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REVIEW ARTICLE

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Potential processes of change in MDMA-Assisted therapy for social anxiety disorder: Enhanced memory reconsolidation, self-transcendence, and therapeutic relationships

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Abstract

Objective: Researchers have suggested that psychotherapy may be enhanced by the addition of 3,4-methylenedioxymethamphetamine (MDMA), particularly in the treatment of disorders wherein interpersonal dysfunction is central, such as social anxiety disorder. We review literature pertaining to three potential processes of change that may be instigated during sessions involving MDMA administration in the treatment of social anxiety disorder.

Design: This is a narrative review that integrates research on the etiology and maintenance of social anxiety disorder and mechanisms of action of MDMA to examine how MDMA may enhance psychotherapy outcomes.

Results: We first outline how MDMA may enhance memory reconsolidation in social anxiety disorder. We then discuss how MDMA may induce experiences of self-transcendence and self-transcendent emotions such as compassion, love, and awe; and how these experiences may be therapeutic in the context of social anxiety disorder. We subsequently discuss the possibility that MDMA may enhance the strength and effectiveness of the therapeutic relationship which is a robust predictor of outcomes across many disorders as well as a potential key ingredient in treating disorders where shame and social disconnection are central factors.

Conclusion: We discuss how processes of change may extend beyond the MDMA dosing sessions themselves.

KEYWORDS
MDMA, memory reconsolidation, processes of change, self-transcendence, social anxiety disorder, therapeutic relationship

1 | INTRODUCTION

Social anxiety disorder (SAD) is a prevalent and disabling disorder characterized by intense fear of being scrutinized or negatively evaluated by others in social situations (American Psychiatric Association [APA], 2013). SAD is the fourth most commonly diagnosed psychological disorder in the United States (Kessler et al., 2005) with onset typically occurring in adolescence and assuming a chronic course even following treatment (Morris et al., 2005). SAD has significant public health costs including

increased workplace absenteeism, lower worker productivity, and unemployment (APA, 2013; Stuhldreher et al., 2014). Furthermore, it often precedes the development of other psychiatric conditions, for example, increasing the risk for the development of major depressive disorder (Adams et al., 2016), and doubling the likelihood of developing an alcohol use disorder (Magee et al., 1996).

Although evidence-based treatments for SAD exist, including medications and therapy, a significant proportion of patients either do not respond or remain considerably symptomatic at the end of treatment (Loerinc et al., 2015; Mayo-Wilson et al., 2014). In terms of pharmacotherapy, meta-analytic evidence supports the conclusion that SSRIs are superior to placebo but also that SSRIs are associated with higher treatment dropout than placebo over the treatment course (Williams et al., 2017). In terms of psychotherapy, cognitive behavioral therapy for social anxiety disorder demonstrates the strongest outcomes (Mayo-Wilson et al., 2014), with other approaches, such as acceptance and commitment therapy (Niles et al., 2014), interpersonal psychotherapy (Stangier et al., 2011), emotion-focused therapy (Shahar et al., 2017), and psychodynamic treatment (Leichsenring et al., 2013) also showing some efficacy.

In the past decade, there has been increased interest in pharmacotherapies to augment the effectiveness of psychotherapy for SAD. For example, d-cycloserine has been tested in several trials and preliminary evidence suggests it may provide a small augmentation effect for exposure therapy targeting social anxiety (Mataix-Cols et al., 2017). In addition, MDMA (3,4-methylenedioxymethamphetamine) has been tested as a means to augment psychotherapy for social anxiety in adults with autism (Danforth et al., 2018). In a randomized, placebo-controlled trial, 12 participants with autism and SAD were treated with two sessions of MDMA-assisted therapy (MDMA-AT) along with non-drug preparatory and integrative psychotherapy. Participants in the MDMA-AT group showed dramatically reduced SAD symptom severity at the post-treatment primary outcome point (between group effect size: $d = 1.4$) after two doses of MDMA, providing preliminary evidence for the efficacy of MDMA as a possible treatment augmentation strategy for SAD.

2 | MDMA AND MDMA-ASSISTED THERAPY

MDMA primarily affects the serotonin, norepinephrine, and dopamine systems (Liechti & Vollenweider, 2001) and stimulates hormonal responses related to oxytocin, vasopressin, prolactin, and cortisol (Emanuele et al., 2006; Mas et al., 1999; Passie et al., 2005). Until MDMA was made illegal in the U.S.A., it had been used as an adjunct to psychotherapy for about a decade. Therapists at the time noted that MDMA created heightened feelings of empathy, reduced patient defensiveness, facilitated direct communication, and helped the processing of traumatic events (Passie, 2018). The first controlled study of MDMA-AT was published in 2011 (Mithoefer et al., 2011) and, in total, five clinical trials of MDMA-AT have been published including one on SAD and four on PTSD (Luoma et al., 2020). A recent pooled analysis of 103 patients from six Phase II clinical trials (Mithoefer et al., 2019) found a large between group difference ($g = 0.8$) compared to placebo at primary end point.

