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Invited review

Positive psychology in the investigation of psychedelics and entactogens: A critical review

Henrik Jungaberle [a, *], Sascha Thal [b], Andrea Zeuch [a], Ansgar Rougemont-Bücking [c], Maximilian von Heyden [d], Helena Aicher [e], Milan Scheidegger [e]

[a] MIND European Foundation for Psychedelic Science, betahaus, Prinzessinnenstr. 19/20, 10969 Berlin, Germany
[b] Faculty of Behavioural and Social Sciences, University of Groningen, Netherlands, Grote Kruisstraat 2/1, 9712 TS Groningen, the Netherlands
[c] Faculty of Science and Medicine, Department of Neurosciences and Movement Science, Laboratory for Psychiatric Neuroscience and Psychotherapy, University of Fribourg, Ch. du Musée 5, Fribourg, Switzerland
[d] FINDER Institute for Prevention Research, Germany, betahaus, Prinzessinnenstr. 19/20, 10969 Berlin, Germany
[e] Neuropsychopharmacology and Brain Imaging, Department of Psychiatry, Psychotherapy and Psychosomatics (DPP), University Hospital of Psychiatry Zurich, Lenggstrasse 31, Postfach 1931, CH-8032 Zurich, Switzerland

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ABSTRACT

Rationale: We reviewed the concepts and empirical findings in studies with psychedelics and entactogens related to positive psychology – the study of healthy human functioning, well-being and eudaemonia. It is an unresolved question how beneficial effects of psychedelics and entactogens are related to the potential risks of these substances – particularly in non-clinical settings.
Methods: We searched in PubMed, PsychINFO and the Cochrane Library for controlled clinical and epidemiological studies which applied concepts from positive psychology. We included N = 77 eligible studies with 9876 participants published before November 1st, 2017: (1) quantitative studies (N = 54), (2) preliminary or exploratory studies and reviews not including meta-analyses (N = 17), and (3) studies evidencing primarily negative results (N = 6).
Results: Positive psychology concepts have been applied for measuring effects of clinical trials, recreational and ceremonial use of psychedelics and entactogens. Psychedelics and entactogens were shown to produce acute and long-term effects on mood, well-being, prosocial behaviours, empathy, cognitive flexibility, creativity, personality factors like openness, value orientations, nature-relatedness, spirituality, self-transcendence and mindfulness-related capabilities.
Conclusions: There is preliminary evidence for beneficial effects of psychedelics and entactogens on measures of positive psychology in clinical and healthy populations, however their sustainability remains largely unresolved. The reported results must be considered preliminary due to methodological restrictions. Since longitudinal data on both positive and adverse effects of psychedelics are lacking, more rigorous and standardized measures from positive psychology should be applied in less biased populations with prospective longitudinal designs to carefully assess the benefit-risk-ratio.
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* Corresponding author. MIND European Foundation for Psychedelic Science, betahaus, Prinzessinnenstr. 19/20, 10969 Berlin, Germany.
E-mail addresses: Henrik.Jungaberle@mind-foundation.org (H. Jungaberle), S.B.Thal@student.rug.nl (S. Thal), Andrea.Zeuch@mind-foundation.org (A. Zeuch), Ansgar.Rougemont-Buecking@unifr.ch (A. Rougemont-Bücking), Maximilian.vonHeyden@finder-research.com (M. von Heyden), Helena.Aicher@mind-foundation.org (H. Aicher), Milan.Scheidegger@bli.uzh.ch (M. Scheidegger).

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1. Introduction

While previous psychedelic research mainly focused on pathophysiological disease models and clinical applications, potential beneficial effects of psychedelics and entactogens on healthy human functioning remain barely investigated. Psychedelics (serotonergic hallucinogens like LSD or psilocybin) and entactogens (like MDMA) are used for basic and clinical research, experimental therapy, but also in recreational and psychospiritual settings. Although the latter practices are illicit or strictly regulated for public health concerns, millions of users worldwide consume psychedelic substances without serious mental health problems (Krebs and Johansen, 2013). There are consistent claims by users and researchers that psychedelics might be useful in improving healthy human functioning (Mackenzie, 2014; Walsh, 1982), however more empirical research is needed to move beyond anecdotal evidence and carefully balance beneficial effects and harm potential.

1.1. Types of studies in the psychedelic field

Basic research with psychedelics is focused on understanding mental functions and their relationship with neuronal processes in the brain (Kyzar et al., 2018). Clinical research emphasizes the improvement of symptom measures in the treatment of diagnosed patients (e.g., Clinician-Administered PTSD Scale (CAPS) in trauma patients or depression scores) where psychedelics and entactogens are predominantly expected to provide valuable pharmacological tools for the augmentation of psychotherapy (Majić et al., 2017; Vollenweider and Kometer, 2010). Studies in non-clinical populations mostly focus on pathologies assumed to be induced by or associated with the misuse of these substances like impairment of memory, psychotic episodes or substance use disorders (Carhart-Harris et al., 2016; Krebs and Johansen, 2013; Nesvag et al., 2015; Rogers et al., 2009).

1.2. Risks and safety issues

Clinical settings supervised by medical doctors and psychotherapists were shown to provide safe environments for the administration of psychedelics and entactogens with marginal risks for severe incidents (Danforth et al., 2016). Yet a systematic evaluation of these risks in naturalistic medical settings still has to be conducted (Heal et al., 2018). In contrast, the recreational use of psychedelics and entactogens in the context of parties, festivals, ceremonies or private homes has generally been considered unsafe – not to speak of the fact that it is illicit to use, own or sell these substances in almost all countries. Globally there is a lack of structured and comparable reporting systems concerning drug-related incidents and deaths. Nevertheless, we see that MDMA related deaths are on the rise in several countries (ibid). Typical risks associated with the recreational use of MDMA include hyperthermia, dehydration, drug interactions, hyponatremia and overdose (Rigg and Sharp, 2018). A study conducted before the rise in media popularity of MDMA estimated the amount of ecstasy related deaths in the US to be about 50 a year (Rogers et al., 2009).

Death due to direct LSD toxicity is unknown (Nichols, 2016). Major risks associated with the recreational use of classical psychedelics are anxiety and panic attacks, manifestation or exacerbation of psychotic disorder and hallucinogenic persisting perception disorders (Baggott et al., 2011; Heyden and Jungaberle, 2017). It is agreed upon that toxicity of LSD, ayahuasca, psilocybin and DMT is generally low. Due to the development of new psychoactive substances like the NBOMe compounds several recent psychedelics have been linked to severe hospitalizations and fatalities (Nichols, 2016).

1.3. Benefits and positive psychology in the investigation of psychedelics and entactogens

Due to such risks LSD and other psychedelics have been listed in Schedule 1 of the US Controlled Substances Act and little attention has been given to the potential of psychedelics to improve peoples' lives through the enhancement of characteristics that are not directly linked to risks and pathologies (Elsey, 2017). Although it is recognized that adverse effects of these substances in uncontrolled settings may entail detrimental ramifications (Carvalho et al., 2014), the focus of the present paper revolves around beneficial effects across different intra- and interpersonal domains. In his review Elsey (2017) concludes that for some people the psychedelic experience may not only produce improvements in mood but may also give access to states of consciousness and insights of great significance to the individual and his social group. With precursors since the 1960ties - like Maslow's theory of self-actualization (Walsh, 1982) - the domain of positive psychology started as a new field of research in the 1990ties. Seligman and Csikszentmihalyi (2000) define positive psychology as "the scientific study of positive human functioning and flourishing on multiple levels that include the biological, personal, relational, institutional, cultural, and global dimensions of life". Peterson (2009) defined it as "the scientific study of what makes life most worth living". Hence, positive psychology provides a valuable conceptual framework to further elucidate the potential beneficial effects of psychedelics and entactogens on healthy human functioning.

Here we investigate the claim that psychedelics and entactogens may produce acute and long-term beneficial outcomes in mental functioning in both clinical and healthy populations by critically reviewing the current research literature. Specifically, we explored how beneficial effects were conceptually defined and empirically measured in these studies, including methodological limitations. Finally, we discuss the consequences of conducting research about psychedelics with concepts from positive psychology highlighting possible avenues for future studies.

2. Methods

An extensive literature search and *critical review* (Grant and Booth, 2009) was conducted including papers until November 1st, 2017. We searched the electronic databases MEDLINE (PubMed), Cochrane Library and PsycINFO with the aim to identify studies that applied concepts related to positive psychology in clinical and epidemiological research on psychedelics and entactogens.Our protocol included (1) randomized controlled clinical and neuroscience studies (Steward & Balice-Gordon, 2014) with transparency in addressing possible biases and rigor in reporting characteristics (Cullum, 2000). (2) From the observational field we included cohort studies, case-control studies, cross-sectional studies and follow-up studies (Sanderson et al., 2007) (Table 1). Our protocol excluded qualitative studies, case reports, opinion papers, field studies as well as treatment or pre-clinical studies that either were not controlled and randomized, that *exclusively* used pathological measurements (like symptom scales) or had only screened for the worsening of clinical parameters in recreational user (Rogers et al., 2009). The following search strings were used: "(psychedelics OR LSD OR psilocybin OR mescaline OR DMT OR dimethyltryptamine OR MDMA OR entactogens OR ayahuasca) AND (social change OR personal change OR transformative OR social transformation OR life changing OR mystical OR altered states of mind OR non-therapeutic OR psychotherapy OR mindfulness OR personality OR personal development OR meaning OR meaningfulness OR insight OR creativity OR problem solving OR prosocial behavior OR psychological well-being OR transpersonal OR psychospiritual growth)."

In the *results* the four categories acute/persistent/personal/social are presented under the heading of the substances ("Psilocybin", "MDMA" etc.). In the *conclusion* the studies are discussed under the headings of positive psychology constructs ("mindfulness", "creativity" etc.).

3. Results

The electronic searches resulted in 2550 hits (2095 in PubMed, 323 in the Cochrane Library, and 132 results in PsychINFO) (Fig. 1). We found N = 77 eligible sources that were subsequently divided into the categories: (1) quantitative empirical studies (N = 54; see Table 1), (2) preliminary or exploratory studies and reviews not including meta-analyses (N = 17; see Table 2), and (3) studies evidencing primarily negative results (N = 6; see Table 3). The count is as follows: 3 treatment/follow-up of treatment studies (n = 38), 54 neurophysiological/neuropsychological or psychological studies (n = 2149), 7 epidemiological studies (n = 7689), 11 reviews and 2 pooled-/meta-analyses. Two of the selected studies were conducted in the 1960ties, 2 studies in the 1970ties, 1 study in the 1980ties, 2 studies in the 1990ties, 8 studies in the 2000s and 62 studies since 2010.

We organized the results in the four categories "acute social change", "persistent social change", "acute personal change" and "persistent personal change". If overlap between the categories occurred, we decided based on main reported findings. Table 1 provides an overview of the selected and reported studies and Table 2 separately lists older, methodologically less elaborate studies and reviews that are mentioned selectively.

Table 2 summarizes studies we excluded because of methodological weakness that are of historical importance.

Table 3 provides a list of negative results within the eligible studies. These are explicitly not the result of an extensive search of negative adverse effects (which would provide much more extensive results). They are rather a byproduct of the search string that was performed to discover concepts and research about positive psychology related to psychedelics.

3.1. Acute social change

This category includes phenomena that are precursors to or directly related to social behaviors.

