17 studies from 2018 to 2020. Kuypers (2020)



IMPORTANT INFORMATION FOR POTENTIAL USERS OF CLEARLIGHT brand "MICRODOSE" LSD

MANUFACTURE:

Utilizing unique variations of modern homeopathic techniques while working in a dry, dark, low-temperature environment, each of these perforated thin sheets of food-grade sterile paper is evenly saturated with a cold solution containing a highly-refined form of pure pharmaceutical Lysergic Acid Diethylamide (LSD), rapidly cold-dried, and immediately sealed in airtight packages. During the drying process, various bells and cymbals are used to ecstatically consecrate each batch. The result of twenty-five years of intense research, these paper squares contain absolutely no binders, buffers, disintegrants, coatings, lubricants, fillers, colors, inks, dyes, sugars, wheat, corn, gelatin, or artificial flavors.

SUGGESTED USES:

These squares are amazingly versatile psychic tools that have a wide variety of uses. For example, there are numerous ways in which these squares may be employed by a bona-fide healer to catalyze a balanced physical/mental restructuring. Some people consider these squares to be an excellent sacrament if used in an appropriate religious setting. These squares may also prove to be of great value to an intelligent user who is seriously interested in exploring her or his creative potential.

DOSAGE:

Each one-quarter inch by one-quarter inch square of paper contains approximately five micrograms of active LSD. This is usually considered to be an extremely low dose (one microgram is one-millionth of a gram). Many, many, many studies of the effects of LSD have been made by the scientific community. The doses given to people by "legitimate" researchers have ranged from ten micrograms to fifteen-thousand micrograms per dose. The dosage most often mentioned in popular literature is one-hundred micrograms. The first measured dose of LSD taken by a human was two-hundred and fifty micrograms. Quite a few of the people who have made a serious study of the subject think that in some cases the appropriate dose is one that weighs between three-hundred micrograms and five-hundred micrograms. Some people seem to feel an effect after taking as little as one-quarter of a single square of CLEARLIGHT brand "MICRODOSE" LSD.

Fig. 1. 'Clearlight' Microdose LSD instructions by jfyf333. Reproduced with permission.

investigated both older and recent microdosing research in a review of 14 papers that specifically focused on the effects of microdosing on depression. The current paper compliments these earlier reviews, providing a comprehensive overview of the largest number of microdosing studies to date. The 44 studies reviewed here span from the early phases of psychedelic research through to very recent studies (January 1955 to April 2021), and cover both treatment and optimisation studies (including an additional 12 papers published since the last review). We outline the key details of each study (Table 2), tabulate their effects across domains of interest (Table 3), and evaluate the strength of evidence for each study (Table 4).

2. Method

2.1. Search procedure

The search procedure and terms were pre-registered on PROSPERO (https://www.crd.york.ac.uk/prospero; ID:171236) and OSF (https://osf.io/t25cy). The final search was completed on 18th April 2021 across five databases (Scopus; PsycINFO; Embase; PubMed; Web of Science). Our broad search strategy was to identify papers that included a term related to any psychedelic substance in the title, plus a term indicating very low doses in the title, abstract or keywords.

The full search terms (Scopus syntax example) were: TITLE (psychedelic OR hallucinogen OR lsd OR psilocybin OR psilocin OR "Lysergic acid diethylamide" OR "Magic mushroom" OR dmt OR mescaline OR trimethoxyphenethylamine OR peyote OR "San pedro" OR dimethyltryptamine OR "2 C-B" OR "2, 5-dimethoxy-4-bromophenethylamine" OR iboga OR ibogaine) AND (TITLE-ABS-KEY("low dose" OR microdose OR microdosing OR "Mini dose" OR "Small dose" OR "Sub-threshold" OR "Sub-perceptual" OR "Sub-acute") or TITLE (dose)).

In addition, to ensure that we captured pre-prohibition research, we included eligible studies reported in Chapter 7 of 'The Science of Microdosing Psychedelics' (Passie, 2019).[3] Finally, we scanned key bibliographies for any additional eligible studies.

Inclusion criteria were: 1) use of 'classical' or serotonergic psychedelics; 2) doses within a microdose range (see Table 1) OR if the dose was not ascertained, reports of effects that were sub-hallucinogenic and/or involved no functional impairment; 3) inclusion of psychological or neurobiological data; 4) reporting of primary empirical data; 5) use of human subjects; and 6) peer reviewed publications.

All screening rounds were conducted independently by both authors. Reference lists across the five databases, Passie (2019), and manual bibliography searches were imported into Covidence (Covidence, 2021), duplicates removed, and titles and abstracts were screened for eligibility (n = 387). Full text screening was conducted on the remaining articles (n = 83), leading to a final sample of 44 included papers (see Fig. 2). Data were extracted by one author and corroborated by the other. Any disagreements during screening were resolved through discussion and consensus.

2.2. Risk of bias

Because of the highly heterogeneous nature of reviewed studies, including early studies that employed outdated methodologies, we were unable to use common Risk of Bias assessments such as the Cochrane Collaboration tool (Higgins et al., 2011). Instead, a tailored risk assessment methodology was developed, based on Murad et al. (2018). Studies were ranked (low, medium, high risk) on the following ten domains: 1) Selection: were selection criteria clear, and were participants selected without bias? 2) Reliability: was the exposure adequately ascertained? 3) Reliability: was the outcome adequately ascertained? 4) Reliability: were outcome measures well validated and reliable? 5)

[3] This chapter reviews all the studies identified by Passie (2019).

Table 2
Study properties.

Author (year)	Drug(s) (doses); placebo-control	Design	Comparisons	Total n (micro dosing n)	Age M (SD) or [range]; % female	Study summary
QUALITATIVE STUDIES						
Johnstad (2018)	Psilocybin MM, LSD, others	Interviews	None	21	early 30s; 0%F	Qualitative interviews of current and former microdosers on their microdosing practices, positive and negative acute effects, and prolonged effects.
Anderson et al. (2019a)*	LSD, psilocybin	Free response survey	BS: LSD v Psilocybin	278	27.8 (8.9); 11%F	Using grounded theory, responses categorised into a 'codebook' of benefits and challenges associated with microdosing LSD and/or psilocybin. Additional survey probed behavioural and substance use improvements.
Andersson & Kjellgren (2019)	LSD, psilocybin, others	Content analysis	None	34 videos, 198 comments	—; 29%F	Analysed YouTube videos and associated comments for self-reports of microdosing practices, motivations, effects, and perspectives.
Fadiman & Korb (2019)	Not specified	Qual analysis of report database	None		[18-80] —	Narrative summary of typical stories and common themes from a large number of qualitative reports and journal entries sent to the microdosingpsychedelics.com information site.
Webb et al. (2019)	LSD, psilocybin MM, 1P-LSD, others	Interviews	None	30	[18-69]; 33%F	Applies narrative identity methods to semi-structured interview responses from regular microdosers regarding microdosing practices, motivations for use, and perceived benefits.
Lea et al. (2020a)	LSD, psilocybin, 1P-LSD	Content analysis	None	714	—; —	Qualitative analysis of content of the microdosing forum on reddit.com. Focuses on benefits, limitations, drug interactions, harm reduction practices, information and support, legal issues, and motivations.
Beaton et al. (2020)	LSD, psilocybin, 1P-LSD	Interviews	None	30	[18-69]; 33%F	Sociological analysis, based on semi-structured interviews with current or former microdosers, which investigated the ways that microdosers excuse or justify their practice.
RETROSPECTIVE SURVEY STUDIES						
Anderson (2019b)*	LSD, psilocybin, others	Cross-sectional survey	BS: Microdosers v Non-microdosers	909 (594)	27.1 (8.8); 15%F	Compares microdosers and non-microdosers on measures of personality, mental health, attitudes, mood, substance use, and divergent thinking.
Hutten et al. (2019a)	LSD, psilocybin, 1P-LSD, others	Cross-sectional survey	BS: Microdose v high dose; Current v former microdosers	1116	28.6 (10); 14%F	Investigates psychedelic use history, dosing schedule, motivations, and negative effects. Some comparisons between current and formal microdosers; also between microdosing and high dose psychedelics.
Hutten et al., (2019b)	LSD, psilocybin, 1P-LSD, others	Cross-sectional survey	WS: Effectiveness ratings of microdosing v conventional treatment	410	28.9 (10.1); 23%F	Investigates microdosers diagnosed with a mental or physiological disorder. Investigated self-rated effectiveness of microdosing for various mental and physiological health diagnoses compared to conventional treatment (pharmacotherapy and psychotherapy) and to high dose psychedelics.
Cameron et al. (2020)	LSD, psilocybin, others	Cross-sectional survey	BS: Current v former microdosers	2347 (383)	35 [18-99]; 49%F	Investigates microdosing prevalence and practices, demographics, self-reported effects (depression, anxiety, memory, focus/attention, sociability, physical factors), and discontinuation motives for current and former microdosers.
Lea et al. (2020b)	Psilocybin MM, LSD, others.	Cross-sectional survey	BS: Psilocybin v LSD	525	34.5 (12.7); 22%F	Investigates demographics; microdosing practices; drug dependence; perceived benefits and harms; motivations; harm-reduction and practices. Some comparisons between LSD and psilocybin microdosers.
Lea et al. (2020c)	Psilocybin, LSD, others	Cross-sectional survey	BS: Current v former microdosers; mental health v other motivations	1102	33 (12.1); 27%F	Investigates current or former microdosers' demographics; motivations; psychiatric history; perceived effectiveness of microdosing for mental health; and comparisons to conventional therapies.
Petranker et al. (2020)	LSD, psilocybin	Cross-sectional survey	None	6753	Not reported for full sample	Investigates respondents in the Global Drug Survey who reported microdosing. Explored benefits and challenges related to microdosing; drug testing behaviours; and relationship between intentions and benefits.
Rosenbaum et al. (2020)*	LSD, psilocybin, others	Cross-sectional survey	BS: Current microdosers v Non-microders	792 (414)	27.1 (8.8); 15%F	Investigates microdosing practices, psychiatric diagnoses, medication use, recreational drug use, and demographics.

