New insights into the clinical and nonclinical effects of psychedelic substances: an integrative
review

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Abstract

After decades of stagnancy, research on psychedelic substances (such as LSD, psilocybin or DMT) has experienced a renaissance over the last 10 years, with various major research programs being conducted across Europe and the United States. This research primarily investigates the potential of psychedelics in the treatment of mental health disorders, their short and long term effects on recreational users, and the neurological and cognitive processes responsible for their effects. The present review provides a concise summary of the most recent insights gained from this research. We briefly outline the history of psychedelic research, the objective and subjective effects caused by these substances, the prevalence and socio-psychological correlates of their use, as well as their potential for harm. Subsequently, we review empirical research on the beneficial effects of psychedelics in clinical samples, focusing on their efficacy in the treatment of major depression, anxiety, and substance use disorders, and discuss research on the proposed neural and cognitive mechanisms behind these effects. We then review research on their effects on healthy subjects, focusing on psychological wellbeing as well as changes in personality, nature relatedness, and creativity. Finally, we review empirical evidence regarding long-term effects of single experiences with psychedelics, and conclude with a brief summary and outlook.

Keywords: Psychedelics, Drugs, Depression, Anxiety, Substance Dependence, Nature Relatedness, Creativity, Wellbeing

Introduction

In 1971, most commonly-used psychedelic (from Greek ψυχή δηλείν, i.e., “mind-manifesting”) substances were classified as Schedule 1 substances by the UN Convention on Psychotropic Substances, labelling them a serious risk to public health without therapeutic value, and thereby effectively stopping scientific inquiries into their effects on humans. This classification caused administrative and legal hindrances and disproportionate costs for academic institutions that made further research on the physiological and mental effects of psychedelics nearly impossible (Nutt et al., 2013). However, with a changing political landscape and new safety protocols in place (Johnson et al., 2008), research on the effects of these substances saw a resurgence over the last two decades, with multiple research programs implemented across Europe (e.g., in the Netherlands, the United Kingdom, and Switzerland) and the United States, and culminating in a host of recent high-impact publications in major scientific outlets. The present review aims at providing a concise summary of the most important insights gained from this research, as well as its current shortcomings, focusing on the effects of psychedelic substances on mental health and wellbeing in clinical samples, and their presumed effects on cognition, behavior, and personality in healthy subjects. We begin with a brief overview of psychedelic substances and their users.

Characteristics of classic psychedelic substances and their users

Classic psychedelic substances (sometimes inaccurately referred to as *hallucinogens*) are characterized by their affinity to the serotonin 2A receptor (5-HT_{2A}) (Vollenweider & Kometer, 2010), and include, for example, the ergot derivate lysergic acid diethylamide (LSD), psilocybin (found in members of the *Psilocybe* mushroom family), and N,N-dimethyltryptamine (DMT)—a

naturally occurring alkaloid found in various plants that are traditionally used, for example, in South American shamanic rituals in the form of a brew called *ayahuasca* (Riba et al., 2003).

These substances have pronounced acute effects on perception, affect, and cognition (Nichols, 2004), with effects notoriously shaped by both subject and environment variables (Carbonaro et al., 2016). Subjective effects include increases in positive mood, a sense of transcendence of time and space, and a sense of ineffability—the difficulty to accurately describe the experience in words. They can further induce what is commonly referred to as a mystical-type experience, characterized by feelings of internal unity (i.e., a sense of undifferentiated being), external unity (i.e., a sense of connectedness to one’s environment), a specific noetic quality (i.e., a sense of an encounter with what one perceives to be objective reality) and a special sense of sacredness pertaining to the experience (MacLean et al., 2012; Barrett et al., 2015). In some cases, psychedelics may cause experiences that are described as spiritual in nature (not unlike non-substance-induced mystical experiences), with users reporting encounters with divine entities or a higher power that in some instances radically alter their belief systems, although it is as of yet unclear what precisely produces these effects (Griffiths et al., 2019, Yaden et al., 2017, Davis et al., 2020). In higher doses, psychedelics can induce a full loss of the concept of self, referred to in the literature as ego dissolution (Tagliazucchi et al., 2016).

Use of these substances is comparably widespread: Roughly 32 million people (approx. 9% of the general population) in the United States alone are estimated to have used a psychedelic substance in their lifetime, with approximately 9.7% of adults between 16 and 34 having used LSD, and 11.8% having used psilocybin (Krebs & Johansen, 2013; see Yockey et al., 2019, for an overview of psychosocial correlates of LSD use). In Europe, the numbers are less conclusive,

with EU surveys estimating lifetime prevalence rates for 15-34-year-old adults to fall between 0.1% and 5.4% for LSD, and 0.3% and 8.1% for psilocybin (EMCDDA, 2012).

