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Authors

Schmid, Yasmin
Bershad, Anya

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Altered States and Social Bonds: Effects of MDMA and Serotonergic Psychedelics on Social Behavior as a Mechanism Underlying Substance-Assisted Therapy

Yasmin Schmid,

Clinical Pharmacology and Toxicology, Department of Biomedicine and Department of Clinical Research, University Hospital Basel and University of Basel, Switzerland

Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland

Anya K. Bershad

Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, California

Abstract

There has been renewed interest in the use of 3,4-methylenedioxy-methamphetamine (MDMA) and serotonergic psychedelics in the treatment of multiple psychiatric disorders. Many of these compounds are known to produce prosocial effects, but how these effects relate to therapeutic efficacy and the extent to which prosocial effects are unique to a particular drug class is unknown. In this article, we present a narrative overview and compare evidence for the prosocial effects of MDMA and serotonergic psychedelics to elucidate shared mechanisms that may underlie the therapeutic process. We discuss 4 categories of prosocial effects: altered self-image, responses to social reward, responses to negative social input, and social neuroplasticity. While both categories of drugs alter self-perception, MDMA may do so in a way that is less related to the experience of mystical-type states than serotonergic psychedelics. In the case of social reward, evidence supports the ability of MDMA to enhance responses and suggests that serotonergic psychedelics may also do so, but more research is needed in this area. Both drug classes consistently dampen reactivity to negative social stimuli. Finally, preclinical evidence supports the ability of both drug classes to induce social neuroplasticity, promoting adaptive rewiring of neural circuits, which may be helpful in trauma processing. While both MDMA and serotonergic psychedelics produce prosocial effects, they differ in the mechanisms through which they do this. These differences affect the types of psychosocial interventions that may work best with each compound.

In recent years, there has been renewed interest in substance-assisted therapy with the entactogen 3,4-methylenedioxy-methamphetamine (MDMA) and classical serotonergic psychedelics to treat various psychiatric disorders (1–6).

Address correspondence to Anya K. Bershad, M.D., Ph.D., at abershad@ucla.edu.

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Specifically, MDMA-assisted psychotherapy has been shown to decrease social anxiety in patients with autism spectrum disorder (7) and reduce posttraumatic stress disorder (PTSD) symptoms in several randomized controlled studies (1,8). There is interest in studying the compound for other indications, including social impairments in schizophrenia (9).

There is growing evidence suggesting efficacy of classical serotonergic psychedelics, including lysergic acid diethylamide (LSD) and psilocybin, in the treatment of depression (2–4), anxiety (due to life-threatening diseases) (5,10–12), alcohol use disorder (6), body dysmorphia (13), and anorexia nervosa (14).

Despite this body of work supporting the clinical efficacy of MDMA- and psychedelic-assisted therapy, little is known about the social mechanisms that may underlie these effects. It is unclear how these compounds interact with psychotherapeutic interventions (a fundamentally social process) or which components of psychotherapy work best to ameliorate symptoms in these contexts. Furthermore, substance-assisted therapy may indirectly treat symptoms by improving social function outside therapy sessions, although these mechanisms remain largely unexplored. Both substance classes impact the reception of and response to social information. These effects have been observed across multiple domains, including impact on self-image in the context of the other (15,16), social reward processing (17–19), responses to negative social input (19–29), and social learning and neuroplasticity (30–33). We have considered these categories of social processing based on a modified version of a review on the use of psychedelics in another clinical context (34). There is accumulating evidence to suggest that social impairments in psychiatric disorders stem from 2 distinct processes, hyperreactivity to negative social stimuli and hyporeactivity to positive social stimuli (35). Accordingly, we created separate categories for these processes. We consider drug effects on one's relationship with oneself (self-image) to be a special case of drug effects on relationships with others (social effects), so we made a separate category for this. Finally, given the observed effects of psychedelics on neuroplasticity, we also wanted to specifically consider these effects in a social context, which gave rise to our final category of social learning and neuroplasticity.