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Table 2 (*continued*)

Author (year)	Drug(s) (doses); placebo-control	Design	Comparisons	Total n (micro dosing n)	Age M (SD) or [range]; % female	Study summary
Bright et al. (2021)	LSD, psilocybin, others	Cross-sectional survey	BS: Microdosers v Yoga v Both v Control	339 (123)	Not reported for full sample	Investigates personality, mental health, wellbeing, and trait absorption between participants who microdose, practice yoga, both, or neither.
PROSPECTIVE OBSERVATIONAL STUDIES						
Prochazkova et al. (2018)	Psilocybin truffles (.22, .33, .44g)	Naturalistic; Longitudinal	WS: Baseline v After dosing	38	31.5 (11.49); 40%F	Quasi experiment in a retreat setting that assessed the acute (90min) effects of a single microdose on convergent thinking, divergent thinking, and fluid intelligence.
Polito & Stevenson (2019)	LSD, psilocybin, others	Survey-based; Longitudinal	WS: Dosing days v Non-dosing days; Baseline v After 6 weeks	98 [63 at endpoint]	[18-56+]; 22%F	Longitudinal study investigating daily effects (e.g., connectedness, creativity, productiveness, wellbeing), and pre-post (6-week) changes in mental health, wellbeing, personality, cognition, creativity, and attention. A secondary study assessed microdosing outcome expectancies.
Dressler et al. (2021)	LSD, psilocybin, others	Survey-based; Longitudinal	WS: Baseline v After 1 month	74 [24 at endpoint]	33 (13.1); 18%F	Longitudinal study investigating the influence of prior microdosing experience and emotional insight on personality changes that may result from microdosing.
Kaertner et al. (2021)	Psilocybin, LSD, others	Survey-based; Longitudinal	WS: Baseline + weekly measures for up to 6 weeks	253 [81 at endpoint]	Not reported for full sample	Longitudinal study with multiple timepoints over 4-6 weeks. Investigated microdosing practices, expectations, mental health, personality, absorption, suggestibility, connectedness, psychological flexibility, resilience, delusional ideation, and subjective drug effects.
Szigeti et al. (2021)	LSD, psilocybin, LSA, DOB, Placebo	Survey-based; Longitudinal	BS: Placebo v Microdosing; WS: Baseline + weekly measures for 4 weeks	240 [191 at endpoint]	34; 19%F	Longitudinal study with self-blinding placebo-controlled protocol and multiple timepoints over 5 weeks. Investigated expectations, suggestibility, cognitive performance, daily effects, emotional state, wellbeing, mental health, connectedness, mindfulness, paranoia, personality and satisfaction. Analysed group differences (placebo v microdose) and the effects of expectancy.
LABORATORY STUDIES						
Abramson et al. (1955)	LSD (0-*225*μg); Placebo	Cross-sectional lab; Non-Blind	BS: Different doses	31 (8)	—; —	Investigates subjective alterations across range of LSD micro- and macro-doses. Post-hoc categorisation of altered state scale reports (Cold Spring Harbor Questionnaire), with 5 categories: euphoria, dysphoria, perceptual distortions, neurosis, psychosis.
Isbell et al. (1956)	LSD (10-*420*μg/70kg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	24	—; 0%F	Clinical trial with addiction inpatients investigated acute psychological and physiological reactions to a range of microdoses and above, and the development and cessation of LSD tolerance.
Greiner et al. (1958)	LSD (4, 7, 12, 20, *40*μg); Placebo	Cross-sectional lab; D-Blind	BS: Placebo v Other doses	14	—; 0%F	Investigates perception, body image, alertness, emotion, thought, mood, galvanic skin conductance, pupil size, heart rate, electroencephalography, and psycho-motor performance following a single dosing session.
Abramson & Rolo (1965)	LSD, psilocybin, psilocin, other (microdoses and above); Placebo	Cross-sectional lab; D- or S-Blind	BS: Placebo v Other doses v Other drugs	6 (5)	[35-45]; 33%F	Investigates intensity of altered states and ability to discriminate substance and dose across multiple psychedelics in microdose range and above.
Muzio et al. (1966)	LSD (6-*40*μg); Placebo	Multiple doses lab; S-Blind	WS: Placebo v Other doses	12 (8)	[19-30]; 50%F	Investigates the impact of various microdoses and higher doses taken just prior to going to sleep, or just prior to first REM phase, on sleep cycles using electroencephalogram, electro-oculogram, and open-ended reports on subjective experience.
Vojtěchovský et al. (1972)	LSD (20μg); Placebo	Multiple doses lab; D-Blind	BS: Placebo v Microdose; WS: Two timepoints	12	—; 50%F	Investigates whether 'threshold' doses could produce schizophrenia-like symptoms, and whether drug could be distinguished from placebo. Participant pairs (with neither, one, or both receiving LSD) were asked to complete a range of social functions in the field (e.g. shopping), and surveys and observation in the lab, and to guess their own and partner's experimental condition.
Fanciullacci et al. (1974)	LSD (*24*μg), psilocybin (1.4mg); Placebo	Multiple doses lab; S-Blind; Quasi-exp	BS: Placebo v LSD v Psilocybin	102	—; 61%F	Clinical trial investigating the hypothesis that Essential Headache (EH) is associated with serotonin sensitivity. On 3 occasions healthy controls and EH sufferers were given LSD, psilocybin, and placebo and acute subjective ratings of mood and perception were recorded.

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Table 2 (*continued*)

Author (year)	Drug(s) (doses); placebo-control	Design	Comparisons	Total n (micro dosing n)	Age M (SD) or [range]; % female	Study summary
Strassman et al. (1994)	DMT (3.5, 7, 14, 28mg/70kg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	11	41.5 (1.5); 9%F	Investigates the subjective effects of microdoses and higher doses of DMT using self-reports of drug effects and alterations in consciousness; and observed behaviours.
Hasler et al. (2004)	Psilocybin (3, 8, 15, 22mg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses; Multiple timepoints	8	29.5 [22-44]; 50%F	Investigates acute effects of 4 different doses + placebo (administered on different days) over 24 hours. Measures focused on subjective reports (ASC, mood), cognitive performance (sustained attention), cardiac function, body temperature, and serology (thyroid-stimulating hormone, prolactin, cortisol, adrenocorticotropic hormone, and standard clinical chemical parameters).
Moreno et al. (2006)	Psilocybin (1.8, 7, 14, 21mg /70kg)	Multiple doses lab; D-Blind	WS: Placebo v Other doses	9 (7)	40.9 [26-62]; 22%F	Clinical trial investigating acute and post-acute subjective effects (drug effects, ASC), and changes in obsessive compulsive disorder symptoms over 24 hours following 4 separate doses alongside minimal psychotherapeutic support in OCD patients.
Wackermann et al. (2008)	Psilocybin (.84mg /70kg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Microdose	9	48.2; 44%F	Investigates the effects of a microdose on time perception (temporal reproduction) by reproducing tone durations (1.5 to 5 seconds; order randomised), and on subject reports (mood and ASC).
Gasser et al. (2014)	LSD (20, 200µg)	Longitudinal lab; D-Blind	BS: Microdose v High dose; WS: Baseline v post v follow up	12 (4)	51.7 (9.1); 36%F	Clinical trial investigating the anxiolytic effects of two dosing sessions using either a high dose or a microdose ("active placebo") alongside psychotherapeutic support in palliative patients.
Forsyth et al. (2016)	Ibogaine (20mg) + paroxetine or placebo	Cross-sectional lab; D-Blind	BS; Pre-loading of SSRI vs Placebo; WS: Baseline v post	21	23.5 [20-40]; 0%F	Investigates changes in mood and cognitive performance (Pro, Anti, Pro/Anti, Simon, Flanker, and 2-back) following ibogaine dosing, and whether SSRI pre-treatment (which inhibits the enzyme that converts ibogaine to its active form) modulated the effects of ibogaine, compared with placebo pre-treatment.
Griffiths et al. (2016)	Psilocybin (1-3mg, 22-30mg /70kg)	Longitudinal lab; D-Blind	BS: Microdose v High dose; WS: Baseline v post v follow up	51	56.3 (1.4); 49%F	Clinical trial investigating acute subjective (drug effects, ASC), cardiovascular, and behavioural effects, and the post-acute effects on mental health and psychosocial function (depression, anxiety, quality of life, various attitudes/beliefs) of a high dose and a microdose ("active placebo") alongside psychotherapeutic support in palliative cancer patients.
Griffiths (2018)	Psilocybin (1, 20, 30mg/70kg)	Longitudinal lab; D-Blind	BS: Microdose v High dose; WS: Baseline v post v follow up	75 (25)	42 [22-69]; 60%F	Investigates acute subjective (ASC, psychosocial attitudes/beliefs), cardiovascular, and behavioural effects, and post-acute effects on psychosocial ratings (attitudes, moods, behaviour, spirituality, relationships, perspectives of dosing session, etc) and spiritual/meditation practices across three group conditions: microdose with standard support, high dose with standard support, and high dose with high support.
Yanakieva et al. (2018)^	LSD (4, 8, 15µg)[1]; Placebo	Multiple doses lab; D-Blind	BS: Placebo v Other doses	48 (36)	62.92 (5.65); 44%F	Investigates acute effects of various microdoses (4 dose conditions, 6 doses each, 3 days apart), on time perception (temporal reproduction; 0.8 to 4 seconds), and subjective reports (drug effects).
Bershad et al. (2019)	LSD (5, 10, 20µg)[1]; Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	20	25 (3); 60%F	Investigates effects of multiple LSD microdoses (4 dosing sessions, at least 7 days apart) on subjective reports (mood, drug effects, mental health, ASC), performance measures (working memory, executive function, social exclusion sensitivity, facial affect processing, convergent thinking), cardiovascular function, and body temperature.
Madsen et al. (2019)	Psilocybin (3, *6*, *12*, *15*, *18*, *24*, *30*mg)	Multiple doses lab; D-Blind	BS: Other doses; WS: Baseline v post	8 (1)	33.0 (7.1); 38%F	Investigates association between Serotonin 2A receptor binding (PET scan), blood plasma psilocin concentration (chromatography and mass spectrometry), and subjective effects (intensity ratings, ASC), with one of seven different doses of psilocybin.
Bershad et al. (2020)	LSD (10µg)[1]; Placebo	Multiple doses lab; D-Blind	WS: Placebo v Microdose	20	25 (4); 50%F	Investigates acute resting state fMRI (2 scans at least 7 days apart: 90 min following placebo or LSD), cerebral blood flow, subjective reports (mood, drug effects, ASC), and cardiovascular function associated with microdosing.
Family et al. (2020)^	LSD (5, 10, 20µg); Placebo	Multiple doses lab; D-Blind	BS: Placebo v Other doses; WS: Multiple timepoints	48 (36)	62.92 (5.65); 44%F	Investigates acute effects of various microdoses (4 dose conditions, 6 doses each, 3 days apart) on adverse events, pharmacokinetics, pharmacodynamics, cognitive performance (reaction time, visual memory, learning, and attention, spatial working memory), balance, proprioception, subjective drug effects, and ASC in older adults.
Hutten et al. (2020)#	LSD (5, 10, 20µg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	24	22.8 (3); 50%F	Investigates acute effects of placebo and 3 different microdosing doses (4 dosing sessions total, at least 5 days apart) on subjective reports (ASC, drug effects, mood), and cognitive performance (sustained attention/vigilance, motor speed, working memory, and visual processing, executive function).
Holze et al. (2021)#	LSD (5, 10, 20µg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	23	23 (3); 48%F	Investigates pharmacokinetics, pharmacodynamics and subjective drug effects of placebo and 3 different microdosing doses (4 dosing sessions total, at least 5 days apart).
Ramaekers et al. (2021)#	LSD (5, 10, 20µg); Placebo	Multiple doses lab; D-Blind	WS: Placebo v Other doses	24	22.7 (2.9); 50%F	Investigates acute effects of 3 different microdosing doses (4 dosing sessions total, at least 5 days apart) on pain tolerance (cold), ratings of dissociation, psychiatric symptoms (somatization, anxiety, and depression), and cardiovascular function.