In established trials, MDMA-AT is typically delivered by a team of two therapists using a combination of non-drug psychotherapy sessions and MDMA dosing sessions. Typically, there are three preparation sessions which involve setting expectations and intentions for treatment, reviewing the patient's history and presenting problem, establishing safety and trust in the therapeutic alliance, the teaching of skills that may be used in dosing sessions, and educating about likely events that might occur in dosing sessions. This is then typically followed by two to three dosing sessions, with three integration sessions occurring after each dosing session. Dosing sessions last approximately 8 h, during which the client receives the investigational drug and spends the session transitioning between states of internally focused attention facilitated by the use of eyeshades and music and externally focused interactions with the therapists. Integration sessions involve processing what occurred in the dosing session, concretizing gained insights or new learning, and translating the experience into meaningful life changes.

3 | PREVIOUS WORK ON MDMA-AT PROCESSES OF CHANGE

The primary goal of this paper is to outline potential processes of change in proposed MDMA-AT for SAD. We choose to use the term 'processes of change' instead of mechanisms of action as it is less restrictive, allowing for feedback loops and bidirectionality, in contrast with the term 'mechanisms', which implies a more linear causal pattern (Hayes et al., 2019). Processes of change can be studied at many levels of analysis, ranging from molecular, neurological, psychological or even sociological levels (Hofmann et al., 2020). Each of these levels of analysis has utility in guiding future treatment development in this domain; however, this paper focuses on the psychological level as it has the most direct relevance to the ongoing development of the psychotherapy component of MDMA-AT. The practical aim of a scientific understanding of processes of change is to guide therapist efforts toward a focus on variables most likely to maximize therapeutic outcomes.

Though many experimental, non-clinical studies have examined the effects of MDMA in humans (for reviews see Feduccia & Mithoefer, 2018; Jungaberle et al., 2018), some of which are reviewed below, processes of change associated with MDMA have been notably understudied. Quantitative data on the subject are sparse, with only one available randomized, controlled trial showing that MDMA-AT resulted in larger changes in the personality trait of openness to experience compared to a placebo condition among people with PTSD (Wagner et al., 2017). The authors proposed that MDMA may have facilitated a tendency toward seeking out new experiences and openness to self-examination, which may have led to improved PTSD outcomes. No authors to date have outlined potential processes of change that might be specific to SAD, but some researchers have noted that MDMA, because of its effects on social

perception and cognition and on social hormones such as oxytocin and prolactin, seems particularly well suited to treat disorders wherein interpersonal dysfunction is central, such as social anxiety, autism, or major depressive disorder (Heifets & Malenka, 2016).

Due to the paucity of the direct study of processes of change in MDMA-AT, this narrative review largely relies on experimental and correlational findings on MDMA and anecdotal reports to hypothesize possible processes of change occurring during MDMA-AT. Where relevant, we also discuss the findings of a qualitative study of perceived benefits of treatment among 19 participants who completed MDMA-AT for PTSD (Barone et al., 2019). It is important to keep in mind that the generalizability of research on MDMA use in experimental and uncontrolled settings to clinical settings may be limited as the effect of MDMA has been shown to be dependent upon the social context in which the drug is used. Drug effects are not independent of the social environment (Alboni et al., 2017) and multiple studies in rodents show that this is also true with MDMA (Hake et al., 2019; Nardou et al., 2019). For example, Nardou et al. (2019) showed that MDMA only increased sensitivity to social reinforcement among mice who received MDMA when in the presence of another mouse, but not in mice receiving the drug while alone. In humans, an experimental study found that participants who were assigned to take a low-dose of MDMA in the presence of other participants reported increased intensity of acute effects of MDMA, such as higher subjective ratings of "feeling the drug" and increased cardiovascular activity, compared to those taking the drug alone (Kirkpatrick & de Wit, 2015). These results imply that the social context of MDMA administration is essential in understanding the effects of MDMA and that the effects of the drug cannot be understood without taking this context into account (Carhart-Harris et al., 2018).