Deficits in social function, including impairment in social cognition and social motivation, represent a key feature of and diagnostic criterion for many psychiatric disorders (36,37) and span the spectrum of psychiatric illness from depression to PTSD to substance use disorders (38–44). The growing field of social neuroscience has begun to shed light on the role of social dysfunction in psychiatry. It has been argued that most psychiatric disorders can be categorized as disorders of social misalignment, in which symptoms interfere with the ability to maintain social attunement with one's social environment (45), and furthermore, that interpersonalized psychiatry, or psychiatry with a focus on the relational, may be a novel and effective way to enhance mental health (46,47). Thus, it is essential to understand how MDMA and classical psychedelics modify social processing and how these effects relate to the clinical efficacy of substance-assisted (psycho)therapy.

In this article, we elaborate on and compare studies that have investigated the effects of MDMA and classical serotonergic psychedelics, focusing on LSD and psilocybin, that may shed light on some of these processes. Our primary focus is on human behavioral data

obtained from healthy volunteers and clinical populations that participated in clinical trials under controlled conditions.

EFFECTS OF MDMA AND PSYCHEDELICS ON SOCIAL PROCESSING AND POTENTIAL ROLE OF THESE EFFECTS IN SUBSTANCE-ASSISTED THERAPY

An overview of the effects of MDMA, LSD, and psilocybin on various dimensions of social and emotional processing can be found in Table S1 in Supplement 2.

Altered Self-Image and Self-Processing

It has been proposed that the idea of the self is foundational to our understanding of the other (48), and drug effects on self-image are an important starting place in the consideration of social effects. Here, we consider altered self-image and self-processing to indicate a change in one's relationship with oneself, which may represent a special case of changing one's relationship with others. Additionally, increased self-focus, shame, feelings of worthlessness, overgeneralized self-blame, distortions of self-experience, and a negative self-image are associated with many different psychiatric diagnoses (39,49–51), and reducing these feelings is a critical component of many therapies (52).

Early trials with MDMA in patient populations suggested that the drug altered patients' sense of themselves such that they felt they were able to better experience their "true nature" (53,54). A more recent placebo-controlled laboratory study investigated this question with healthy volunteers and showed that MDMA (1.5 mg/kg) increased ratings of authenticity or the degree of congruence between the ideal and real self (15). Perhaps related to the construct of authenticity, it has been suggested that MDMA may reduce shame in individuals who have endured trauma. Similarly, lower levels of internalized shame have been reported in patients with histories of childhood trauma who self-administer psychedelics with therapeutic intention (55). To our knowledge, the effects of MDMA and psychedelics on shame have not been directly tested in any controlled trials. However, patients with alcohol use disorder who received psilocybin reported that it enhanced self-compassion and self-awareness (56). Another study investigated the effects of MDMA on the drop in self-esteem induced by simulated social rejection and showed that MDMA (0.75 and 1.5 mg/kg) significantly buffered this decrease (57). A large body of evidence suggests that both MDMA and serotonergic psychedelics dose dependently increase empathy toward others (19–21,58–61) (Table S1 in Supplement 2). However, they may also improve empathy toward oneself, thereby facilitating therapeutic change.

Loss of Ego Boundaries and Modulation of Self-Processing.—Mystical experiences are difficult-to-operationalize, but important, aspects of the psychedelic experience that may also be related to altered self-image and increased connectedness (62). These experiences typically involve an experience of unity with other forms of existence (63), which is related to the phenomena of ego dissolution and oceanic boundlessness, commonly reported dose-dependent and transient experiences that occur following psychedelics (64–66). Both unity and ego dissolution suggest that serotonergic

psychedelics alter the sense of self and lead to reduced self-other differentiation and self-referential processing, effects that may be therapeutic in some contexts (67). Ego dissolution is thought to involve alterations in resting-state network activity (68), and some functional magnetic resonance imaging studies have reported that psilocybin (2 mg intravenous) (69) and LSD (75 μg and 100 μg) (70,71) decreased functional connectivity within the default mode network, which represents the higher-level self and is activated during self-referencing (72,73). One study observed a correlation between self-reported ego dissolution and decreased activity in the default mode network following intravenous administration of LSD (75 μg) (70); however, this could not be replicated in another study following oral administration of LSD (100 μg) (71). Psilocybin reduced the integrity of the salience network, which represents the embodied self (74), and LSD (100 μg) diminished anticorrelated activity between the default mode network and the dorsal attention network, hypothesized to represent the boundary between subject and object, and with the salience network (75). Preller *et al.* (16) showed that self-processing was also altered during social interaction following LSD in healthy volunteers. Administration of LSD (100 μg) reduced self-other differentiation and blunted responses to self-initiated compared to other-initiated social interactions in the posterior cingulate cortex and the angular gyrus, which were correlated with changes in the 5-Dimensional Altered States of Consciousness scale score “changed meaning of percepts” (16). The decrease in self-other differentiation was prevented by pretreatment with the serotonin 2A receptor antagonist ketanserin (16).

