References

Hutcheson JD, Setola V, Roth BL, et al. (2011) Serotonin receptors and heart valve disease: It was meant 2B. *Pharmacol Ther* 132: 146–157.

Ly C, Greb AC, Cameron LP, et al. (2018) Psychedelics promote structural and functional neural plasticity. *Cell Rep* 23: 3170–3182.

Kornfeld A and Fadiman J (2013) Psychedelic induced experiences. In: HL Friedman and G Hartelius (eds).*The Wiley-Blackwell Handbook of Transpersonal Psychology*. New York: Wiley/Blackwell, pp. 352–366.

Wacker D, Wang S, McCorvy JD, et al. (2017) Crystal structure of an LSD-bound human serotonin receptor. *Cell* 168: 377–389.e12.

Commentary

Torsten Passie

Psychedelics and creativity

I would recommend not mentioning just these very few anecdotal cases in respect to creativity and psychedelics. There are some good studies and reviews about the subject (Hartmann, 1969) on 40 prominent painters at the German Max Planck Institute of Psychiatry in Munich and the review on the subject by Krippner (1985).

When it comes to the very few studies looking for low doses of psychedelics and creativity (review in Passie, 2019), no study revealed any significant/relevant effects under controlled scientific conditions (e.g. McGlothlin et al., 1967). The study of Prochazkova et al. (2018) claimed (under weakly controlled conditions in respect to dosing and environment) increased lateral thinking, which has been discussed as a marker of creativity. This study employed doses of psilocybin that were above the perceptible level (4–8 mg p.o.). However, increased lateral thinking does not mean that the drugged subjects have shown increased creativity in a valid sense, e.g. creating more original painting.

Definitions: Microdosing and minidosing

I do not agree with the authors' narrow definition, since it does not reflect fully what is used in the literature and the appropriate Internet entries. It has been proposed that the term 'minidosing' could be used to separate the approach of taking small perceptible doses. It is also clear that many authors and Internet entries suggest the practice of just taking one dose at a time rather than a few ones consecutively as, for example, seen with the Fadiman scheme. This is also valid for taking a tenth or a twentieth of a usual dose. However, the issues related to definitions point towards the question/definition of what is considered a 'full dose'. In the case of LSD, some authors reasonably argue that 150 µg is a full dose (especially in females), whereas others consider 250 µg a full dose. This is a significant issue, because 15 µg is usually not perceptible by most subjects, but a dose of 25 µg is for most subjects (as shown in some scientific studies). Therefore, the definition has to be sharpened before scientific consensus can be reached and the evidence from so-called microdosers disseminated on the Internet as well as studies of anecdotal evidence (e.g. Johnson, 2018), which suffers from such inaccuracies, can be taken seriously.

Dosing of dried mushrooms

Plant/fungal material is generally quite unreliable for calculating a dose. I do not agree with the author's statement that 3.5 g *P. cubensis* is 'a usual recreational dose'. Most recreational users take 1 to 2.5 g as a recreational dose, which is also recommended in most books in the field. From my experience, and the research studies of Abramson and Rolo (1967), I would state that a dose of psilocybin below 3 mg is below the perceptible range. Usually, doses above this level can become apparent. For example, Prochazkova et al. (2018) used 4–8 mg psilocybin, i.e. more than a microdose, thus, more consistent with the definition of what might be considered a minidose.

The most used dosing regime and effects of micro- and minidosing

It can be easily seen in Internet entries that most subjects who take microdoses recreationally for 'bettering performance' take doses that give them some perceptible effects. Even a microdosing proponent like Paul Austin recommends doses where you can feel/perceive some alterations to some extent. How would you better your performance if nothing can be felt from a dose?

Following my comprehensive research into this topic (Passie, 2019), I have never come across anything about a 'workaholic approach' (dosing during weekdays, but not on weekends) as suggested by the authors. This also does not make much sense form a pharmacological point of view, because tolerance to LSD develops very quickly. Be reminded, that the US military has dosed soldiers with increasing daily doses to try to make them 'immune' to LSD's effects (Ketchum, 2006).

I think that a minidose (e.g. 20 to 50 µg LSD), in contrast to a microdose (which I define as something below 20 µg LSD, e.g. 5–15 µg), makes a significant difference in terms of recreational as well as scientific studies as it definitely alters psychological functioning and the cognitive system.

However, this alteration is not in any way equivalent to stimulants like Ritalin or amphetamine as is sometimes reported anecdotally. It is more a dissociation from the environment and the person itself. Cognitive abilities have been proven to be compromised in

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many studies with LSD and psilocybin employing a very low dose range (Passie, 2019). It is also important to register these (potentially) distracting effects. There are also a few scientific reports of people who have been given very low doses of LSD for treating depressive mood. These had negative results with very few patients experiencing a small improvement.