4 | POSSIBLE PROCESSES OF CHANGE IN MDMA-AT FOR SOCIAL ANXIETY DISORDER

This paper reviews literature relevant to three interdependent processes of change we hypothesize may be instigated during dosing sessions and further consolidated during integration sessions. We focus first on the possibility that MDMA may enhance memory reconsolidation in SAD, an idea that has been previously discussed in relation to PTSD (Feduccia & Mithoefer, 2018). We then discuss how MDMA may induce experiences of self-transcendence and self-transcendent emotions, such as compassion, love, and awe and how these experiences may be therapeutic in the context of SAD. Finally, we discuss the possibility that MDMA may enhance the strength and effectiveness of the therapeutic relationship (Johansen & Krebs, 2009), potentiating corrective emotional and interpersonal experiences in which socially anxious patients feel safe enough to behave authentically, facilitating greater openness to acceptance and warmth from their therapist. While these processes are presented separately for clarity in this paper, we hypothesize that they are interrelated and influence each other.

This paper focuses primarily on events that occur during dosing sessions. Yet the content of integration sessions is also likely to be central in further reinforcing and elaborating processes initiated during dosing sessions. Similarly, the content of preparation sessions is likely to influence the chance that these processes are likely to occur during dosing sessions. In addition, there may be drug-related effects that are more delayed, such as those found in a series of studies in mice by Nardou et al. (2019), which showed that MDMA increased sensitivity to social rewards for at least two weeks post-dosing. This suggests that, among humans, MDMA may affect responses to social reinforcement for an undetermined period after the acute drug has left the body and that this potential process of change may interact with the person's social context in the weeks after dosing. Due to space constraints, we only focus on these three processes and how they may unfold during dosing sessions; we do not mean to imply that activities in integration sessions are not important or that other processes of change may not also be central.

4.1 | Enhanced memory reconsolidation

Memory reconsolidation refers to a type of neuroplasticity that occurs when a memory is reactivated, initiating a critical period during which the memory trace is destabilized and then can be modified and updated with new information before being consolidated again into long term memory (Elsey et al., 2018). Memory reconsolidation has been proposed as a common mechanism across many psychotherapy approaches (e.g., Lane et al., 2015) and has been specifically proposed as a mechanism in the context of MDMA-AT (Feduccia & Mithoefer, 2018). We seek to outline how this process may relate to SAD.

People with SAD have a large bank of readily accessible implicit and explicit memories of being shamed, humiliated, rejected, ostracized and generally devalued. Experiences with maltreatment are a generalized risk factor for the development of SAD (Bruce et al., 2012; Simon et al., 2009; Wong & Rapee, 2016), with emotional abuse and neglect being associated with symptom severity in patient samples with SAD (Bruce et al., 2012; Simon et al., 2009) and prospectively predicting the onset of SAD (Kessler et al., 1997). Social victimization among peers may be a particularly strong risk factor for the development of social anxiety (Norton & Abbott, 2017a, 2017b; Sansen et al., 2015). One study of people with SAD found that 98% reported aversive early experiences with peers (Norton & Abbott, 2017b).

At least partially as a result of these salient experiences, people with SAD exhibit enhanced retrieval of negative autobiographical memories and reduced availability of positive autobiographical memories (Stopa & Jenkins, 2007). Compared to non-anxious controls, people with SAD recall positive memories with impoverished detail (Moscovitch et al., 2011) and negative memories with greater internal detail and a higher degree of self-relevance (Moscovitch et al., 2011, 2018). People with greater social anxiety also tend to recall more self-defining negative memories and memories related to social anxiety (Krans et al., 2014). Recall biases may also affect recent

memories, with research showing that people higher in social anxiety tend to recall positive feedback about a social task more negatively over time (Glazier & Alden, 2017) compared to people low in social anxiety. The recall of negative memories, particularly those related to victimization, has been shown to heighten physiological arousal among people with SAD, with those who reported past experiences of peer victimization demonstrating higher skin conductance to recall of negative memories (Sansen et al., 2015).

More easily accessible negative memories also appear to be related to the prevalent intrusive negative self-imagery found in most people with SAD (Chiupka et al., 2012). The vast majority of people with SAD report negative self-imagery in social situations (Homer & Deeprose, 2017; Moscovitch et al., 2011, 2018), with most reporting that the imagery is linked to identifiable autobiographical memories (Hackmann et al., 1998, 2000; Moscovitch et al., 2011). Preliminary evidence suggests that the occurrence of this negative self-imagery linked to autobiographical memory might be a causal factor in the maintenance of SAD (Makkar & Grisham, 2011). Together, the above findings implicate the important role of autobiographical memory and self-imagery in maintaining SAD and suggest that targeting these memories and attempting to alter parameters associated with them (their meaning, current levels of intrusiveness) may be particularly important in treatment for SAD. Relatedly, several studies have shown preliminary benefits of a technique called imagery rescripting that involves engaging with negative autobiographical memories while inserting novel imagery and emotional experiences (Knutsson et al., 2019; Langkaas et al., 2017; Nilsson et al., 2012; Reimer & Moscovitch, 2015; Wild & Clark, 2011). Rescripting interventions have been shown to alter imagery and memory details and the appraisal of the meaning of the memory, as well as reduce intrusiveness, vividness, and negative affect associated with target memories (Reimer & Moscovitch, 2015; Romano et al., 2020).

