MIND FOUNDATION

Microdosing psychedelics

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Here's a thought-provoking question: Would you rather take a high dose of LSD or psilocybin sporadically to dissolve the boundaries between yourself and the universe, or just a tiny amount regularly to become more creative and excel at intellectually demanding tasks? The latter option has recently garnered the attention of biohacking communities, where it is popularized as *microdosing.* At the recent Interdisciplinary Conference of Psychedelic Research (ICPR2020), researchers investigating microdosing practices and effects shared their findings and suggested that microdosing might not actually be the right tool for performance enhancement.

What's behind the microdosing trend?

The stimulant effects of low doses of LSD have been known since Albert Hofmann himself suggested it as an alternative to Ritalin.1 Today, microdosing enthusiasts may come to the practice with a far greater variety of motivations. One of their primary drivers is the promise that regularly using "sub-threshold" ("won't get you high") amounts of psychedelic substances – will enhance cognition and memory.2 Indeed, members of online microdosing hubs (e.g. Reddit, TheThirdWave) enthusiastically report positive effects related to their cognitive performance and creativity. Scientists refer to these benefits collectively as *nootropic effects.* Others are more focused on the mental health and well-being benefits: users with depression and anxiety claim microdosing helps with their symptoms, and healthy users report it helps put them in a more positive mood.

The true cognitive benefits of microdosing remain elusive, however, as microdosers worldwide turn a blind eye to the limited yet growing body of evidence against their claims. This lack of clarity is compounded by researchers who simultaneously emphasise the novelty and the limitations of their work. While there have been around a dozen published studies in the past couple of years that examine the many supposed benefits of microdosing,3 it is not uncommon for researchers to claim theirs is the first of its kind. They will also commonly

state that while they find no difference between placebo pills and microdoses, these results are preliminary, and they need more research before they are certain that microdosing truly has no performance-enhancing effects. When will this moment of certainty come?

Notes from the researchers at the 4th Interdisciplinary Conference on Psychedelic Research (ICPR2020)

The recent virtual conference ICPR2020 provided important insights into the latest psychedelic research trends. With a variety of speakers covering topics ranging from philosophy to neuroscience to politics, the September conference provided participants with a holistic, level-headed view of all the newest research.

ICPR2020 proved once again how important microdosing has become in the psychedelic science community: the conference accorded it two whole sections and five separate lectures. True to the "interdisciplinary" tag in the conference title, these talks ranged from fundamental biological research examining the pharmacology of microdosing (Tobias Buchborn from Imperial College London) to psychology-based studies examining the influence of microdosing on artistic and aesthetic sensibilities (Michiel Van Elk, PhD, from Leiden University).

The remaining three speakers presenting microdosing-related work were Nadia Hutten, PhD, from Maastricht University, Neiloufar Family, PhD, from Eleusis Ltd, and Balazs Szigeti, PhD, from Imperial College London. All three of them showed results pertaining to the effects of microdosing on both well-being and cognition. Szigeti and his group have a paper in preparation, while the Eleusis and Maastricht studies were recently published. 4,5

Microdosing study design 101

In order to understand the results, it's important to understand the methodology of these studies and the similarities and differences in their experimental setup. Importantly, the Maastricht University and Eleusis studies involved microdosing LSD in a clinical setting, while the Imperial study was surveying at-home microdosers (using any sort of psychedelic, but most commonly LSD and psilocybin), albeit with an innovative twist. Additionally, Maastricht researchers followed the acute effects of psilocybin microdoses for up to 8 hours after ingestion, while the other two studies followed participants for a month. In these month-long studies, microdosing schedules were based on the protocol that popularised microdosing in the first place, stemming from James Fadiman's 2011 book "The Psychedelic Explorer's Guide."6 According to this protocol, microdoses of LSD or psilocybin are taken every 3 days for a month.

The laboratory setting imposes limitations on sample size, so the Maastricht and Eleusis studies were done with under 50 participants, while Szigeti's remote, self-blinding study had no such limitations and included almost 200 microdosers. This would make it, with certain disclaimers, the largest placebo-controlled microdosing study to date.

Comparing these studies is further complicated by differences in setting, number and age of participants (20-somethings in Maastricht, 60-somethings at Eleusis), and the cognitive parameters that were measured. All three studies looked at participants' attention spans and measured their reaction times, but Eleusis and Imperial added some visual and spatial memory tests. The Imperial study measured the most cognitive parameters, with additional tasks that tested deductive reasoning, spatial planning, and mental rotation.