The effects of MDMA on mystical-type experiences have also been directly compared to the effects of LSD in healthy volunteers. While a high dose of MDMA (125 mg) increased self-reported ego dissolution and some ratings on the Mystical Experiences Questionnaire and the 5-Dimensional Altered States of Consciousness scale, it did not raise them to the extent that LSD did (76). This suggests that while MDMA may alter one’s self-perception, it may do so in a way that is less associated with mystical-type experiences and acute alterations of consciousness.

Both LSD and psilocybin appear to produce lasting effects beyond their acute drug response in healthy volunteers and patients, including increased openness, increased trait levels of prosocial attitudes, and positive attitudes about self (77–83), which appear to be at least partially associated with the extent of acute alterations of mind and mystical-type experiences (77,80,83). While MDMA produces similar effects on openness, and it has been suggested that this effect may predict therapeutic outcomes in PTSD (84), MDMA does not produce mystical-type experiences similar to those that have been repeatedly associated with therapeutic outcomes for serotonergic psychedelics [e.g., (5,12)].

Responses to Social Reward

Altered social reward processing is a common but difficult-to-treat symptom of psychiatric illness (85). Deficits in social reward processing may affect any stage of social interaction, from anticipated reward or reward seeking to acute responses to social reward to ongoing effort to maintain social relationships (86,87). One way in which MDMA and psychedelics may act to facilitate psychotherapy and improve social functioning is by enhancing affective, behavioral, or neural processes at any stage of response to social reward. This effect may

also play a role in substance-assisted therapy because it may improve patient engagement during sessions.

Perhaps the simplest way to investigate the effects of drugs on social reward seeking is by examining its effects on the self-reported desire to socialize. Many studies conducted with healthy volunteers have shown that MDMA (75–125 mg or 1–2 mg/kg) increased ratings of feeling "sociable," "friendly," "talkative," "close to others," and "loving" [e.g., (15,20,21,88–90)] summarized in Regan *et al.* (17). Kirkpatrick *et al.* (90) showed that MDMA increased the frequency with which participants chose to socialize versus participate in a nonsocial activity (90). Similarly, healthy volunteers who received LSD (100 and 200 μg) reported dose-dependent subjective empathogenic and prosocial effects, including increased ratings of "happiness," "closeness to others," and "trust" (18,19). Interestingly, increases in self-reported connectedness were already observed after administration of a very low dose of LSD (10 μg) (91).

Beyond self-reporting, behavioral paradigms can measure responses to social rewards. Studies have shown that MDMA increased social seeking behavior as measured by attention bias (92,93). During the presentation of socially rewarding stimuli, MDMA increased positive affective responses to emotional faces as measured by facial electromyography (25) and increased ventral striatal responses to images of happy faces (29). The way in which participants allocate resources on behavioral tasks may indicate ongoing effort to engage in and maintain relationships and can indicate how rewarding they find prosocial behavior. MDMA enhanced cooperation during a prisoner's dilemma task (94) and increased generosity toward friends on a welfare tradeoff task (95). Both MDMA and LSD increased prosocial resource allocation in the social value orientation task (19,21), which suggests that these drugs increase the rewarding properties of prosocial behavior. One final, less-studied dimension of social reward is responses to pleasant social touch. One study showed that MDMA (0.75 mg/kg and 1.5 mg/kg) increased pleasantness ratings of standardized social touch (93).

Overall, a considerable evidence supports the ability of MDMA to boost responses to social reward at all stages of social interaction. In the case of serotonergic psychedelics, there is some evidence that these compounds may facilitate positive responses to socially rewarding stimuli. However, the evidence is not as robust as it is for MDMA, and more research is needed in this area.