Experimental studies of fear conditioning in rats and mice have suggested that MDMA may facilitate memory reconsolidation of fear memories (Hake et al., 2019; Young et al., 2015). Possible neurobiological mechanisms for how MDMA may enhance memory reconsolidation include altered action in the medial pre-frontal cortex and amygdala (Carhart-Harris et al., 2015) and a 5-HT-dependent reduction in Brain Derived Neurotropic Factor (BDNF; Hake et al., 2019), a neurotropin important for memory reconsolidation (Bekinschtein et al., 2014). In addition, basic science shows that MDMA alters memory functioning in a variety of ways (for a review see Feduccia & Mithoefer, 2018). In humans, MDMA appears to diminish the encoding of emotional information (Doss et al., 2018) and enhance the vividness of positive autobiographical memories (Carhart-Harris et al., 2014), with MDMA potentially reducing the recollection of specific details of emotional events, rather than the ability to recall the event itself (Doss et al., 2018). This could be helpful in the treatment of intrusive imagery commonly found in SAD (Chiupka et al., 2012) if upsetting memories are re-encoded with weakened associations to emotionally evocative details.

We posit that MDMA-AT may facilitate memory reconsolidation through a) enhancing the activation of relevant memory traces and b) intensifying the prediction errors that are central to updating these memory traces. With respect to the former, the activation of a relevant memory trace is necessary for reconsolidation. Several etiological models of SAD have recently emphasized that the fear most central to the maintenance of SAD is that the authentic, core self is undesirable, deficient, or inadequate and that this self, if revealed to others, will trigger ostracism, rejection, and further shame (Elliott & Shahar, 2018; Moscovitch, 2009). Accordingly, the therapeutic context needs to facilitate the activation of memory traces consistent with this core fear in order for SAD-relevant reconsolidation to occur, but it is important to note that activation of the memory trace in session does not necessarily need to entail the recall of explicit autobiographical memories. In humans, activated memory traces may be primarily explicit or implicit in nature, with implicit memory referring to the influence of prior events on current experience and behavior in the absence of explicit recall or awareness of the experience that led to that learning (Lane et al., 2015), and explicit memory referring to events that are recalled with awareness (e.g., autobiographical memory). Regardless of the cue, when this fear is activated, autobiographical memories are likely to arise since this central fear involves a perceived inadequate self and is linked autobiographical (traumatic) memories.

We hypothesize that MDMA may serve both to elicit the cue for the core fear memories that need reconsolidation while also fostering a strong prediction error. A prediction error is a mismatch between expected and current event and is thought to be essential for reconsolidation to occur (Fernández et al., 2017). If the core fear of people with SAD is that revealing the authentic self will lead to ostracism, rejection, and shame, then a strong prediction error would conceivably occur if the authentic self is revealed and these events do not occur. MDMA tends to elicit an experience of authenticity (Baggott et al., 2016; Passie, 2018) in its users, thus conceivably activating the core memory traces that need to be reconsolidated in SAD. However, under the effects of MDMA, rather than the typically accompanying feelings of fear, the person with SAD is instead likely to experience feelings of peace, safety, or even love (Studerus et al., 2010). This would conceivably foster a strong prediction error that may facilitate memory reconsolidation. A prediction error in which outcomes of current events do not match with expectations is thought to be a particularly strong signal to update an aversive memory trace (Elsey et al., 2018) and the experiences of safety, love, and increased perception of empathy from others (Jungaberle et al., 2018) typically elicited by MDMA, simultaneously occurring in a context of felt authenticity, would run counter to the expectations of people with SAD. In addition, because MDMA can induce this experience for several hours, this may allow for a more prolonged period of learning compared to the more limited moments of feeling connected and cared for in more typical talk therapy. In addition, because MDMA increases people's focus on social and emotional content (Kamilar-Britt & Bedi, 2015; Wardle et al., 2014), this may further facilitate memory reconsolidation relevant to core fears. The extended focus on social and emotional content related to social fears might also facilitate the elaboration of autobiographical

memories with new, more adaptive information that may not have been available at the time the original memory was laid down, such as an awareness of the social context surrounding the events or the development of a more compassionate, nuanced perspective of the events. Later integrations sessions might then help bridge this learning to other parts of the person's life and social situations.

