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# MDMA-assisted therapy for treatment of PTSD and beyond

**Edited by**
Rick Doblin, Gul Dolen, Peter Schuyler Hendricks, Berra Yazar-Klosinski, Lisa Jerome, Julie Wang and Jennifer Mitchell

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# MDMA-assisted therapy for treatment of PTSD and beyond

**Topic editors**

Rick Doblin — Multidisciplinary Association for Psychedelic Studies, United States
Gul Dolen — Johns Hopkins University, United States
Peter Schuyler Hendricks — University of Alabama at Birmingham, United States
Berra Yazar-Klosinski — Multidisciplinary Association for Psychedelic Studies Public Benefit Corporation, United States
Lisa Jerome — Other, San Jose, United States
Julie Wang — Multidisciplinary Association for Psychedelic Studies, United States
Jennifer Mitchell — University of California, San Francisco, United States

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# Table of contents

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EDITED BY
Jennifer Mitchell,
University of California, San Francisco,
United States

REVIEWED BY
C. White,
University of Connecticut,
United States
Jason Luoma,
Portland Psychotherapy Clinic,
United States

*CORRESPONDENCE
William Barone
wbarone4@gmail.com

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# Facing death, returning to life: A qualitative analysis of MDMA-assisted therapy for anxiety associated with life-threatening illness

William Barone[1]*, Michiko Mitsunaga-Whitten[2], Lia Osunfunláyò Blaustein[3], Phillip Perl[4,5], Marisa Swank[6] and Thomas Cody Swift[7]

[1]Lucin Psychology Consultation, Oakland, CA, United States, [2]Kintsugi Psychotherapy LLC, Boulder, CO, United States, [3]The JFK School of Psychology, National University, Pleasant Hill, CA, United States, [4]MAPS Public Benefit Corporation, San Jose, CA, United States, [5]University of California, San Francisco, San Francisco, CA, United States, [6]Department of Psychosocial and Psychoanalytic Studies, University of Essex, Colchester, United Kingdom, [7]School of Medicine, Johns Hopkins University, Baltimore, MD, United States

Anxiety associated with life-threatening illness (LTI) is a pervasive mental health issue with a wide impact. A spectrum of traditional pharmacotherapies and psychotherapies are available, but offer varying success in reducing symptoms and improving quality of life. We explore a novel therapy for this condition by assessing prominent thematic elements from participant narrative accounts of a pilot phase 2 clinical trial of 3,4 Methylenedioxymethamphetamine-Assisted Therapy (MDMA-AT) for treating anxiety associated with LTI. Semi-structured qualitative interviews were conducted with a subset of adult participants 3 months following completion of this trial. This qualitative analysis sought to complement, clarify, and expand upon the quantitative findings obtained from the clinical trial to further understand the process and outcomes of the treatment. Interviews were coded and analyzed using an Interpretative Phenomenological Analysis (IPA) methodological framework. Participants described in detail their experiences from before, during and after the trial, which were analyzed and categorized into thematic clusters. Specifically, participants explored what they felt were important elements of the therapeutic process including processing trauma and grief, exploring mystical and existential experiences, engaging with the present moment with reduced physiological activation, and facing illness and existential fears. Outcomes of the treatment included increased ability to cope with LTI, reduced psychological symptoms, improved vitality and quality of life, and feeling more resourced. Participant narratives also showed a reconnection to life and greater

emotional resilience in response to trauma and medical relapse. These findings are compared to similar treatments for the same indication. Limitations and challenges encountered in conducting this study are discussed along with implications for theory and clinical treatment.