Responses to Negative Social Input

MDMA and serotonergic psychedelics not only enhance responses to positive social stimuli and social reward but also reduce responses to negative social stimuli, thereby alleviating the negative processing bias that occurs in many psychiatric disorders (39,96,97). Here, we consider the effects of these compounds on affective and perceptual responses to negative social cues, including social rejection and images of emotional faces.

Social Exclusion.—In healthy volunteers, MDMA (1.5 mg/kg) ameliorated the expected drop in mood and self-esteem following simulated social rejection in the Cyberball task (57). Similarly, it reduced social anxiety in healthy volunteers and adult patients with autism

(7,15). Consistent with the effects of MDMA, healthy volunteers who received psilocybin (0.215 mg/kg) reported reduced feelings of exclusion during the Cyberball task, although they were aware of the simulated exclusion (98). Additionally, in these participants, a decrease in the neural response to social exclusion was noted in the dorsal anterior cingulate cortex and the middle frontal gyrus (98), brain regions that typically exhibit increased activity toward social pain that results from social rejection (99,100). Interestingly, neural changes were associated with self-reported changes on the 5-Dimensional Altered States of Consciousness scale "experience of unity" after psilocybin, which suggests that psychedelic-induced alterations in self-processing and mystical states are also crucial for changes in socialinteraction processing (98). Mixed results were observed for low doses of LSD. In healthy participants, repeated administration of low doses of LSD (26 μg, 4 times at 3- to 4-day intervals) reduced negative mood ratings during exclusion (101). This effect was already observed during the first session at peak drug effects and was similar at session 4 but was not noted at the follow-up session 3 to 4 days after the last drug administration (101). In contrast, no acute changes in social exclusion measures were observed in healthy participants who received several low doses of LSD (6.5, 13, and 26 μg LSD) (102).

Moderate doses of psilocybin (0.215 mg/kg) have been shown to induce a change in goal-directed behavior toward positive cues. Psilocybin-induced increases in reaction times for negative and neutral words were higher than for positive words, and error rates for negative words were higher than for positive words in an emotional go/no-go task (26). Ketanserin did not prevent these effects (26). No effect was observed when psilocybin was repeatedly ingested at low doses (0.7 g of dried psilocybin-containing truffles), even though participants were presented with pictures of emotional faces as go/no-go stimuli (103).

Overall, it seems that higher doses of psilocybin and MDMA have similar effects on feelings of exclusion. Microdosing of LSD does not appear to produce analogous effects, but the impact of comparable doses would need to be tested to establish a reliable comparison of psilocybin and MDMA.

Emotion Recognition.—Recognition of facial expressions, which provides information concerning the internal emotional states and intentions of others, is crucial in social cognition. Several studies have investigated the effects of MDMA and classical psychedelics on the recognition of emotional facial expressions in healthy volunteers, and the results have suggested that these drugs positively bias emotion recognition. Using the Reading the Mind in the Eyes Test, a high dose of MDMA (125 mg) enhanced reading of positive emotions from the eye region (104) and impaired recognition of negative emotions while leaving identification of neutral stimuli unaffected (104). However, studies that used lower doses of MDMA (75 mg, 0.75 mg/kg, 1.5 mg/kg) observed no effects on the Reading the Mind in the Eyes Test (59,105). Most studies have used a version of the facial Emotion Recognition Task and have shown that MDMA impairs the recognition of negative emotions (including sadness, anger, and fear) across a range of doses in a dose-dependent manner (20–25). Besides impaired recognition of negatively valenced emotions, several studies have shown increased misclassification of emotions as "happy" following MDMA administration (22,23). Interestingly, only 1 study has examined sex differences, and it showed that MDMA-induced decreases in the correct identification of negative emotions occurred only

in women (21), suggesting that there may be sex differences in responses to MDMA that may be relevant to its therapeutic use. Additionally, the decrease in fear recognition was inversely correlated with MDMA exposure (21).