In sum, we hypothesize that MDMA-AT dosing sessions may elicit relevant core fears that serve to maintain SAD while simultaneously promoting new emotional experiences that then lead to a new memory trace via reconsolidation (Lane et al., 2015). We further elaborate on how MDMA might enhance this prediction error in the section on the therapeutic relationship. Effectively studying memory reconsolidation in the context of MDMA-AT likely requires measurement across a variety of levels including cognition, behavior, genetic, and peripheral and central physiology as well as across multiple domains with each level (Fernández et al., 2017). Furthermore, it may require multiple conditions aimed specifically at experimentally manipulating the variables thought to lead to reconsolidation. Acknowledging these complexities, an example of a face valid measurement approach at the cognitive level may be the use of structured interview methods to assess changes in the content (i.e., specific positive or negative details) and appraisals (i.e., the meaning ascribed to the event) related to core memories of shame and rejection identified by the client before and after dosing and integration sessions (Romano et al., 2020).

4.2 | Self-transcendent experiences and emotions

The functioning of the self is considered central to most models of SAD (Clark & Wells, 1995; Elliott & Shahar, 2018; Gilboa-Schechtman et al., 2020; Hofmann, 2000; Moscovitch, 2009). While conceptualizations of the self are numerous, one common distinction is between: 1) the self as content, sometimes referred to as the self-as-object (Gilboa-Schechtman et al., 2020), conceptualized self (Luoma et al., 2017) or simply as "me;" and 2) the self-as-subject (Gilboa-Schechtman et al., 2020), sometimes referred to as the observer self (Luoma et al., 2017), perspective-taking-self (Mchugh & Stewart, 2012), or the "I." Most models of SAD focus on the content of the self, with less attention paid to the functioning of the subjective self or the I from which we experience. Repeated experiences of social mistreatment and shame, combined with difficulty in achieving adequate levels of interpersonal validation and reduced social efficacy result in the development of a sense of self as inadequate, inferior, and flawed (Elliott & Shahar, 2018). Research has demonstrated that SAD is more highly correlated with shame than are other anxiety disorders (Cândea & Szentagotai-Tăta, 2018) and that the self-concept of people with SAD is generally negative (Anderson et al., 2008) and manifested in heightened self-criticism (Cox et al., 2004), beliefs relating to social inferiority (Gilbert, 2000), greater negative self-related imagery (Makkar & Grisham, 2011), and heightened access to negative autobiographical memories (Stopa & Jenkins, 2007).

In contrast, much less research focuses on the functioning of the subjective self or the 'I' in SAD, despite its potential importance. A notable exception is research on attentional biases, which show that SAD is associated with a general tendency to attend to threat-related cues (Bar-Haim et al., 2007) and a difficulty focusing attention on positive and affiliative cues (Taylor et al., 2011). These biases may be due to the documented tendency for people who perceive themselves as low in social rank to monitor more for social threat (Gilboa-Schechtman et al., 2020). People with SAD tend to focus more on their own behavior, whether that is in the form of heightened self-consciousness or increased self-focused attention to interoceptive cues in social situations (Norton & Abbott, 2015). Neuroscientific findings also show that the insula, which is associated with interoceptive processing, is more active in people with SAD (Stein, 2015). In sum, there are various alterations in the function of the self that are associated with SAD both at a content and process level.

MDMA may help address some of these self-related difficulties through fostering experiences with self-transcendence. MDMA often produces strong positive emotions and, most importantly in this discussion, *self-transcendent* positive emotions. Self-transcendent positive emotions represent a subset of positive emotions and include compassion, awe, gratitude, appreciation, inspiration, admiration, and love. Experimental research on MDMA administration shows that the single most commonly experienced phenomenon under MDMA is a blissful state characterized by feelings of pleasure, peace, and love (Studerus et al., 2010). Clinical observations indicate that MDMA often fosters an attitude toward the self and one's experiences characterized by positive feelings such as compassion (Passie, 2018) as shown in participant reports such as, "…with MDMA, I feel, even though I'm crying, I feel good" (Barone et al., 2019).