3.1.1. Psilocybin

Study participants under the influence of psilocybin report positive changes in mood (Grob et al., 2011). This positive effect on mood was found to be associated with reduced responses to negative stimuli subsequent to acute psilocybin administration (Kometer et al., 2012; Schmidt et al., 2013; Vollenweider and Kometer, 2010). A functional magnetic resonance imaging (fMRI) study by Kraehenmann et al. (2015), showed decreased right amygdala response to neutral ($p < 0.001$) and negative ($p = 0.001$) stimuli and increases in self-reports of positive mood ($p = 0.001$) in people under the influence of psilocybin. Preller et al. (2016) found decreased neural reactivity to self-reported social exclusion in the dorsal anterior cingulated cortex (dACC; $p < 0.05$) and the middle frontal gyrus ($p < 0.05$) in healthy subjects after the administration of psilocybin. Therefore, it was hypothesized that psilocybin reduces the processing of social pain. Pokorny et al. (2017) assessed how multiple facets of empathy and hypothetical decision making are acutely influenced by psilocybin in healthy volunteers. Both implicit ($p < 0.05$) and explicit ($p < 0.01$) emotional empathy were significantly affected by psilocybin compared to placebo. While

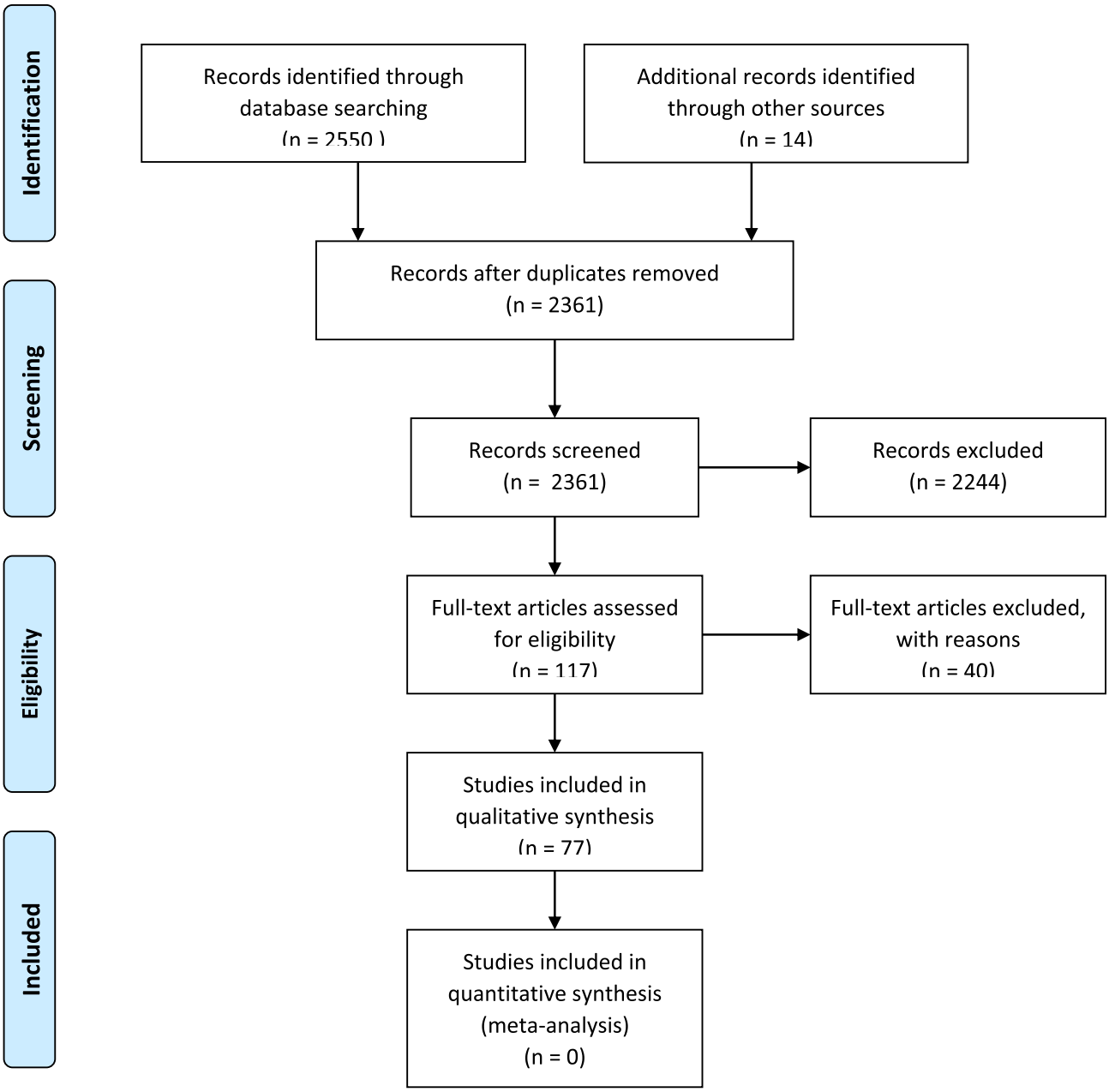

Fig. 1. Literature search flow diagram.

moral-decision making was not influenced by psilocybin, heightened implicit emotional empathy was found to be related to the altered meaning of percepts induced by psilocybin ($p < 0.01$).

3.1.2. *Lysergic acid diethylamide (LSD)*

Similar effects were reported using Lysergic acid diethylamide (LSD) in a laboratory study by Mueller et al. (2017). Using fMRI, LSD was shown to decrease right medial prefrontal cortex and left amygdala responses during the presentation of anxiety inducing stimuli ($p < 0.05$). This suggests that altered emotional processing under the influence of LSD relies on modulatory effects on cortico-limbic neurocircuitries. In line with this result, Dolder et al. (2016) found that LSD reduced the identification of fearful and sad faces on the Face Emotion Recognition Task (FERT; $p < 0.001$). Additionally, acute social changes after administration of LSD included enhancements in perceived closeness to others ($p < 0.001$), openness ($p < 0.001$), trust ($p < 0.001$), desire to be with other people ($p < 0.001$), prosocial behavior ($p < 0.05$), as well as explicit ($p < 0.001$) and implicit ($p = 0.01$) emotional empathy (Dolder et al., 2016; Schmid et al., 2015).

3.1.3. *Methylenedioxymethamphetamine (MDMA)*

There is evidence that Methylenedioxymethamphetamine (MDMA) improves users' self-reported perception of and responses to emotional stimuli with social content (Hysek et al., 2012), influences how people talk about significant others (Baggott et al., 2015), increases empathy for positive emotional situations and enhances interpersonal empathy in social interactions (Wardle and De Wit, 2014). Stewart et al. (2014) found MDMA to improve users' perception of trustworthiness ($p < 0.05$) and co-operative behaviors ($p < 0.05$), possibly contributing to the enhancement of empathy. Empathy on the Multifaceted Empathy Test (MET) was

Table 1
Overview of quantitative studies with positive psychology measures.

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Sampedro et al. (2017)	Ayahuasca	Within-subject comparison	16; non-clinical sample	• Increases in non-judging ($p = 0.011$) and non-reacting ($p = 0.02$) • Increased Experience Questionnaire scores ($p < 0.003$) • Correlations between glutamate + glutamine reductions and increases in the "Non-Judging" subscale of the Five Facets Mindfulness Questionnaire (FFMQ) ($r = -0.589$, $p = 0.044$) • Increases in superior rostral ACC-PCC connectivity correlated with increases in Non-Judging ($r = 0.604$, $p = 0.013$) and Non-Reacting ($r = 0.522$, $p = 0.038$) on the FFMQ • Increased anterior cingulated cortex connectivity in the medial temporal lobe correlated with increased scores on the Self-Compassion questionnaire ($r = 0.514$, $p = 0.042$) and increases in Non-Judging ($r = 0.637$, $p = 0.008$) and Non-Reacting ($r = 0.656$, $p = 0.006$) on the FFMQ • In the two month follow-up: Decreased glutamate + glutamine in the posterior cingulated cortex correlated with differences in Non-Judging ($r = -0.74$, $p = 0.009$); Increased anterior cingulated cortex connectivity in the medial temporal lobe ($r = 0.566$, $p = 0.035$) and the superior rostral ACC-PCC ($r = 0.637$, $p = 0.008$) correlated with Non-Judging	• Small sample size • No placebo-control • No control for time-effects • All participants had previous experience with Ayahuasca • Participants evidence high base-line scores of multiple mindfulness facets • Correlation analysis should be considered preliminary • Only sub-acute state of Ayahuasca effects were investigated
Barbosa et al. (2016)	Ayahuasca	Cross-sectional, case-controlled	57; non-clinical sample	• Positive correlation between number of Ayahuasca sessions attended in the previous 12 month and DUREL-assessed Organizational Religious Activity ($r = 0.39$, $p = 0.034$) • Increasing total lifetime months of regular attendance at Ayahuasca rituals age was linked to a decreased likelihood of lifetime past use of alcohol to intoxication ($p = 0.034$) • Ayahuasca users evidence fewer role limitations due to health problems on the Medical Outcomes Study Short Form-36 ($p = 0.035$) • Depression and confusion scales indicated lower levels of depressive ($p = 0.043$) and confusion ($p = 0.032$) states in Ayahuasca users on the Profile of Mood States •Increase in Agreeableness ($p = 0.028$) and Openness ($p = 0.037$) on the Big Five Inventory • Longer lifetime attendance Ayahuasca use was associated with lower impairments in daily life caused by physical health problems assessed by the Medical Outcomes Study Short Form-36 ($p = 0.032$) • No group differences across neuropsychological variables, except: Decreased susceptibility to proactive interference during verbal learning ($p = 0.04$) on the California Verbal Learning Test in Ayahuasca users	• Cross-sectional design makes study vulnerable to selection bias • Multiple comparisons increase the likelihood of type I error
Kuypers et al. (2016)	Ayahuasca	Within-subject	26; non-clinical sample	• No significant effect found for Pattern/line meanings test • Increase in divergent ($p = 0.023$) and decrease in convergent thinking ($p = 0.017$) on the picture concept test	• Quasi-experimental design limits the conclusions that may be drawn
Soler et al. (2016)	Ayahuasca	Within-subject	25; non-clinical sample	• Increase in the MINDSENS composite index ($p = 0.016$) • The Five Facets Mindfulness Questionnaire (FFMQ): increases in two facets of the FFMQ indicating a reduction in judgmental processing (Non-Judge; $p = 0.01$) of experiences and in inner reactivity (Non-React; $p = 0.034$) • Experiences Questionnaire (EQ): increase in decentering ability ($p = 0.007$)	• Small sample size • All participants had prior experience with Ayahuasca • Absence of control-group • Only one dose of Ayahuasca was given, subjective effects of Ayahuasca are dose-dependent
Bouso et al. (2015)	Ayahuasca	Matched between-group comparison	44; non-clinical sample	• Decreased harm avoidance ($p = 0.044$) • Increased self-transcendence ($p < 0.001$) • Differences in cortical thickness (CT) in midline structures of the brain, with thinning in the posterior cingulate cortex (PCC) • CT values in PCC were inversely correlated with intensity ($r = -0.444$; $p = 0.038$) and duration ($r = -0.492$; $p = 0.02$) of prior use of Ayahuasca and with scores on self-transcendence ($r = -0.479$; $p = 0.024$)	• No direct causation can be established

