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Microdosing psychedelics has no impact on cognitive function in naturalistic settings

Abstract

Background and aim: Subjective and anecdotal accounts link ingestion of psychedelic microdoses, quantities small enough to retain perceptual clarity, to enhanced cognitive function and performance. In this study we review current evidence, test the link between domains of cognitive function and microdosing psychedelics and evaluate a remote testing approach for cognitive function. Methods: In an observational within-subjects design, we repeatedly assessed 17 participants during their microdosing regimen using the CNSVS neurocognitive battery in a naturalistic setting. Results: We found that neither the day of microdosing, nor the day after microdosing are significantly linked to enhanced or diminished performance on processing speed, sustained attention, inhibitory control, set shifting, working memory, visual memory and verbal memory. Conclusion: Microdosing psychedelics may act on psychological rather than neurocognitive pathways to induce a subjective feeling of performance enhancement. The use of remote cognitive batteries might benefit longitudinal cross-cultural studies by reducing participant burden.

Keywords: microdosing, psychedelics, cognitive function, experience sampling

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Microdosing psychedelics has no impact on cognitive function

Psychedelics such as psilocybin and LSD are currently proposed and tested for clinical applications to treat autism, Alzheimers disease, substance use, mood, and trauma-related disorders. Additionally, studies have demonstrated their anti-inflammatory properties, alterations in brain functional connectivity and increases in neuroplasticity by raising Brain-Derived Neurotropic Factor (BDNF).[1–6] While most therapeutic applications and investigations include medium to large doses, microdosing has become a recent trend among people aiming to enhance their cognitive, emotional, and social functioning irrespective of levels of psychopathology. Microdosing refers to the ingestion of psychedelic substances in low doses, below the threshold for perceptual alteration and in a way that does not impair normal functioning with the aim of improving well-being.[7] A recentstudy by Rootman et al.,[8] reports that 58.1% of microdosers named enhancing learning capacity, and 44.6% decreasing procrastination as their primary motive for microdosing.

Cameron et al.,[9] conducted an online survey on the subjective effects of microdosing and found that 59% of their sample experienced a subjective improvement of attention and focus, 26% no effect and 15% worsening of attention. In terms of memory, 39% felt an improvement of memory, 46.5% found no effect and 15% worsening of memory.

While anecdotal accounts of enhanced cognitive effects after microdosing are abundant and people report subjective cognitive benefits, evidence regarding the efficacy of microdoses to enhance cognitive function are scarce and mixed. In the present study, we will briefly review current literature about the relationships between microdosing and several neurocognitive domains and test their relationship in a within-subjects longitudinal design using remote neurocognitive testing and the experience sampling method. A thorough review spanning multiple domains of cognitive function does not currently exist. This paper is the first to summarize the current literature on low-dose psychedelics that spans multiple domains including attention, executive functions, and memory. Our main contribution lies in the observational approach, allowing subjects to continue their microdosing practice in a naturalistic setting while using remote cognitive assessments to provide insight into their cognitive function and the experience sampling method to capture psychological variables. In this way our study extents the literature by testing and evaluating an approach to study pharmacological alterations as well as behavioral, cognitive, and emotional phenomena in a way that does not require participants to alter their habitual behavior to adapt to an experimental setting, effectively enhancing ecological validity.

Processing speed

Processing Speed refers to the capacity to incorporate novel information with a motor responses. It functions as a measure of cognitive efficiency and has been related to regularaging as well as neurological deficits, intelligence and white matter integrity.[10] Its most common measure is the Digit Symbol Substitution Test, which is a composite measure indicating healthy functioning across several domains including attention, visual perception, executive functions, and motor speed. While sacrificing specificity, the test has been shown to be quite sensitive to brain impairments, clinical disorders, acute intoxication with alcohol and benzodiazepines, sleep deprivation and cognitive change in major depression.[11] Due to the sensitivity of processing speed measured by the DSST, it may be well situated to pick up changes induced by low doses of psychedelics, especially since previous research has implicated serotonergic hallucinogens, similar to SSRIs, with the attenuation of cognitive decline during depression.[12,13] The task shows a grid with numbers 1-9 and a corresponding symbol. The participant is then prompted with a symbol and is required to respond with the correct number for a fixed period of time. The symbols appear in random order and the participants performance is measured by the amount of correct responses given in the time period. One study by Barrett et al.,[14] tested 20 healthy participants on the DSST under placebo, 10, 20, 30 mg/70kg psilocybin on 4 different occasions. These medium to large doses produced impairments of processing speed but not accuracy, while also impairing memory regarding substitutions. Two studies have employed the DSST as

