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The Viability of Microdosing Psychedelics as a Strategy to Enhance Cognition and Well-being - An Early Review

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ABSTRACT

Psychedelic substances are currently experiencing a renaissance in interest for both therapeutic as well as recreational applications. It has been proposed that microdosing, i.e., ingesting sub-perceptual doses of a psychedelic, could confer some of the benefits of these substances to users while minimizing the risks associated with full-dose use. This review aimed to summarize and examine the extant literature on psychedelic microdosing. Exploratory evidence published to date indicates a variety of benefits reported by microdosers including improvements in mood, focus, and creativity, with some null reports, and a minority of people reporting selective negative consequences such as increased anxiety and physiological discomfort. Methodological limitations of current evidence, however, make definitive conclusions hard to draw. Recommendations for future research are given.

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Introduction

Despite their continued illegality in most parts of the world, many have observed that psychedelic substances have been experiencing a resurgence of interest in both therapeutic as well as recreational applications in recent years (Carhart-Harris et al. 2018; Sessa 2008). Good research remains scarce and difficult to do, owing to the substances' legal status and lingering social stigma, but slow progress is being made. Therapeutically, recent research indicates that psychedelics could play a beneficial role in the treatment of substance dependence (Johnson, Garcia-Romeu, and Griffiths 2017; Krebs and Johansen 2012; Thomas et al. 2013), end-of-life anxiety and depression (Gasser, Kirchner, and Passie 2014; Griffiths et al. 2016), treatment-resistant depression (Carhart-Harris et al. 2017; Osório et al. 2015), and obsessive-compulsive disorder (OCD; Moreno et al. 2006). Recreationally, psychedelic use has been associated with increases in openness (MacLean, Johnson, and Griffiths 2011; Schmid et al. 2015), prosocial behavior and attitudes (Griffiths et al. 2018), positive affect and emotion (Kometer et al. 2012), and boosts in creativity and problem-solving ability (Harman et al. 1966), as well as mystical experiences capable of effecting lasting changes in subjective evaluations of personal meaning and significance (Griffiths et al. 2008). Despite these promising results, psychedelic trips can also be immensely challenging experiences (Carbonaro et al. 2016), and, in rare cases, have been associated with enduring psychological problems like panic attacks, flashbacks, and hallucinogen persisting perception disorder (HPPD; Martinotti et al. 2018). Although most studies documenting negative effects to date have emphasized the relatively low risk compared to other drugs, the intense experiences occasioned by full-dose psychedelic use are not always desirable.

In contrast, microdosing is the practice of ingesting sub-perceptual doses of a psychedelic, usually defined as between one tenth and one twentieth of a normal dose (Fadiman and Korb 2019). Researchers have proposed that this practice may provide a strategy to access the potential benefits of these substances while minimizing the risks associated with full-dose use (Anderson et al. 2019b; Fadiman and Korb 2019; Johnstad 2018). The present paper summarizes the literature on microdosing in order to investigate whether it can be a viable strategy to improve cognitive functioning and well-being, and to analyze any potential risks that may be associated with the practice.

Methods

In order to find relevant studies, I searched Scopus, Pub-med, ProQuest, Google Scholar, and sEURch for the following search terms: microdosing AND (psychedelics OR lsd OR psilocybin OR mdma OR dmt OR mescaline OR psychoactive). The search was originally

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performed on 11 May, 2019, and amended on 12 November, 2019. Additional *ad hoc* searches were performed at a later date to identify full-dose psychedelic studies that included a microdose control condition. Titles and abstracts were read to determine the relevance of the studies to the present research question. Studies were excluded if they did not report novel results (e.g., review articles), if they were not published in a scientific journal (i.e., popular press), and if they did not involve the effects of microdosing psychedelics on humans (e.g., animal studies). Twenty-one documents met inclusion criteria and were read fully. Additional searches of the reference lists of selected studies did not yield further sources. The final selection of sources consists of eleven observational studies, one quasi-experimental study, and nine experimental studies. An overview of all included publications can be seen in Table 1. Due to the relative paucity of research in this area, much of the evidence to date remains qualitative in nature. Since qualitative data should be treated as exploratory, and only quantitative data as possessing the inferential strength to confirm or disconfirm hypotheses, the subsections of this review are structured in order of increasing evidential strength, and indications have been added to clarify the quantitative or qualitative nature of every cited study.