In contrast to widespread beliefs, partially fueled by the sensationalized media reports dating back the 1960s, newer research attests to the relative safety and tolerability of classic psychedelic substances (Nichols, 2016) that many scholars consider to be among the least harmful and addictive recreationally-used drugs, both when it comes to physical and mental health (Nutt, 2007). In fact, in an analysis of a large representative sample from the National Survey on Drug Use and Health (NSDUH), Johansen and Krebs (2015) found no correlation between lifetime psychedelic substance use and markers of mental wellbeing, while a more inclusive analysis by Hendricks and colleagues (2015) in fact revealed a significant *negative* association between lifetime use of these substances and self-reported psychological distress and suicidality. This negative association was further substantiated by Argento and colleagues (2017) in a longitudinal, community-based study, who found that lifetime psychedelic drug use was associated with a reduce in suicidality of 60%. Likewise, across multiple years of the NSDUH, Hendricks and colleagues found a negative association between psychedelic use and criminal behavior such as theft and assault (2018), as well as prison recidivism (2014). Male users of psychedelics were also found to be less likely to perpetrate intimate partner violence than were non-users (Thiessen et al., 2018).

This is not to say that using psychedelics comes without any risk. While Ross and colleagues (2016) reported that no adverse long-term side-effects were observed across the more than 2000 participants who partook in psychedelic research studies as of 2016, these substances can cause severe acute emotional distress, especially (but not exclusively) when used in a less controlled environment and without proper support or opportunities for integration of the

experience (Carbonaro et al., 2016; Carhart-Harris et al., 2018b). In fact, acute negative effects are relatively common, even in controlled laboratory studies. For example, in one psilocybin administration study, 31 % of participants reported having experienced periods of acute anxiety during the treatment, which did however not persist beyond the session (Griffiths et al., 2006; 2008). Notably, however, especially in clinical applications, there is a possibility that the emergence of negative affective states may actually contribute to the therapeutic efficacy of psychedelics (similar to how psychotherapy may at times involved unpleasant affective states), although at least one study suggest that an experience of dread during the psychedelic experience negatively predicts treatment outcomes (Roseman et al., 2018). Yet, more research is needed to better understand the relationship between these variables.

In addition, some case studies suggest that psychedelics may cause what is known as a type-2 hallucinogen persisting perception disorder (HPPD)—a presumably chronic condition characterized by visual snow, afterimages, and corresponding difficulties concentrating (e.g., Hermle et al., 2012). Due to the anecdotal nature of most case reports and a lack of rigorous empirical investigations, the prevalence of this disorder is as-of-yet unknown. In fact, some research suggests that in many patients, subclinical visual HPPD symptoms were already present before intoxication, but may have been aggravated by anxiety associated with the intake of an arousing substance. If the condition is real, however, it is likely not specific to the use of psychedelic substances, and the prevalence is estimated to be very low (approx. 1/50,000 cases; Halpern et al., 2016). Lastly, given the potentially stressful nature of the psychedelic experience, use of these substances is typically considered not advisable for people with a genetic predisposition for psychosis (Abraham, et al., 1996), though evidence for a causal link between use of psychedelics and onset of psychosis is lacking.

Still, with media coverage about the ongoing research on psychedelics continually on the rise, more and more people seek out these substances in hope of gaining spiritual insights, getting new perspectives on life, or dealing with psychological distress and trauma, be it in the form of ayahuasca retreats in South America, legal psilocybin retreats in the Netherlands, or in the form of underground psychedelic-assisted psychotherapy (Sessa & Fischer, 2015).

Clinical effects of psychedelic substances.

Very soon after its discovery, by the late 1950s (e.g., Smith, 1958), therapists began using LSD in therapeutic sessions to explore its potential in treating conditions such as alcoholism or depression (for an overview see Pahnke et al., 1970; Rucker et al., 2016). Contemporary research suggests that serotonergic psychedelics can indeed have a variety of decidedly positive effects when used in clinical settings (Hartogsohn, 2016), predominantly focusing on their anxiolytic and antidepressant properties in the treatment of major depression disorder (MDD), (end-of-life) anxiety disorders, and substance use disorder (see Johnson et al., 2019 for a comprehensive review). Clinical trials typically involve administering a psychedelic substance to thoroughly-screened participants in a controlled and comfortable setting under the guidance of trained professionals. Sessions last approximately 4-9 hours, depending on substance and dosage, and commonly involve pre- and post-treatment assessment of relevant variables, as well as long-term follow-ups. In most clinical studies, use of psychedelics is embedded within a psychotherapeutic context, in which participants receive 11-12 hours of psychotherapy alongside the pharmacological treatment.