Self-transcendent positive emotions have been shown to increase perceptions of social connectedness (Shiota et al., 2007), prosocial behavior (Goetz et al., 2010; Piff et al., 2015), and encourage individuals to transcend their own momentary needs and desires and focus on those of another (Stellar et al., 2017). Self-transcendent emotions are also central to binding people to others, whether that is with a partner, children, or larger groups. Self-transcendent emotions generated through practices such as loving-kindness meditation have been shown to result in increased high frequency heart rate variability, an indicator of improved cardiac response (Lumma et al., 2015), reduced self-criticism (Shahar et al., 2015), and greater social connectedness (Hutcherson et al., 2008; Kok & Fredrickson, 2015; Kok & Singer, 2017). Since self-transcendent positive emotions focus attention on the needs and welfare of others, they may be helpful in reducing the rigid and excessive self-directed attention found in SAD (Stellar et al., 2017). To be clear, we would not necessarily expect that MDMA would reduce self-focused attention during dosing session, since an internal focus is typically encouraged during such treatment (Mithoefer, 2014). However, we would anticipate that this internal self-focusing during dosing sessions would be less characterized by the critical self-monitoring aimed at threat management typical of SAD,

but rather a more mindful and open state of self-reflection that occurs in a state of felt safety (Kirschner et al., 2019; Liotti & Gilbert, 2011). In addition, neuroscience has found that receptors connected to oxytocin and prolactin are particularly prevalent in brain regions related to self-transcendent emotions (Landgraf & Neumann, 2004), suggesting the possibility that the oxytocin and prolactin release documented in MDMA administration may explain, at least partially, how MDMA fosters self-transcendent positive emotions.

MDMA also appears to foster self-transcendent experiences (STEs), which incorporate self-transcendent positive emotions, but are broader in scope. STEs involve periods of reduced self-salience and an increased sense of connectedness (Yaden, 2017). They may also help decrease internal focus and enhance positive self-representations of people with SAD (Gilboa-Schechtman et al., 2020). During STEs, the normative experience of being a bounded, separate self is reduced; the sense of a separate self may even dissolve completely in more extreme STEs, such as mystical experiences (Nour et al., 2016). In Yaden et al.'s view (2017), self-transcendence has both an "annihilational" component that refers to a dissolution of a bodily sense of self and self-boundaries and a "relational" component characterized by a sense of oneness with something beyond the self, often with other people or one's environment. This second aspect of self-transcendence appears most relevant to the experience of MDMA as it commonly evokes an experience of unity characterized by feeling part of a larger whole, feeling one with the environment, and a sense that the future and past are dissolving into an all-encompassing now (Studerus et al., 2010). Induction of strong experiences of interconnection and feelings of closeness with others may create more enduring shifts toward a sense of shared humanity and interconnection with others, which may be helpful for people with SAD who typically feel different from and inferior to others, disconnected, prone to rejection, and lonely. One study of people in treatment for SAD found that people who reported seeing themselves as closer to others had better treatment outcomes, suggesting that shifts toward a greater sense of closeness and similarity to others may improve outcomes (Meuret et al., 2016)

Some of the self-transcendent emotions and experiences in MDMA-AT may occur in the form of self-compassion, which is likely to be particularly helpful in relation to the high levels of shame experienced by people with SAD. Experimental research has shown that self-compassion increases when people take MDMA/ecstasy (Kamboj et al., 2015, 2018) and experiences with self-compassion are commonly reported in MDMA-AT as shown in qualitative reports like, "It was really that first MDMA session that we had…where I was able to clearly see that I had a big disconnect in compassion that I had for myself. In fact, I didn't have, really, any compassion for myself, other than maybe enough just to want to try to get help," (Barone et al., 2019).

Self-compassion refers to experiencing feelings of caring and kindness toward oneself, an understanding, nonjudgmental attitude toward one's inadequacies and failures, and a recognition that one's own experience is part of the common human experience (Neff, 2003). This last aspect of self-compassion is transcendent in that it involves seeing or experiencing oneself as part of a larger whole of humanity in which one's own perceived flaws or inadequacies lose salience when embedded in a larger context. Individuals with SAD report lower self-compassion compared to healthy controls and among those with a SAD diagnosis, greater self-compassion has been related to decreased fear of positive and negative evaluation (Werner et al., 2012) and reduced social anxiety severity (Makadi & Koszycki, 2020). Further, increases in self-compassion through meditation practice have been shown to reduce anticipatory anxiety related to a public speaking task among individuals high, but not low, in social anxiety (Hake et al., 2017) and an experimental study showed that women who participated in a self-compassion exercise prior to a public speaking task demonstrated lower physiological markers of social stress than women across two other control conditions (Arch et al., 2014). There is also some preliminary data suggesting that treatments incorporating self-compassion practices may be helpful in the treatment of SAD (Boersma, et al., 2015; Koszycki et al., 2016). Taken together, these findings suggest a beneficial buffering effect of self-compassion from which socially anxious individuals were not previously benefiting.