Results

General effects

The general effect of a psychedelic microdose has been described as "a really good day" (Waldman 2017). Although information is scarce, a number of observational, qualitative studies have provided preliminary statistics on the distribution of general effect patterns in their respective populations. Specifically, Fadiman and Korb (2019) designed a website offering a microdosing protocol for people interested in conducting a self-study. The protocol recommended microdosing every third day (i.e., a microdosing day followed by two non-microdosing days) for a period of one month. Among the hundreds of participants that have sent in narrative reports (a specific number of participants is not provided), they report that roughly 80% of accounts were positive or neutral in content. Another recent study involving an online questionnaire administered to volunteers on psychedelic-focused online fora (n = 1116) reported that about one fifth of participants who reported microdosing also reported experiencing negative effects (Hutten et al. 2019a). Unfortunately, the study did not specify what those negative effects were, beyond stating that they were more commonly psychological rather than physiological, and limited to the acute. Additionally, the study found that the most commonly reported reason for stopping a microdosing practice was not the experience of negative effects, but rather the feeling that the practice was ineffectual.

Johnstad (2018) interviewed 21 participants recruited through internet fora and noted that patterns of results became clear, so that new information was deemed unlikely to emerge. He reported mostly positive experiences, especially in the domains of depression and anxiety, among some null reports. However, he also reported a number of challenges participants faced. Among these, besides overdosing experiences and concerns about long-term consequences, were reports of backfiring effects associated with more long-term use. More precisely, some participants felt that the benefits obtained by microdosing early on actually reversed and served to exacerbate their mental health problems after a longer period of use.

Fossos-Wong et al. (2018), investigating self-reported comorbid drug use in college students, found that almost 69% of people who reported microdosing in the past year also reported at least one negative consequence of the practice. However, similar to the overdosing concerns reported by Johnstad (2018), the most commonly cited negative consequence was the experience of hallucinations (44.2%). Since these are most likely a result not of microdosing *per se*, but rather of a failure to dose correctly, it can be argued that it should not count as a negative consequence of microdosing itself. Moreover, the consequences of microdosing were not the primary focus of this study, and the portion of the study that did examine microdosing effects focused exclusively on negative consequences, possibly leading to an overly pessimistic conclusion. Nonetheless, since this study is the only one in the literature striking a more negative tone, it is included in the present review with these considerations in mind.

Lastly, in terms of negative effects of microdosing, several qualitative studies have found that the most frequently cited concerns had nothing to do with microdosing itself, but were consequences of the illegality and/or stigma associated with the substances (Anderson et al. 2019a; Lea, Amada, and Jungaberle 2019). Such concerns included the difficulty of having to measure doses oneself, having to hide the practice from others, and uncertainty about the purity of the substances due to reliance on the black market. In summary, evidence collected to date indicates that many microdosers experience positive effects with some people reporting no discernible effects and a number of reported challenges that will be discussed in later sections.

Table 1. Overview of existing microdosing studies (categorized in order of increasing evidential strength).