a measure of processing speed in response to microdoses of LSD. Hutten et al.,[15] enrolled 24 healthy participants in a within-subjects-design with four levels: 5, 10, and 20 micrograms LSD, placebo. They measured information-processing speed using the Digit Symbol Substitution Test (DSST), they found that the highest dose, 20 mcg of LSD significantly impaired processing speed as measured by the total correct substitutions but not accuracy as measured by ratio of correct substitutions to total substitutions. Another investigation into processing speed has been conducted by Bershad et al.,[16] using the DSST. 20 participants received a weekly dose of placebo, 6.5, 13, 26 micrograms of LSD but showed no significant change in processing speed. Both studies showed non-significant but slight increases in total codings, while Hutten et al.,[15] showed a decrease with the largest dose. Generally, accuracy seems to be unaffected by small or large doses, while speed may follows a dose-dependent impairment. It is possible that small microdoses might increase, while minidoses impair performance in this complex task.

Attention

Sustained Attention refers to processes that enable performance over an extended period of time including the capacity to stay vigilant, select a target of attention and maintain this target over a specific duration.[17] One way to measure sustained attention is the continuous performance task in which participants are asked to watch a repeated demonstration of stimuli and respond only if they see a particular one. One example is using letters of the alphabet, where participants see random letters of the alphabet but are instructed to only respond via button press if the letter "B" appears.

The evidence for alterations of sustained attention in response to serotonergic psychedelics is scarce and mixed. Two studies indicate an impairment of sustained attention after noticeable (small to large) doses of psilocybin. In a 2003 study by Umbricht et al.,[18] a medium dose of psilocybin (0.28mg/kg) reduced the overall hit rate in a continuous performance task in which the 18 healthy participants were supposed to react only to a specific two letter combination among distractors from the whole alphabet. Another study by Vollenweider et al.,[19] gave 16 healthy subjects the Frankfurt Attention Inventory, a pen and paper test resulting in a composite score that includes a sustained attention score under the influence of 115 (minidose), 215 (medium), and 315 µg (high) of psilocybin against placebo. They found similarly decreased performance in all psilocybin conditions and the most pronounced impairment 105 minutes compared to 180 and 360 minutes after administration. The most nuanced study regarding sustained attention was conducted by Hutten et al.,[15] enrolled 24 healthy participants in a within-subjects-design with four levels: 5, 10, and 20 micrograms LSDversus placebo. They measured sustained attention using a psychomotor vigilance task, in which participants had to react to a stimulus as quickly as possible for 100 randomly triggered trials within 10 minutes. Overall, they found no significant difference between doses, however, the authors indicate that there might be considerable inter-individual differences, since 76% of observations under 5µg and 74% of 20µg showed significantly less attentional lapses (not reacting to the stimulus), resulting in enhanced attention for a majority of individuals in the study.

Executive functions

Executive functions are generally at play when there is something to do that requires effortful attention, concentration & behavior. The three main components are inhibitory control, cognitive flexibility, and working memory.[20] Inhibitory control, as measured by the stroop test, is the capacity to focus on a specific stimulus, inhibit an impulsive response and engage in a controlled one instead. The evidence for an effect of psychedelics on inhibitory control is mixed. A meta-analysis by Basedow et al.,[21] investigating the effect of serotonergic psychedelics on neuropsychological functioning regardless of dose, found improved performance on incongruent trials of the stroop task. One randomized, double-blind and counterbalanced experimental study by Quednow et al.,[22] showed that a medium dose of psilocybin could impair reaction time and produce more errors in the incongruent condition of the stroop task. A study closest approaching microdosing was done by Cavanna et al.,[23] in which they administered a minidose (0.5g) of mushrooms to 34 participants and measured their inhibitory control using the Go/No Go task as well as the stroop task. While scores on the Go/No. Go task did not change, participants showed impaired reaction time in incongruent trials of the stroop task.

Cognitive Flexibility, as measured by the shifting attention test, refers to the ability to quickly and accurately adapt behavior to changing demands of a task, such as in sorting a stack of cards according to color (black/red) and then switching to sort according to number (odd/even). The evidence regarding cognitive flexibility concerning doses that would qualify as microdoses or minidoses is lacking altogether. A few studies, however, can hint towards expected effects. One study by Pokorny et al.,[24] investigated the effect a medium large dose of LSD (100 µg) in a double-blind, randomized, placebo-controlled within subjects design on the IED task, which is similar to the Wisconsin Card Sorting Test. LSD increased the error rates and the reaction time during set-shifting trials. Two studies looked at the after effects of administering psychedelics. In the context of open-label psilocybin-assisted therapy for depression, Doss et al.,[12] employed the PCET, another set-shifting task similar to the WCST before, 2 weeks, and 4 weeks after one medium-high and one high dose of psilocybin. Psilocybin reduced the amount of perseverative errors 2 and 4 weeks after dosing. One study that investigated the effect on inhibitory control and set shifting during the afterglow of a minidose of LSD (50µg) by Wießneret al.,[25] found an impairment of set shifting but not in inhibitory control 24h after dosing.