Similarly, LSD and psilocybin have consistently been shown to impair the recognition of negative facial expressions in healthy volunteers (19,26,27). Specifically, LSD (100 and 200 μg) significantly impaired recognition of fearful faces and tended to impair recognition of sad faces on the facial Emotion Recognition Task (19), whereas psilocybin (0.115 and 0.215 mg/kg, respectively) attenuated recognition of negative emotional states on the Reading the Mind in the Eyes Test (26) and impaired encoding of fearful faces as evidenced by decreased N170 event-related potentials, an effect that was more pronounced during conscious than nonconscious visual processing (27). Interestingly, pretreatment with ketanserin decreased psilocybin-induced increases in error rates for negative faces (26). One week after treatment with psilocybin (10 and 25 mg, separated by 1 week), patients who had treatment-resistant depression demonstrated significantly faster reaction times in response to dynamic facial emotional stimuli, which were correlated with improvements in anhedonia (106). Conversely, low doses of LSD (26 μg) decreased positive ratings of positive emotional images, but neither facial emotion identification nor social exclusion were affected (102). Repeated administration of low doses of LSD did not affect emotional face ratings, but the highest dose used (26 μg) induced a slight decrease in false alarm rates for recognizing fear in the emotional faces task using a forced-choice design (101). Similar to social exclusion, this effect was already observed at the first and last drug sessions but was not sustained (101).

In healthy volunteers, MDMA (1.5 mg/kg) reduced amygdala responses to threatening faces (29). Similarly, reduced amygdala and right medial prefrontal cortex reactivity toward fearful stimuli have been observed after the intake of 100 μg of LSD during the pharmacological and subjective peak, and the decrease in amygdala reactivity was associated with the acute drug effects (28). Similarly, psilocybin acutely attenuated amygdala reactivity toward negative but also toward neutral stimuli from the International Affective Picture System, which was related to psilocybin-induced increases in positive mood in healthy volunteers (107). A similar effect on emotional face processing was observed when electrical neuroimaging analyses were used for visual evoked potentials. Specifically, psilocybin exhibited temporal selective effects, with decreased activity within the amygdala and parahippocampal gyrus toward fearful and neutral faces initially being followed by a decrease in activity toward happy faces (108). Reduced amygdala reactivity was observed 1 week after but not 1 month after psilocybin administration in healthy volunteers (109). In contrast, in patients with depression, one study reported an increase in right amygdala reactivity toward fearful faces the morning after psilocybin administration, which was predictive of therapeutic improvement 1 week after psilocybin administration (110).

Overall, both MDMA and serotonergic psychedelics have consistently been shown to reduce reactivity to negative facial expressions across behavioral and neural domains in healthy volunteers.

Social Neuroplasticity and Trauma Processing

In addition to considering the acute effects of MDMA and psychedelics on social processing, it is important to consider how these compounds may act to catalyze a change in social processing or to enhance social learning and neuroplasticity. Social learning profoundly shapes our responses and adaptation to life's challenges by influencing behaviors, beliefs, and well-being through interactions with others. Social learning is intricately linked to neuroplasticity and trauma processing because the brain's ability to adapt and rewire is influenced by the social environments and interactions we experience, ultimately shaping how traumatic events are processed.

In preclinical and limited clinical studies, both single and repeated administration of MDMA and classical psychedelics have been shown to enhance neuroplasticity or increase markers of neuroplasticity such as BDNF (brain-derived neurotrophic factor) (32,111). In rats, repeated MDMA administration reduced behavioral markers of anxiety and increased hippocampal BDNF expression (33). Likewise, psilocybin in mice decreased cued fear conditioning, promoted neurogenesis, and enhanced hippocampal neuroplasticity (112,113). Intriguingly, recent preclinical studies found that a single dose of MDMA, LSD, and psilocybin could reopen a critical period for social reward learning, with varying durations for each drug and a notably longer duration for LSD than psilocybin and MDMA. Notably, the impact of MDMA was linked to oxytocinergic transmission, while LSD and psilocybin relied on serotonin 2A receptor activation for similar effects (30,31).

Assessing neuroplasticity in humans is more challenging, and most studies conducted with healthy participants that measured peripheral BDNF have yielded mixed results. Holze *et al.* (76) observed no elevation in BDNF after MDMA (125 mg). Some studies have observed increases in BDNF after LSD (64,114) and psilocybin (64,114,115) while several others have not (116–118). It is unclear whether peripheral BDNF is a suitable marker for detecting psychedelic-induced neuroplasticity in humans, and alternative approaches are needed. Notably, administration of ketanserin also did not prevent LSD-induced increases in BDNF (64,119).