Note: Doses in italics are considered higher than a microdose. 1 = These studies administered LSD tartrate. For ease of comparison we have presented the equivalent dose of LSD base, using the ratio of 1µg base : 1.3µg tartrate (Holze et al, 2021). Papers marked by *, #, and ^ describe the same or overlapping datasets. 'Multiple doses' = a study where participants received a drug on multiple occasions (usually at different doses) but measurement focused on acute effects. 'Longitudinal' = a study where participants received a drug on multiple occasions but measurement focused on enduring effects (i.e., changes from baseline to study endpoint). BS = between-subjects comparison. WS = within-subjects comparison.

Causality: were alternative causes that may explain the observation ruled out? 6) Causality: was there a dose-response effect? 7) Causality: was follow-up long enough for outcomes to occur? 8) Transparency: was the study described with sufficient details to allow other investigators to replicate the research? 9) Transparency: were the study design, analyses, and hypotheses pre-registered? and 10) Transparency: was the data made publicly available? Each rank within each domain was precisely operationalised with specific criteria (available at https://osf.io/w8cq4/). Both authors independently assessed Risk of Bias and any discrepancies were resolved through discussion and consensus.

3. Results

3.1. Study properties

Table 2 summarises the design and aim of all studies. Studies were organised in four categories based on their methodology: a) Qualitative studies, which involved interviews, free response questionnaires, and analyses of internet forums or videos (7 studies); b) Retrospective survey studies, which involved online questionnaires that asked participants to report on past microdosing experiences (9 studies); c) Prospective studies, which collected measures related to microdosing at multiple timepoints either online or in a naturalistic setting (5 studies); and d) Laboratory studies, which investigated the acute effects of microdoses administered in a controlled setting (23 studies).

Sample size ranged from 4 to 1116 microdosing participants. Most studies explored multiple different psychedelics (21 studies), LSD only (13 studies), or psilocybin only (7 studies). A minority of studies focused on other psychedelics like DMT (1 study) and ibogaine (1 study). The vast majority of studies specifically exploring microdosing were published in the last few years, with 30 of the 44 reviewed studies published in 2018 or later.

We note that the studies were highly variable with respect to the inclusion and type of comparison condition. Most qualitative studies did not contain any comparison condition, as is appropriate and common with such study designs. Retrospective survey studies frequently included a comparison between current microdosers and non-microdosers, but these were uncontrolled self-reports. Prospective studies relied on within-subject comparisons, and apart from Szigeti et al. (2021), did not have any placebo control. Only a subset of lab studies had rigorous placebo control comparison conditions. However, one critical point to bear in mind is that these different types of studies may not have investigated microdosing effects in comparable ways. Specifically, qualitative, retrospective and prospective studies investigated the accumulative effects of regular microdosing over a sustained period. Conversely, lab studies have focused on the acute effects of a relatively small number of doses (1−6). As such, although lab studies had a greater level of experimental control, these studies may not provide a complete picture of the way microdosing effects develop over time.

3.2. Motives for microdosing

Several studies assessed respondents' reasons for microdosing. A wide variety of motives were reported, including performance enhancement, mood enhancement, and curiosity (Hutten et al., 2019a); treatment of health conditions (Hutten et al., 2019b); self-fulfilment, coping with negative situations, and increasing social connection (Beaton et al., 2020); improving mental health, personal/spiritual development, and enhancing cognitive performance (Lea et al., 2020b). In general, participants reported confidence that microdosing fulfilled these aims (e.g., Anderson et al., 2019a; Cameron et al., 2020; Petranker, Anderson, Maier et al., 2020). There were also indications that microdosing is being used as an adjunct or substitute to conventional medications for mental and physical health issues by a considerable proportion of individuals (Hutten et al., 2019b; Lea et al., 2020b, 2020c).

3.3. Effects of microdosing

Table 3 shows the reported outcomes from all studies, separated by study type (row sections) and six outcome domains (columns). Before discussing the reviewed results, a few methodological points. We have only coded effects related to doses in the plausible microdosing range indicated in Table 1. Some studies - particularly qualitative and cross-sectional studies – report a wide range of effects associated with microdosing, and in some cases the proportion of respondents indicating certain effects was relatively small or unclear. In such cases, we have coded the themes and outcomes emphasised by the authors. One lab based study, by Hutten et al. (2020), reported both group level and individual level effects of microdosing; we have only coded group level effects in this table. For quantitative studies, we have included only statistically significant results. This table does not show variables that were not found to relate to microdosing. Many studies deployed large batteries of tasks and did not always report on variables that were unaffected by microdosing. Accordingly, any impression of consistency may be inflated. Finally, we report here findings for all types of studies. However, we note that the quality of evidence varied amongst studies (see 'Risk of Bias' below). Many findings come from self report studies without rigorous experimental controls. With this in mind, null findings from well controlled lab based studies may be particularly important for evaluating conflicting evidence and characterising the true effects and limitations of microdosing. Consequently, we have emphasised relevant null findings from recent lab-based studies in the following sections.

3.3.1. Mood and mental health

Improved mood associated with microdosing was found across numerous qualitative (Anderson et al., 2019a; Fadiman and Korb, 2019; Johnstad, 2018; Lea et al., 2020a; Webb et al., 2019), retrospective survey (Anderson et al., 2019b; Hutten et al., 2019a; Lea et al., 2020b; Petranker et al., 2020), prospective (Szigeti et al., 2021), and lab studies (Abramson et al., 1955; Hutten et al., 2020; Isbell, 1959; Vojtěchovský et al., 1972). Microdosing was also frequently linked with lower depression scores (Cameron et al., 2020; Griffiths et al., 2016; Hutten et al., 2020; Kaertner et al., 2021; Lea et al., 2020a; Polito and Stevenson, 2019). However, one survey study found higher levels of depressive symptoms associated with microdosing (Bright et al., 2021), and three well controlled lab studies found no acute changes in depression, negative affect, or positive affect scores on the dosing day (Bershad et al., 2019, 2020; Ramaekers et al., 2021).

Findings related to anxiety and stress were mixed, with reports of decreased anxiety or stress in six of the reviewed studies (Anderson et al., 2019a; Griffiths et al., 2016; Kaertner et al., 2021; Polito and Stevenson, 2019; Rosenbaum et al., 2020; Szigeti et al., 2021), increased anxiety or stress in four studies (Andersson and Kjellgren, 2019; Gasser et al., 2014; Isbell, 1959; Ramaekers et al., 2021), and both increases and decrease in anxiety found in three studies (Hutten et al., 2020; Lea et al., 2020a, 2020b).

Improvements in substance misuse was another recurrent finding, although this was assessed in only a minority of studies. Qualitative studies showed microdosing was thought by respondents to be linked to reductions in smoking (Johnstad, 2018), and substance use (Anderson et al., 2019b; Webb et al., 2019). Additionally, one retrospective survey study found that microdosers reported lower levels of substance use disorders yet higher rates of recreational substance use (Rosenbaum et al., 2020). No lab studies have assessed substance misuse effects yet.

Microdosing was also linked to improved general mental health in two qualitative (Andersson and Kjellgren, 2019; Johnstad, 2018) and two retrospective survey studies (Hutten et al., 2019b; Lea et al., 2020c). Microdosing was associated with reduced OCD severity in a small clinical trial (Moreno et al., 2006), and with increased dissociation in a lab study with healthy volunteers (Ramaekers et al., 2021).

Some of these results need to be treated with caution; for example reduced pre-post depression scores linked to the microdosing condition

Table 3
Microdosing Effects.

	Mood / Mental Health	Wellbeing / Attitude	Cognition / Creativity	Personality	Changes in Conscious State	Neurobiological / Physiological
QUALITATIVE STUDIES						
Johnstad, 2018	± mental health + mood - smoking	+ energy	+ focus	+ openness + extraversion + sociability		-pain + insomnia
Anderson et al., 2019b	+ mood - anxiety - substance use	+ self-efficacy + positive habits ± energy	+ creativity			+ discomfort
Andersson & Kjellgren, 2019	+ mental health + anxiety	+ insight	+ cognitive performance + creativity		+ altered state	+ sensory acuity + discomfort
Fadiman & Korb, 2019	± affect		+ productivity + creativity	+ sociability		
Webb et al., 2019	+ mood - drug dependence	+ wellbeing	+ creativity	+ sociability		
Lea et al., 2020a	+ mood - depression ± anxiety	+ insight + health habits	+ mindfulness + cognitive performance + creativity	+ sociability		+ discomfort
Beaton et al., 2020	-substance use	+ self-fulfilment -negative mood		+ sociability		
RETROSPECTIVE SURVEY STUDIES						
Anderson et al., 2019a	- negative emotionality	- dysfunctional attitudes + wisdom	+ creativity	+ open-mindedness		
Hutten et al., 2019a	+ negative psychological effects					+ discomfort
Hutten et al., 2019b	+ mental health					- pain - physical disorders
Cameron et al., 2020	- depression		+ focus + memory	+ sociability		
Lea et al., 2020b	+ mood ± anxiety		+ cognitive performance	+ sociability	+ unpleasant psychedelic effects + dreams	+ discomfort
Lea et al., 2020c	+ mental health					- pain
Petranker et al., 2020	+ mood	± energy	+ creativity -focus	+ sociability		- discomfort
Rosenbaum et al., 2020	- anxiety disorders ± substance use disorder					
Bright et al., 2021	+ depression + stress	+ wellbeing		+ absorption + openness		
PROSPECTIVE OBSERVATIONAL STUDIES						
Prochazkova et al., 2018			+ convergent thinking + divergent thinking			
Polito & Stevenson, 2019	- depression - stress		- mind wandering	+ absorption + neuroticism		
Dressler et al., 2021				+ conscientiousness - neuroticism		
Kaertner et al., 2021	- depression - anxiety	+ wellbeing + resilience + nature relatedness		+ agreeableness - neuroticism + sociability		
Szigeti et al., 2021	+ mood - anxiety	+ energy	+ creativity		+ drug effects	