Working memory

Working memory, as measured by the 2n-back task, is considered part of the executive functions and refers to the capacity to hold information in mind and manipulate it according to immediate needs and goals including, but not exclusively, to store information in long-term memory.[20] A to-date thorough overview of the effect of classical psychedelics on memory has been published in a review paper by Healy.[26] The author included 14 publications until May 24, 2020. 9 publications investigated LSD, 4 psilocybin, 1 ayahuasca. In the studies in which low doses have been administered, no effect on working memory has been observed, whereas with mini- and high doses impairments generally increasedfor most memory tests including with an n-back working memory test. A subset of four tests across the 14 studies showed no impairment even at mini doses for working memory: psilocybin impaired spatial working memory at 0.25 mg/kg but not at 0.115 or 0.215 mg/kg across two studies. Digit span was not impaired with 50, 72 & 200 µg of LSD, while other memory tests showed decreased performance. Overall, this review indicates a dose-dependent impairment of memory due to classical psychedelics, however there are some exceptions to this impairment regarding working memory. The only study that specifically investigated the influence of microdosing on working memory has been conducted by Bershad et al.,[16] using an 2n-backtask. 20 participants received a weekly dose of placebo, 6.5, 13, 26 micrograms of LSD but showed no change in working memory performance.

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Explicit memory

Explicit memory refers to those processes of memory that entail the deliberate storage of information about objects, events, or facts (declarative memory) as well as autobiographical content (episodic memory).[27] In this way, explicit memory differs from implicit memory that entails unconscious learned motor responses such as riding a bicycle or playing an instrument.[28] Both visual as well as verbal memory are part of the explicit, declarative memory. Visual Memory as measured by the visual memory test refers to the capacity to store abstract geometric shapes in short-term and long-term memory. Healy's[26] review on the effect of classic psychedelics on memory also included studies investigating visual and verbal memory. The evidence regarding visual memory turns out to be old and mixed as Sloane & Doust[29] found no significant difference in visual memory between 40µg LSD and control, while Jarvik et al.,[30] found impaired visual object recall under 50 and 100 mcg of LSD. Silverstein[31] asked participants to reproduce simple geometric figures from memory after 72µg of LSD and found significant impairment. Studies employing verbal memory paradigms are similarly scarce. Verbal Memory as measured by the verbal memory test refers tot he capacity to store words in short-term and long-term memory. Jarvik et al.,[30] administered 4 verbal memory tests and did not find impairment at 50µg but only at 100 mcg for recall of word opposites, sentences, paired associates and recall nonsense syllables but not forrecognition of nonsense syllables. The 2018 study by Barrett et al. showed a similar pattern.

They tested verbal memory using a memorization, recall and recognition task and found a significant impairment in free recall when comparing 10, 20, 30 mg/70kg psilocybin to placebo. They found no impairment in word recognition. While evidence regarding visual memory remains mixed, verbal memory impairments seem to occur with doses larger than microdoses for free recall tasks, while leaving recognition intact.

Most of the studies that have investigated the effects of psychedelics on cognitive function have taken place in restrictive experimental conditions that required participants to visita laboratory at a specific time, refrain from other habitual substance use habits such as coffee or cigarettes and may have therefore created artificial conditions that are not representative of actual effects in the daily lives of mircrodosing practitioners. Since we allow participants to conduct psychological and neurocognitive tests in naturalistic conditions, we don't derive hypotheses strictly from previous research. If microdosing psychedelics has an effect on cognitive function in our within-subjects comparison, we expect each outcome measure to differ on the day of the microdose, the day after microdose and any off days.

Methods

Data was obtained in an observational within-subjects longitudinal design over 28 days.

Participants

20 respondents started the study of which 18 respondents (4 male, 14 female) between 19and 57 (median 22) years old from Eurasia, America and Africa completed the study after being enrolled in two waves from February 20 to March 5 and May 12 to May 21, 2020. Participants were recruited in the university of the researchers and through social media. Participants were incentivized with a gift card and a report on their own data. Ethical approval of the Ethics Review Board of the authors' university was obtained and all participant signed a written agreement upon enrolling the study.