Mood disorders.

The dominant line of clinical research on psychedelics focuses on patients suffering from mood disorders; oftentimes those who did not respond well to classic treatment options. In one of

the first open label studies investigating the potential of psychedelics in the treatment of MDD, Osório and colleagues (2015) found that a single dose of ayahuasca reduced depressive scores of six patients by up to 82% on a variety of measures, an effect replicated with 17 patients of a psychiatric unit who suffered from recurring depression (Sanches et al., 2016). In a placebo-controlled follow-up study on 29 patients diagnosed with treatment resistant depression, similar antidepressant effects were observed after a single ayahuasca dose, persisting up to seven days post-treatment (Palhano-Fontes et al., 2019). Investigating the antidepressant effects of smoked 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT; structurally related to N,N-DMT), Davis and colleagues (2019) likewise observed reductions in self-reported anxiety and depression.

A separate line of research has focused on psilocybin as an especially promising candidate for the treatment of patients with mood disorders. An open label study found a reduction of depressive symptoms in 12 patients suffering from moderate-to-severe treatment resistant depression after a single dose of psilocybin (Carhart-Harris et al., 2016), with results persisting up to six months post-treatment (Carhart-Harris et al., 2018). In addition, sustained improvements in anxiety and anhedonia were observed. Patients themselves responded positively to the treatment, noting the absence of unpleasant long-term side-effects commonly encountered with classic treatment options (Watts et al., 2017). Based on these initial results, the US Food and Drug Administration granted psilocybin-assisted therapy the status of a potential “breakthrough therapy”, indicating that “the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)” (FDA, 2019). It should be noted, however, that research on the effects of these substances in the treatment of mood disorders is still in its infancy, and in need of further studies with larger sample sizes and more detailed follow-up analyses to make any conclusive statements. It is also important to note that while psychedelics

revealed great potential in treating MDD, a treatment that combines classic psychotherapy (and potentially even certain meditation techniques, Heuschkel & Kuypers, 2020) with use of psychedelic substances is likely to be more efficient and safer than administration of the substances alone (Greenway et al., 2020).

Anxiety in patients suffering from life-threatening medical conditions.

In a number of double blind, randomized, placebo-controlled studies (with different active control substances), similar positive results were obtained for the treatment of anxiety disorders. In particular, this area of research revolves around the treatment of patients suffering from anxiety and depression due to life-threatening medical conditions—a phenomenon that is encountered, for example, in 30-40% of all cancer patients in hospitals, and that is responsible for a variety of negative treatment outcomes (Mitchell et al., 2011). Grob and colleagues (2011) found a significant reduction in existential anxiety in a small group of patients suffering from advanced-stage cancer, one and three months after receiving two doses of psilocybin. These findings were replicated in a cross-over design with a larger sample by Griffiths and colleagues (2016), who found a significant reduction of anxiety in more than 80% of their participants six months after treatment with a single high dose of psilocybin. Similar findings were reported—in conjunction with psychotherapy—for a parallel study by Ross and colleagues (2016). Constituting the first study involving administering LSD to humans since the 70s, Gasser (2014) likewise reports a reduction of trait anxiety in participants with life-threatening diseases two months after receiving a 200-microgram dose of LSD, with no adverse side-effects, in an open-label crossover study establishing the safety and tolerability of LSD in clinical settings.

Substance use and substance dependence disorders.

A third line of clinical research investigated the potential of psychedelics in the treatment of substance use or dependence disorders (Bogenschutz & Pommy, 2012; Bogenschutz & Johnson, 2016; Sessa, & Johnson, 2015), a notion that was already investigated in the 70s with promising results (Krebs & Johansen, 2012). Specifically, Johnson and colleagues (2014) reported that multiple moderately high doses of psilocybin (in combination with cognitive behavioral therapy) significantly reduced smoking in 14 patients with tobacco dependence. Although the lack of a control group does not allow for drawing conclusive inferences, following the treatment, 80% of their participants were still smoking abstinent after six month, with 67% remaining abstinent 30 months post treatment, many of whom positively noted the lack of affect-related withdrawal symptoms (Johnson et al., 2017).