(*continued on next page*)

Table 3 (*continued*)

LABORATORY STUDIES						
Abramson et al., 1955	+ euphoric signs			+ neuroticism		
Isbell et al., 1956	+ euphoria + anxiety				+ drug effects	+physiological changes
Greiner et al., 1958	± mood	- motility	- alertness - control - thought	± sociability		
Abramson & Rolo, 1965					+ drug effects	
Muzio et al., 1966						+ REM sleep
Vojtěchovský et al., 1972	+ euphoria + smiling				+ drug effects	
Fanciullacci et al., 1974	± mood				+ drug effects + perceptual distortion	
Strassman et al., 1994	+ affect		+ altered cognition		+ intensity + somaesthesia - volition	
Hasler et al., 2004	+ intensification of moods				+ drug effects	
Moreno et al., 2006	- OCD					
Wackermann et al., 2008			+ time perception			
Gasser et al., 2014	+ anxiety					
Forsyth et al., 2016			+ selective attention			
Griffiths et al., 2016	- depression - anxiety - psychiatric symptoms	- death transcendence + coherence				+ blood pressure + visuals
Griffiths et al., 2018		+ forgiveness			+ exp rated drug effects	
Bershad et al., 2019		+ vigor	- control		+ drug effects + blissful state + experience of unity	+ blood pressure
Madsen et al., 2019					+ drug effects	
Yanakieva et al., 2019			+ time perception			
Bershad et al., 2020						+ thalamus connectivity + amygdala connectivity + blood pressure
Family et al., 2020					+ drug effects - vigilance	+ dizziness + body changes
Hutten et al., 2020	+ happy		± concentration - productive		+ altered state + drug effects	
Holze et al., 2021					+ drug effects	
Ramaekers et al., 2021	+ anxiety + dissociation					- pain + somatization + blood pressure

in Griffiths et al. (2016) and lower pre-post OCD scores in the microdosing condition in Moreno et al. (2006), may be attributable to substantial psychotherapeutic support and expectancy effects associated with the administration of the microdose (which was used in these studies as the 'placebo' group). Also, higher depression scores in the microdosing group in Bright et al. (2021) may be attributable to self-medication motivations, relative to controls. Notably, most survey studies did not probe the duration of effects following microdosing, so it is unclear whether the above findings relate to fleeting or sustained changes in mood and mental health.

3.3.2. Wellbeing and attitudes

Three qualitative studies (Anderson et al., 2019b; Beaton et al., 2020; Webb et al., 2019), and one retrospective survey study (Bright et al., 2021) showed increases in the overlapping constructs of wellbeing, self-fulfilment, self-efficacy, and resilience. Additionally, one prospective study showed increases in reports of wellbeing and resilience over the course of a 4-week period of microdosing, with this finding partially accounted for by expectation (Kaertner et al., 2021). No lab-based studies have investigated wellbeing yet.

Other findings relevant to wellbeing included two qualitative studies that found increases in themes of self-insight (Andersson and Kjellgren, 2019; Lea et al., 2020a); one retrospective survey study that showed increases in wisdom, and decreases in a measure of dysfunctional attitudes (Anderson et al., 2019b), and two qualitative studies that showed improved physical health and other habits (Anderson et al., 2019a; Lea et al., 2020a).

Findings related to energy levels and vigor were somewhat mixed. Microdosing was linked to reports of increased energy in a qualitative study (Johnstad, 2018) and in a placebo controlled prospective study (Szigeti et al., 2021); a well-controlled lab study also found increases of vigor (Bershad et al., 2019). In two retrospective survey studies from the same group, 11–45% of respondents reported that microdosing was related to increased energy, while 8–10% reporting decreases in energy (Anderson et al., 2019a; Petranker, Anderson, Maier et al., 2020). Finally, two lab studies found no evidence of group level changes in vigour, arousal or fatigue (Bershad et al., 2019; Hutten et al., 2020).

3.3.3. Creativity and cognition

There are several indications that microdosing may be associated with increases in creativity. In a quasi-experimental, open-label study, Prochazkova et al. (2018) reported increases in both convergent and divergent thinking following ingestion of psilocybin-containing truffles in a retreat setting. Similarly, in an online study by Anderson et al. (2019b) participants who microdosed scored higher on a divergent thinking task compared to a non-microdosing control condition. There were also six accounts of self-reported increases in creativity following microdosing (Anderson et al., 2019a; Andersson and Kjellgren, 2019; Fadiman and Korb, 2019; Lea et al., 2020a; Petranker et al., 2020; Webb et al., 2019). A placebo-controlled prospective study (Szigeti et al., 2021) did find an increase in creativity, however, another prospective study (Polito and Stevenson, 2019) and one lab-based study (Bershad et al., 2019) found no effects.

Several studies have shown changes in neurocognitive behavioural tasks following microdosing. Specifically, evidence from two well-controlled lab studies have shown that both LSD (Yanakieva et al., 2019) and psilocybin (Wackermann et al., 2008) impact time perception, with participants systematically generating shorter responses in a time reproduction task (i.e., microdoses were associated with faster subjective time perception). In another lab-based study, Forsyth (2016) investigated the effects of microdoses of ibogaine on a large battery of cognitive tasks but found only slight improvements in selective attention. Similarly, Hutten et al. (2020) found that some participants improved performance on a psychomotor vigilance task (indicating improved selective attention), but that both performance on a working memory task and self-rated concentration were reduced following microdoses of LSD. Two contemporary controlled lab studies found no acute changes in concentration on dosing day (Hutten et al., 2020; Yanakieva et al., 2019), and one controlled lab study found no acute change in working memory, visuospatial processing, attention, and convergent thinking (Bershad et al., 2019).

Psychometric measures also indicated various changes in cognition. In studies collating microdosers' self-reports, claims of increased attention, mindfulness, and ability to focus were common (Andersson and Kjellgren, 2019; Cameron et al., 2020; Fadiman and Korb, 2019; Johnstad, 2018; Lea et al., 2020a, 2020b). Similarly, in a prospective study by Polito and Stevenson (2019), reports of mind wandering decreased following six weeks of microdosing. Participants administered microdoses of DMT (0.04 −0.05 mg/kg) in Strassman's (1994) study rated cognition items on the Hallucinogen Rating Scale higher than placebo. However, there is evidence from controlled lab studies that microdosing may have some negative impacts on cognition. Bershad et al. (2019) reported impaired cognitive control following a relatively large microdose of LSD (equivalent to 20 μg base) and in an early lab study Greiner (1958) reported reductions in alertness, control and thought that persisted over the course of a day when participants were administered 20 μg of LSD, and for several hours when given 7 μg LSD (although these results were based on just 4–6 participants).

3.3.4. Personality

Although there have been reports of positive personality change following ingestion of psychedelics at high doses (Erritzoe et al., 2018), this was less consistent in studies of microdosing. With regards to changes in the classic big five personality traits, one qualitative study (Johnstad, 2018), and two retrospective survey studies reported increases in openness (Anderson et al., 2019b; Bright et al., 2021), whereas four prospective studies (Dressler et al., 2021; Kaertner et al., 2021; Polito and Stevenson, 2019; Szigeti et al., 2021) and one lab study (Griffiths et al., 2016) did not find any change in openness. Johnstad (2018) reported improved extraversion. Polito and Stevenson (2019) found an increase in neuroticism, but this was not repeated in two subsequent studies: Dressler et al. (2021) found a decrease in neuroticism and an increase in conscientiousness; Kaertner et al. (2021) found a decrease in neuroticism and an increase in agreeableness. Lab studies have seldom investigated personality change, as most of these experiments have focused on acute rather than persisting changes. An exception is Abramson et al. (1955), who reported that participants taking LSD in a lab setting frequently showed acute neurotic signs.

Much more consistent were increases in interpersonal feelings, attitudes, and behaviours (coded as sociability in Table 3). One early lab study (Greiner et al., 1958), one prospective study (Kaertner et al., 2021), three survey studies (Cameron et al., 2020; Lea et al., 2020b; Petranker, Anderson, Maier et al., 2020), and nearly all of the qualitative studies reported improved relationships and interpersonal connection (Beaton et al., 2020; Fadiman and Korb, 2019; Johnstad, 2018; Lea et al., 2020a; Webb et al., 2019). However, one controlled lab study found no increase in sensitivity to social rejection during acute effects (Bershad et al., 2019) and one prospective study found no increase in social connectedness compared to placebo (Szigeti et al., 2021).

Finally, one cross sectional study (Bright et al., 2021) and one prospective study (Polito and Stevenson, 2019) found an increase in absorption, although a second prospective study reported no change (Kaertner et al., 2021).

3.3.5. Changes in conscious state

Despite the common anecdotal claim that microdosing is subperceptual (e.g., Woods, 2016), there was consistent evidence that microdosing did lead to changes in subjective awareness. In a qualitative analysis of videos about microdosing, Andersson and Kjellgren (2019) described a change in psychophysiological state characterised by heightened presence and perceptual clarity, which they claimed was a *prerequisite* for the beneficial effects of microdosing. However, changes

Table 4
Risk of Bias.