Type of study	Study	Overview
Observational, qualitative	Anderson et al. 2019a	Analysis of narrative reports as well as targeted online questioning; provides distribution of benefits and drawbacks reported by participants
	Andersson, Persson, and Kjellgren 2017	Searches of internet fora indicating a possible benefit of psychedelic microdoses for migraines and cluster headaches
	Fadiman and Korb 2019	Offered microdosing self-study protocol for interested participants; provides anecdotal reports and some statistics
	Fossos-Wong et al. 2018	Investigated comorbid drug use in students; reports correlational statistics on comorbidity as well as negative consequences of microdosing
	Hutten et al. 2019a	Online questionnaire administered to participants recruited through online fora concerning participants' motivations and negative effects from microdosing
	Johnstad 2018	Conducted interviews with 21 microdosers recruited through internet fora; provides anecdotal reports
	Lea, Amada, and Jungaberle 2019	Analyzed the content of comments and threads in a subreddit devoted to microdosing; provides qualitative taxonomies of motivations, benefits, and limitations/adverse effects
	Sewell, Halpern, and Pope 2006	Conducted interviews with 53 cluster headache patients who had self-medicated with sub-perceptual psychedelic doses
Observational, quantitative	Anderson et al. 2019b	Questionnaire-based study of current and former microdosers recruited through social media
	Hutten et al. 2019b	Online questionnaire administered to participants recruited through online fora concerning participants' self-rated effectiveness of microdoses for mental and physiological disorders
	Polito and Stevenson 2019	Systematic tracking of healthy microdosers; daily e-mail reports as well as tests on nine domains of psychological functioning at baseline and at 6-week follow-up
Quasi-experimental	Prochazkova et al. 2018	Repeated-measures design; administered a divergent thinking task, a convergent thinking task, and a fluid intelligence task to participants before and during a microdose in an open-label natural setting
Experimental	Bershad et al. 2019	Placebo-controlled, double-blind, repeated measures experimental study on the effects of varying small doses of LSD on mood, focus, creativity, and physiological measures
	Family et al. 2019	Investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of microdoses of LSD (5, 10, 20 µg) in healthy older adults under placebo-controlled, double-blind conditions
	Gasser et al. 2014a	Administered either 200 or 20 µg of LSD with therapy to patients diagnosed with life-threatening diseases to investigate the drug's effect on anxiety; no placebo-condition; double-blind
	Griffiths et al. 2016	Double-blind study administering either a low dose (1 or 3 mg/70 kg) or a high dose (22 or 30 mg/70 kg) of psilocybin to patients with life-threatening cancer to investigate effects on depression and anxiety; no placebo-condition
	Griffiths et al. 2018	Double-blind study administering psilocybin in varying doses and with varying levels of support (1 mg/70 kg with standard support, 20 and 30 mg/70 kg with standard support, or 20 and 30 mg/70 kg with high support for spiritual practice) to participants who practiced meditation or other spiritual practices; no placebo condition
	Hasler et al. 2004	Double-blind placebo-controlled dose-effect study administering placebo, 45, 115, 215, and 315 µg/kg of psilocybin to healthy humans; tested both psychological and physiological effects; $N = 8$
	Moreno et al. 2006	Double-blind study administering 25, 100, 200, and 300 µg/kg of psilocybin to $N = 9$ patients diagnosed with obsessive-compulsive disorder; no placebo condition
	Wackermann et al. 2008	Study 1 did not include a microdose condition; Study 2 administered 12 µg/kg of psilocybin or placebo to $N = 9$ participants under double-blind conditions to investigate subjective effects on time perception
	Yanakieva et al. 2018	Placebo-controlled, double-blind experimental study of the effects of LSD microdoses on time perception

Creativity

Multiple studies attest to an improvement of creativity associated with microdosing. Qualitatively, Fadiman and Korb (2019) and Johnstad (2018), as well as a recent content analysis of the subreddit r/microdosing on the online forum Reddit (Lea, Amada, and Jungaberle 2019), and a detailed analysis of the distribution of qualitatively reported microdosing effects (Anderson et al. 2019a) all reported that feelings of improved creativity were a common feature in the accounts they analyzed. Though their methods were exploratory, their results offer a promising finding warranting further investigation. In terms of quantitative studies, Anderson et al. (2019b) administered a battery of online questionnaires and tasks assessing aspects of personality, attitudes, mental health, and creativity to participants both with and without microdosing experience, and found higher creativity scores among both current and former microdosers when compared to participants without such experience. However, since this study included both current and former microdosers, it cannot be established that the effects observed were a result of a microdosing practice. It is equally possible that more creative people are more likely to seek out the microdosing experience.