Measures

Information on demographics, as well as other measures not relevant for the current study, were collected one day before start of the study during an in person or zoom meeting in which participants were instructed on how to fill in questionnaires through the App and how to conduct the cognitive tests. Starting with the first day of the study until day 28, we collected responses about participants microdosing behavior, their sleep, and other psychological variables reported elsewhere[32, 33] using repeatedly scheduled questionnaires through the EthicaData App. In addition, it was possible for participants to submit information on their own will, resulting in a maximum of 30 observation days. EthicaData is approved by the Ethics Review Board of the researchers' university in terms of compliance with GDPR regulations.

Microdosing information

Information about our participants microdosing habits were assessed through a daily self-report questionnaire that captured the microdose Day ("Have you taken a microdose?") with three levels: "I have taken a dose today" (MD 1), "I have taken a dose yesterday" (MD 2) and "I did not take a dose today or yesterday"(MD 0). Participants could further specify the time, substance and quantity with which they microdosed: "LSD", "Psilocybin Mushrooms", or "Psilocybin Truffles", whereby LSD was reported in micrograms (µg) and Mushrooms and Truffles in grams (g).

Sleep

Information about our participants sleep quality was assessed each morning with the question: "How would you rate your sleep quality overall?", answerable on a scale of 0 (Very Bad) to 3 (Very Good).

Positive & negative emotion

Participants reported their emotions by answering "Thinking about yourself and how you felt today to what extent did you generally feel [...]?" about 23 emotions on a scale between and 0-21. For further information see specifics reported elsewhere.[32,33] An index of positive and negative emotion was calculated by averaging all positive emotions and negative emotions respectively.

Cognitive function

In addition to questionnaires, we measured the cognitive functions processing speed, attention, executive function, and memory using the CNSVS neurocognitive battery.[34] Participants could complete their cognitive tests independent of their location using their own computer. Participants were instructed to conduct an even amount of assessments over the three relevant microdose days: Day of microdose, the day after and off-days. They were also instructed to conduct each test in similar conditions and not deviating from this setting for subsequent tests (such as sticking to testing in the morning). All participants completed a first practice session during the introductory meeting in order to clarify any open questions, to make sure that instructions were clear, and to minimize practice effects during the period of the study. Participants had the opportunity to conduct 4 assessments per week, resulting in a maximum of 16 possible tests over the period of the study. The estimated total duration of each assessment battery was about 25 minutes.

Processing speed

Processing speed was measured with the Symbol-Digit-Coding task. In this task, participants see an instructional grid that associates

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specific symbols to the numbers from 2 to 9. Participants are prompted with symbols for which they are required to press the corresponding number buttons as shown in the instructional grid for about 4 minutes. We subtracted errors from total correct responses for the analysis.

Attention

Sustained Attention was measured as part of the 4-Part-Continuous-Performance test, consisting of 3 steps: First, a simple reaction time task. Second, reacting to one specific figure out of different ones, similar to the classical continuous performance task, and third, a one-back task i.e. reacting only if the stimulus is repeated twice. A composite score was calculated by subtracting incorrect responses from correct responses.

Executive function

Cognitive flexibility was assessed with the Shifting Attention Test, in which subjects are asked to match a stimulus depending on shape or color, while rules change unpredictably. A composite score was calculated by subtracting incorrect responses from correct responses. Additionally, the reaction time to correctly respond was used for analysis.

Inhibitory control was measured with the Stroop Test, in which subjects are asked to react to words written in the same color as the word and subsequently to words written in a different color from the word. We used the stroop effect (congruent reaction time subtracted fromincongruent reaction time) as outcome measure for analysis.

Working Memory was assessed in the form of a 2n-back task as part of the 4-Part- Continuous-Performance Task of the CNSVS battery, where the subject is asked to respond only if the prompted shape is the same as 2 trials ago. A composite score was calculated by subtracting incorrect responses from correct responses.

Memory

Verbal Memory was assessed with the Verbal Memory Test of the CNSVS battery, which prompts 15 words for 2 seconds each. Subjects are required to respond to these words among 15 new words. After all other tests were completed, at the end of the battery, a delayed recall trial takes place. We used the sum of all correct hits and passes as well as the overall reaction time foranalysis. Visual Memory was assessed with the Visual Memory Test of the CNSVS battery, which prompts 15 shapes for 2 seconds each. Subjects are required to respond to the previously memorized shapes among 15 new shapes. A delayed recall trial takes place at the end of the battery. We used the sum of all correct hits and passes as well as the overall reaction time for analysis.