Microdosing research limitations (and how to overcome them)

“Set and setting” has been a traditionally important phrase in psychedelic science, referring to the phenomenon that the mindset and the circumstances in which people take psychedelic drugs will influence their effects. This is well-known and applied in high-dose psychedelic research: participants in the famous psilocybin cancer trials, for example, got to have their psychedelic experiences in a “lab” mimicking a cosy living room.7 This gives some assurance that the experience won’t be negatively affected by the subtle discomfort people often feel in overtly clinical atmospheres.

When it comes to microdosing, however, giving the lab a makeover may not suffice. Most of the anecdotally claimed benefits of microdosing become most apparent in the long run, as people are just living their lives. Will they get better at work and problem-solving? Will they start more creative endeavours? Will their relationships prosper? These are not things researchers are able to gauge when they have participants come to their lab. Spending the whole day in the lab, having taken only a “sub-threshold” dose of a drug, might even put people in a slightly agitated mood that could tamper with their well-being and cognition. Still, a double-blind, placebo-controlled trial is the gold standard for any pharmacological study, especially for those involving mind-altering substances. These studies allow us to distinguish the mind’s intrinsic suggestibility from the physiological effects of the drug and are, therefore, indispensable.

Before it was possible to conduct rigorous, placebo-controlled studies with psychedelics, the only way to find out about participants’ microdosing experiences was the humble questionnaire.3 In the Imperial self-blinding study, Szigeti and colleagues elevated the classic online survey to a placebo-controlled form. Instead of collecting data post-hoc, the researchers asked their at-home microdosing participants to carefully organise a month’s worth of microdoses in capsules and place the unlabeled capsules in envelopes marked only with QR codes. They also needed to prepare an equal number of QR code-labelled envelopes with empty, placebo capsules. They then had to shuffle all the envelopes, randomly pick out half of them for a month’s worth of use, and send the researchers the QR codes. This way the researchers knew, based on the QR codes, whether the participants were taking a microdose or a placebo, while the participants themselves were none the wiser.

The most prominent limitation of the self-blinding study is that it relies on the participants procuring their own LSD or psilocybin for the study, meaning there’s no way to tell what amount they’re actually taking and whether the substances are pure. The effects of this limitation, however, are largely alleviated by the large sample (191 participants completed the study, compared to 20-50 in the lab-based studies). Most importantly, the self-blinding study design has a major advantage, allowing us a glimpse into the effects of microdosing in a natural, everyday setting, while also providing a placebo control.

Nootropics and no-tropics

The reported nootropic effects of microdosing are manifold: improvements in concentration, creativity, spiritual awareness, productivity, language, and visual capabilities.8 So, did all these claims hold up when put to the test in the lab (in the Eleusis and Maastricht study) and in a placebo-controlled at-home setting (Imperial College)?

Briefly: no.

Two of the three placebo-controlled studies presented at the ICPR2020 conference found no significant differences in cognitive performance between the placebo control and the microdoses of LSD or psilocybin. Only the Maastricht study found positive effects of LSD on visual attention, yet the Eleusis study did not find effects on visual attention in a different task.

In the self-blinding study from Imperial, there was no difference in cognitive ability when participants took microdoses, neither acutely (2-5h after ingesting the pill), nor at the end of the four-week regimen. The researchers did, however, find a significant susceptibility to the placebo effect. They asked their microdosers an important question: “Do you *think* you’ve taken a microdose?”

When the participants thought they had taken a microdose, whether or not the pill was actually a placebo, they felt a greater sense of well-being, more mindful, and more satisfied with their lives. Presented with a placebo, the mind can “cheat” thoughts and moods, but it can’t cheat a cognitive test: whether or not they thought they had taken a performance-enhancing drug, and whether or not they’d actually taken one, the participants’ test scores remained the same.

But the scientists weren’t convinced. Balazs Szigeti, the lead researcher in the self-blinding study, suspects that if microdosing had such wide-ranging positive effects like people anecdotally claim, they should have been seen in such a large sample. Still, he doesn’t exclude the possibility that further research might uncover small, specific positive effects. For example, the researchers in Maastricht found that microdosing can be beneficial for sustained attention – though while this result is promising, the study from Eleusis showed no increase in performance on a similar attention test.