In sum, MDMA-AT regularly induces experiences of self-transcendence and self-transcendent emotions, which may have a range of therapeutic effects on people with SAD, including reducing sensitivity to social-evaluative threat, increasing self-compassion, reducing self-focused attention, increasing a sense of interconnection with and similarity to others, and increasing attention to positive social events. Researchers wishing to study self-transcendent experiences in MDMA-AT might consider measures such as state and trait versions of the Self-Compassion Scale (Neff, 2003), Ego Dissolution Inventory (Nour et al., 2016), Nondual Awareness Dimensional Assessment (Hanley et al., 2018), Gratitude Questionnaire (McCullough et al., 2002), the blissful, unity, and percepts subscales of the Altered States of Consciousness Rating Scale (Studerus et al., 2010), the Inclusion Of Other In The Self Scale (Aron et al., 1992), Small Self Scale (Piff et al., 2015), or modified Differential Emotions Scale (Fredrickson et al., 2003).

4.3 | Enhanced therapeutic relationship

A strong therapeutic relationship has been identified as centrally important for all forms of psychotherapy (Norcross & Lambert, 2018). The therapeutic relationship has many qualities, including those related to the working environment (agreement on task and goals) and those related to the therapist-patient emotional bond (empathy, positive regard, congruence, attachment). Meta-analytic studies have consistently shown that all of these relationship elements are associated with favorable treatment outcomes. A robust set of meta-analytic studies has shown that the therapeutic alliance, a construct that includes both the therapist-patient bond and agreement on tasks and goals, is predictive of positive outcomes

(Flückiger et al., 2018). Other meta-analytic studies specifically focusing on relationship qualities show similar associations with outcome, such as empathy (Elliott et al., 2018), positive regard and affirmation (Farber et al., 2018) and congruence/genuineness (Kolden et al., 2018). In addition, some models of therapy hold that the alliance is central in fostering therapeutic change in SAD (Elliott & Shahar, 2018; Leichsenring et al., 2013).

Only few studies directly examine the association between the alliance and outcomes within SAD samples. These studies have shown mixed results, with some studies showing a positive association between the alliance and outcome (Haug et al., 2016; Kivity et al., 2020) and some studies reporting no such association (Mörtberg, 2014; Woody & Adessky, 2002). However, the sample sizes of these studies on alliance in SAD were relatively small, some of them were on group therapy, and some showed limited variability in some aspects of the alliance (e.g., Mörtberg, 2014), thus limiting the statistical power to detect effects typically found in the rest of the literature and introducing potential statistical confounds related the measurement of alliance in group treatments. It is also possible that the alliance, especially the bond component, may matter less in structured treatments like CBT that make up the bulk of the research cited above (Mörtberg, 2014). Given the strength of the findings about outcome-alliance associations transdiagnostically, it seems likely the alliance is important in treating SAD, though this has not been directly proven.

Our hypothesis is that MDMA may particularly enhance the therapeutic relationship, and specifically the therapist-patient emotional bond by initiating several processes. MDMA typically induces a state in which people feel safe around others and less sensitive to rejection, as shown in studies showing that MDMA reduces the effects of simulated rejection experiences (Bershad et al., 2016). Anecdotal reports suggest that this extends to therapeutic situations as shown in patient reports that MDMA was "very calming. That's the safest I've probably ever felt" and "I (felt) like you [the therapist] would be able to walk through hell with me." (Barone et al., 2019). MDMA-AT has been observed to reduce threat sensitivity (Baggott et al., 2016), increase disclosure in therapy, and enable people to receive both praise and criticism with more acceptance (Passie, 2018). This may help reduce the keeping of secrets that can interfere with therapy (Farber et al., 2019), which can also help the client feel more authentic. The tendency for MDMA to reduce fear in social situations may also generalize to reduced fear of compassion that is common in people with SAD and often functions as a barrier to receiving compassion from the therapist (Gilbert et al., 2011) and from oneself.

MDMA also induces friendly, playful, and loving feelings towards others (Bedi et al., 2010) and may promote prosocial behavior and generosity (Kamilar-Britt & Bedi, 2015). Accordingly, clients ingesting MDMA are likely to engage in warm and positive expressions toward therapists that will in turn trigger greater expressions of affiliative emotions from therapists, as research shows that affiliative behavior cues affiliative behavior in others (Markey et al., 2003; Sadler et al., 2009), at least in part through the operation of the mirror neuron system (Jeon & Lee, 2018). The tendency for MDMA to strengthen responses (measured at both a subjective and neurophysiological level and often called emotional empathy) to positive interpersonal situations and emotional expressions of others (Bedi et al., 2009; Hysek et al., 2014; Jungaberle et al., 2018; Kuypers et al., 2017; Wardle & De Wit, 2014; Wardle et al., 2014) may make therapist expressions of positive emotion such as compassion and liking more salient at both a visceral and cognitive level. This may also be enhanced by the tendency for MDMA to make people perceive others as more empathic of them (Bershad et al., 2016).