Author	Sample size (n)	Study type	1. Selection	2. Reliability: Exposure	3. Reliability: Outcome	4. Reliability: Measures	5. Causality: Alternative	6. Causality: Dose-Response	7. Causality: Timeline	8. Transparency: Reporting	9. Transparency: Pre-reg	10. Transparency: Open data	RoB Total
Bershad et al.(2019)	20	Lab	Low	Low	Low	Low	Low	Low	Low	Low	Med	High	0.13
Family et al. (2020)	48	Lab	Low	Low	Low	Low	Low	Low	Low	Low	Med	High	0.13
Yanakieva et al. (2018)	48	Lab	Low	Low	Low	Low	Low	Low	Low	Low	Med	High	0.13
Holze et al. (2021)	23	Lab	Low	Low	Low	Low	Low	Low	Low	Low	High	High	0.17
Hutten et al. (2020)	24	Lab	Low	Low	Low	Low	Low	Low	Low	Low	High	High	0.17
Ramaekers et al. (2021)	24	Lab	Low	Low	Low	Low	Low	Low	Low	Low	High	High	0.17
Bershad et al. (2020)	20	Lab	Low	Low	Low	Low	Low	High	Low	Low	Med	High	0.21
Forsyth et al.(2016)	21	Lab	Low	Low	Low	Low	Low	High	Low	Low	Med	High	0.21
Gasser et al.(2014)	12	Lab	Low	Low	Low	Low	Med	Med	Low	Low	Med	High	0.21
Griffiths et al. (2016)	51	Lab	Low	Low	Low	Low	Med	Med	Low	Low	Med	High	0.21
Griffiths et al. (2018)	75	Lab	Low	Low	Low	Low	Med	Med	Low	Low	Med	High	0.21
Moreno et al.(2006)	9	Lab	Low	Low	Low	Low	Low	Med	Low	Low	High	High	0.21
Hasler et al.(2004)	8	Lab	Med	Low	Low	Low	Low	Low	Low	Low	Med	High	0.25
Szigeti et al. (2021)	240 [191 at endpoint]	Prospective	Low	Med	Med	Low	Low	High	Low	Low	High	Low	0.25
Anderson et al. (2019b)	909	Qualitative	Low	High	High	Med	High	High	Low	Low	High	Low	0.29
Polito and Stevenson (2019)	98 [63 at endpoint]	Prospective	Low	Med	Med	Low	Med	High	Low	Low	High	Low	0.29
Kaertner et al. (2021)	253 [81 at endpoint]	Prospective	Low	Med	Med	Low	Med	High	Low	Low	High	Med	0.33
Madsen et al. (2019)	8	Lab	Med	Low	Low	Low	Med	Low	Low	Low	High	High	0.33
Prochazkova et al. (2018)	38	Prospective	Low	Low	Low	Low	High	High	Low	Low	High	High	0.33
Strassman et al.(1994)	11	Lab	Med	Low	Low	Med	Low	Low	Low	Med	High	High	0.38
Dressler et al. (2021)	74 [24 at endpoint]	Prospective	Low	High	High	Low	High	High	Low	Low	High	Low	0.42
Petranker et al. (2020)	6753	Retrospective	Low	High	High	Med	High	Med	Low	Low	Low	High	0.42
Rosenbaum et al. (2020)	792	Retrospective	Low	High	High	Med	Med	High	Low	Low	High	Low	0.42
Anderson et al.(2019a)	278	Retrospective	Low	High	High	Low	Med	High	Low	Low	Low	High	0.46
Cameron et al.(2020)	2347	Retrospective	Low	High	High	Med	High	High	Low	Low	High	Low	0.46
Isbell et al. (1956)	24	Lab	Med	Low	Low	High	Low	Low	Low	High	High	High	0.46
Bright et al. (2021)	339	Retrospective	Low	High	High	Low	Med	High	Low	Med	High	High	0.50
Greiner et al.(1958)	14	Lab	Med	Low	Low	High	Med	Low	Low	High	High	High	0.50
Hutten et al. (2019b)	410	Retrospective	Low	High	High	Med	High	High	Low	Low	High	Med	0.50
Muzio et al. (1966)	12	Lab	High	Low	Low	Med	Low	Low	Low	Med	High	High	0.50
Wackermann et al. (2008)	9	Lab	High	Low	Low	Low	Low	Med	Low	Med	High	High	0.50
Hutten et al. (2019a)	1116	Retrospective	Low	High	High	Med	High	High	Low	Low	High	High	0.54
Lea et al. (2020b)	525	Retrospective	Low	High	High	Med	High	High	Low	Low	High	High	0.54
Lea et al. (2020c)	1102	Retrospective	Low	High	High	Med	High	High	Low	Low	High	High	0.54
Fanciullacci et al. (1974)	102	Lab	High	Low	Low	High	Low	Low	Low	High	High	High	0.58
Webb et al. (2019)	30	Qualitative	Low	High	High	Med	High	High	Low	Med	High	High	0.58
Abramson and Rolo, 1965	6	Lab	High	Low	Low	High	Med	Low	Low	High	High	High	0.63
Beaton et al. (2020)	30	Qualitative	Low	High	High	High	High	High	Low	Med	High	High	0.63
Abramson et al. (1955)	31	Lab	High	Low	Low	High	Med	Med	Low	High	High	High	0.67
Vojtěchovský et al. (1972)	12	Lab	High	Low	Low	High	Low	High	Low	High	High	High	0.67
Andersson and Kjellgren, 2019	NA	Qualitative	Med	High	High	High	High	High	Low	Med	High	Med	0.71
Lea (2020a)	714	Qualitative	Med	High	High	High	High	High	Low	Med	High	High	0.75
Johnstad (2018)	21	Qualitative	Med	High	High	High	High	High	Low	High	High	High	0.79

Risk of bias categories were as follows: **1**) Were selection criteria clear, and were participants selected without bias? **2**) Was the exposure adequately ascertained? **3**) Was the outcome adequately ascertained? **4**) Were the outcome measures well validated and reliable? **5**) Were other alternative causes that may explain the observation ruled out? **6**) Was there a dose–response effect? **7**) Was follow-up long enough for outcomes to occur? **8**) Was the study described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice? **9**) Was the study design, analysis, and hypotheses pre-registered? **10**) Was the data made publicly available? Note: Fadiman & Korb (2019) was not assessed for risk of bias, as this project explicitly aimed to collect data outside of the framework of standard experimental controls (see Fadiman, 2017 for details).

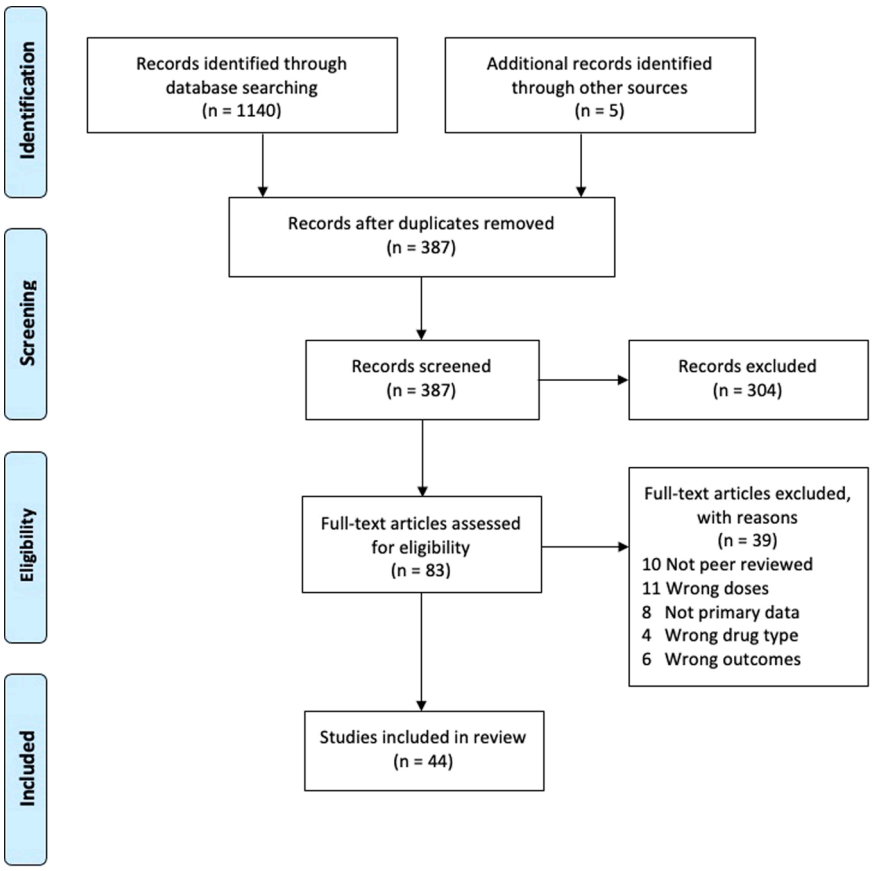

Fig. 2. PRISMA diagram, indicating the numbers of publications at different stages of the review process.

in conscious state were not always linked to benefit: Lea et al. (2020b) reported that unwanted psychedelic effects were the primary negative outcome associated with microdosing, with over 70% of microdosers in that study reporting that they sometimes felt like they were 'mildly tripping', and a similar proportion reporting unusually vivid dreams.

A focus of several of the older lab studies was to investigate whether participants and/or researchers could distinguish very low doses of psychedelics from placebos or other non-psychedelic substances. Four of these studies found evidence of drug effects in the microdosing condition (Abramson and Rolo, 1965; Isbell, 1959; Vojtěchovský et al., 1972). More recent lab studies have included self-ratings of overall drug intensity (or positive and negative drug effects), and have consistently found higher scores for microdoses compared to placebo (Bershad et al., 2019; Family et al., 2020; Hasler et al., 2004; Holze et al., 2021; Hutten et al., 2020; Madsen and Knudsen, 2020; Strassman et al., 1994), with two controlled lab studies reporting non-significant trends (Bershad et al., 2020; Yanakieva et al., 2019). Based on these findings, it appears that microdoses were associated with ratings of approximately 30% of scale maxima for drug intensity ratings, compared to ratings of $< 10\%$ for placebos. By comparison, Holze et al. (2020) reported that 100 ug of LSD was rated at 87% of the scale maximum for subjective drug effects. In addition to increased intensity, Strassman et al. (1994) also reported increased somaesthesia (i.e., interoceptive and tactile sensations) and reduced volition following DMT microdoses.

Griffiths et al. (2018) used a microdose of psilocybin as a control condition in a study of psychedelic induced mystical experiences. Although the outcomes reported in this condition were minimal, therapist ratings of participants' behaviour indicated some drug effects. Finally, self-rated intensity of drug effects was the only measure that differentiated between microdoses and placebo, after controlling for expectation in Szigeti et al.'s (2021) self-blinded prospective study.

Some studies have used the 5D-ASC (Studerus et al., 2010) as a more detailed psychometric measure of alterations in consciousness. Hutten et al. (2020) showed a dose-response effect across four out of the five primary dimensions of this scale, with 20 μg of LSD leading to significant increases on each dimension (apart from *auditory alterations*) compared to placebo, and 10 μg of LSD only increasing the *anxious/fearful* dimension. Similarly, Bershad et al. (2019) found increases in the *blissful state* and *experience of unity* sub-dimensions following 13 μg of LSD tartrate, and Family et al. (2020) found a dose dependent relationship in the reduction in *vigilance* subscale (i.e., drowsiness and reduced alertness) following LSD microdosing. However, another lab study found no acute changes in 5D-ASC scores following 13 μg of LSD tartrate (Bershad et al., 2020).

Finally, in one lab study, Fanciullacci et al. (1974) found that headache patients were considerably more likely to have acute psychological, affective and perceptual alterations following microdoses of both psilocybin and LSD, compared to healthy controls. This finding is intriguing in the context of reports that high dose psychedelics may offer relief for otherwise difficult to treat headache symptoms (Andersson et al., 2017; Sewell et al., 2006).