Addressing these concerns of directionality is the only quasi-experimental study conducted on psychedelic microdosing to date. Prochazkova et al. (2018) assessed measures of general intelligence (Ravens Progressive Matrices), divergent thinking (Alternative Uses Task), and convergent thinking (Picture Concept Task) in visitors to a psychedelic festival in the

Netherlands as part of an on-stage presentation. The latter two tasks were presumed to be indicators of creativity. Participants completed all three tasks once before drug consumption, and once under the presumed influence of an estimated microdose of psychedelic truffles. Results showed significant improvements in both convergent and divergent thinking with no significant changes in fluid intelligence. The authors interpreted their findings as suggesting that psychedelic substances may help creativity by improving task transitioning processes in the brain. Although this study did not include a placebo control group and was not conducted under laboratory conditions, it presents the strongest evidence of creativity boosts in psychedelic microdosing to date.

In contrast, one observational study found no changes in creativity among microdosing participants, neither in self-report measures on acute microdose effects, nor at a 6-week post-rating of a more objective creativity task (Polito and Stevenson 2019). Additionally, Bershad et al. (2019) administered four single doses of LSD to 20 volunteers in an experimental, double-blind, placebo-controlled setting (doses: 0, 6, 13, and 26 µg) and similarly failed to find differences in creative performance on a Remote Associations Task beyond a marginal increase in attempts for the highest dose. Since the highest dose also significantly increased ratings on a "feel high" scale, however, it can be argued that it should not qualify as a microdose. In summary, then, the existing evidence on creativity changes associated with microdosing is mixed.

Focus and productivity

Part of the reason for the recent resurgence of psychedelic substances appears to be a movement, originally started in Silicon Valley, of microdosing to improve focus and productivity at work (Sahakian, d'Angelo, and Savulich 2018). Until recently, however, no published research was available to bear out these anecdotal reports. In the past two years, several qualitative studies have provided exploratory data on the issue. Fadiman and Korb (2019) detailed reports of increased productivity and less procrastination in microdosing participants. The interview study conducted by Johnstad (2018), as well as the subreddit content analysis (Lea, Amada, and Jungaberle 2019), and the questionnaire-based study by Anderson et al. (2019a), all present self-reported accounts of cognitive improvements in microdosers including enhanced productivity and efficiency, and a decrease in mental fog. The latter study also reported accounts of impaired focus. However, as the authors point out, negative accounts regarding this variable were outweighed by positive ones in an almost 2:1 ratio.

Polito and Stevenson (2019), analyzing both daily e-mail reports of participants (n = 98) and comparing a battery of questionnaires assessing nine domains of functioning at baseline and at a 6-week post-rating (n = 63), also found lower levels of distractibility and increased absorption at follow-up. This study offers the first systematic piece of evidence for long-term effects of microdosing as opposed to the acute effects reported on active microdosing days or the day after. On the other hand, the experimental, placebo-controlled study by Bershad et al. (2019) mentioned earlier found neither effects on working memory function, nor on focus and productivity compared with lower doses and a placebo, except for a marginal increase in vigor in the highest-dose condition. As previously mentioned, this higher dose does not meet the traditional definition of a microdose. Similarly, Family et al. (2019) administered six doses of either a placebo, 5, 10, or 20 µg of LSD to healthy older adults and found very minimal effects on cognition except for a linear dose-dependent increase in vigilance reduction, dizziness, and sleepiness. However, as the authors note, the fact that volunteers were confined to bed on microdosing days could have been a confounding factor.

A final aspect tangentially related to focus and productivity is the subjective experience of time in microdosing subjects. Yanakieva et al. (2018; using a subset of the Family et al. [2019] sample) have conducted one of only five experimental, placebo-controlled studies on human microdosing to date on this topic. An experimental paradigm requiring participants to estimate the duration of a computer-based stimulus found that people under the influence of an LSD microdose tended to overestimate supra-second intervals. However, this finding was restricted to the 2000–4000 millisecond range and is at odds with previous research showing that full doses of psilocybin and LSD tend to lead to underestimation of supra-second time intervals (Aronson, Silverstein, and Klee 1959). Additionally, Wackermann et al. (2008), utilizing a similar experimental paradigm requiring the reproduction of time intervals between 1.5 and five seconds, reported a significant increase in the loss rate of internal time representation in psilocybin microdoses (12 µg/kg) compared to placebo.