(*continued on next page*)

Table 1 (*continued*)

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Bouso et al. (2012)	Ayahuasca	Placebo-controlled, Between-subject comparison	243; non-clinical sample	• Increased Reward Dependence ($p = 0.009$) and Self-Transcendence ($p < 0.001$) • Decreased Harm Avoidance ($p < 0.001$) and Self-Directedness ($p = 0.002$) • Lower scores on psychopathological measures of the Symptom Checklist-90-R SCL-90-R ($p = 0.009$) • Better performance on the Stroop test, the Wisconsin Card Sorting Test and the Letter-Number Sequencing task from the WAIS-III, and better scores on the Frontal Systems Behavior Scale • Higher scores on the Spiritual Orientation Inventory ($p < 0.001$), the Purpose in Life Test ($p < 0.001$) and the Psychosocial Well-Being test ($p < 0.001$) • Overall differences with controls were maintained one year later	• Groups were not matched in premorbid IQ. It is thus impossible to determine whether the differences in neuropsychological tests were preexisting or due to the use of Ayahuasca • The quantity of variables analyzed may have increased the occurrence of type I error • Common problems associated with self-report questionnaires and the motivational aspects • Assessed individuals may have been those who did not experience negative neuropsychiatric consequences derived from Ayahuasca use, because subjects experiencing adverse consequences may have given up Ayahuasca use
Frecska et al. (2012)	Ayahuasca	Test-retest measures	61; non-clinical sample	• Increased highly original solutions and phosphenic responses on visual components of the Torrance Tests of Creative Thinking ($p < 0.05$) • Ayahuasca affectioned individuals exhibited more phosphenic solutions already at the baseline ($p < 0.05$)	• Use of mixture compound which is unreliable in terms of dose and blood level • No causal, only correlational evidence • No ethnically comparable, placebo-control group went through the same preparation procedure • Neuropsychologically unclear why Ayahuasca users produced more original solutions
Barbosa et al. (2009)	Ayahuasca	Within-subjects	23; non-clinical sample	• Santo Daime group: Reduction of the intensity of minor psychiatric symptoms on the Clinical Interview Schedule - Revised Edition ($p = 0.005$), improvement of mental health on the Short Form-36 Health Survey Questionnaire ($p = 0.027$), and increased novelty seeking ($p = 0.025$) on the Temperament and Character Inventory-125 items • Uniào do Vegetal group: Decrease in physical pain on the Short Form-36 Health Survey Questionnaire ($p = 0.044$), and decreased reward dependence ($p = 0.017$) on the Temperament and Character Inventory-125 items • In the entire sample reward dependence was positively correlated with the frequency of Ayahuasca use ($r = 0.505$, $p = 0.014$)	• Small sample size • Naturalistic study and thus limited control of variables
Cakic et al. (2010)	DMT	Online self-report survey	121; non-clinical sample	• Self-reported increase in psychospiritual insight (75.5%)	• Potentially biased sample due to snowball sampling • Poly drug use of participants
Kamboj et al. (2015)	Ecstasy/MDMA	Within-subject, counterbalance-comparison	20; non-clinical sample	• Gradual reduction in scores on the negative affect subscale of the Positive and Negative Affect Scale ($p < 0.001$, $\eta^2 = 0.33$) • Increased energy, euphoria, jaw clenching, sensitivity to colors, trust, wanting to be with others, compassion for others, closeness to others, empathy, self-confidence and self-compassion (p-values ≤ 0.036, $\eta^2 > 0.16$)	• Convenience sample • No blinding • Several participants tested positive for recreational/medicinal compounds • Participants did not show all of the effects expected of MDMA • Ecstasy use was assessed, thus cannot unequivocally be attributed to MDMA alone
Stewart et al. (2014)	Ecstasy	Independent group, repeated Measure	39; non-clinical sample	• Increased face trustworthiness ratings ($p < 0.05$) of facial stimuli • Increased cooperative behavior on dictator ($p < 0.05$) and ultimatum games ($p < 0.05$) • No group-differences after 3 days • Standard acute ecstasy effects (euphoria, energy, jaw clenching) • Negative effects (less empathy, compassion, more distrust, hostility) after 3 days	• No translation to clinical setting because it's a naturalistic study
Mueller et al. (2017)	LSD	Double-blind, randomized, placebo-controlled	20; non-clinical sample	• Reduced reactivity of the left amygdala and the right medial prefrontal cortex relative to placebo during the presentation of fearful faces ($p < 0.05$) • Negative correlation between addition, there was a significant negative correlation between amygdala blood oxygen-level dependent response to fearful stimuli and subjective drug effects ($r = -0.46$; $p < 0.05$)	• Double-blinding was unblended by psychedelic drug effects • Measures of negative affect were not included in analyses • Only moderate dose of LSD was used

Schmid and Liechti (2017)	LSD	Double-blind, randomized, placebo-controlled, crossover	16; non-clinical sample	• Persisting Effects Questionnaire (PEQ): positive attitudes about life and/or self ($p < 0.001$), positive mood changes ($p < 0.01$), altruistic/positive social effects ($p < 0.001$), positive behavioral changes ($p < 0.01$), and well-being/life satisfaction ($p < 0.001$) significantly increased at 1 and 12 months and were subjectively attributed by the subjects to the LSD experience; No changes in negative attitudes, negative mood, antisocial/negative social effects, or negative behavior • Mysticism Scale (MS): increased the total score ($p < 0.001$) • Death Transcendence Scale (DTS): ratings of mystical experiences significantly increased 1 and 12 months after LSD administration ($p < 0.01$ and $p < 0.001$ respectively) • NEO-Five Factor Inventory (NEO-FFI): Only Conscientiousness was affected after 12 ($p < 0.05$) but not after 1 month • State-Trait Anxiety Inventory (STAI): No changes • Mystical Experience Questionnaire (MEQ30) total scores correlated with changes in well-being/life satisfaction 12 months after LSD administration ($r = 0.6$, $p < 0.05$); Altered States of Consciousness Rating Scale total score correlated with positive changes in mood ($r = 0.56$, $p < 0.05$), behavior ($r = 0.53$, $p < 0.05$), and well-being/life satisfaction ($r = 0.53$, $p < 0.05$) on the PEQ at 12 months • After 12 months, 10 of 14 participants rated their LSD experience as among the top 10 most meaningful experiences in their lives	• No true control condition for long-term effects of LSD thus effects may be due to expectations of positive long-term changes • Small sample, not sufficient power to detect small personality changes • German translation of the questionnaires was not validated • Study was conducted in healthy subjects and results cannot be generalized to patient groups
Carhart-Harris et al. (2016)	LSD	Within-subjects, placebo-controlled	20; non-clinical sample	• Heightened mood • High scores on the Psychotomimetic States Inventory (PSI; $p < 0.001$) • Increased optimism ($p = 0.005$) and trait openness ($p = 0.03$) two weeks after LSD • No changes in delusional thinking ($p > 0.05$)	• Relatively short duration of follow-up period • Single-blind design • No active placebo-control • MRI and MEG scans may have influenced the experience
Dolder et al. (2016)	LSD	Double-blind, random-order, placebo-controlled cross-over	40; non-clinical sample	• Feelings of happiness ($p < 0.001$), trust ($p < 0.001$), and closeness to others ($p < 0.001$) • Enhanced implicit ($p = 0.01$) and explicit ($p < 0.001$) emotional empathy on the Multifaceted Empathy Test (MET) • Impaired the recognition of sad and fearful faces on the Face Emotion Recognition Task (FERT; $p < 0.001$) • Enhanced desire to be with other people ($p < 0.001$) and increased prosocial behavior on the Social Value Orientation (SVO) test ($p < 0.05$)	• Dose effects were studied in different participants instead of within-subject • Only emotion recognition was used as a measure of response to emotions and stimuli used were artificial
Lebedev et al. (2016)	LSD	Balanced-order, placebo-controlled	19; non-clinical sample	• Pronounced global effect on brain entropy ($p < 0.001$) in sensory ($p < 0.001$) and hierarchically higher ($p < 0.001$) networks across multiple timescales • Shifts in brain entropy predict enduring increases in trait openness ($p = 0.035$) and were moderated by music ($p < 0.001$) • Shifts in the orbitofrontal ($p = 0.048$) and superior frontoparietal ($p = 0.026$) networks were greatest when ego-dissolution was reported	• Order of the music scan was not counterbalanced making it impossible to separate its effects from that of psychodynamics • Some participants had substantial experience with psychedelics prior to the study
Liechti et al. (2017)	LSD	Double-blind, placebo-controlled, cross-over	40; non-clinical sample	• LSD-induced alterations of consciousness (Alteration of Consciousness - ASC total score) were significantly correlated ($r = 0.87$; $p < 0.001$) with ratings of mystical experience (Mystical Experience Questionnaire - MEQ) • Scores of the MEQ positive mood scale were strongly linked with scores on the ASC experience of unity ($r = 0.85$; $p < 0.001$) and blissfulness state ($r = 0.8$; $p < 0.001$) scales	–
Tagliazucchi et al. (2016)	LSD	Randomized, placebo-controlled, within-subject	15; non-clinical sample	• Increase in functional connectivity observed under LSD correlated with subjective reports of "ego dissolution." in the right ($r = 0.71$, $p = 0.003$) and left ($r = 0.64$, $p = 0.01$) angular gyrus and the right ($r = 0.81$, $p < 0.001$) and left ($r = 0.75$, $p = 0.001$) insular cortex	• Significant differences in head motion between conditions • Strict criteria to combat motion artifacts reduced sample size • Analysis of ego dissolution based on a single numerical report by experienced users of psychedelics • Potential unblinding in participants due to their prior LSD experience
Kaelen et al. (2015)	LSD	Within-subject, placebo-comparison	10; non-clinical sample	• Emotional response to music is enhanced by LSD ($p = 0.006$), especially wonder ($p = 0.027$), transcendence ($p = 0.027$), power ($p = 0.027$), and tenderness ($p = 0.027$)	• Limited sample size • Enhanced suggestibility of LSD may have contributed to the effect

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Table 1 (*continued*)