In another example of potential specific effects, the self-blinding study results show a slight, but statistically insignificant trend towards increased capability for mental rotation. “More studies should reproduce our findings before a firm conclusion could be reached, but in my opinion, the cognitive benefits of microdosing do not look promising”, concludes Szigeti.

Taken together, all the findings from ICPR2020 might lead recreational microdosers to ask themselves: “Am I performing better, or do I just think I am?”

Not all is placebo: clinical potential of microdosing

The unglamorous truth is, research to date has shown that the best, most reliable nootropic is… cardiovascular exercise.9 Different drugs that supposedly boost your brain have come in and out of style. Modafinil, the most popular one, was even proven to be mildly effective at enhancing attention and memory, particularly in performing complex tasks.10 But none of the nootropics’ effects are even remotely close to “unlocking the full potential of the human brain” in the way depicted in the movie *Limitless.* Psychedelics are no exception.

While it may not significantly alter cognitive performance, microdosing might still be beneficial for the brain in other ways. Nadia Hutten’s research at Maastricht University demonstrated that microdosing does lead to acute increases in BDNF (Brain-Derived Neurotrophic Factor), a molecule important for neuroplasticity.11 And at Eleusis Ltd, Neiloufar Family researches how microdosing might prove helpful in treating early Alzheimer’s disease. Her clinical research is led by the hypothesis that low doses of LSD can increase BDNF signalling and thus increase neuroplasticity, which would help protect the ageing brain from decay.11

This is not even the only mechanism through which LSD microdoses could act as neuroprotectants. Drugs that act on the serotonin 5HT-2A receptor, including LSD, have proven anti-inflammatory effects, and neuroinflammation is strongly implicated in Alzheimer’s pathology.13 When asked to comment on performance-enhancing effects, Neiloufar Family says, “I am not concerned that LSD did not have a nootropic effect on healthy adults, because a nootropic effect in a healthy population is not necessary for a drug that otherwise has a therapeutic effect in a patient. If you look at other drugs that help with cognition, like atomoxetine for ADHD, it doesn’t have nootropic effects in healthy people but is effective in treating ADHD.”

The future of microdosing research

As the popularity of microdosing increases, the psychedelic research community needs to prioritise conclusively answering one more question: **is it safe in the long run?** Research conducted thus far looked at participants' health for brief periods of up to a month at a time, but people in internet microdosing hubs sometimes promote daily use of low doses of psychedelics over months and years. Acute adverse effects are rare and include occasional increases in anxiety and restlessness (common contraindications of stimulants), but long-term adverse effects are virtually unknown.

When thinking about long-term effects, it is wise to take note of the case of fen-phen (fenfluramine), a popular weight loss drug in the 90s that turned out to come with significant cardiac risks. Fen-phen can lead to heart disease by acting on its primary target, the 5HT-2B receptor.12 Most psychedelic drugs have the 5HT-2A receptor as their primary target, but they are not completely specific and can activate the 5HT-2B as well. Does that mean chronic microdosing over many months and years, can lead to negative cardiac outcomes? More research is needed.

We still don't know if microdosing can significantly improve brain health, or if the reported emotional well-being benefits are based entirely on the placebo effect, or if doing it for months or years at a time can damage your heart. When it comes to the nootropic benefits, the evidence is rather inconclusive. While one study found improved sustained attention after LSD, another did not find this effect. And, after all, maybe the tasks used to measure cognitive performance are simply not capturing the effects microdosers are reporting – maybe we are yet looking in the wrong place.

Further research is in the works as Balazs Szigeti's self-blinding study at Imperial enters its second phase, and the Beckley/Maastricht Research Programme starts a new study using neuroimaging tools to investigate the effects of repeated microdoses more closely and objectively.

These new studies could lead to establishing the mechanisms of how microdosing can make our brains healthier and more resilient to ageing. But from what we have seen so far, they could also strengthen the case against microdosing for superhuman cognitive abilities. In the scientific exploration of the benefits of psychedelics, wanting both a psychologically and neurologically transformative experience at a high dose and a biohack from a microdose might simply be too much to ask.

For more on this and many other issues in psychedelic research, be sure to check out our INSIGHT 2021 conference program and pre-conference workshops.

Disclaimer: This post was edited in April 2021. Before, the post stated that 'none of the three studies on microdosing found positive effects on cognitive performance.' However, as it is stated in the post, the Maastricht study found a positive effect on sustained attention in the Psychomotor Vigilance Task.

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