Mood and general well-being

Both qualitative and quantitative studies have provided information on the effects of microdosing on mood and related topics. Qualitatively, early studies have reported effects such as an elevation of mood, increases in energy and self-efficacy, more openness toward friends

and family, improved attitude toward life, and extroversion (Anderson et al. 2019a; Fadiman and Korb 2019; Johnstad 2018; Lea, Amada, and Jungaberle 2019). Quantitatively, Anderson et al. (2019b) reported lower dysfunctional attitudes and negative emotionality, and increased wisdom and open-mindedness in current and former microdosers compared to a control group without microdosing experience. As already noted, however, the directionality of effects in this study is particularly unclear. Polito and Stevenson (2019) found decreases in stress at the 6-week follow-up, but also reported increases in neuroticism in some participants at the same assessment.

Finally, two experimental studies that investigated higher-dose psychedelic effects but included low-dose conditions for comparison are relevant here. Griffiths et al. (2018), who did not include a full placebo condition in their comparison of high and low doses of psilocybin in combination with other spiritual practice, reported that participants in the low-dose condition did attribute some changes on variables such as "positive behavior changes" and "positive mood changes" to their psychedelic experiences at a 6-month follow-up. However, the absence of a placebo condition, and the fact that many participants were likely led to expect a transformative experience, make interpretation of these results difficult. In contrast, Hasler et al. (2004), who did include a full placebo condition, reported slight drowsiness, increased sensitivity, and intensification of preexisting mood states amidst many null findings on mood and well-being in their lowest psilocybin condition (45 µg/kg; sample of $N = 8$). Similarly, the experimental studies by Bershad et al. (2019) and Wackermann et al. (2008) found no or only very few noteworthy alterations on mood and emotional processing.

Mental health

General

Anderson et al. (2019a) reported reduced use of substances such as caffeine, alcohol and tobacco in the qualitative reports they analyzed, while Johnstad (2018) presented qualitative evidence for improvements in conditions such as obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and narcolepsy. Hutten et al. (2019b), who designed a quantitative online questionnaire asking participants to rate the effectiveness of microdosing for mental health and physiological issues in comparison to both conventional treatments and full-dose psychedelic experiences ($N = 410$), found that participants rated microdosing as significantly more effective than conventional treatments for conditions such as ADD/ADHD and anxiety disorders. Finally, Moreno et al. (2006) reported some improvements in OCD symptoms for microdoses of psilocybin (25 µg/kg) in an experimental setting. However, no placebo condition was included, and symptom reductions were not significantly different across dose conditions, increasing concerns about possible expectancy effects.

Depression

Although generally dwarfed by the seemingly strong anti-depressive effects of full psychedelic doses (Hutten et al. 2019b), the literature to date includes some indications that psychedelic microdoses may also help with depression and depressive symptoms. In addition to the qualitative self-report studies suggesting this (Fadiman and Korb 2019; Johnstad 2018; Lea, Amada, and Jungaberle 2019), an anti-depressive effect was observed by both Polito and Stevenson (2019), as well as a study on depressive symptom reduction of cancer patients after high and low doses of psilocybin (Griffiths et al. 2016). In the latter study, although again dwarfed by the much higher efficacy of full doses, 32% of patients that had only received the low dose still exhibited a clinical response regarding their depression (defined as a 50% measure reduction relative to baseline) after the experience.

Anxiety

The evidence surrounding the effects of microdosing on anxiety is a little more contested. In terms of qualitative evidence, Johnstad (2018) presented reports of participants experiencing relief from especially social anxiety, while both Fadiman and Korb (2019) and Fossos-Wong et al. (2018) reported incidences of increased anxiety in the accounts they analyzed. In the latter study, 35% of people who reported microdosing in the past year also reported experiencing an increase in anxiety at least once. Additionally, both Lea, Amada, and Jungaberle (2019) and Anderson et al. (2019a) received reports saying both that microdosing helped with anxiety, as well as reports saying the opposite. In the latter study, the balance between positive and negative accounts regarding anxiety was found to be almost equal. However, this only held for open-ended questioning about benefits and challenges. When asked more directly whether microdosing had helped with anxiety issues, 59.2% of participants in the same study answered affirmatively.