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Schmid et al. (2015)	LSD	Double-blind, randomized, placebo-controlled, crossover	16; non-clinical sample	• Positive relationship between intensity ratings of the experience and emotional arousal to music ($r = 0.79$, $p = 0.006$) and increases in feelings of transcendence ($r = 0.79$, $p = 0.006$) • Increased ratings of oceanic boundlessness ($p < 0.001$), "experience of unity ($p < 0.001$), and "blissful state" ($p < 0.001$) • Increased subjective well-being ($p < 0.05$), excitation ($p < 0.001$), inactivity ($p < 0.01$), introversion ($p < 0.001$), dreaminess ($p < 0.001$), happiness ($p < 0.001$), closeness to others ($p < 0.001$), openness ($p < 0.001$), and trust ($p < 0.001$)	• Difficulties in maintaining the blinding • Emotions were not assessed in pre- and post-ratings • Only a single dose of LSD was used • No dose-response data • Subjective effects of LSD unblended the assignments • Expectations may have influenced the results • Effect of LSD in recreational settings may differ from laboratory settings • Endocrine measures only performed at two time-points during the expected peak drug effect
Lyvers & Meester (2012)	LSD & Psilocybin	Online self-report questionnaire	337; non-clinical sample	• Use of LSD ($p < 0.001$) and psilocybin ($p = 0.04$) significantly predicted scores on the Mysticism scale explaining 11% of the variance in scores • Use of LSD ($p < 0.001$) significantly predicted scores on the Mystical Experience Questionnaire explaining 12% of the variance in scores	• Convenience sample • Common biases due to self-report questionnaire
Kuypers et al. (2017)	MDMA	Pooled analysis of six placebo-controlled within-subject studies	118; non-clinical samples	• Increased emotional empathy ($p = 0.008$, partial $\eta^2 = 0.06$) on the Multifaceted Empathy Test (MET) • Empathy was most pronounced during presentation of positive emotions ($p = 0.001$, partial $\eta^2 = 0.09$) on the MET • MDMA-induced empathy enhancement on the MET, i.e., concern for positive emotions ($r = 0.26$, $p = 0.005$) and arousal for positive emotions ($r = 0.2$, $p = 0.04$) was positively related to MDMA blood concentrations	• Pooling of studies revealed inconsistencies in the data • Studies administered different tasks despite those for which data was compared, i.e., participants of different studies were exposed to different demands • Study instructions may have differed between studies
Wagner et al. (2017)	MDMA	Double-blind, placebocontrolled, randomized, open-label cross-over	16; clinical sample from Mithoefer et al. (2011)	• Interaction between change in Openness and Clinician-Administered PTSD Scale (CAPS) scores: Those who had the greatest increase in Openness also demonstrated greater decreases in PTSD symptoms as measured by the CAPS ($p = 0.029$) • Enduring changes in both Openness ($p = 0.032$) and Neuroticism ($p = 0.003$) when comparing baseline personality traits with long-term follow-up traits	• See Mithoefer et al. (2011) • Possible expectancy effect • Main outcome measures are based on subjective reports
Baggott et al. (2016)	MDMA	Within-subjects, double-blind, randomized, placebo-controlled	12; non-clinical sample	• Increased feelings of authenticity ($p = 0.006$) • Decreased social anxiety ($p = 0.019$) • Increased comfort describing emotional memories (fixed effects of condition ($p = 0.024$) and emotion ($p = 0.014$))	• Small sample size and power • Not controlled for temporal duration of autobiographical memories • No active placebo control
Baggott et al. (2015)	MDMA	Two-session, within-subject, double-blind	35; non-clinical sample	• Linguistic Inquiry and Word Count: Increased use of social ($p = 0.008$) and sexual ($p = 0.046$) words • Participants spoke more about death ($p = 0.002$) • Psychological statements decreased ($p < 0.001$) and non-psychological statements increased ($p = 0.003$) • Machine learning: Increased use of social words and words relating to both positive and negative emotions	• Bag-of-words approach does not pay attention to work order or context • Not controlled for range of emotional memories that were recorded
Clark et al. (2015)	MDMA	Within-subject, counterbalanced, double-blind, placebo-controlled	21; non clinical-sample	• Increased prosocial ($p = 0.02$, $\eta^2 = 0.08$) and stimulated feelings ($p = 0.001$, $\eta^2 = 0.12$) • Prosocial effects correlated with stimulated feelings and measures of sympathetic activity using pre-ejection period but not with respiratory sinus arrhythmia	• Small sample size • Not powered to detect small correlations between autonomic functions and subjective effects • All participants had prior experience with MDMA • Participants took MDMA alone not in groups which may decreases generalizabilty to real-life settings
Kirkpatrick et al. (2015)	MDMA	Within-subjects, randomized, placebo-controlled	32; non clinical sample	• Welfare Trade-Off Task: Participants were significantly more generous toward the Friend compared to the Stranger, regardless of MDMA dose ($p < 0.001$); MDMA (1.0 mg/kg) increased generosity toward a friend ($p < 0.05$) but not a stranger; MDMA (0.5 mg/kg) slightly increased generosity toward a stranger, only among female participants ($p < 0.05$)	• All participants had prior MDMA experience

Frye et al. (2014)	MDMA	Counter-balanced double-blind, placebo-controlled	35; non-clinical sample	• Decreased effect of simulated social rejection on self-reported mood ($p < 0.05$) and self-esteem ($p < 0.05$) • Decreased perceived intensity of rejection ($p < 0.001$)	• All participants had prior experience with MDMA • Simulated rejection manipulation did not elicit any autonomic response • Simulation of rejection does not reflect all aspects of real-world rejection • MDMA was taken alone not in a social group which may change the results • Tasks were not administered during peak of drug effects
Hysek et al. (2014)	MDMA	Double-blind, random-order, cross-over, placebo-controlled	32; non-clinical sample	• Enhanced explicit ($p = 0.019$) and implicit ($p = 0.047$) emotional empathy in the Multifaceted Empathy Test • Increased prosocial behavior in the Social Value Orientation test in men ($p = 0.008$) • Impaired identification of negative emotions, including fearful ($p < 0.001$), angry ($p = 0.007$), and sad ($p = 0.01$) faces, in the Facial Emotion Recognition Task in women ($p < 0.001$)	• No dose − response study was performed • Blinding did not work for most participants • Relatively large number of statistical comparisons was used for the evaluation of social cognition
Kirkpatrick et al. (2014)	MDMA	4-session, within-and-between-subjects, double-blind, placebo-controlled	65; non-clinical sample	• Increased feelings of "Friendly" and "Insightful" (both $p < 0.001$) • Impaired recognition of angry and fearful facial expressions (both $p < 0.01$), recognition of happy and sad faces was not affected on Morphed Facial Expression Task • Larger doses: Increased desire to be with others ($p < 0.05$) on Social Choice Task	• Behavioral measures not obtained at optimal times to detect oxytocin effect • placebo and oxytocin nasal spray formulations differed slightly, different sensations may have influenced subject expectations • All participants had prior MDMA experience • Drug dose
Wardle and De Wit (2014)	MDMA	Double-blind, counterbalanced placebo-controlled, within-subject	36; non-clinical sample	• Increased scores for loving on Visual Analog Scale ($p = 0.004$) • Slowed perception of angry expressions ($p = 0.03$) • Increased psychophysiological responses to happy expressions: Decreased corrugator activity to happy faces ($p = 0.04$), increased zygomatic responses to happy expressions ($p = 0.02$) • Increased ratings of empathy ($p = 0.05$) • Increased desire to take the drug again ($p < 0.001$) • Drug effects were not strongly related to desire to take the drug again	• Small and homogeneous sample • Limited generalizabilty because DSM-IV disorders and heavy drug use were screened out • All participants evidenced previous use of MDMA • Some effects of the substance may not be detectable in the study setting • Measure of abuse potential was a single self-report item
Wardle et al. (2014)	MDMA	Double-blind, placebo-controlled	101; non-clinical sample	• Increased positive ratings of positive social pictures ($p = 0.02$) • Reduced positive ratings of non-social positive pictures ($p = 0.009$)	• Relative homogeneous sample • DSM-IV disorders and heavy drug use were screened out • Artificial nature of stimuli • All participants had prior experience with MDMA • There may have been an expectancy effect
Hysek et al. (2012)	MDMA	Double-blind, placebo-controlled, within-subjects	48; non-clinical sample	• Reading the Mind in the Eyes Test: Enhanced the accuracy of mental state decoding for positive stimuli ($p < 0.05$), impaired mind reading for negative stimuli ($p < 0.01$), and no effect on mind reading for neutral stimuli • Increased subjective prosocial effects, including feelings of being more open, talkative, and closer to others (all $p < 0.001$)	−
Bedi et al. (2010)	MDMA	Within-subjects, double-blind, randomized, placebo-controlled	21; non-clinical sample	• Increased ratings of feeling "loving" ($p = 0.004$; $\eta^2 = 0.21$) and "friendly" ($p = 0.001$; $\eta^2 = 0.26$) • Increased loneliness ($p = 0.008$) • Increased playfulness ($p = 0.001$; $\eta^2 = 0.31$) • Decreased accuracy of facial fear recognition ($p = 0.008$; $\eta^2 = 0.18$)	• All participants had prior experience with ecstasy or MDMA • Behavioral tasks used might not be sensitive to all unusual social effects attributed to MDMA • Difficult to determine the specificity of findings to social stimuli • Dose was adjusted to the body weight for MDMA but not for METH
Bedi et al. (2009)	MDMA	Double-blind, placebo-comparison	9; non-clinical sample	• Increased self-reported sociability ($\eta^2 = 0.28$) • Attenuated left amygdala response to angry facial expressions ($p = 0.052$) • Amygdala response to fearful facial expressions not affected • Enhanced ventral striatum response to happy expressions ($p < 0.005$)	• Small sample size • All participants had prior ecstasy exposure • Short periods between sessions • No blood plasma measurements were obtained

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Table 1 (*continued*)

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Dumont et al. (2009)	MDMA	Double-blind, randomized, crossover, placebo-controlled	15; non-clinical sample	• Increase in subjective prosocial feeling, i.e., subjective amicability ($p = 0.002$) and subjective gregariousness ($p = 0.018$) • Prosocial feeling i.e., subjective amicability ($p = 0.001$) and subjective gregariousness ($p = 0.049$) were correlated with variation in oxytocin levels	• Oxytocin concentrations were measured in blood not cerebral spinal fluid oxytocin concentrations • Subjective not objective prosocial effects • MDMA was administered as a fixed dose and not according to body weight to reduce variance in oxytocin concentrations • Current design cannot determine whether oxytocin really mediated MDMA's prosocial effects
Pokorny et al. (2017)	Psilocybin	Double-blind, randomized, placebo-controlled, within-subject	24; non-clinical sample	• Increased scale scores for all subscales of the Altered States of Consciousness Rating Scale except anxiety (all $p < 0.001$, except spiritual experience $p < 0.05$) • Increased positive affect ratings ($p < 0.05$) • Increased explicit ($p < 0.01$) and implicit ($p < 0.05$) emotional empathy • No increase in cognitive empathy • Increase in implicit emotional empathy was significantly linked to changed meaning of percepts induced by psilocybin ($p < 0.01$)	–
Preller et al. (2016)	Psilocybin	Double-blind, randomized, counter-balanced, cross-over	21; non-clinical sample	• Increased ratings on all Altered States of Consciousness Rating Scale scales ($p < 0.05$) • Participants reported a reduced feeling of social exclusion ($p < 0.01$), the neural response to social exclusion was decreased in the dorsal anterior cingulate cortex (dACC) ($p < 0.05$) and the middle frontal gyrus ($p < 0.05$) • Reduced neural response in the dACC was significantly correlated with Psilocybin-induced changes in social exclusion processing ($r = 0.53$, $p < 0.02$) and decreased aspartate (Asp) content ($r = -0.56$, $p < 0.02$)	• Results of pharmacological MRI studies may be susceptible to drug effects on cerebral vasoactivity • Reduction of BOLD signal in the dACC reported in the current study might relate to a general reduction of neuronal activity due to psilocybin • There are conflicting results between PET and fMRI regarding resting state activity in the ACC after psilocybin use
Ross et al. (2016)	Psilocybin	Double-blind, placebo-controlled, crossover	29; clinical-sample	• Sustained benefits in spiritual significance ($p < 0.01$) and Well-Being/Life-Satisfaction ($p < 0.001$), as well as improved attitudes towards death ($p < 0.05$). • Mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression	• Relatively small sample size • Non-nationally representative cancer patient population • Crossover design limited the interpretation of clinical benefits
Garcia-Romeu et al. (2014)	Psilocybin	Within-subject comparison	15; non-clinical sample	• 80% of participants evidenced biologically verified smoking abstinence at 6-month follow-up • 40% reported challenging psilocybin experiences	• Small and homogeneous sample • Aspects beside mystical experiences were not measured but could have potentially influenced the results
Kraehenmann et al. (2015)	Psilocybin	Double-blind, randomized, counterbalance cross-over	25; non-clinical sample	• Increase in positive mood ($p = 0.001$) • Decreased right amygdala activation to neutral ($p < 0.001$) and negative ($p = 0.001$) stimuli • Attenuation of right amygdala reactivity to negative stimuli was associated with increase in positive mood state	–
Schmidt et al. (2013)	Psilocybin	Double-blind, within-subject, placebo-controlled	42; non-clinical sample	• Impaired the encoding of fearful faces as expressed by a reduced N170 over parieto-occipital brain regions ($p < 0.001$) • No effect on the N170 in response to happy faces	–
Kometer et al. (2012)	Psilocybin	Double-blind, randomized, placebo-controlled	17; non-clinical sample	• Increased mood ($p < 0.001$; $\eta^2 = 0.509$) • Attenuated recognition of facial expressions dependent on the valence ($p < 0.05$; $\eta^2 = .254$) • Increase in goal directed behavior toward positive relative to negative cues ($p < 0.05$) • Facilitation of positive sequential emotional effects ($p < 0.01$; $\eta^2 = .135$)	–
Griffiths et al. (2011)	Psilocybin	Double-blind, quasi-random, placebo-controlled	18; non-clinical sample	• 39% experienced extreme anxiety and fear • 72% had a mystical experience • 61% of volunteers considered the psilocybin experience the single most spiritually significant experience of their lives, 83% rated it in their top five. • 94% and 89% of volunteers, respectively, indicated that the experiences increased their well-being or life satisfaction and positively changed their behavior at least moderately	• Generalizability of the findings is limited by the study population • Most of the participants reported weekly participation in religious or spiritual activities before the study