3.3.6. *Neurobiological and physiological effects*

Only one study assessed neurobiological changes following microdosing. In a detailed exploration of the effects of microdoses of LSD on the brain, Bershad et al. (2020) found changes in resting state connectivity between the amygdala and a series of brain regions that have been associated with depression (i.e., increased connectivity with the right angular gyrus, right middle frontal gyrus, cerebellum; and decreased connectivity with the postcentral gyrus and superior temporal gyrus). Although this is a single preliminary finding, these results are compatible with both findings from research on the effects of high dose psychedelics (Mueller et al., 2017), and potential mechanisms for the efficacy of traditional antidepressants (S. E. Murphy et al., 2009).

Although we did not specify somatic changes as inclusion criteria for this review, a range of effects from psychophysiological to somatic were reported in the reviewed studies. The most consistently reported of these was reduction in perceived pain. This has been found in a qualitative study (Johnstad, 2018) and two survey studies (Hutten et al., 2019b; Lea et al., 2020c). However, the clearest evidence comes from a well-controlled lab study by Ramaekers et al. (2021), who found that 20 μg of LSD were associated with significant increases in the duration that participants could tolerate aversive exposure to cold, and that participants rated the experience as significantly less painful and unpleasant compared to placebo. Relatedly, there was also one qualitative report of increased sensory acuity (Andersson and Kjellgren, 2019).

Notably, two large scale survey studies (Hutten et al., 2019b; Lea et al., 2020c) found that microdosers rated the effectiveness of very low dose psychedelics as greater than conventional treatments for physical disorders (e.g., migraines, chronic pain). This led some users to reduce or entirely cease standard medications (e.g., Lea et al. reported that 27.5% of affected respondents stopped taking pain medication).

Despite these positive reports, negative physical outcomes were also relatively common during or following microdosing in self reports. Qualitative accounts noted insomnia (Johnstad, 2018), physical discomfort (Anderson et al., 2019a; Andersson and Kjellgren, 2019) and other unwanted physiological effects (e.g., headache, fatigue, nausea; Lea et al., 2020a). In a survey study, Hutten et al. (2019a) found that approximately 6% of microdosers experienced negative physiological effects. Similarly, Lea et al. (2020b) found relatively common reports of trouble sleeping, overstimulation and headache. Finally, Petranker et al. (2020) found that physiological discomfort was common among psilocybin microdosers, but not among microdosers using LSD (or similar substances).

Five reviewed studies showed autonomic changes following microdoses (e.g., increased galvanic skin responses, pupil changes, increased blood pressure; Bershad et al., 2019, 2020; Greiner et al., 1958; Isbell, 1959; Ramaekers et al., 2021). Griffiths et al., (2016, 2018) also reported findings suggestive of increased cardiovascular response following microdosing, but these were not formally compared to a no drug condition. However, Hasler et al. (2004) found no autonomic changes associated with microdoses of psilocybin. Ramaekers et al. (2021) and Family et al. (2020) additionally reported minor unpleasant physical symptoms such as somatization and dizziness. Finally, in a study of the impact of LSD on sleep, Muzio et al. (1966) suggest that low doses of LSD may lead to prolonged REM phase sleep, although doses were inconsistently grouped together in that paper and it is not clear if the reported outcomes are truly representative of effects in the microdose range.

3.4. Risk of bias

The reviewed studies showed a wide range of Risk of Bias (RoB) scores (Table 4). There were several patterns related to study type and year of publication. All studies from the first generation of psychedelic research (in our selection, from 1955 to 1974) scored higher on RoB than the median RoB, whereas all contemporary laboratory studies scored lower than the median RoB. Prospective studies tended to have lower RoB scores than retrospective survey studies, which in turn tended to have lower RoB scores than qualitative studies. Several of the included studies were aimed at investigating the effects of high dose psychedelics and used a microdose condition as a placebo (Forsyth et al., 2016; Gasser et al., 2014; Griffiths et al., 2016, 2018; Madsen et al., 2019; Moreno et al., 2006). Despite being rigorously designed for their intended purpose, these studies did not include any additional comparator conditions that could be used to evaluate the effectiveness of microdosing, and so these studies scored higher for risk in our assessment (this is not a comment on their overall study quality, only on suitability for evaluating microdosing specifically). Also, it's worth noting that any contribution of expectancy to the effects of microdosing is likely to be different in trials specifically evaluating microdoses (i.e., where a low dose is framed as potentially effective) compared with those that used microdoses as controls (i.e., where a low dose is framed as ineffective).

In terms of categories of risk, selection bias was not a risk in most studies, with clear selection criteria and random samples. Reliability and causality biases were mixed, with high bias mostly associated with certain types of study designs, and not design flaws (e.g., retrospective survey studies have inherent risk of reliability and causality bias). Notably, transparent research practices were an area of high risk for most microdosing studies. Although reporting methods were typically rigorous, very few studies followed open science practices. Only two studies were formally pre-registered and only six studies provided open datasets. No studies provided both pre-registration and open data.

Ranked categories of bias risk for microdosing studies were as follows:

1. lack of preregistration (most common risk)
2. lack of open data
3. lack of dose-response effect
4. lack of controlled alternatives
5. lack of controlled outcome assessment
6. lack of controlled exposure to drug
7. lack of reliable measures; poor reporting fidelity
8. unclear or unbiased selection
9. inadequate time to follow up (least common risk)

A correlation investigating the association between number of citations (Google scholar citations as of 3 June 2021) and RoB scores indicated that papers with lower risk of bias were more cited ($r = -0.32$, $p = .040$). This was also the case when controlling for year of publication ($r = -0.37$, $p = .017$). This indicates that more rigorous microdosing studies were more likely to be cited.

4. Discussion

This systematic review considered all empirical research on microdosing from 1955 to 2021 to produce what we believe is the most comprehensive summary of findings on microdosing psychedelics to date. This review included numerous studies not reported in previous reviews that were either from the first wave of psychedelic research or very recently published. We found that despite considerable differences in research standards from the time of pre-prohibition research to now, the older lab studies were consistent with contemporary research, with similar findings related to changes in conscious state and improvements in mood. Overall, the studies reviewed used a diverse range of methods and measures, and reported a large number of outcomes. There were several themes that stood out across these studies.

4.1. Key effects of microdosing

Although there are emerging questions about the degree to which microdosing effects can be explained by expectation (see 4.3), several lines of evidence indicate direct drug effects in the microdose range. In particular, multiple studies indicated beneficial changes in cognitive processing, and improved indicators of mental health. Here we summarise the most promising evidence from both lab and self-report studies (see Table 5).

4.1.1. Effects found in both self-report and lab studies

Some of the clearest evidence for changes in cognition from lab-based microdosing research relates to alterations in time perception. This has been demonstrated in two well-controlled lab studies (Wackermann et al., 2008; Yanakieva et al., 2019). Although on its own, a finding of altered perception of time does not have immediately obvious clinical or optimisation benefits, reliable changes in this capacity do

typically imply the involvement of attention and working memory (Yanakieva et al., 2019). However, lab findings directly related to attention and working memory are mixed. Bershad et al. (2019) found no evidence of changes to working memory (n-back task). Similarly, both Bershad et al. and Hutten et al. (2020) found no changes in general cognitive functioning using a digit span substitution task. Hutten et al. did find that the majority of participants showed improved attention in a psychomotor vigilance task following 5 μg and 10 μg of LSD, but not after 20 μg. In any case, untangling the mechanisms that underlie temporal processing following microdosing is a promising avenue for future research.

Reduced pain perception is another finding that has been demonstrated in a well-controlled lab study (Ramaekers et al., 2021), and several self-report studies (Hutten et al., 2019b; Johnstad, 2018; Lea et al., 2020c). Reduced sensitivity to physiological pain is likely also a factor driving other self-reported physical and mental health outcomes.

A further common finding, particularly in lab studies, was that microdosers report a variety of acute subjective alterations to their conscious state when microdosing (e.g., Abramson et al., 1955; Andersson and Kjellgren, 2019; Holze et al., 2021; Madsen et al., 2019; Szigeti et al., 2021). This contradicts the popular narrative that microdosing is a sub-perceptual phenomenon. Beyond questions of accurately defining the practice of microdosing, this finding calls into question the veracity of blinding in placebo-controlled trials (see 4.3).

Although time perception, pain reduction, and changes in conscious state are not commonly mentioned in popular reports, these are consistent findings from controlled lab and self-report studies, and together provide good evidence of direct neurocognitive effects of psychedelics taken in the microdose range. Further evidence of neuropharmacological effects of microdosing comes from the only imaging study to date, which found evidence of altered neural connectivity that was associated with affective changes after microdosing with LSD (Bershad et al., 2020).

4.1.2. *Effects found in self report studies but not well investigated in lab studies*

There were a wide range of promising findings from self-report studies that have not been well explored in lab settings. Most notably, there have not yet been any clinical trials of microdosing. There is strong and consistent evidence from qualitative, survey, and prospective research that microdosing may improve mental health (particularly depression and anxiety), including reports that microdosing is perceived by users to be more effective than existing treatments (Hutten et al., 2019b; Lea et al., 2020c, 2020a). Microdosing was also commonly reported to relieve physical discomfort, and reduce substance use. The possible clinical impact of microdosing is an underexplored area with considerable potential impact for future research to address.

There are currently mixed findings related to creativity. Several self-report studies (Anderson et al., 2019a, 2019b; Andersson and Kjellgren, 2019; Fadiman and Korb, 2019; Lea et al., 2020a; Petranker et al., 2020; Webb et al., 2019), and two prospective studies (Prochazkova et al., 2018; Szigeti et al., 2021) have indicated that microdosing may increase creativity, however the only lab study to investigate this topic found no change (Bershad et al., 2019). More research is needed before confident conclusions can be drawn.

Other promising findings that have not yet been explored in well-controlled lab studies relate to the potential for microdosing to optimise or enhance functioning in healthy individuals. In particular, self-report studies have indicated: beneficial changes in specific attentional capacities, such as increases in absorption and decreased mind wandering; increased wellbeing and insight; positive personality changes; and greater connection to nature.

4.1.3. *Effects reported in self report studies; investigated but not confirmed in lab studies*

There were several promising self-report findings that, so far, have not been confirmed in lab studies. These include improved mood, sociability, cognition, and emotional processing. However, a critical factor to consider when evaluating the current microdosing literature is that all lab studies to date have focused on acute changes following a single dose, or a small number of doses. By contrast, many of the findings reported in qualitative, survey and prospective studies are accumulative effects that result from lengthy periods of microdosing. This means that it is prudent to be cautious when interpreting null findings from current lab studies. For example, two well controlled studies by Bershad et al., (2019, 2020) reported no acute change in mood following microdoses of LSD, whereas multiple self-report studies indicate marked improvements in mood (see Table 3). It may be the case the microdosing has no immediate, acute effect on mood but that regular microdosing does lead to sustained, gradual mood improvements. By way of comparison, traditional antidepressant medications can take a number of weeks for the full effects to emerge. It would not be very informative to assess the effectiveness of fluoxetine after a single dose. Well controlled lab studies that investigate the long term effects of microdosing are needed to properly test sustained impacts (and there is at least one such study currently underway; R. J. Murphy et al., 2021).