Analysis

The analysis has been performed in RStudio with the lme4 package. Descriptives were given about microdosing data of our participants and an overview of the adherence to the remote tests. To analyse the effect of microdosing on cognitive function we have used a multilevel model, allowing intercepts to vary across individuals. For each of the previously described outcome measures, we have first created a null model without predictors, a linear model with only an intercept and an unconditional model with only an intercept as predictor and compared this unconditional model to the null and linear model using anova. If the unconditionalmodel had a better fit than both the null model and the linear model, microdose Day (MDDay) with three levels: Day of the microdose (MD 1), the day after a microdose (MD 2), and off-days (MD 0) was added as a predictor. To control for effects of sleep and motivation on cognitive performance (Sweet, 2011), we added variables of sleep quality and positive as well as negative emotion to the model in a stepwise way.

Results

Our 18 final participants each microdosed at least one, at most nine and a median of five times throughout the study period resulting in a total of 100 microdosing occasions. The minimum, mean, median, and maximum quantity across 40 occasions with mushrooms were 0.05g, 0.163g, 0.15g, and 0.3g respectively. In 39 occasions of LSD microdosing the minimum was 5µg, mean 13.6µg, median 15µg, and maximum 30µg. In two occasions in which participants microdosed with Truffles, they administered 1g each.

The initial 20 participants conducted a total of 148 cognitive tests that had at least one valid score in any cognitive domain. The minimum per participant was one test, the median seven tests, mean 7.4 and the maximum 16 tests. The average length of a test battery was 25.12 minutes. Only four tests were shorter than 10 minutes and six longer than 32 minutes, which might have occured due to technical difficulties or short breaks participants took and have resulted in partially valid test scores. There was considerable variation in the time at which participants conducted their tests. After accounting for timezone differences, we calculated an average time and the standard deviation from this average time for each participant. The earliest average time of testing was 07:55 in the morning and the latest 21:43 in the night. The median average time of testing across participants was 16:18 in the afternoon. Standard deviations for each participant ranged from circa 10 minutes to about 10 hours with most individuals regularly conducting their tests within about 2 to 4 hours. For an overview of the timing of each remote testing session see Figure 1 in the appendix. For the following analysis we only used test scores that were valid and conducted on days on which participants also reported their microdosing behavior. This resulted in a minimum amount of two, median of six and maximum of 15 cognitive test batteries per participant and a sum of 100 to 104 usable test occasions over the period of the study.

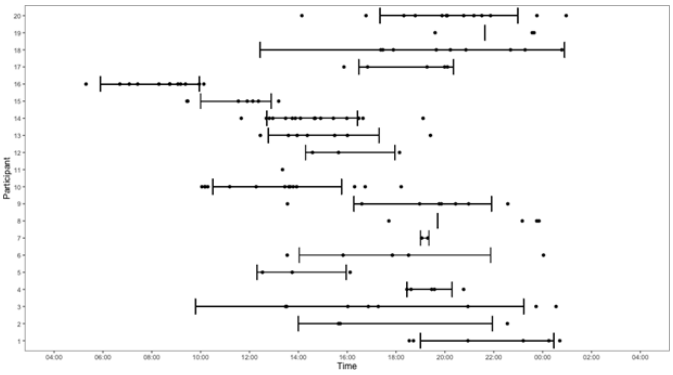

Figure 1 Time of remote cognitive testing by participant.

Note: *Dots represent single testing sessions, error bars represent mean±SD for each participant.*

Processing speed

Considering all datapoints without missing values in Microdosing Day and Processing Speed our analysis included 104 observations nested in 17 individuals. The unconditional modelshowed significantly better explanation of our data than the null-model or a linear model. The intraclass correlation showed that about 34% of variance is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model,

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indicating that MDDay had no significant effect on processing speed. This remained the case when controlling for sleep quality (n=91) and negative and positive emotion (n=67).

Sustained attention

Included were 100 observations nested in 17 individuals. The unconditional model explained our data significantly better than null-model or a linear model. The ICC indicated that 30% of variance is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model, indicating that MDDay had no significant effect on sustained attention. This remained the case when controlling for sleep quality (n=87) and negative and positive emotion (n=63).

Inhibitory control

Included were 103 observations nested in 17 individuals. The unconditional model explained our data significantly better than null-model or a linear model. The ICC indicated that 50% of variance is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model, indicating that MDDay had no significant effect on inhibitory control. This remained the case when controlling for sleep quality(n=90) and negative and positive emotion (n=66).

Cognitive flexibility

Included were 103 observations nested in 17 individuals for both accuracy and reaction time. The unconditional model explained our data significantly better than null-model or a linear model for both accuracy and reaction time. The ICC indicated that 52% of variance for accuracyand 54% of variance for reaction time is situated between individuals. Adding a fixed effect of microdose day to the model for accuracy and variance showed no better fit than the respective unconditional model, indicating that MDDay had no significant effect on cognitive flexibility. This remained the case when controlling for sleep quality (n=90) and negative and positive emotion (n=66).