What is plausible (and has been experienced by this author) is that a minimal sympathomimetic effect (for sure not compatible with any sort of usual stimulant!), which might be still there up to 20 hours after a 10- to 15-µg dose of LSD, can cause problems with falling asleep, especially in sensitive persons. It is of interest how long it takes following intake for effects to occur. One could think of a train of effects induced in the organism, which is pushed on and may influence the organism even after virtually all of the substance has left the organism.

I definitely do not see the Fadiman protocol (5–15 µg LSD every third day) as the most used approach. It might be viewed as the most widely known, but by far (!) the most 'microdosers' use one occasional dose, not a regular intake. This also makes it very questionable what effects can be/are felt or not, especially when it comes to taking 10 µg just a few times per year (which is apparently what most users do). As Fadiman's coworker on his more or less systematic Internet surveys, Sophia Korb has mentioned in a lecture (conference 'Beyond Psychedelics', Prague 2018) that they know of just three persons who have dosed regularly (according to the Fadiman protocol) for more than 3 weeks. These three subjects were terminal cancer patients and felt quite normal up to day 50. Between days 50 and 60 they all became much more psychologically labile, i.e. having larger mood changes (in the positive as well negative direction, with daily fluctuations), as measured using the PANAS scale.

To my mind, the study published by Horsley et al. (2018) does not have any seriously calculable implications for humans. Its limitations should be discussed.

Possible alterations of gene expression and receptor proteins

There are serious doubts that the repeated doses of LSD, which have been used in rodents, are comparable to microdoses in humans. I am not an expert on interspecies scaling, but, for example, (just by simplified arithmetic) the studies by Martin et al. (2014) have used doses which are 12,000 times higher than a microdose in humans. According to a recent review (Sharma et al., 2009), it appears not to be congruent with scientific data to state that the dose used by Martin et al. (2014) is in any way comparable to a microdose in humans. Therefore, to date we know nothing about possible changes in gene expression induced by regular LSD intake in humans.

I doubt that the gene/BDNF changes which were found with very high daily doses in animals can be scaled up to humans using microdoses every few days. Issues of adaption and tolerance should be discussed in this respect.

Receptors are proteins. These proteins and others might be altered by repeated intake of, e.g. LSD, even in very low doses (Buchborn et al., 2016). Even if this is somewhat speculative, it seems probable.

On the possible induction of cardiovascular valvopathy

In respect to a possible induction of cardiovascular valvulopathy by chronic 2-HT2R activation, it is worth mentioning that the studies of Bender and Sankar (1968) in the 1960s involved doses of 100 µg LSD for up to 35 months on a daily basis without any observable damage. However, their methods of investigation might not have been sensitive enough to detect damage. It is also true that just a very small part of the patient population taking ergot compounds (e.g. methysergide) do in fact develop valvulopathy. It is also worth mentioning that if a valvulopathy is detected in a patient, in all cases it disappears within a short time after stopping the medication. There is just one case documented in the literature where surgery was necessary (Graham, 1967).

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References

Abramson H and Rolo A (1967) Comparison of LSD with methysergide and psilocybin on test subjects. *J Asthma Res* 3: 81-96

Bender L and Sankar DVS (1968) Chromosome damage not found in leukocytes of children treated with LSD-25. *Science* 159: 749.

Buchborn T, Grecksch G, Dieterich DC, et al. (2016) Tolerance to lysergic acid diethylamide: overview, correlates, and clinical implications. In: VR Preedy (ed.) *Neuropathology of Drug Addictions and Substance Misuse*, Volume 2. New York: Academic Press, pp. 846–858.

Graham JR (1967) Cardiac and pulmonary fibrosis during methysergide therapy for headache. *Am J Med Sci* 254: 1–12.

Hartmann RP (1969) *Malerei aus Bereichen des Unbewußten. Künstler experimentieren unter LSD*. Köln: Dumont.

Horsley RR, Palenicek T, Kolin J, et al. (2018) Psilocin and ketamine microdosing: Effects of subchronic intermittent microdoses in the elevated plus-maze in male Wistar rats. *Behav Pharmacol* 29: 530–536.

Johnson MW, Griffiths RR and Hendricks PS (2018) The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. *Neuropharmacology* 142: 143–166.

Krippner S (1985) Psychedelic drugs and creativity. *J Psychoactive Drugs* 17: 235–246.

McGlothlin WH, Cohen S and McGlothlin MS (1967) Long lasting effects of LSD on normals. *Arch Gen Psychiatry* 17: 521–532.

Martin DA, Marona-Lewicka D, Nichols DE, et al. (2014) Chronic LSD alters gene expression profiles in the mPFC relevant to schizophrenia. *Neuropharmacology* 83: 1–8.

Passie T (2019) *The Science of Microdosing Psychedelics*. London: Psychedelic Press.

Prochazkova L, Lippelt DP, Colzato LS, et al. (2018) Exploring the effect of microdosing psychedelics on creativity in an open-label natural setting. *Psychopharmacology* 235: 3401–3413.

Sharma V and McNeill JH (2009) To scale or not to scale: the principles of dose extrapolation. *Br J Pharmacol* 157: 907–921.