Grob et al. (2011)	Psilocybin	Within-subject, double-blind, placebo-controlled	12; clinical sample	•Significant reduction of anxiety 1 ($p = 0.001$) and 3 ($p = 0.03$) months following treatment on the State-Trait Anxiety Inventory • Significant improvement of mood on the Beck Depression Inventory after 6 months ($p = 0.03$) • Increased measures of feeling of oceanic boundlessness ($p < 0.001$), anxious ego dissolution ($p = 0.049$), and auditory alterations ($p = 0.03$) on the 5-Dimension Altered States of Consciousness Profile	• Blinding did not work • No independent control group • Variability in extent of contact with participants after treatment
MacLean et al. (2011)	Psilocybin	Within-subject, placebo-comparison, quasi-randomized	52; non-clinical sample	• Increases in Openness following a high-dose psilocybin session ($p = 0.023$, $\eta^2 = 0.10$) • Follow-up tests evidenced that only those who had a mystical experience evidenced increased in Openness ($p = 0.002$) • No significant changes in Neuroticism, Extraversion, Agreeableness, and Conscientiousness • Participants who had mystical experiences during their session, increases in openness remained in a one-year follow-up ($p = 0.05$, $\eta^2 = 0.13$)	–
Griffiths et al. (2008)	Psilocybin	Follow-up	36; non-clinical sample	• 58% and 67%, respectively, of volunteers rated the psilocybin-occasioned experience as being among the five most personally meaningful and among the five most spiritually significant experiences of their lives • 64% indicated that the experience increased well-being or life satisfaction • Measures of personality, affect, quality of life and spirituality assessed across the study showed no difference from screening except for one scale measuring mystical experiences	• Generalizability of the findings is limited by the study population • All of the participants reported at least intermittent participation in religious or spiritual activities before the study
Griffiths et al. (2006)	Psilocybin	Double-blind, counterbalanced comparison	36; non-clinical sample	• Increased Anxiety or fearfulness ($p < 0.01$), Joy/intense happiness ($p < 0.001$), Peace/harmony ($p < 0.001$) • Increases in all subscales of the Mysticism Scale and the States of Consciousness questionnaire by $p < 0.001$ • Increases of positive attitudes about life and/or self and/or self ($p < 0.001$), positive mood changes ($p < 0.001$), altruistic/positive social effects ($p < 0.001$), and positive behavior changes ($p < 0.001$) on the Persisting Effects Questionnaire	• The extent to which the study population limits the generalizability of the results is unknown
Carbonaro et al. (2016)	Psilocybin mushrooms	Online self-report survey	1993; non-clinical sample	• 76% reported increased well-being and life satisfaction • 8% reported decreased well-being and life satisfaction • 84% reported to have benefitted from the challenging portions of the session • 46% would repeat the session • Degree of difficulty of the experience correlated positively with degree of personal meaning ($r = 0.41$, $p < 0.001$), spiritual significance ($r = 0.20$, $p < 0.001$), and enduring well-being ($r = 0.11$, $p < 0.001$) • Personal meaningfulness correlated positively with spiritual significance ($r = 0.58$, $p < 0.001$) and enduring well-being ($r = 0.39$, $p < 0.001$) • Spiritual significance correlated positively with enduring well-being ($r = 0.46$, $p < 0.001$)	• High rate of non-completion • Difficulty in assessing truthfulness of responses • Non-diverse population • Prevalence of challenging experience cannot be derived from the results • Sample was likely biased towards positive attitudes about psychedelics (convenience sample)
Forstmann & Sagioglou (2017)	Classic psychedelics	Online self-report questionnaire	1487; non-clinical sample	• Increased self-reported engagement in pro-environmental behavior ($p < 0.001$) mediated by people's degree of self-identification with nature ($p < 0.001$)	• No causal, only correlational evidence • Measurements of pro-environmental behavior are based on self-reports
Johnson et al. (2017)	Classic psychedelics	Anonymous, cross-sectional, online self-report survey	358; non-clinical sample	• 38% reported continuous smoking cessation after psychedelic use, among them, 74% reported >2 years' abstinence • 28% reported a persisting reduction in smoking, among them, 62% reported >2 years of reduced smoking • 34% reported temporary smoking reduction and eventual relapse and rated their experience as lower in personal meaning ($p = 0.03$) and spiritual significance ($p = 0.004$) • All participants reported less significant withdrawal symptoms • Changes in life priorities/values were the most important psychological factor related to smoking cessation/reduction	• Convenience sample data cannot be verified • Data are retrospective and thus subject to recall bias • Identity and dosage of psychedelics used cannot be confirmed
Sweat et al. (2016)	Classic psychedelics	Correlational	68; non-clinical sample	• Those reporting classic psychedelic use with mystical experience evidenced faster times on the functional fixedness task ($p = 0.02$, $d = -.87$) and greater lifetime mystical experience ($p = 0.01$, $d = .93$)	• No causal, only correlational evidence • Small sample size • Sample consistent only of students • No inferences about the durability of the proposed effect can be made

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Table 1 (*continued*)

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
					• No recency of use was assessed • Results are limited to functional fixedness as a proxy for creativity, i.e., one facet of the construct • Possible that greater specificity in the measurement of mystical experience may have yielded different results
Nour et al. (2017)	Psychedelics	Self-report online questionnaire	893; non-clinical sample	• Lifetime psychedelic use positively predicted liberal political views ($p = 0.001$), openness ($p < 0.001$), and nature relatedness ($p < 0.001$) • Lifetime psychedelic use negatively predicted authoritarian political views ($p = 0.002$) • Experienced ego dissolution positively predicted liberal political views ($p < 0.001$), openness ($p < 0.001$), and nature relatedness ($p < 0.001$) • Experienced ego dissolution negatively predicted authoritarian political views ($p = 0.005$)	• Cross-sectional study: No causal, only correlational evidence • Homogeneous sample, limited generalizability
Lerner and Lyvers (2006)	Psychedelics	Cross-cultural comparison, self-report questionnaire	183; non-clinical sample	• Increased scores on mystical believes ($p < 0.001$), life values of spirituality ($p < 0.001$), empathy ($p < 0.001$), and concern for others ($p = 0.001$), concern for environment ($p = 0.001$), and creativity ($p = 0.03$) • Decreased scores on financial prosperity ($p = 0.001$)	• No causal, only correlational evidence

shown to be most distinct upon presentation of positive emotions compared to negative emotions ($p = 0.001$, partial $\eta 2 = 0.09$) (Kuypers et al., 2017). Bedi, Hyman and De Wit (2010) measured correlates of prosocial reactions under the influence of MDMA. Subjective changes were assessed through self-report ratings of affective states and tasks in which participants identified emotions from images of faces, pictures of eyes, and vocal cues. The higher dose of MDMA (1,5 mg/kg) increased ratings of "loving" ($p = 0.004$, $\eta^2 = 0.21$) and "friendly" ($p = 0.001$, $\eta^2 = 0.26$), whereas the lower dose of MDMA (0.75 mg/kg) increased "loneliness" ($p = 0.008$). In another study (Bedi et al., 2009), a higher dose of MDMA (1.5 mg/kg) increased self-reported sociability ($\eta^2 = 0.28$) compared to lower dose MDMA (0.75 mg/kg) and placebo. Higher dose MDMA (1.5 mg/kg) attenuated left amygdala response to angry facial expressions ($p = 0.052$), but MDMA did not affect amygdala reactivity to fearful expressions. Lower dose MDMA (0.75 mg/kg) enhanced ventral striatum response to happy expressions relative to placebo ($p < 0.005$). Clark et al. (2015) linked MDMA's prosocial effects to measures of sympathetic activity while Dumont et al. (2009) found that prosocial feelings, i.e. subjective amicability ($p = 0.001$) and subjective gregariousness ($p = 0.049$), were correlated with variation in oxytocin levels. Participants in a study by Hysek et al. (2012) showed enhanced accuracy in decoding positive stimuli ($p < 0.05$) but decreased ability to decode negative stimuli ($p < 0.01$) on the Reading the Mind in the Eye Test. Similar effects were reported by Kirkpatrick et al. (2014). Wardle and de Wit (2014) hypothesized MDMA to induce 'socially selective' effects which then influence prosocial behavior through increases in the ability to judge and compare closeness with others and social contact. In addition, under the acute influence of MDMA self-reported mood and self-esteem may be influenced to a lesser degree by social rejection (Frye et al., 2014). Baggott et al. (2016) found evidence that positive effects of MDMA on self-evaluation might be due to the perception of increased authenticity which in turn potentially facilitates emotional and autobiographic disclosure. In summary, a number of pro-social feelings and behaviors might be fostered under the acute influence of MDMA (Frye et al., 2014).

3.2. Acute personal change

3.2.1. Lysergic acid diethylamide (LSD)

Kaelen et al. (2015) found LSD to significantly enhance participants' emotional response to music compared to placebo ($p = 0.006$). Schmid et al. (2015) showed LSD to produce acute increases in subjective well-being ($p < 0.05$), happiness ($p < 0.001$), openness ($p < 0.001$), and trust ($p < 0.001$). Tagliazucchi et al. (2016) used fMRI to depict heightened global connectivity within the brain, particularly in the thalamus and high-level association cortices of participants under the influence of LSD. These increases in global connectivity were found to correlate with subjective reports of 'ego dissolution' which is conceptually related to positive psychology constructs like "flow" and "spirituality".