Sociability is another finding commonly shown to improve in self-report studies but that was not supported by Bershad et al.'s (2019) lab study. Again, a state-based measure tapping immediate responding after a single exposure to microdosing may not be informative regarding enduring trait-like changes that might result from repeated exposures. We suggest that although mood and social connection have not yet been confirmed in lab-based research, considering the weight of evidence from self-report studies, these are domains where it would be worthwhile to explore enduring changes in controlled studies.

Other self-report findings that were not confirmed in lab studies included improvements in cognition, creativity, and emotional processing. The evidence base around these constructs is less consistent and these may be less of a priority for future research.

4.2. *Microdosing is related to bidirectional effects*

A recurrent and noteworthy finding, both within and across studies, was opposing or bidirectional effects. That is, in some cases microdosing appeared to be related to both increases and decreases on the same measures. For example, Hutten et al. (2020) showed that several variables significantly increased in some participants but decreased in others, as a function of drug dose (including attentional lapses, cognitive function, mood, and energy). Some survey studies also showed bidirectional effects (e.g., Lea et al., 2020b; Rosenbaum et al., 2020), with notable emphasis on this pattern of findings within Anderson et al. (2019a), who report bidirectional findings associated with anxiety and cognitive effects in particular.

This pattern of findings, not unique to psychedelics, may in some cases be an interaction between drug effects and expectancy or other

Table 5
Current evidence for microdosing effects.

Effects found in both self-report and lab studies	Effects found in self-report studies but not well investigated in lab studies	Effects found in self-report studies; investigated but not confirmed in lab studies[a]
• Altered time perception • Pain tolerance • Changes in conscious state	• Improved mental health • Reduced substance use • Increased absorption • Reduced mind wandering • Personality changes • Insight • Nature relatedness • Wellbeing • Improved creativity	• Improved mood • Social connection • Improved cognition • Enhanced emotional processing • Increased energy

[a] Note: Lab studies to date have investigated only acute effects. Sustained effects related to microdosing have not yet been explored in lab-based studies.

contextual factors (e.g., anxiety may increase or decrease depending on how conducive the physical environment is), and thereby vary within the same individual in different contexts. In other cases, bidirectionality may be attributed to subtypes of people that respond to microdoses in specific and consistent ways (for example, microdosing may reduce anxiety symptoms in some people, and increase anxiety symptoms in others). For example, recent research has identified individual differences in enzymatic activity that impact on certain individuals' capacity to metabolise LSD (Luethi et al., 2019).

If bidirectionality is explained by contextual factors, future research should attempt to determine contexts that better support beneficial effects. If instead bidirectionality relates to population subtypes, then future research should attempt to ascertain predictive markers for certain responses, conduct subtype analyses, and thereby determine who is likely to benefit from microdosing.

4.3. Placebo control in microdosing studies is seldom adequate

Less than half of the reviewed studies were placebo-controlled (17 of 44 studies). All 17 of these placebo-controlled studies were either single- or double-blind. However, only 5 of these assessed the success of the blind (i.e., 71% did not assess the blind), only two studies (different samples from the same lab) achieved a reasonable degree of blinding (Bershad et al., 2019, 2020), and none used active placebos. In most studies that assessed blinding, participants often correctly guessed the difference between placebo and microdose. As microdosing in the typical dose range often produces noticeable changes to conscious awareness (see 3.3.5) which would cause the blind to be broken, it is possible that many placebo-controlled microdosing studies that did not explicitly assess blinding failed to achieve it. Accordingly, it is difficult to distinguish between the role of drug expectancy and drug effects of microdosing within the reviewed studies. Note, control conditions that don't assess or maintain adequate blinding may still control for other extra-pharmacological factors.

Despite this, two recent studies have suggested that the effects of microdosing may be wholly or predominately caused by expectation. First, Kaertner et al. (2021) showed in a prospective, self-report study, that baseline expectations predicted positive outcomes. Second, Szigeti et al. (2021) used an innovative 'self-blinding' citizen science design to compare microdosing and placebo conditions, and found little evidence of any difference between the two conditions across many of the commonly-reported effects of microdosing (e.g., improved mood, well-being, social connectedness, cognitive performance, mindfulness). Szigeti et al. also analysed data according to which experimental condition participants guessed they were in and found that despite the lack of overall group differences, there were significant differences between those who guessed they had microdosed compared with those who guessed they had taken a placebo (regardless of which substance they had taken). The authors of both studies interpret their results to indicate that many of the reported effects of microdosing are driven by expectancy.

However, we highlight seven issues that cast doubt on a predominant role of expectancy in these findings. First, blinding in microdosing research has been mostly ineffective. As highlighted above, this is the case for almost all studies to date. In particular, over 70% of all guesses were correct in Szigeti et al. (2021), and participants accurately guessed they had consumed a microdose at double the rate predicted by chance (i.e., blinding in the microdose condition was limited). This means that we don't have a clear picture of what the real placebo component is from many of these studies.

Second, there are likely to have been substantially asymmetric expectations between experimental groups in many microdosing studies. In other words, guessing is not independent of drug effects. In Szigeti et al. (2021) participants correctly guessed the placebo condition only marginally better than chance, but correctly guessed they were in the microdose condition at twice the rate expected due to chance. In addition, correct guesses increased with higher doses, and participants indicated various acute drug effects as the reasons for breaking the blind in the microdose condition. This suggests that correct microdose guesses, in addition to being more frequent, were likely made with higher confidence than correct placebo guesses (given the acute drug effects). If this is the case, it implies considerably different levels of expectancy between the conditions. Moreover, participants who reported acute drug effects in Szigeti et al. (2021) were more likely to have had an 'effective dose' that could produce changes in other outcome variables compared with those reporting no acute drug effects (see sixth point below), confounding any distinctions between guess confidence and direct microdosing effects.

Third, previous microdosing studies suggest that the magnitude of expectancy effects may be small. Although Kaertner et al.'s (2021) study showed that expectancy contributed to changes on each outcome variable, the proportion of variance explained by expectancy was relatively modest (8% for wellbeing; 7% for depressive symptoms; 5% for anxiety). In contrast, the main analyses showed relatively large effect sizes for overall changes from baseline to the end of the study period (wellbeing $\eta p2 = 0.18$; depressive symptoms $\eta p2 = 0.31$; anxiety $\eta p2 = 0.24$). Relatedly, in a controlled lab study, Hutten et al. (2020) found that although the majority of participants (74%) increased performance on a cognitive attention task, most participants (63%) believed that they had decreased performance. In other words, many participants' beliefs about their change in performance were in direct opposition to their actual change in performance. These findings suggest that although expectation is important, it may not be the main mechanism driving microdosing effects.

Fourth, spurious attributions may have impacted participants' guesses in Szigeti et al. (2021). Szigeti et al. imply that participants' guesses (or expectations) cause changes on the outcome variables. But it may be that (for at least some participants) observed changes in outcome variables lead to particular guesses. Specifically, in the absence of acute drug effects, *any* observed effects that occur for unrelated reasons may be misattributed to the study. If a participant notices improved mood they may misattribute this to being in the microdosing condition (regardless of their actual experimental condition). Similarly, a participant who notices worsened mood may misattribute this to being in the placebo condition. That is, changes due to spurious causes may have led participants to make an incorrect guess regarding experimental condition, which would appear indistinguishable from the scenario where the condition a participant guesses drives the expected changes. This means that differences between the guessed conditions may have been inflated by causes unrelated to expectancy.

Fifth, commonly found bidirectional effects may obscure group differences. As outlined in the previous section, microdosing may affect subgroups of individuals in opposite ways. If a subset of individuals increase on a particular variable but others decrease (e.g., Hutten et al., 2020), potentially interesting patterns of results may be obscured by group level analyses. If the placebo component of a particular effect is consistent across individuals, in the context of strong bidirectional drug effects, this component may survive group aggregation, whereas the highly variable drug effects may not. This would lead to an overestimation of placebo effects.

Sixth, participants in both Kaertner et al. (2021) and Szigeti et al. (2021) were self-selected and highly motivated microdosers. These individuals presumably undertook legal risks to obtain psychedelic substances and went to considerable effort to prepare these in the appropriate dose for these studies. The majority of participants in both studies rated themselves as strong advocates of psychedelics and most also reported previous experience with high dose psychedelics. As such, these samples were unlikely to be representative of the wider populations, and likely also possessed positive expectations about the effects of low dose psychedelics. Considering this, it is not clear whether claims regarding the role of expectation in these studies might also apply to less motivated populations (more broadly, self-selection biases are a concern

for many reported microdosing findings: see 4.6).

Seventh, and perhaps mostly importantly, studies that suggest strong expectancy effects may have investigated *ineffective* doses in a large proportion of participants. Both Kaertner et al. (2021) and Szigeti et al. (2021) relied on self-reports with uncontrolled and variable doses. Kaertner et al. found no discernible acute drug effects in about 20% of participants; and Szigeti et al. reported at least 20% of participants in the microdose condition incorrectly guessed they were in the placebo condition, implying that these participants did not notice any subjective effects. Lab based research has shown that the threshold dose for acute effects on conscious state varies widely across individuals (Holze et al., 2021), and also that the dose-response relationship for various putative changes related to microdosing varies widely (Hutten et al., 2020). This suggests that the intensity of acute subjective effects may provide a proxy indicator of an individual's sensitivity to other microdosing outcomes. If this is the case, it is likely that some proportion of participants not reporting subjective effects did not take effective doses. This means that genuine differences due to the pharmacological effects of microdosing were likely obscured by participants in the microdosing condition who took ineffective doses. Furthermore, ineffective doses would inflate differences between guess conditions, as some participants in the microdose condition would guess they are in the placebo condition due to ineffective dosing rather than expectancy.

With these issues in mind, we suggest that claims that microdosing is largely a placebo-driven effect (e.g., Siebert, 2021) are premature. The above studies show that expectancy does contribute to the overall effect of microdosing, but we cannot yet be confident about the magnitude of the expectancy effect, or its relative importance compared to the pharmacological effects of microdosing. To confidently resolve these questions, future studies should employ active-placebos and assess adequate blinding to tease apart the effects attributable to microdosing (including any that depend on acute drug effects) from a placebo response. Specifically, in an ideal scenario, an active placebo would lead to participants breaking blind at a rate close to chance. In this case investigators could be confident that any differences that were found between a microdose and a placebo condition would not be driven by expectancies.

Furthermore, studies could ensure effective doses by titrating the dose to achieve some minimal acute drug effects with no loss of function, and develop methods to identify subtypes of individuals with specific response profiles towards separating 'responders' from 'non-responders'.