While it is more difficult to assess plasticity effects on social learning and behavior in human studies, recent work has examined the effects of MDMA on memory and fear extinction in humans. Carhartt-Harris *et al.* (120) showed that MDMA (100 mg) enhanced positive ratings of good memories and reduced negative ratings of bad memories during an autobiographical memory task (120). Another study with healthy human volunteers showed that MDMA (125 mg) facilitated fear extinction and retention of fear extinction (23). Thus, MDMA may help promote social learning and neuroplasticity that benefits recovery from psychiatric illnesses, including trauma-related disorders.

Similarly, a functional magnetic resonance imaging study in which autobiographical recollections were measured following psilocybin (2 mg intravenous) showed increased self-reported ratings of vividness of recalled autobiographical memories (121), which indicates that memories could be relived more vividly and pleasantly. Intriguingly, memory vividness was significantly correlated with subjective well-being 2 weeks later (121). In healthy volunteers, LSD (100 μg) has also been shown to increase social adaptation, most likely due

to altered feedback processing, but only when the opinions of others were similar to one's own (122). Pretreatment with ketanserin prevented LSD-induced increased activity in the medial prefrontal cortex during feedback processing (122).

Continuing to investigate the effects of these drug classes on social learning and memory is an important future direction for the field. Paradigms that can be carried out in a controlled laboratory setting such as social object relocation tasks (123) and social influence learning tasks (122) may be particularly valuable in this area.

Overall, there is strong, although predominantly preclinical, evidence in support of the ability of both MDMA and serotonergic psychedelics to induce neuroplasticity, with some evidence in human volunteers suggesting that MDMA modifies memory and fear extinction and that classical psychedelics may modify memory and affect social feedback. Additional research is needed to assess the potential impact of neural plasticity on trauma processing in human volunteers and establish the effects of both substance classes in clinical populations.

DISCUSSION

Summary and Therapeutic Implications

This comparative narrative review elaborates on the effects of MDMA and classical serotonergic psychedelics on various dimensions of social behavior in an effort to understand how these drugs may act as therapeutic adjuncts. We examined similarities and differences across 4 realms of social processing, including altered self-image, responses to social reward, responses to negative social input, and social learning and neuroplasticity. MDMA and classical psychedelics exert overlapping effects on socioemotional processing and social learning but also differ in some critical ways. These differences may affect the types of psychosocial interventions best suited for each substance class.

Both substance classes have been shown to alter one's self-image, but they may do so in different ways. Whereas for serotonergic psychedelics, this effect appears to be linked to the experience of mystical states and acute alterations of consciousness, MDMA appears to produce its effects on self-image independently of these processes. Interestingly, MDMA does not elicit pronounced alterations of the mind similar to classical psychedelics (76) but displays many similar social effects, suggesting that prosocial effects and prototypical psychedelic effects are dissociable. This finding is relevant to clinical contexts when a negative self-image and increased self-focus are barriers to patient treatment, such as in depression, PTSD, substance use disorder, and body dysmorphic disorder (39,49–51).

MDMA has been shown to reliably increase responses to social reward across multiple domains. While there is some emerging evidence that serotonergic psychedelics may also facilitate such responses, MDMA appears to induce a unique combination of prosocial and motivating properties. Impaired response to social reward, or social anhedonia, is a transdiagnostic psychiatric symptom and causes significant functional impairment (36). Psychosocial interventions have been tested for this symptom, but the effects are limited by poor patient motivation (124). The ability of MDMA to enhance social reward and

motivation could be leveraged in a clinical context if the drug were used as an adjunct to time-limited psychosocial training.

Both substance classes have robust and reproducible effects on responses to negative social input, thereby ameliorating a negative processing bias. These effects are observable in responses to simulated social exclusion and emotion recognition and have implications for how these compounds may act therapeutically. It has been suggested that antidepressants such as selective serotonin reuptake inhibitors (SSRIs) work partly by altering the negative processing bias in response to social cues (125). This theory makes sense in the context of medications such as SSRIs that are taken daily for extended periods of time. It is less clear how reducing a negative processing bias acutely facilitates therapeutic change with compounds like MDMA or serotonergic psychedelics that are typically administered only several times. One hypothesis is that these compounds may help induce receptiveness to social feedback from a therapist during a therapeutic session.