3.2.2. Ayahuasca and DMT

The Amazonian plant tea ayahuasca (Labate and Jungaberle, 2011) was described to acutely decrease inner reactivity ($p = 0.034$) and judgmental processing ($p = 0.01$) in a non-controlled study, which are considered classical goals and beneficial effects associated with mindfulness practice (Soler et al., 2016). Conversely, ayahuasca increased cognitive flexibility, i.e. creative divergent thinking, in a quasi-experimental design ($p = 0.023$; Kuypers et al., 2016). Sampedro et al. (2017) reported increases on certain subscales (nonjudging and nonreacting) of the Five Facets Mindfulness Questionnaire (FFMQ) 24 h after ayahuasca administration. Magnetic resonance spectroscopy (MRS) illustrated

Table 2
Preliminary, exploratory studies and reviews.

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Dominguez-Clavé et al. (2016)	Ayahuasca	Narrative-review	–	• Similarities with mindfulness-based therapy • Increased mindfulness facets related to (self-)acceptance and the ability to take a detached view of one's own thoughts and emotions (decentering) • Neuroimaging studies after an Ayahuasca intake have reported activation in areas associated with emotional processing and memory formation • Promising therapeutic tool by enhancing self-acceptance and allowing safe exposure to emotional events	–
Gasser et al. (2015)	LSD	12-months follow-up, qualitative interview	10; clinical sample	• Reported insightful, cathartic and interpersonal experiences, accompanied by a decrease in anxiety (77.8%) and an increase in quality of life (66.7%)	• See Gasser et al. (2015) • Small sample size • No control-group for follow up
Chunko (1973)	LSD	Self-report questionnaire	2500; non-clinical sample	• 96.3% of all LSD, etc. users have had, what is termed, a bad trip, at one time or another • 93.4% of all LSD, etc. users generally enjoyed the experience • 97.3% of current LSD, etc. users felt that the experience had influenced their outlook on life, 89.2% of this group saw LSD, etc. usage as the only means of attaining this outlook on life • 50.3% found that the use of LSD, etc. caused a predominately religious or mystical experience	• Limited statistical specifications
Turek et al. (1974)	MDA	Exploratory study	10; non-clinical sample	• Psychedelic experience questionnaire: Experience of unity (54%), sacredness (57%), objectivity and reality (57%), transcendence of time and space (46%), positive mood (60%), ineffability (62%) • Modified Linton-Langs Questionnaire: Meaning change (45%), somatic change (32%), disturbed time sense (29%), affect change (25%), alteration of thinking (15%), loss of control (14%), body image change (14%), and perceptual change (5%)	• Limited sample size • No p-values or effect sizes
McDaniel (2017)	MDMA	Qualitative Review	–	• Increased patience, helpfulness, understanding, spirituality, response to immorality • Greater meaning • New life goals	–
Bershad et al. (2016)	MDMA	Narrative review	–	• Appraisal of social stimuli and (naturalistic) social interactions • Shared and distinctive effects on social processing and social behavior • Increased self-reported feelings of trust and generosity, responses to social and emotionally stimuli, empathy, social and emotional themes in spontaneous speech	–
Kamilar-Britt and Bedi (2015)	MDMA	Systematic review	49 Studies	• Increased feelings of social affiliation and social approach • Decreased identification of negative facial expressions (cognitive empathy) • Blunted responses to social rejection • Enhanced responses to others' positive emotions (emotional empathy)	–
Harman et al. (1966)	Mescaline	Exploratory study	27: non-clinical sample	• Lowering of defenses, reduction of inhibitions and anxiety • Ability to see the problem in the broadest terms • Enhanced fluency of ideation • Heightened capacity for visual imagery and fantasy • Increased ability to concentrate • Empathy with external processes and objects heightened • Empathy with other people heightened • Data from “unconscious” more accessible • Enhanced sense of “knowing” when the right solution appears	• Limited statistical specifications

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Table 2 (*continued*)

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Hasler et al. (2004)	Psilocybin	Within-subject	8; non clinical sample	• Psilocybin dose dependently increased scores of all Altered States of Consciousness Rating Scale core dimensions. • One participant reacted with transient anxiety • 50% reduction of performance in the Frankfurt Attention Inventory • Increase in "general inactivation", "emotional excitability", and "dreaminess" were the only domains of the Adjective Mood Rating Scale	• Low number of participants
Pahnke (1966)	Psilocybin	Exploratory study	20; non-clinical sample	• Experience of transcendence, external and internal unity, sacredness, and paradoxicality • Persisting positive attitude and behavior changes	• See Doblin (1991)
Carhart-Harris et al. (2014)	Psychedelics	Narrative review	–	• Distinction can be made between two different modes of cognition: Primary and secondary consciousness	• Insufficient consideration of the phenomenological content of the relevant altered states of consciousness
Vollenweider and Kometer (2010)	Psychedelics	Narrative review	–	• Transcendent peak (mystical-type) experience (key role in the therapeutic outcome) and which was rated as among the most personally meaningful experiences, occurs in most cases only in supportive settings and after high-dose administration of psychedelics • Drugs that increase neuroplasticity, could be particularly efficient in combination with psychotherapeutic interventions	–
Sessa (2008)	Psychedelics	Narrative review	–	• Enhancement of creativity is an area that may have potential benefits for furthering the understanding of neuroscience	–
Walsh (1982)	Psychedelics	Qualitative review	5; non-clinical sample	• Significant number of people feel that may have positive effects on their personal psychological growth • Opening to new realms of experience and belief • Deeper understanding of psychology, religions, spirituality • Important insights	• Qualitative experience reports
Riedlinger & Riedlinger (1994)	Psychedelics & Entactogens	Narrative review	–	–	–
Letheby (2015)	–	Narrative review	–	• Psychedelic transformation seems to be transparent and meaning-involving	–
Doblin (1991)	–	Long-term follow-up, Self-report questionnaire	16; non-clinical sample	• Persisting positive changes	• Only the psilocybin but not the control participants participated in this study

Table 3
Negative effects in the selected literature.

Reference	Substance(s)	Study design	Sample size, *n*	Outcome	Limitations
Hittner and Schachne (2012)	Ecstasy	Meta-analysis	17 studies	• Association between ecstasy use and risky sexual behavior evidences a small to moderate sized effect (mean weighted $r = 0.211$, $p < 0.05$) • Mean effect size for the early (1986–2000, n = 5, mean weighted $r = 0.292$), middle (2001–2006, n = 7, mean weighted $r = 0.263$) and later (2008–2011, n = 5, mean weighted $r = 0.082$) studies indicated a decreasing trend ($p < 0.001$)	• The random-effects approach is restricted to analyzing the data at hand • Extent to which the magnitude of effect accurately characterizes individuals in the population is an empirical question
Wunderli et al. (2017)	MDMA	Cross-sectional, between-group comparison	107; non-clinical sample	• Considerably lower mean hair concentrations of stimulants, opioids, and hallucinogens were detected in primary compared to polydrug users • Group differences between controls and polydrug MDMA users on measures of attention ($p = 0.003$, $d = 0.7$), working memory ($p < 0.001$, $d = 0.96$), declarative memory ($p < 0.001$, $d = 1.21$), and executive functions ($p < 0.001$, $d = 0.86$) • Group differences between controls and primary MDMA users only in working memory ($p = 0.034$, $d = 0.52$) and declarative memory ($p = 0.004$, $d = 0.9$) performance	• Self-reports measures were used for alcohol, nicotine, and cannabis consumption • Possible that cognitive differences are based on preexisting differences and that predispositions are responsible for drug use and cognitive impairments
Parrott (2014)	MDMA	Narrative review	–	• Increased cortisol release may enhance stress response in individuals • Regular usage can also lead to serotonergic neurotoxicity and memory problems, changes in sleep, reduced immunocompetence, depression and other forms of psychiatric distress, occupational problems, neurohormonal changes, reduced happiness and greater everyday stress • Immediate effects include a wide range of mood changes, emotional excitation and sensitivity, apprehensiveness anxiety, and fear-of-loss of thought control • Post MDMA-effects include feelings of anhedonia, lethargy, anger, depression, anxiety, insomnia, greater susceptibility to pain, and appetite reductions	–
Wagner et al. (2015)	MDMA	Between-group comparison	96; non-clinical	• Attention and information processing speed: Interaction effect of age of first use and cumulative lifetime dose ($p = 0.045$), interaction effects on the corresponding between-subjects effects were found for the first part of the trail-making test ($p = 0.026$, $\eta^2 = 0.056$) and the digit symbol test ($p = 0.022$, $\eta^2 = 0.059$) • Early onset of use is connected to a larger discrepancy between higher and lower cumulative lifetime dose of scores reached on the digit symbol test, than a later start of consumption • Main effect of age of first use ($p = 0.011$) on episodic memory on the Lern- und Gedächtnistest • Test of between-subject effects delivered significant results for the recognition performance of the Auditiv-Verbaler Lerntest ($p = 0.001$, $\eta^2 = .114$).	• Sample size was small (due to authors) • Frequency of use or average use were not reported • No control group was used • participants were aware of the fact that this study addressed MDMA use • No causal, only correlational
Bosch et al. (2013)	MDMA	Between-groups	38; non clinical sample	• Impairment immediate ($p = 0.042$, Cohen's $d = 0.66$) and delayed recall ($p < 0.001$, Cohen's $d = 1.13$), learning performance ($p = 0.001$, Cohen's $d = 1.04$), and recall consistency ($p = 0.001$, Cohen's $d = 1.05$) on Rey Auditory Verbal Learning Test • Decreased regional cerebral brain glucose metabolism (rMRGlu) in the right and left dorsolateral prefrontal cortex (DLPFC; both $p = 0.001$) and inferior parietal cortex ($p < 0.001$), bilateral thalamus (both $p = 0.001$), right hippocampus ($p = 0.001$), right precuneus ($p < 0.001$), right cerebellum ($p < 0.001$), and pons ($p = 0.001$) • Learning and recall were positively correlated with rMRGlu predominantly in bilateral frontal and parietal brain regions • Recognition was additionally related to rMRGlu in the right mediotemporal and bihemispheric lateral temporal cortex • Cumulative lifetime dose of MDMA was negatively correlated with rMRGlu in the left dorsolateral and bilateral orbital and medial PFC, left inferior parietal and right lateral temporal cortex	• Drug consumption was inferred from subjective reports • High prevalence of polydrug use in study population • Tobacco use was significantly higher in MDMA users • Abstinence duration from different drugs was highly variable • Very high consumption (2 tablets per week on average)
Moreno-López et al. (2012)	MDMA	Correlational	49; non-clinical sample	• No correlations between the amount of MDMA use and brain metabolism measures • Negative correlations between the duration of MDMA use and brain metabolism in the left postcentral and inferior parietal gyrus, the right inferior frontal gyrus (pars triangularis) extending to the dorsolateral prefrontal cortex; the right superior temporal pole extending to the middle part of this region (all $p < 0.001$)	• Participants were all polydrug users of: Cocaine, heroin, alcohol, MDMA, and Cannabis • Not controlled for the use of nicotine • No causal, only correlational evidence • Findings could be due to premorbid brain alterations or the results of the interaction between the premorbid alterations and the neurotoxic effects of drug use

decreases in glutamate and glutamine which correlated with increases in the nonjudging subscale of the FFMQ ($r = -0.589$, $p = 0.044$). Two month later, results still pointed to a tendency towards elevations in nonjudging.