Similarly, initial evidence was found for the efficacy of psilocybin in the treatment of alcohol dependency. Bogenschutz and colleagues (2015) conducted a proof-of-concept study, in which 10 participants received two doses of psilocybin during a 12-week treatment program, decreasing their number of drinking days and heavy drinking days for up to 36 weeks post-treatment. More recently, a survey study found that naturalistic use of psychedelic substances outside of treatment settings similarly predicted subsequent reduction in self-reported alcohol use amongst a sample of people who struggled with dependency (Garcia-Romeu et al., 2019).

Other research programs currently investigate the usefulness of psilocybin assisted therapy in the treatment of various substance use disorders, such as opioid dependence (Argento et al., 2019). For example, although correlational in nature, Pisano and colleagues (2017) found that lifetime users of psychedelics were 40% less likely to have used opiates in the year prior to year their study was conducted. Yet, even more so than for studies on depression and anxiety,

additional, rigorously-controlled studies are necessary to make more conclusive statements about the effects of psychedelics in the treatment of substance dependence and substance use disorders.

Processes underlying the effects of psychedelics.

Although the neural underpinnings of the psychedelic experience have been researched for a while (e.g., Carhart-Harris et al., 2012), the exact mechanisms underlying the effects of psychedelics on mental health are not yet fully understood (see Muttoni et al., 2019 for a detailed review). On a neurological level, it is speculated that, among other pathways, psychedelics can inhibit amygdala reactivity and thereby attenuate the elevated levels of threat processing that are associated with depression (e.g., Kraehenmann et al., 2015), manifesting, for example, in a decreased sensitivity in encoding fearful faces (Dolder et al., 2016). They can further decrease resting-state connectivity within the default mode network (Carhart-Harris et al., 2012)—a brain network assumed to play a role in our concept of self, but also in negative self-referential thought in patients suffering from mood disorders (Sheline et al., 2009; Greicius et al., 2007). In fact, default-mode network disintegration under the effects of LSD (specifically, when experiencing ego dissolution) was found to negatively predict ruminative thought—that is, reflection about oneself in the past (Speth et al., 2016), a critical component of MDD (Hamilton et al., 2015).

Yet, crucially, an important factor for their therapeutic potential seem to be the subjective effects that psychedelics cause—specifically the aforementioned mystical-type experiences (see Barrett & Griffith, 2017 for a detailed discussion). In many of the studies investigating the effects of psychedelics on depression (Carhart-Harris et al., 2018) and anxiety (Ross et al., 2016), subjective qualities of the experience predicted therapeutic efficacy of the treatments. Across some of these studies, aspects of mystical-type experiences mediated effects of the substances on positive outcomes, whereas sensory perceptual effects did not (Roseman et al., 2018). Other

analyses suggest that a sense of connectedness (to oneself, others, and the world) (Watts et al., 2017), perceived insights gained from the experience (Carhart-Harris et al., 2018), and experiences of emotional breakthrough (Roseman et al., 2019) contribute to the effects. Likewise, in a large-scale cross-sectional survey, Davis and colleagues (2020) found that self-reported mystical-type experiences predicted lower levels of depression and anxiety following a psychedelic experience, and that this effect was mediated by higher levels of psychological flexibility.

Similarly, the effects of psychedelics on patients suffering from substance use or dependence disorders seem to partly rely on mystical type experiences. For example, participants who had stronger mystical-type experiences after treatment with psilocybin were more likely to be successful in quitting smoking (Garcia-Romeu et al., 2014). Additionally, in the survey study detailed above, higher doses of psychedelics predicted greater mystical experience and subjective insights gained from the experience, which positively predicted meaningfulness of the experience, and which in turn was negatively related to problematic drinking behavior (Garcia-Romeu et al., 2019).

Non-clinical effects of psychedelic substances

Yet, since most people who use psychedelics do so outside of a clinical setting, how do these substances and the corresponding mystical-type experiences affect healthy individuals?