As for quantitative evidence, Hutten et al. (2019b) reported that participants rated microdosing as both more effective than traditional treatments, and less effective than higher psychedelic doses for treatment

of anxiety disorders, while two full-dose experimental studies that included microdosing control conditions obtained conflicting results. Although the study on cancer patients found a 24% clinical response rate on anxiety after the low-dose session, it also reported that 15% of patients experienced an episode of anxiety during the session (Griffiths et al. 2016). Gasser et al. (2014a), also investigating a sample of people suffering from life-threatening illnesses, administered 20 μg of LSD in combination with therapy as a control condition to a high dose of LSD (200 μg), and found slight increases in both state and trait anxiety for people in the low-dose condition. However, the sample size in the low-dose condition was extremely small (n = 4). Moreover, as with other primarily full-dose psychedelic studies, the possible expectation of participants of having a full-blown psychedelic experience could have presented as a confounding factor, as the low-dose condition was used as a *de facto* placebo condition. In summary, then, it remains unclear what effect psychedelic microdoses may have on anxiety issues.

Physiological effects

The research concerning the physiological effects of psychedelic microdosing remains almost exclusively qualitative. One issue often brought up in popular discussion is a potential buildup of tolerance to the substances. Johnstad (2018) presented conflicting reports in this respect, and implied that effects might differ depending on microdose frequency. Even with daily ingestion, however, only some participants reported a significant buildup of tolerance, while others reported no tolerance. The only consistent finding in this study was that a microdose frequency of a few times per week did not seem to lead to any substantial tolerance effect.

As for acute physiological effects of microdosing, Johnstad (2018) reported reductions in migraines for some participants, which has been further reinforced by two qualitative self-report studies investigating sub-hallucinogenic doses of psychedelics as a last resort treatment for chronic migraine and cluster headaches (Andersson, Persson, and Kjellgren 2017; Sewell, Halpern, and Pope 2006). The quantitative study of Hutten et al. (2019b) found that participants rated microdosing as a more effective treatment than conventional options for nervous system diseases like migraines and cluster headaches. In contrast, there have also been qualitative reports of insomnia (Johnstad 2018), increased heart rate (Fossos-Wong et al. 2018), mild to severe headaches and nausea (Lea, Amada, and Jungaberle 2019), and physiological discomfort (Anderson et al. 2019a). Mild headaches in response to LSD microdoses were also found in the experimental study by Family et al. (2019), and the full-dose experimental study by Griffiths et al. (2016) reported that 12% of patients in the low-dose condition experienced physiological discomfort.

Finally, no research to date has examined any potential long-term physiological effects beyond the qualitative observation that microdosers have sometimes credited the practice with increasing their exercise, sleep, and healthy eating (Anderson et al. 2019a; Lea, Amada, and Jungaberle 2019). Although the toxicity of psychedelic substances has generally been found to be low (e.g., van Amsterdam, Opperhuizen, and Brink 2011), the risk of possible adverse physical consequences in the long run warrants separate inquiry in the future. Since 5-HT_{2B} agonists (including LSD and psilocybin) have been suggested to be implicated as a potential mediating factor in valvular heart disease (Cavero and Guillon 2014), one target of future research should be to investigate the possible cardiovascular effects of a long-term microdosing practice.

Discussion

This study summarized the extant literature on the topic of psychedelic microdosing. Overall, the evidence indicates a variety of benefits including improvements in mood, focus, and creativity, with some people experiencing no discernible effects or expressing concerns about selective negative consequences like increased anxiety. However, many of the samples drawn in the cited studies were convenience samples and therefore likely biased and unrepresentative of the general population. One possible consequence is underrepresentation of people who may have tried microdosing, but stopped due to experiencing either negative or no effects. Such persons would have been less likely to appear in the cited studies than a person who experienced only positive consequences of microdosing. Furthermore, research on long-term effects is nonexistent and much remains unknown in this area.