3.2.3. Methylenedioxymethamphetamine (MDMA)

MDMA was found to increase self-reported ratings of self-compassion and to decrease self-criticism (Kamboj et al., 2015).

3.3. Persistent social change

We included results that were sustainable for at least two weeks with a range up to several years. We pooled psychometric variables of prosocial personal attitudes into this category, too, since they are highly predictive of prosocial behaviors (e.g. openness).

3.3.1. Classical psychedelics

Forstmann and Sagioglou (2017) conducted a general population online study with 1487 participants that demonstrated self-reported engagement in pro-environmental behaviors that were predicted by respondents' past experiences with classical psychedelics ($p < 0.001$). Their degree of self-identification with nature statistically accounted for the relationship ($p < 0.001$). The authors hypothesized that incorporation of nature into one's self-construal (possibly facilitated by psychedelics) may account for the effects on pro-environmental behavior. Yet the causality of this relationship must be further investigated. Furthermore, Schmid and Liechti (2017) outline that LSD experience produced long lasting subjective effects of prosocial and altruistic behaviors in participants ($p < 0.001$). In a 14-month follow-up to their 2006 study, Griffiths et al. (2008) reported significant increases in self-ratings of long-lasting positive social effects and behaviors following psilocybin administration in hallucinogen-naïve adults.

3.3.2. Methylenedioxymethamphetamine (MDMA)

Wagner et al. (2017) conducted a two-year follow-up study to a phase two trial on MDMA-assisted psychotherapy for treatment resistant PTSD. Results indicated long-term increases in openness ($p = 0.032$) and persistent decreases in neuroticism ($p = 0.003$) on the NEO-PI-R Personality Inventory on the personal effect side.

3.4. Persistent personal change

3.4.1. Classical psychedelics

Lerner and Lyvers (2006) assessed the values, beliefs, and emotional empathy of users of psychedelics. Compared to users of non-psychedelic drugs and non-illicit drug-using social drinkers, psychedelic users exhibited increased values of spirituality ($p < 0.001$) and “mystical beliefs” ($p < 0.001$) as well as concern for others ($p = 0.001$), while displaying less appreciation of financial prosperity ($p = 0.001$). However, due to study limitations these findings may be due to personality characteristics preceding the use of psychedelics. In addition, Sweat et al. (2016) found lifetime users of classical psychedelics to exhibit greater creativity than non-users ($p = 0.02$, $d = -0.87$). Nour et al. (2017) found lifetime use of psychedelics to positively predict liberal political views ($p = 0.001$), openness ($p < 0.001$), and nature relatedness ($p < 0.001$) and to negatively predict authoritarian political views ($p = 0.002$).

Changes in life values subsequent to psychedelic experiences, may account for continuous smoking cessation and reduction and were clinically associated with less severe affective withdrawal symptoms (Johnson et al., 2017). This is further reinforced by an open-label pilot-study by Garcia-Romeu et al. (2014) using psilocybin in the treatment of smoking addiction. Measures of mystical experiences and participants' ratings of spiritual significance and personal meaning of the psilocybin sessions was significantly related to smoking cessation.In two double-blind controlled studies of psilocybin MacLean et al. (2011) found a significant enhancement of the big-five trait openness (measured with the NEO inventory) in participants subsequent to a high-dose session with psilocybin ($p = 0.023$, $\eta^2 = 0.10$). In a one-year follow-up, measures of openness continued to be above baseline in those who had reported a significant mystical experience during the psilocybin session ($p = 0.05$, $\eta^2 = 0.13$). This may imply that mystical experience mediated by psilocybin potentially facilitate sustainable adult personality change. In a methodologically improved version of Pahnke (1966) with a non-theologian clientele Griffiths et al. (2006) demonstrated, that psilocybin lead to increases in self-rated measures of mystical experiences ($p < 0.001$). Additionally, a 14-month-follow-up study was conducted evaluating participants' psilocybin experiences to be important in terms of personal meaning and to constitute one of the five most spiritually significant events of their lives (Griffiths et al., 2008, 2011). Similar findings are reported in a study by Ross et al. (2016). Expanded states of consciousness are known to sometimes entail acute distress such as anxiety during the acute drug effects. Nevertheless, in an online survey Carbonaro et al. (2016) found 84% of the participants to endorse having benefited from their most challenging experience with psilocybin mushrooms.

3.4.2. Lysergic acid diethylamide (LSD)

Lebedev et al. (2016) used fMRI to evidence global increases in brain entropy ($p < 0.001$), regarding sensory ($p < 0.001$) and hierarchically higher networks ($p < 0.001$), subsequent to LSD administration. Such modulations – as well as experienced ego-dissolution during the LSD-state – predicted an enhancement in the personality trait openness measured two weeks after LSD administration ($p = 0.035$).

Carhart-Harris et al. (2016) examined the psychological effects of LSD administration. Improved psychological well-being was measured two weeks after the LSD experience. The authors hypothesized that heightened mood may be a secondary effect to an essential alteration in the quality of cognition. Schmid and Liechti (2017) found that LSD may result in long lasting subjective effects of improved mood ($p < 0.01$), life satisfaction ($p < 0.001$) and an overall positive view on life ($p < 0.001$). In a preliminary dose-response relationship study Lyvers and Meester (2012) concluded that LSD experiences significantly predicted scores on the Mysticism Scale ($p < 0.001$).

3.4.3. Ayahuasca and DMT

Two other psychedelics demonstrated the potential to induce psychospiritual experiences are ayahuasca (a concoction containing DMT among potentially numerous other psychoactive and emetogenic compounds) and one of its psychoactive ingredients *N,N*-Dimethyltryptamine (DMT). Both should be investigated and treated as two different substances.Cakic et al. (2010) reported an increase in “psychospiritual insights” by 75.5% for smoked DMT as well as ayahuasca in an online questionnaire study. Bouso et al. (2012) compared measures of neuropsychological performance, life attitudes, personality and psychopathology of regular users of ayahuasca from several Brazilian ayahuasca churches and controls actively participating in non-ayahuasca religions. Compared to non-users, regular users of ayahuasca exhibited increased ratings of self-transcendence ($p < 0.001$), decreased harm avoidance ($p < 0.001$), and self-directedness ($p = 0.002$), lower psychopathology scores on the Symptom Checklist-90-R (SCL-90-R; $p = 0.009$), superior performance on the Frontal System Behavior Scale, the Letter-Number Sequencing task (from the WAIS-III), as

well as the Stroop test and the Wisconsin Card Sorting Test. In addition, they demonstrated higher scores on the Purpose of Life Test ($p < 0.001$), the Psychological Well-Being test ($p < 0.001$) and the Spiritual Orientation Inventory ($p < 0.001$). These differences remained significant at a one-year follow-up. Similarly, Barbosa et al. (2016, 2009) found a reduction of the intensity of minor psychiatric symptoms ($p = 0.005$) on the Clinical Interview Schedule, improved mental health ($p = 0.027$) on the Short Form-36 Health Survey Questionnaire, and decreased levels of depression ($p = 0.043$) and confusion ($p = 0.032$) in members of ayahuasca churches. Using fMRI Bouso et al. (2015) found reduced cortical thickness in the posterior cingulate cortex (PCC) in participants who regularly used ayahuasca. Findings suggest a negative correlation between PCC cortical thickness, one of the key nodes of the Default Mode Network (DMN), and measures of spirituality (transpersonal feelings) and self-transcendence ($r = -0.479$; $p = 0.024$). This is in line with the finding of Carhart-Harris et al. (2014), who found reduced activity of the PCC being linked to acute experiences of ego dissolution. Although these findings are merely correlational, they suggest that psychedelics may have the potential to induce brain structure modifications which are associated with persistent personal changes.

Frecska et al. (2012) found participants' visual creativity to be enhanced after the repeated ingestion of ayahuasca in a ritual setting ($p < 0.05$). The number of original solutions and phosphenic responses to the visual components of the Torrance Test of Creative Thinking was significantly increased ($p < 0.05$) after the end of a two-week long ceremony series – which is usually interpreted as associated with creative problem solving. Nevertheless, participants in the ceremonies already displayed more phosphenic solutions at baseline, possibly due to exhibiting more life-time psychedelic experiences than controls or personality traits making them more inclined for psychedelic experiences.

4. Discussion

Positive psychology is a domain of scientific inquiry that emerged in the late 1990ties but has numerous antecessors in the history of science and philosophy (Compton and Hoffman, 2012). It highlights the importance of well-being, happiness and eudaemonia that support healthy human functioning. It is related to resilience research and salutogenesis (Kröninger-Jungaberle and Grevenstein, 2013). Interestingly, there are numerous anecdotal claims and preliminary scientific data about sustainable positive effects of psychedelics on aspects of healthy human functioning (Elsey, 2017). Such claims motivate recreational and ceremonial uses of these substances, however, more empirical research is needed to further investigate possible beneficial effects and individual risk factors associated with the widespread use of these substances. To guide future research hypotheses, we critically reviewed studies using constructs from positive psychology related to psychedelics and entactogens.

5. Study selection

Our analysis included 77 studies with a search string focused on concepts related to positive psychology (e.g. well-being, introspection, prosocial behavior, empathy, mindfulness, self-transcendence, creativity and personality factors like openness). We found 3 treatment/follow-up of treatment studies (n = 38), 54 neurophysiological/neuropsychological or psychological studies (n = 2149), 7 epidemiological studies (n = 7689), 11 reviews and 2 pooled-/meta-analyses (Tables 1–3). Two of the selected studies were conducted in the 1960ties, 2 studies in the 1970ties, 1 study in the 1980ties, 2 studies in the 1990ties, 8 studies in the 2000s and 62 studies since 2010.

6. Summary of results

6.1. Beneficial effects on emotional processing and prosocial attitudes

Acute changes in mood and psychological well-being have been reported as an effect of the administration of classical psychedelics like psilocybin (Grob et al., 2011) including altered neural responses to negative or fearful stimuli (Kometer et al., 2012; Kraehenmann et al., 2015; Schmidt et al., 2013; Vollenweider and Kometer, 2010). Reduction of fronto-limbic neural reactivity and altered emotional processing of aversive or negative valenced stimuli was also found after LSD administration (Dolder et al., 2016; Mueller et al., 2017). Conversely, MDMA increased ventral striatal reactivity to positive valenced stimuli (Bedi et al., 2009, 2010). This is in line with the notion, that under the acute influence of MDMA self-reported mood and self-esteem may be influenced to a lesser degree by social rejection (Frye et al., 2014). Neural markers of increased brain entropy as well as the experience of ego-dissolution under the influence of LSD were specifically predictive of enhancements in the personality trait openness two weeks after LSD administration (Lebedev et al., 2016). Similarly, long-term increases in openness were reported in a 2-year-follow up after a clinical MDMA trial (Wagner et al., 2017) as well as following a high-dose psilocybin session that was persistent for participants who had reported a significant mystical experience during the session (MacLean et al., 2011). For LSD, improved psychological well-being and long lasting subjective effects of improved mood, life satisfaction and an overall positive view on life have been described (Carhart-Harris et al., 2016; Schmid and Liechti, 2017), similar findings including lower psychopathology scores were reported for regular ayahuasca use in ritual contexts (Bouso et al., 2012). The later study, though, is typical of using rather selective convenient samples that were not sufficiently tested for pre-existing conditions (Dolder et al., 2016; Mueller et al., 2017; Bedi et al., 2009, 2010; Frye et al., 2014).