Multiple double-blind crossover studies found that psilocybin (as well as LSD; Liechti et al., 2017), can reliably induce dose-dependent mystical-type experiences with pronounced personal significance in healthy participants (Griffiths et al., 2011; see Gandy et al., 2019 for an overview), around 60% of which considered the experience to be among the most meaningful experiences of their lives (Griffiths et al., 2006; 2008; Barrett et al., 2015). These experiences

were found to have positive effects on participants' subjective well-being and quality of life (Griffiths et al., 2006; 2008), trait openness to experience (MacLean et al., 2011; see also Lebedev et al., 2016 for similar effects with LSD), mindfulness (e.g., Madsen et al., 2020; Soler et al., 2016) and—in combination with meditation and other spiritual practices—on prosocial attitudes and behaviors (Griffiths et al., 2017). Further, in these studies, mystical-type experiences were found to positively affect people's sense of connectedness to both themselves and others (Griffith et al., 2017; Watts et al. 2017). In addition, a recent study by Barrett and colleagues (2020) revealed that a single high dose of psilocybin had positive effects on mood in healthy subjects, which remained elevated up to one month post-treatment.

More recently, a large-scale field study investigated the relationship between naturalistic psychedelic use, interpersonal connectedness, and well-being at various multi-day mass gatherings in the UK and USA. The study found that recent use of psychedelics, but not other substances, positively predicted self-reported transformative (and thus presumably mystical-type) experiences. These psychedelic-induced experiences were positively related to perceived connectedness to other humans as well as positive mood (Forstmann et al., 2020).

Similarly related to connectedness and feelings of external unity, lifetime use of classic psychedelics was found to be positively linked to nature relatedness (i.e., an incorporation of nature into one's self-construal) and thereby to ecological behavior (Forstmann & Sagioglou, 2017; Kettner et al., 2019). In particular, psychedelics-induced mystical-type experiences (Kangaslampi et al., 2020) and feelings of ego dissolution (Nours et al., 2017) were found to be strongly associated with people's self-reported change in their relationship to nature following a psychedelic experience. Given the established link between nature relatedness and mental well-being, positive affect, and perceived meaning in life (e.g., Nisbet et al., 2011), these findings may

help shed more light on the antidepressant effects of psychedelics discussed above. While initial investigations have been made (Lyons & Carhart-Harris, 2018), convincing evidence for a causal relationship between psychedelic substance use and nature relatedness or ecological behavior, however, is still lacking.

Based on initial data gathered in the 1960's (Harman et al., 1966) and contemporary views that consider creativity a dynamic form of cognition (Girn et al., 2020), another line of research seeks to investigate the link between use of psychedelics (which are thought to promote dynamic cognition; Tagliazucchi et al., 2014) and creativity or creative problem solving (Sessa, 2008). Although correlational in nature, Sweat and colleagues (2016) provided initial support for a link between lifetime use of psychedelics and creative problem solving on a functional fixedness task, with additional correlational evidence provided by Davis and colleagues (2020). Frecska and colleagues (2012) also assessed various aspects of creativity in a sample of 40 participants before and after repeated use of ayahuasca in a ceremonial setting, observing higher scores on visual creativity post-treatment. Similarly, 26 participants of a spiritual retreat showed enhanced divergent thinking and decreased conventional convergent thinking during the acute effects of ayahuasca (Kuypers et al., 2016). Yet, to date, no rigorous placebo-controlled studies were conducted, and evidence for a causal link between psychedelic substance use and increased creativity remains scarce.

Lastly, it should be noted that psychedelics may be used in the study of more basic cognitive processes. Specifically, due to their distinct neurological effects, they may prove to be useful utensils for researching effects on working and episodic memory, associative learning, or visual perception (Barrett et al., 2018, 2020b).

Long-term effects of psychedelics

Importantly, given a lack of longitudinal data, it remains a challenge to accurately assess the duration of the therapeutic efficacy of psychedelics in the treatment of the various disorders discussed above, as well as of the purported beneficial changes to well-being, cognition, and personality in healthy subjects. Providing a positive outlook, in the first studies on psilocybin and MDD, the significant reduction in scores on self-reported depressive symptoms was still observable after 6 months, with comparably stable effect sizes across this timespan (Carhart-Harris et al., 2018). Similar long-term effects were reported for the studies on psilocybin and end-of-life anxiety, in which 87% (Ross et al., 2016) and 82% (Griffiths et al., 2016) of patients suffering from life-threatening cancer reported increased life satisfaction six months post treatment—an effect that was primarily attributed to less perceived hopelessness and existential anxiety. In contrast, for example, in the ayahuasca study by Sanches and colleagues (2016) discussed above, a follow-up with some of their patients revealed that while participants considered the experience to be among the most important of their lives, self-reported reduction in depressive symptoms was limited to a few weeks (Dos Santos et al., 2018).