Working memory

Included were 100 observations nested in 17 individuals. The unconditional model explained our data significantly better than null-model or a linear model. The ICC indicated that 29% of variance is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model, indicating that MDDay had no significant effect on working memory. This remained the case when controlling for sleep quality(n=87) and negative and positive emotion (n=63).

Visual memory

Included were 104 observations nested in 17 individuals. The unconditional model explained our data significantly better than null-model or a linear model. The ICC indicated that 32% of variance of the accuracy and 30% of variance of the reaction time is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model, indicating that MDDay had no significant effect on visual memory. This remained the case when controlling for sleep quality (n=91) and negative and positive emotion (n=67).

Verbal memory

Included were 104 observations nested in 17 individuals. The unconditional model explained our data significantly better than null-model or a linear model. The ICC indicated that 50% of variance of the accuracy and 21% of variance of the reaction time is situated between individuals. Adding a fixed effect of microdose day to the model showed no better fit than the unconditional model, indicating that MDDay had no significant effect on verbal memory. This remained the case when controlling for sleep quality (n=91) and negative and positive emotion (n=67).

Discussion

In the current observational study we investigated the effect of microdosing on cognitive function in a naturalistic setting. Microdosing has not affected any of the domains of cognitive function tested in this study. According to our results microdosing neither diminishes nor improves the cognitive functions processing speed, sustained attention, inhibitory control, cognitive flexibility, working memory, visual memory, and verbal memory. This is in contrast to some of the previous research that indicated that microdoses of LSD could improve processing speed and sustained attention in some people Hutten et al.,[15] as well as the mixed findings regarding effects of medium and minidoses on inhibitory control[21–23] and cognitive flexibility.[12,24] The lack of change in cognitive flexibility during microdosing might suggest that the previously reported afterglow effect that persists for several days or weeks after administration of medium doses has an effect that is different from the acute effect of microdosing.[25] The findings regarding explicit (visual and verbal) memory as well as working memory were in line with previous research.

It is curious that both subjective reports and molecular mechanisms support enhanced cognitive function, yet these seem not to translate into measurable performance increases in the daily lives of our participants. One possibility is that the cognitive effects are cumulative over a sustained period of time and therefore require longer tracking of participants. Support for this cumulative effect comes from evidence in regular Ayahuasca users, who have been drinking the psychedelic brew at least twice a month for 15 years. When compared to controls, these regular users showed better inhibitory control measured by the stroop test and cognitive flexibility measured by the Wisconsin-Card-Sorting-Test at two measurement occasions one year apart.[35] Another possibility is that our current distinction between neurocognitive domains and the established measures thereof are not sensitive to the changes induced by psychedelics in naturalistic settings. While this conclusion can not be ultimately ruled out, to draw a broad picture of microdosing effects, we employed composite tests such as processing speed which require multiple different cognitive functions on the one hand and tests for the lowercognitive functions of inhibitory control, cognitive flexibility, and specific types of memory on the other hand. All in all, this suggests that the effect of subjectively enhanced cognitive performance might arise from a psychological rather than a neurocognitive mechanism. The idea that non-biological factors contribute to the effects of psychedelics is not new. Hartogsohn[36] has discussed how set (mindset including thoughts, mood and emotions) and setting (surrounding physical, legal, and social environment), similar to the placebo response in other therapeutic interventions, shape expectations that can alter psychedelic experiences. A prospective study has already shown that positive expectancy scores at baseline predicted improvements in well-being through microdosing.[37] It remains unclear what individual differences might contribute to the susceptibility to such expectation effects and whether those vary depending on the dose.

This study fortifies the previous literature showing that acute cognitive impairment due to psychedelics might appear in a dose-

dependent manner. Here we show that microdoses administered in a naturalistic setting do not reach a threshold that impairs or improves functioning. It is important to note that all of the participants in our study have already had experience with microdosing and therefore had not have to go through excessive testing of whichdoses might be too much for daily life. Using our remote testing approach we have successfully addressed challenges that arise in strict experimental studies that do not allow individual variation in susceptibility to psychedelic substances to be accounted for. In naturalistic settings, microdosing practitioners commonly go through a trial and error process of finding the dose in the first few dosing days. The use of remote testing along with an experience sampling method has shown to be a powerful tool to address such challenges of generizability of experimental studies. Since our participants were instructed to complete the cognitive tests at a time that was suitable and sustainably repeatable for them instead of limiting them to academic working hours, we have seen that some participants conducted those tests even late at night or early in the morning before starting their regular days. This added flexibility might allow early risers or nightowls to participate in studies that are otherwise challenging to integrate in their daily routines.