If the reported acute effects of LSD and MDMA may play a beneficial role in the augmentation of psychotherapeutic processes or psychospiritual practices remains to be further investigated. Concerning long-term effects on personality factors like openness future studies should investigate the role of social amplification that may play a role in sustaining these effects. Particularly MDMA was found to increase self-reported ratings of self-compassion and to decrease self-criticism in a study with recreational users (e.g. Kamboj et al., 2015). However, it remains unclear which social and psychological factors mediate and sustain or discontinue these effects under real life conditions.

6.2. Social cognition, empathy and prosocial behaviors

Acute social changes after LSD administration included enhancements in perceived closeness to others, openness, trust, desire to be with other people, prosocial behavior, as well as explicit and implicit emotional empathy (Dolder et al., 2016; Schmid et al., 2015). Notably, Schmid and Liechti (2017) outline that LSD experience produced lasting subjective effects of prosocial and altruistic behaviors that were sustained after 12 months. Pokorny et al. (2017) reported heightened implicit emotional empathy that was related to the altered meaning of percepts induced by psilocybin. MDMA was also found to enhance prosocial feelings and behaviors as well as interpersonal empathy in social interactions (Frye et al., 2014; Wardle and De Wit, 2014). Acute prosocial changes were further demonstrated in brain imaging studies depicting

heightened ventral striatum reactivity to happy facial expressions and reduced amygdala reactivity to angry faces (Bedi et al. 2009, 2010). Baggott et al. (2016) found evidence that positive effects of MDMA on self-evaluation could be due to the perception of increased authenticity. Finally, Frye et al. (2014) and Wardle and De Wit (2014) concluded that MDMA partially improves the judgement of social situations and induces socially selective effects which then improve prosocial behavior. In conclusion, converging evidence suggests that serotonergic psychedelics and entactogens increase prosocial behaviors and attitudes, which makes them suitable tools to support psychotherapeutic processes. However, it remains to be shown how sustainable these effects are in the medium or long-term interval and whether overuse may be also associated with negative effects on social functioning.

6.3. Cognitive flexibility, creativity, and problem solving

Enhanced cognitive flexibility, creativity, and imagination are generally found in psychedelic states, with long-term increases in creative problem-solving abilities and personality trait of openness (Lebedev et al., 2016; Sweat et al., 2016). Specifically, ayahuasca may have the potential to increase cognitive flexibility through divergent thinking (Kuypers et al., 2016) and enhanced visual creativity (Frecska et al., 2012). Two double blind controlled studies found a significant enhancement of imagination, creativity and aesthetic appreciation in participants after a high-dose session with psilocybin (MacLean et al., 2011). These preliminary findings motivate further systematic research into the potential of psychedelics to enhance cognitive flexibility and problem-solving capacity. Specifically, acute vs. long-term effects need to be clearly distinguished, since performance on neurocognitive tasks might be affected under the acute influence of psychedelics, while divergent and more associative styles of thinking might be facilitated through repeated exposures.

6.4. Changes in life-values and orientations

Changes in core life-values and behavioral attitudes were found in several observational studies with psychedelic users. Psychedelic users scored higher on values of spirituality as well as concern for others, while displaying less appreciation of financial prosperity, compared to users of non-psychedelic drugs and non-illicit drug-using social drinkers (Lerner and Lyvers, 2006). Conversely, classical psychedelic induced changes in life values may account for reductions in addictive behaviors (Johnson et al., 2017). Experience with classical psychedelics was further related to increased self-identification with nature and actual pro-environmental behaviors (Forstmann and Sagioglou, 2017). Finally, higher scores in spirituality and better psychosocial adaptation as reflected by some attitudinal traits such as Purpose in Life and Subjective Well-Being were found in ritual users of ayahuasca (Bouso et al., 2012). In conclusion, there is preliminary evidence that psychedelic use is associated with changes in core life values that might be associated with prosocial and pro-environmental behaviors, however more longitudinal studies are needed to further corroborate those changes over time (Forstmann and Sagioglou, 2017).

6.5. Psychospiritual experiences and mindfulness-related capabilities

Increased levels of self-transcendence (Bouso et al., 2012) and reduced cortical thickness in the posterior cingulate cortex (PCC) were found in regular ayahuasca users (Bouso et al., 2015). This suggests that PCC cortical thickness, a key node of self-referential information processing in the brain, is inversely correlated to measures of spirituality and self-transcendence. This longitudinal finding is in line with the observation that reduced activity of the PCC is linked to acute experiences of ego dissolution under the influence of psychedelics (Carhart-Harris et al., 2014). At the whole brain level, heightened global connectivity particularly in thalamo-cortical networks was found to be correlated to subjective reports of “ego dissolution” under LSD (Tagliazucchi et al. (2016), which is in line with the entropic brain hypothesis (Carhart-Harris et al., 2014). States of ego-dissolution or self-transcendence are a central characteristic of mystical-type experiences that are frequently reported in psilocybin subjects (Griffiths et al., 2006). Notably, psilocybin users mostly rate these among the five most significant spiritual experiences of their lives (Griffiths et al., 2008). Converging evidence highlights the relevance of mystical-type experience and participants' ratings of spiritual significance and personal meaning of the psilocybin sessions to mediate therapeutic outcomes in clinical studies with psychedelics (e.g. smoking cessation: Garcia-Romeu et al., 2014). In a one-year follow-up of MacLean et al.'s (2011) two double blind controlled studies, measures of openness continued to be above baseline in those who had reported a significant mystical experience during the psilocybin session. Lerner and Lyvers (2006) found psychedelic users exhibited increased values of spirituality and “mystical beliefs”. In a dose-response study Lyvers and Meester (2012) concluded that LSD experiences correlates positively with the Mysticism Scale. Notably, Mystical Experience scores correlated with changes in well-being and life satisfaction 12 months after LSD administration in another study (Schmid and Liechti, 2017). Apart from inducing acute and intense mystical-type experiences that may be perceived deeply meaningful or transformative by the participants, psychedelics were also found to increase mindfulness-related capabilities. For instance, elevated levels of mindfulness, self-compassion, and “decentering” that refers to the capacity to observe thoughts and emotions as transitory mental events without being trapped by them, was found after ayahuasca intake (Sampedro et al., 2017; Soler et al., 2016). In conclusion, the induction of transformative mystical-type experiences and mindfulness-related capabilities may both contribute to the noted increases in wellbeing and mood following exposure to psychedelics.

7. Potential roles of psychedelics in revealing brain mechanisms associated with positive personal and societal change processes

As reviewed above, psychedelics and entactogens appear to show potential for the study of bio-psycho-social mechanisms of acute and persistent personal and social change. In supportive environments, these substances promote feelings of trust, empathy, bonding, closeness, tenderness, forgiveness, acceptance, and connectedness (Belser et al., 2017; Carhart-Harris et al., 2017; Watts et al., 2017). There is an increasing number of studies exploring the neurobiological basis of prosocial feelings and their impact on psychological health and wellbeing. Hence, the use of entactogens and psychedelics may be informative to further explore quantitative changes in brain network dynamics by means of specific pharmacological interventions to identify neurocircuitries of prosocial feelings that serve personal growth and well-being. Specifically, drug-induced experiences of “ego-dissolution” and changes in self-referential processing systems show considerable promise as predictors of long-term behavioral change in terms of more adaptive emotion regulation and increased pro-social attitudes and behaviours (Griffiths et al., 2006). Recently, the concept of brain entropy was introduced to characterize the phenomenology of psychedelic states and their underlying neurodynamics (Carhart-Harris et al., 2014). Drug-induced altered states of consciousness

may thus open new avenues for the investigation of how broadband alterations in functional network connectivity and global brain plasticity drive beneficial outcomes such as increased cognitive flexibility, emotion regulation, and mindfulness-related capabilities. Hence, psychedelics and entactogens may represent a novel category of pharmacological tool compounds, that enable the safe investigation of psychological and neural mechanisms associated with neurobehavioral change processes in empirically controlled and supervised settings.

8. Harm reduction and ethical challenges

Many users from the therapeutic, recreational or ceremonial field claim (Elsey, 2017) to experience effects on "positive human functioning and flourishing" (Seligman and Csikszentmihalyi, 2000). While a risk-oriented discourse may prevail in public media (Hoffman and Slater, 2007), in clandestine discourses (e.g. on drug online forums) there seems to be a dominance of users that are biased towards positive experience or self-treatment (Soussan et al., 2018). These users often set the social norms in those drug savvy subcultures (ibid.). A critical and harm-reduction focussed voice that acknowledges potential gains, but is supporting to distinguish real benefits from illusionary gains is an asset for the prevention of problematic drug use.

Regarding future research on positive psychology we conclude that studies should not only measure and report positive psychology constructs. Both ethically and in terms of unknown side-effects it seems necessary to monitor risk perception and behaviours as well as neuropsychological abilities of users. There is also serious criticism about distortions of reality from "positive illusions": a form of high positivity is correlated with the incapability to critically self-reflect and prejudice (Wong, 2011).

Following the range of potentially positive effects associated with psychedelics or entactogens as reviewed here, an ethical debate seems appropriate that discusses the clinical admission of patients to safe and supervised psychedelic-assisted treatments. Moreover, the access of healthy people to such potential benefits of psychedelics needs to be debated.

9. Limitations

The studies reviewed above vary considerably in methodology and study designs. To further corroborate this preliminary evidence about beneficial effects of serotonergic psychedelics and empathogens on healthy human functioning, more randomized controlled studies with specific hypotheses are needed. Most reported studies used within-subject designs (Table 1), probably because it is more convenient in terms of resources. Small sample sizes and the use of convenient samples make generalization of the results difficult for many studies (e.g. Bedi et al., 2009; Cakic et al., 2010). Most of the designs are correlational and thus inadequate to allow for causal inferences. For ethical reasons, the majority of study participants had prior experience with psychedelic substances which further limits the generalization of the results. A larger number of the studies reported very specific convenient samples including rather experienced, poly-drug users from white European and American cultural backgrounds.

Most imaging studies reported here allowed for statistically sufficient control of the experimental variables. On the other hand, controlled laboratory studies render inferences about naturalistic settings difficult. We thus provided a combination of naturalistic, epidemiological, and laboratory studies, in order to collect a wide range of preliminary evidence to guide future study designs.

10. Future research on factors related to positive psychology

Based on this review we conclude that psychedelics and entactogens are 1) valuable pharmacological tools to measure psychological states or behaviors that advance the understanding of brain function and mental phenomena. 2) First clinical studies show that efficacy of psychedelics and entactogens in reducing pathological symptoms is related to measures of positive psychology, and 3) there is preliminary evidence that for a part of the population psychedelics and entactogens sustain and enhance healthy human functioning including emotional responsiveness, cognitive and social abilities and psychospiritual practices such as mindfulness. However, since observational studies suffer from selection biases, these findings cannot be applied to the general population and further longitudinal or controlled study designs need to carefully assess the benefit-risk-ratio to inform drug policy and regulations. Particularly prospective, randomized and controlled studies clarifying causal relationships between the use of those substances, genetical predispositions, personality traits and environmental factors are needed.

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