However, given the small sample sizes of most of the clinical studies, it is difficult to make conclusive statements regarding potential long-term effects. To address this concern, Romeo and colleagues (2020) recently published a first meta-analysis on the available data, comprising a total of eight clinical studies involving the administration of psilocybin, LSD, or ayahuasca, all of which assessed depressive symptoms at various times post-treatment. The authors note that although one should be cautious when interpreting the results of the analysis due to the low number of data points and inadequate statistical power, psychedelics may indeed contribute to a rapid improvement of depressive symptoms for up to six months. In a similar vein, in their recent review on long-term effects of psychedelics, Aday and colleagues (2020) state that

their search “documented robust positive and enduring effects of psychedelic treatment on measures of depression across several studies and research groups” (p. 15). They do, however, note that some studies required patients to abstain from their antidepressant medication, while others did not or did not specify whether this was the case.

When it comes to non-clinical samples, multiple studies report that participants consistently rated their psychedelic experience to be among the top five most meaningful experiences of their lives, with the majority of them reiterating this sentiment 14 months post treatment, further reporting increased well-being and life satisfaction as a result of their experience (Griffiths et al., 2008). Similarly, six month post psilocybin treatment (embedded within a meditation/spiritual practice program), participants in another study revealed significant increases on, for example, measures of interpersonal closeness, gratitude, meaning in life, and forgiveness (Griffiths et al., 2017).

A more recent study by Barrett and colleagues (2020) involving healthy subjects investigated persisting effects of psilocybin on multiple aspects of mental well-being. Results indicate that, while short term effects of psilocybin administration included an increase in positive mood, a decrease in negative mood, a decrease in trait anxiety, and a reduction in neural responses to negative affective stimuli, only the effects on positive mood and trait anxiety persisted at the one month follow-up. Likewise, in the large-scale field study by Forstmann and colleagues (2020), predictive power of psychedelic substance use on positive mood was robust for very recent substance use (within the last 24 hours), yet declined for moderately recent use (within the past week).

Conclusion and outlook

Over the last years, numerous research efforts (only a selection of which we could include in this review) have begun and continue to investigate various hypothesized positive effects of classic, serotonergic psychedelic substances, in both clinical and nonclinical samples. In the clinical context, research primarily focused on the potential of psychedelics in the treatment of mood disorders, anxiety, and substance use disorders, and on the investigation of the underlying neurological and cognitive processes. Much is still to be learned about these substances, especially when it comes to how precisely they unfold their therapeutic potential, the duration of their treatment efficacy, as well as the potential downsides of their use. Nevertheless, the present results are more than promising. Most notably, the positive effects of psychedelics on MDD and anxiety are typically the result of a single, medium-to-large dose of a psychedelic substance. This stands in stark contrast to established medications for these conditions, for example serotonin reuptake inhibitors, that bring with them a host of unwanted and potentially burdensome side-effects for the patient, and that have been shown to lose effectiveness over time (Uher & Pavlova, 2016).

Similarly, studies on healthy subjects revealed promising findings, suggesting a relationship between use of psychedelics, transformative experiences, mood, creativity, and feelings of connectedness with oneself, others, and nature. Notably, while mystical-type experiences seem to play a crucial role in these effects, little is known about which personality traits or environmental variables (despite dosage) may facilitate the occasion of such experiences and which aspects of these experiences may be responsible for their effects. Future research may therefore aim at establishing more precise criteria for what constitutes a mystical-type experience, develop more tools to accurately assess them, and determine their antecedents and precise mechanism of action.

Although causality of most of the effects in healthy subjects has not yet been convincingly established, results tentatively suggest that controlled use of psychedelics may have unique positive effects on people's well-being and their relationships with others and the world around them. As a result, psychedelics begin to play a role in the philosophical debate on moral enhancement (e.g., Earp, 2018).

However, while some of the research projects discussed now employ double blind, placebo-controlled study designs, many of them are still open label studies, and almost all of them suffer from small sample sizes and a lack of rigorous long term follow-ups. In addition, some exclusively rely on self-selected samples. As such, more studies are needed that overcome the present shortcomings in order to arrive at a clearer picture of the capabilities and limitations of psychedelic substances, including detailed meta-analyses of past studies.

On a political level, the present (albeit early) findings raise the question whether the ongoing restrictions and prevailing harsh legal repercussions in association with possession of psychedelic and other psychoactive substances in most European countries are still appropriate for scientifically oriented societies, or whether a re-evaluation should be considered for the sake of removing hurdles for academic institutions in their endeavor to determine the potential of these substances.

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