The combination of enhanced response to social reward and reduced response to negative social input may facilitate the therapeutic alliance during a substance-assisted session. Therapeutic alliance is a crucial factor in various psychotherapy approaches, and there is robust evidence supporting a predictive relationship between therapeutic alliance and psychotherapy outcomes for several mental disorders (126). Acutely reduced fear recognition, decreased amygdala reactivity, and modulated functional connectivity of the amygdala may facilitate the processing of negative information (19,28,29,107,127,128), and feelings of closeness and trust may enhance the patient-therapist relationship, leading to a better therapeutic alliance (18,19,129). Additionally, social connectedness may also be directly related to mood-enhancing effects, as has been shown for psychedelic use in naturalistic settings (130). Thus, effects of MDMA and psychedelics on social processing may not only facilitate therapeutic alliance in clinical settings but also directly affect treatment responses. Consistent with this statement, previous research has shown that the strength of the therapeutic alliance is predictive of emotional breakthrough and mystical-type experiences and hence antidepressant response following psilocybin-assisted therapy (131).

There is accumulating preclinical evidence that supports the ability of both MDMA and serotonergic psychedelics to induce social neuroplasticity (30–32,111). There is also some evidence from studies with healthy human volunteers that suggests that MDMA modifies memory and fear extinction (23,120) in addition to consistent evidence suggesting that the drug reduces reactivity to fearful faces [reviewed in (17)]. These effects indicate that the compounds may not only be helpful in the context of the psychotherapy that is currently being tested for PTSD (1) but may also be helpful during other types of therapies that directly target fear-related symptoms, such as exposure therapy or cognitive processing therapy. More research is needed to establish the sociobehavioral effects of serotonergic psychedelic-induced plasticity in human volunteers and to establish the effects of both substance classes in clinical populations. It will also be critical to explore the duration of an eventual window of plasticity and social learning.

Limitations and Outlook

The social dimension of psychiatric disorders is becoming increasingly recognized as an important direction of investigation. This narrative, nonsystematic review suggests that MDMA and classical serotonergic psychedelics including LSD and psilocybin show promise for affecting several domains of socioemotional processing. Reassuringly, effects observed in highly controlled laboratory studies have also been observed in naturalistic studies in other contexts, including other serotonergic psychedelics (132–134). Overall, the effects of classical serotonergic psychedelics on social processing appear to be dose dependent rather than substance dependent. However, direct comparisons of various psychedelics that include MDMA are lacking. Additionally, it remains to be investigated whether psychedelic compounds that act as serotonin 2A receptor agonists, which show neuroplastic and antidepressant activity in rodents but lack prototypical hallucinogenic properties, will show similar changes in human social behavior (135). Underlying neuropharmacological mechanisms of MDMA and psychedelics are discussed in detail in Supplement 1, but future studies should further investigate the role of specific serotonin receptor subtypes in social behavior.

While there is a developing body of work focusing on the effects of these compounds on social processing, the social paradigms tested thus far are very basic, focusing on simple responses. Several recent reviews highlighting the importance of social neuroscience in psychiatry have suggested that investigating the whole complex social interaction, including behavioral, physiological, and neural synchrony, is an essential next step for the field (136,137).

Furthermore, neither the long-term effects of MDMA and psychedelics on social processing have been determined nor have the effects of prolonged administration of these substances. These effects may differ from acute effects in a way that is similar to SSRIs, which acutely improve recognition of fearful and happy faces (125), but chronic administration of SSRIs reduces the recognition of fearful faces (138).

Currently, it remains largely unknown whether and how MDMA- and psychedelic-induced alterations in social functioning translate to patients. To our knowledge, few studies have assessed changes in socioemotional processing in patients receiving MDMA- and/or psychedelic-assisted psychotherapy [primarily for depression, e.g., (106,110)]. It will be necessary for future research to investigate whether selective modulation of specific facets of these effects may be leveraged in targeted therapeutic interventions. However, it is important in this context to acknowledge the potential risks that are associated with the social effects of these compounds, including the increased patient vulnerability they may confer (139).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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YS and AKB performed the literature analysis and wrote the manuscript. All authors read and approved the final manuscript and agreed to be accountable for all aspects of the work.

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