Additionally, remote testing allowed us to enrol participants from Europe, North America, and Africa simultaneously. As shown in Figure 1, there was considerable variability in the time our participants have conducted their cognitive tests. While most participants conducted tests in theafternoon, some people conducted them early in the morning and others late in the evening.

Assuming people were motivated to perform well during these cognitive tests, there might be considerable benefit in remote testing to allow inter-individual differences in timing of cognitively demanding tasks to be captured in scientific studies. Further, the regularity of each participant in conducting their tests differed strongly across individuals. One reason for this might be that participants needed to use a laptop or computer for their tests, which might not always be around. Without further speculating about why there was so much variation, our data shows how restricting fixed appointments for experimental testing can be when conducting longitudinal research. Through the use of this self-organized remote testing approach we have strongly minimized the burden on participants, allowing them to live their lives as close as possible to usual conditions, while gathering valuable data in the process.

The main strength of the current study is the strong ecological validity of our findings as well as the multilevel design that allows for tracking changes between as well as within participants over time. One large limitation is the lack of control of experimental conditions, as variables such as distance from monitor, and hardware differences between participants could not be controlled. Our longitudinal design with repeated measures may have accounted for some of the downside of this limitation. Additionally, we have not used any placebo controls and have not accounted for expectation effects, which has become common practice in recent studies of psychedelics. A further limitation is the necessity for a large sample size and incentives to increase compliance to attain a sufficient amount of completed tests. Finally, the use of remote cognitive tests in naturalistic settings in combination with experience sampling methods bears a promising opportunity to conduct large cross-cultural longitudinal studies that track intraindividual changes in response to pharmacological treatment, especially with large sample sizes.

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None.

Conflicts of interest

There is no conflicts of interest.

References

1. Barrett FS, Krimmel SR, Griffiths RR, et al. Psilocybin acutely alters the functional connectivity of the claustrum with brain networksthat support perception, memory, and attention. *Neuroimage*. 2020;218:116980.
2. Barrett FS, Preller KH. *Disruptive Psychopharmacology*. Springer International Publishing; 2022
3. Bedford P, Hauke DJ, Wang Z, et al. The effect of lysergic acid diethylamide (LSD) on whole–brain functional and effective connectivity.*Neuropsychopharmacology*. 2023;48(8):1175–1183.
4. Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain afterpsilocybin therapy for depression. *Nature Medicine*. 2022;28(4):844–851.
5. De Vos, CMH Mason, NL Kuypers, et al. Psychedelics and Neuroplasticity: A Systematic Review Unraveling the Biological Underpinnings of Psychedelics. *Frontiers in Psychiatry*. 2021;12:724606.
6. Dos Santos RG, Osório FL, Crippa JAS, et al. Antidepressive, anxiolytic, and antiaddictive effects of ayahuasca, psilocybin and lysergic acid diethylamide (LSD): A systematic review of clinical trials published in the last 25 years. *Therapeutic Advances in Psychopharmacology*. 2016;6(3):193–213.
7. Kuypers KPC, Ng L, Erritzoe D, et al. Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. *Journal of Psychopharmacology*. 2019;33(9):1039–1057.
8. Rootman JM, Kryskow P, Harvey K, et al. Adults who microdose psychedelics report health related motivations and lower levels of anxiety and depression compared to non– microdosers. *Scientific Reports*. 2021;11(1):22479.
9. Cameron LP, Nazarian A, Olson DE. Psychedelic Microdosing: Prevalence and Subjective Effects. *Journal of Psychoactive Drugs*. 2020;*52*(2):113–122.
10. Sweet LH. Information Processing Speed. In: JS Kreutzer, J Deluca, B Caplan, editors. *Encyclopedia of Clinical Neuropsychology*. 2011. pp. 1317–1318.
11. Jaeger J. Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. *Journal of Clinical Psychopharmacology*. 2018;38(5):513–519.
12. Doss MK, Považan M, Rosenberg MD, et al. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. *Translational Psychiatry*. 2021;11:574.
13. Magaraggia I, Kuiperes Z, Schreiber R. Improving cognitive functioning in majordepressive disorder with psychedelics: A dimensional approach. *Neurobiology of Learning and Memory*. 2021;183:107467.
14. Barrett FS, Carbonaro TM, Hurwitz E, et al. Double–blind comparison of the two hallucinogens psilocybin and dextromethorphan: Effects on cognition. *Psychopharmacology*. 2018;235(10):2915–2927.
15. Hutten NRPW, Mason NL, Dolder PC, et al. Mood and cognition after administration of low LSD doses in healthy volunteers: A placebo controlled dose–effect finding study. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*. 2020;41:81–91.
16. Bershad AK, Schepers ST, Bremmer MP, et al. Acute Subjective and Behavioral Effects of Microdoses of Lysergic Acid Diethylamide in Healthy Human Volunteers. *Biological Psychiatry*. 2019;86(10):792–800.