4.4. The current state of microdosing research

Despite various methodological limitations and possible expectancy effects outlined above, there are reasons to continue to develop microdosing science. There have now been eight modern, placebo-controlled laboratory studies specifically focused on the effects of microdosing, six of which tested multiple doses within the microdose range. Importantly, all of these studies show clear dose-dependent changes across a range of measures (see Table 5). Another consistent outcome in these lab studies is that participants report subjective effects following doses in the microdosing range. These findings together provide evidence of psychopharmacological effects. That is, microdosing appears to be doing something. A key question for researchers is whether these effects of microdosing have clinical or optimisation benefits beyond what might be explained by placebo or expectation.

Regardless of whether the effects of microdosing are primarily based on expectation or pharmacology, there is evidence that microdosing is having a considerable impact on peoples' lives. Prevalence estimates vary, but a surprisingly high proportion of those who use illicit drugs report microdosing. One study, which did not specifically target psychedelic users, found 17% of respondents reporting recreational drug or alcohol use had microdosed (Cameron et al., 2020), and approximately 7% of respondents to the 2019 Global Drug Survey reported microdosing (Petranker et al., 2020). Furthermore, microdosers believe that the practice is more effective than traditional treatments for physical and mental health issues (Hutten et al., 2019b), with a considerable proportion (e.g., more than 50% in Lea et al., 2020c) ceasing traditional medications after commencing microdosing. In this regard, microdosing represents a common practice with implications for health behaviours.

4.5. Open questions and the future of microdosing

As microdosing science becomes a more established field, the next phase of work must focus on well-controlled confirmatory research. Assessing individual predictors, expectancies, and contextual factors within active-placebo controlled designs will be key to determining reliable findings and their mechanisms. Indeed, the common finding of bidirectional effects (e.g., Anderson et al., 2019a), subgroup differences (e.g., greater sensitivity to LSD in essential headache sufferers in Fanciullacci et al., 1974) and also substantial individual variability in response (e.g., Hutten et al., 2020) suggest that until the field has made some initial progress on individual response prediction, aggregate data will lose many signals in the noise. Furthermore, a general question associated with all microdosing research is whether and to what degree the effects depend on acute subjective experience of the microdose effects, and if they do, how to conduct adequately blinded studies.

One key area that has been under-studied is the safety profile of long-term microdosing (Kuypers et al., 2019). Occasional ingestion of much higher doses of psychedelic substances are physiologically safe for most people (Nichols, 2016), and a well-controlled microdosing study specifically assessing safety found that six low doses of LSD, taken at 4 day intervals, were well tolerated with no differences in adverse events, vital signs, blood markers, and psychiatric parameters from placebo (only mild to moderate headaches were related to microdosing; Family et al., 2020). However, safety concerns have been raised regarding chronic administration of very low doses over many months or years, as is common in naturalistic microdosing practice. While these concerns have not been directly tested, chronic administration of serotonin 2B receptor agonists have been shown to cause valvular heart disease (Hutcheson et al., 2011), and commonly microdosed psychedelics are known to activate this receptor subtype with high affinity (Besnard et al., 2012; Wacker et al., 2017). Future research should investigate this, and other potential health risks associated with chronic and long-term administration of microdoses of psychedelics.

4.6. Recommendations for the next phase of microdosing science

We conclude with nine suggestions to guide the next phase of microdosing research.

4.6.1. Accurately measure substance and dose

Researchers should clearly specify the substances and dose ranges that are being investigated. An assumption of some qualitative, cross-sectional, and observational studies of microdosing has been that there are common effects across various serotonergic psychedelics. As outlined above, there has also been some uncertainty as to what dose constitutes a microdose. To increase the precision of microdosing science we need to focus on identifying substance-specific psychopharmacological effects. While we hope that the suggestions for plausible microdosing ranges provided in Table 1 will assist with this, further research is required to definitively ascertain perceptual threshold doses, and substance specific outcomes.

4.6.2. Distinguish and evaluate frequency and dosing schedule

There is likely a substantial distinction to be drawn between the acute effects of one or a few administrations of a microdose versus the sustained effects of regular and longer-term microdosing practice. Most reviewed survey studies reported on regular and longer-term practice, whereas the reviewed lab studies assessed the acute effects of one to six administrations. Future survey studies should clearly assess the

frequency and duration of microdosing practice, and future lab studies should systematically vary these. Relatedly, although a common practice in the wild and in research studies is to microdose approximately every three days, to date there have been no formal comparisons of different dosing schedules and we have no empirical evidence to support the relative efficacy of any particular dosing regimen. This is an important variable to test in future research.

4.6.3. Reframe microdosing as frequently supra-perceptual

Given that one of the most consistent findings amongst the papers we reviewed was that microdosing was associated with identifiable subjective drug effects, we suggest that researchers avoid describing microdosing as sub-perceptual. Instead, we suggest that acute subjective effects should always be measured and microdosing could be defined as *sub-hallucinogenic with no loss of functionality*.

4.6.4. Control for placebo response

It is critical that studies investigating the effects of microdosing control for participant expectations. While many lab-based studies incorporate placebo-controlled designs, many do not assess the integrity of the blind. Given typical microdoses produce noticeable acute subjective drug effects, we suggest that one important way of controlling expectations would be for future studies to incorporate active-placebo controls (e.g., low doses of diphenhydramine or tetrahydrocannabinol) and assess blinding veracity. Metrics such as the Bang Blinding Index allow sensitive evaluation of the relative blinding efficacy of each experimental condition, and may be particularly suited to microdosing research (Bang et al., 2004; Muthukumaraswamy et al., 2021). Controlling drug expectancy need not be limited to laboratory research: Szigeti et al. (2021) have demonstrated that it is possible to control for expectancy and implement placebo blinding within observational microdosing studies.

4.6.5. Explore response prediction

One clear theme to emerge in the reviewed microdosing literature is bidirectional effects: within and across studies, a large number of variables have been shown to both decrease and increase following microdosing. Whether bidirectional effects are a function of stable individual differences (e.g., some people consistently become more anxious and others less anxious following microdosing) or situational factors (e.g., dose, mindset, physical setting, time of day, etc), future studies should explore these and other potential predictors of subgroup effects. Better response prediction may substantially speed up progress in microdosing science. As discussed above, bidirectional effects may cancel each other in group aggregates, and so it may be productive to investigate changes in variance or absolute shift from baseline in addition to mean score differences. Moreover, better response prediction may substantially improve the usefulness of microdosing science by determining real and reliable benefits and harms in subgroups of people.

4.6.6. Improve specificity of measured effects

Future microdosing research should focus on assessing specific cognitive and other capacities. Early anecdotal and qualitative reports suggested that microdosing might have a very broad range of positive impacts on individuals' lives. This has led microdosing researchers to investigate relatively broad, ill-defined, or complex constructs such as wellbeing and quality of life. On balance, the studies in this review have not shown strong evidence of changes in these domains. By contrast, there is compelling evidence that microdosing may impact specific cognitive functions such as time perception and pain perception. Promising directions for future research may be to focus on identifying other unexplored lower-level cognitive functions that may be responsive to microdosing, and investigate whether the cognitive capacities that are influenced by microdosing have clinical or practical utility (for example, through clinical trials or ecologically relevant performance-based measures).

4.6.7. Explore clinical applications

Reported improvements in mental and physical health were some of the most common findings across all types of self report studies. The potential application of microdosing as a clinical tool, particularly as a treatment for depression has been identified previously (Kuypers, 2020), but no clinical study has yet taken place. The original reports from Fadiman that catalysed the current popularity of microdosing were clearly focused on the clinical utility of low dose psychedelics (e.g., Fadiman, 2017), yet this has not been a major focus of most empirical research. This is an obvious gap that should be addressed.

4.6.8. Recruit representative samples

Most microdosing research to date suffers from selection bias, with samples comprised of enthusiastic microdosing volunteers. This may have had a considerable impact on research findings to date. Future research would benefit from large, demographically diverse samples that better represent the population at large.

4.6.9. Conduct long-term longitudinal studies

To date there has been little longitudinal research on the effects of microdosing. Only four prospective studies were identified in this review, and these all looked at effects over a time span of six weeks or less. Moreover, most of the controlled microdosing-specific studies tested different doses once each on the same volunteers, which does not resemble recurrent or sustained microdosing practice. Two controlled studies randomised participants to a specific dose that was administered six times (Family et al., 2020; Yanakieva et al., 2018), which goes some way to exploring repeat dosing, yet still does not resemble naturalistic practice. As long-term safety and efficacy remain unknown, and regular long-term use is already the de facto approach to microdosing in the community, carefully controlled studies that investigate the impacts of microdosing over longer time spans are needed.

4.6.10. Assess safety

More research is needed into the safety of microdosing. Although psychedelics in general have a very good safety profile, the usage pattern associated with microdosing – i.e., regular, ongoing use – is quite different to the way that high dose psychedelics are typically consumed. One study has shown that microdosing appears to be safe for older individuals (Family et al., 2020), however this study focused mainly on acute effects. Little is known about potential risks related to long term chronic use, with some notable concerns regarding cardiac valvulopathy associated with chronic serotonin 2B receptor activation (Hutcheson et al., 2011). Definitively assessing these risks may require investigation of very long term microdosing.

4.6.11. Practice open science

Despite specific calls for transparency in psychedelic research (Petranker et al., 2020), the microdosing literature to date has not been particularly open. As microdosing science moves beyond the initial exploratory phase, it is necessary for the field to shift toward emphasising scientific rigour and replication. To facilitate this, we encourage researchers to pre-register their hypotheses, methods, and analytic plans, and to share de-identified data at the time of publication.

Microdosing research appears to be at an inflection point. As might be expected, the initial studies that arose in response to the recent popularisation of microdosing were qualitative or survey-based, cross sectional, retrospective investigations, in which people already engaged in the practice have reported on their motives and experiences. Such studies are exploratory in nature, with minimal experimental control. This hypothesis-generating phase of research has led to a large body of knowledge about the characteristics of microdosers and the perceived effects of this practice. A consistent theme from these studies is that microdosers report considerable and varied benefits, and that microdosing can lead to behaviour change. This phase of research is now being followed by well-controlled lab studies and research that places a

greater emphasis on teasing apart the influence of expectation and drug effects. Alongside widespread practice in the community and some early signals in the data, a more rigorous science of microdosing is now emerging to investigate acute and long-term benefits and risks, mechanisms of change, response prediction, and differences across substances, doses and dosing regimens. With the above recommendations in mind, microdosing science is set to mushroom into a productive field of enquiry over the coming years.

Data Availability

Supplementary materials for this project can be found at https://osf.io/xmqg7/.

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