This enhanced therapeutic relationship should potentiate new (corrective) interpersonal and emotional learning (Christian et al., 2012) and memory reconsolidation. As discussed above, memory reconsolidation first requires that the memory is activated. If the core fear of people with SAD is that the exposure of a seemingly flawed and inferior self will result in rejection and shaming from others, then the therapeutic situation in MDMA-AT is likely to enhance and prolong contact with cues that normally elicit this fear, thus potentiating learning. In addition, MDMA may enhance the expectancy mismatch needed for memory change through reconsolidation. If the person with SAD expects that revealing their authentic self will result in rejection, mistreatment, or shame, a strong prediction error would presumably occur as MDMA enhances the likelihood the therapist will be experienced as fully and unconditionally accepting, caring, warm, safe, and compassionate.

Additionally, some models propose that optimal reconsolidation and learning is activated in the context of enough arousal to activate relevant memory traces, but also moderate enough to allow an experience of safety during the therapeutic interaction (Lane et al., 2015; Siegel, 1999). MDMA may help keep the person in this optimal zone of learning by fostering a sense that one is being authentic, thereby triggering core fears related to shame, while simultaneously creating a sense of safety in the relationship. As illustrated by one MDMA-AT patient, "I felt like I had the ability and tools, whereas before I was unarmed, unarmored, and had no support. And this type of environment, with [the therapists], the catalyst drug, and everything else, it felt as though I had backup. Now it was safe, and I had my tools and weapons to be able to tackle the obstacles that I never had before." (Barone et al., 2019).

Finally, the extended period of authentic connection with the therapist and intense experience of a dosing session could lead to lasting improvements in the therapeutic relationship. The resulting stronger relationship could be subsequently helpful in facilitating whatever additional gains could be made during following non-dosing integration sessions. This deeper connection and corrective experience may also serve as a prototype of more meaningful social relationships for people with SAD in their own lives. Researchers examining therapeutic alliance in MDMA dosing sessions might consider state measures of authenticity such as the Self Experiences Questionnaire (Plasencia et al., 2011), closeness with therapists such as by utilizing the Inclusion of Other in the Self Scale (Aron et al., 1992), or measures of therapeutic alliance such as the Working Alliance Inventory (Tracey & Kokotovic, 1989) or the Agnew Relationship Measure (Cahill et al., 2012), a less commonly used measure

of the therapeutic alliance that seems more appropriate to the relatively non-directive context of dosing sessions and which includes a subscale related to feeling free to disclose personal material to the therapist.

5 | CONCLUSION

Now that clinical trials are establishing the efficacy of MDMA-AT, it is time that researchers pay more attention to identifying possible processes of change relating to MDMA-AT. Scientific progress cannot come exclusively from randomized trials showing that a treatment works at the group level, it must also come from examining how different interventions affect different, theory-driven processes of change hypothesized to occur during treatment. This approach could enable clinical scientists to more effectively tailor in-session interventions delivered in dosing sessions to capitalize on relevant therapeutic processes enhanced by MDMA, thereby potentially improving clinical outcomes. Current trials of MDMA-AT generally feature a non-directive approach that emphasizes the role of an inner-healing intelligence purported to be activated by MDMA (Mithoefer, 2014). However, the one pilot trial that incorporated a more structured approach, cognitive-behavioral conjoint therapy, appeared promising, suggesting more structured interventions might be successfully coupled with MDMA (Monson et al., 2020). An empirical understanding of processes of change could guide how to incorporate other psychotherapy models into MDMA-AT that target processes of change found to be important in research. Research on process-outcome relationships holds the potential to guide therapist intervention based on empirical observation, an important supplement to current practice that is largely guided by clinical experience and theory. For example, if evidence eventually supported the change processes described in this paper, findings related to memory reconsolidation might be capitalized on by facilitating the activation of explicit autobiographical memories, implicit memory traces, or feelings related to the core fear of shame and rejection in SAD, while coupled with elements aimed at maximizing expectancy violations, such as imagery rescripting (Reimer & Moscovitch, 2015) or similar in-session imaginal exposure work. Alternately, if self-transcendent emotions were linked to positive outcomes, this could suggest that integration sessions might attempt to capitalize on self-transcendent experiences to build more self-compassion through experiential exercises such as chair work or meditative practices (Luoma & LeJeune, 2020). As another example, therapists might utilize an enhanced therapeutic bond to facilitate in-session self-transcendent emotions via strategic self-disclosure. We hope that by integrating a variety of lines of research, this paper will guide new predictions that stimulate future research on MDMA-AT for SAD and beyond.

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CONFLICTS OF INTEREST

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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