17. Cohen RA. Sustained Attention. In: JS Kreutzer, J deluca, B Caplan, editors. *Encyclopedia of Clinical Neuropsychology.* 2011. P. 2440–2443.
18. Umbricht D, Vollenweider FX, Schmid L, et al. Effects of the 5–HT2A Agonist Psilocybin on Mismatch Negativity Generation and AX–Continuous Performance Task: Implications for the Neuropharmacology of Cognitive Deficits in Schizophrenia. *Neuropsychopharmacology*. 2003;28(1):1.
19. Vollenweider FX, Csomor PA, Knappe B, et al. The Effects of the Preferential 5–HT2A Agonist Psilocybin on Prepulse Inhibition of Startle inHealthy Human Volunteers Depend on Interstimulus Interval. *Neuropsychopharmacology*. 2007;32(9):9.
20. Diamond A. Executive Functions. *Annual Review of Psychology*. 2013;64(1):135–168.
21. Basedow LA, Riemer TG, Reiche S, et al. Neuropsychological Functioning in Users of Serotonergic Psychedelics – A Systematic Review and Meta–Analysis. *Frontiers in Pharmacology*. 2021;12:739966.
22. Quednow BB, Kometer M, Geyer MA, et al. Psilocybin–induceddeficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. *Neuropsychopharmacology*. 2012;37(3):630–640.
23. Cavanna F, Muller S, de la Fuente LA, et al. Microdosing with psilocybin mushrooms: A double–blind placebo–controlled study. *Translational Psychiatry.* 2022;12:307.
24. Pokorny T, Duerler P, Seifritz E, et al. LSD acutely impairs working memory, executive functions, and cognitive flexibility, but not risk–based decision–making. *Psychological Medicine*. 2020;50(13):2255–2264.
25. Isabel Wießner, Olivieri R, Falchi M, et al. LSD, afterglow and hangover: Increased episodic memory and verbal fluency, decreased cognitive flexibility. *European Neuropsychopharmacology*. 2022;58:7–19.
26. Healy CJ. The acute effects of classic psychedelics on memory in humans. *Psychopharmacology.* 2021;238(3):639–653.
27. Schuh J. Declarative Memory. In: JS Kreutzer, J deluca, B Caplan, editors. *Encyclopedia of Clinical Neuropsychology.* 2011. P. 781–783.
28. Glisky EL. Implicit Memory. In: JS Kreutzer, J deluca, B Caplan, editors. *Encyclopedia of Clinical Neuropsychology.* 2011. pp. 1301–1302.
29. Sloane B, Doust JWL. Psychophysiological Investigations in Experimental Psychoses: Results of the Exhibition of D–Lysergic Acid Diethylamide to PsychiatricPatients. *Journal of Mental Science*. 1954;100(418):129–144.
30. Jarvik ME, Abramson HA, Hirsch MW. Lysergic Acid Diethylamide (LSD–25):VI. Effect upon Recall and Recognition of Various Stimuli. *The Journal of Psychology.* 1955;39(2):443–454.
31. Silverstein AB. Effects of Lysergic Acid Diethylamide (LSD–25) on Intellectual Functions. *Archives of Neurology and Psychiatry*. 1958;*80*(4):477.
32. Pop I, Dinkelacker J. Microdosing psychedelics – Does it have an impact onemodiversity? *Journal of Psychedelic Studies.* 2023a;7(1):29–35.
33. Pop I, Dinkelacker J. Unlocking the self: Can microdosing psychedelics make onefeel more authentic? *Nordic Studies on Alcohol and Drugs.* 2023b;145507252311753.
34. CNS Vital Signs, LLC. *CNS vital signs interpretation guide*. CNS Vital Signs Website.
35. Bouso JC, González D, Fondevila S, et al. Personality, Psychopathology, Life Attitudes and Neuropsychological Performance among Ritual Users of Ayahuasca: A Longitudinal Study. *Plos ONE.* 2012;7(8):e42421.
36. Hartogsohn I. Set and setting, psychedelics and the placebo response: An extra– pharmacological perspective on psychopharmacology. *Journal of Psychopharmacology.*2016;30(12):1259–1267.
37. Kaertner LS, Steinborn MB, Kettner H, et al. Positive expectations predict improved mental – health outcomes linked to psychedelic microdosing. *Scientific Reports*. 2021;1–11.

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