One issue that needs further research is the possible role of placebo effects. Two arguments against a placebo-based explanation have been proposed. Firstly, Johnstad (2018) suggested that the patterns of reports obtained in his exploratory study regarding both dosing regimens as well as effect patterns may be too specific to be due to placebo or nocebo effects. For example, placebo-based explanations may not explain why many people find specific dosing regimens effective but have had bad experiences with others. Secondly, Polito and Stevenson (2019) conducted a follow-up study in which they asked participants to

detail their expectations of microdosing effects, and found no association between people's expectations and the actually experienced effects from their first study. If people do not expect the rather specific effects that microdosing seems to have on them, the likelihood that these effects can be completely explained as a placebo seems reduced.

On the other hand, Anderson et al. (2019a) note that, in their sample, almost every effect that was mentioned as an advantage (e.g., increased energy) was also mentioned as a disadvantage (e.g., impaired, or too much, energy), suggesting that the phenomenon of microdosing may be heavily influenced by expectations and placebo. However, the authors point out that individual genetic and epigenetic differences may also account for some of these data. Taking into account the few placebo-controlled studies conducted so far, a general trend in the literature seems to be that the more scientifically rigorous the evidence, the more minimal and measured the results.

Another question that needs to be resolved is in how far microdoses resemble full doses in terms of their underlying brain mechanism. Since one is ingesting the same substances, a reasonable expectation would be that the brain would be affected in a similar way (i.e., same receptors, same mechanism). However, it is a common experience of researchers that analogies from full doses do not commonly hold for microdoses and vice versa. For example, Johnstad (2018) did not consistently find a buildup of tolerance to microdoses even with daily ingestion, whereas it has been reported that daily ingestion of full doses of LSD leads to a complete absence of acute effects as early as the fourth day of consecutive use (Buchborn et al. 2016). In contrast, many of the reported effects (e.g., mood improvements, anti-depressive effects) seem similar between doses at least in terms of direction. Neuroimaging studies could help determine to what extent analogies between full doses and microdoses are appropriate. In terms of anti-depressive effects, for example, it has been proposed that the effect of a full psychedelic dose on the default-mode network (DMN) might be an important mechanism in the apparent efficacy of (particularly) psilocybin to treatment-resistant depression (Ruban and Kołodziej 2018). Clarifying whether and to what degree microdoses of the same substance affect the DMN may aid our understanding of how and why microdoses could or could not have similar anti-depressive properties.

Lastly, it is important to note that there is no consensus on the precise definition of a microdose. In terms of psilocybin, for example, the experimental evidence here reviewed ranges in their definition of a "very low dose" from 12 µg/kg body weight (i.e., 0.84 mg/70 kg; e.g., Wackermann et al. 2008) to 45 µg/kg body weight (i.e., 3.15 mg/70 kg; e.g., Hasler et al. 2004). In some of the studies using the higher end of this spectrum, participants selectively reported some perceptual distortions and visual illusions (Griffiths et al. 2016; Hasler et al. 2004), violating the working definition employed by many researchers requiring a microdose to be sub-perceptual. Even without the perceptual aspect, however, it is still a reasonable expectation that there might be significant differences between a dose of 1/10th of a normal dose, and a dose of 1/20th. Failing to distinguish these two dose levels may make comparisons between studies more difficult. Standardized experimental procedures are needed to address confusion and confounds related to this issue. Research experiments within this 1/10th to 1/20th range may find the dose that maximizes the effects of the substances while still preserving the sub-perceptual nature of the experience. With regards to LSD, for example, Bershad et al. (2019) recently suggested a threshold dose of 13 µg. In terms of psilocybin, the range still seems ambiguous (i.e., somewhere between 14 and 43 µg/kg or 1 and 3 mg/70 kg).

Owing to the continued illegality and stigma surrounding psychedelic substances, methodologically strong research continues to be difficult due to lack of official approval and the high cost of legally acquiring the substances (Polito and Stevenson 2019). Preliminary evidence on the phenomenon of microdosing looks promising, but a trend toward more minimal results in more scientifically rigorous data provides reason for caution. Therefore, future research should prioritize double-blind, placebo-controlled, experimental paradigms as well as longitudinal studies.

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