KEYWORDS

MDMA-assisted therapy, life-threatening illness, psycho-existential distress, existential anxiety, Interpretative Phenomenological Analysis (IPA), death and dying, psychedelics, 3,4 methylenedioxymethamphetamine (MDMA)

## Introduction

The experience of being diagnosed with a life-threatening illness (LTI), receiving treatment, and even achieving remission can be incredibly stressful and traumatic for individuals and their support systems (1). It is not uncommon for individuals at various stages in the treatment process to develop a "chronic, clinically significant syndrome of psychosocial distress" that can present as symptoms of depression, anxiety, or posttraumatic stress disorder (PTSD) (2, 3). These symptoms have been found to occur in nearly half of patients with LTI, and can negatively impact functioning, quality of life, treatment adherence, and prognosis (2, 4). While there have been advances in treating the physical manifestations of cancer and other LTI, more support is needed in helping patients cope with the psychological and existential distress related to these conditions (5).

In recent decades, a resurgence of research into psychedelic-assisted therapies has aimed to provide novel approaches for indications that have traditionally been challenging to treat (6, 7). One area of focus in this field of study has been the exploration of using either psilocybin or lysergic acid diethylamide (LSD) in combination with psychotherapy to treat distress associated with LTI (3, 8–11). In multiple phase 2 clinical trials, researchers demonstrated the potential of a course of therapy aided by either psilocybin or LSD to safely and effectively reduce anxiety and depression in this population (3, 8–11).

Although pharmacologically and qualitatively different from classic psychedelics like psilocybin and LSD, 3,4 methylenedioxymethamphetamine (MDMA) has shown promise as an adjunct to psychotherapy for treating various conditions (12–17). Given the evidence of MDMA-assisted therapy (MDMA-AT) in successfully treating trauma and anxiety-related conditions, as well as its methodological similarities to psilocybin and LSD-assisted therapies, a pilot phase 2 clinical trial was employed to assess the safety, efficacy, and feasibility of MDMA-AT for treating anxiety and other psychological distress associated with LTI (5, 18). The trial assessed participants' scores on a range of standard quantitative measures for issues including anxiety, post-traumatic growth, and depression from before and after a treatment course that included two manualized 8-h therapy sessions combined with either MDMA or an inactive placebo (lactose) (5, 18). Quantitative findings indicated improvement for the majority of participants on primary and secondary outcome measures; however, this was a pilot feasibility study and due to a small sample size was not powered to reliably detect statistically significant between-group differences (18).

While these quantitative outcomes provide important information about the trial, qualitative studies of previous psychedelic-assisted therapy clinical trials have indicated that participants may experience therapeutic mechanisms and treatment outcomes that are not fully captured by the quantitative measures alone (19–21). Quantitative methods are not intended to provide in-depth explorations of participants' lived experiences and perspectives; rather, they focus on quantifiable treatment outcomes (22). Qualitative research has provided an important alternative perspective in exploring psychedelic-assisted therapies, as many aspects of the psychedelic experience and treatment outcomes cannot be properly captured by traditional quantitative measures (19–21).

This qualitative follow-up study was employed to provide an in-depth exploration into participants' experiences and outcomes from the MDMA-AT clinical trial for treating anxiety and other psychological distress associated with LTI. This qualitative study analyzed the 3-month post-treatment follow-up interviews of a subset of participants from this clinical trial (18). These interviews sought to explore the experience of participants before, during, and following this clinical trial, as well as document their perceptions of MDMA-AT as a treatment for psychological distress associated with LTI. The aims of this study were as follows: (1) to complement, clarify, and expand upon the quantitative findings of the clinical trial (5, 18); (2) to identify key themes in participant experiences and treatment outcomes from the trial to better understand the therapeutic process; (3) to identify perceived mechanisms of the treatment leading to sustained reductions in mental health symptoms and/or improvements to quality of life; (4) and assess the similarities and differences to similar treatments that are used for this indication.

# Methods

The individuals interviewed for this retrospective qualitative follow-up study were participants in the Multidisciplinary Association for Psychedelic Studies (MAPS)-sponsored pilot phase 2 clinical trial investigating MDMA-AT as a treatment for anxiety associated with LTI. All of the semi-structured qualitative interviews were conducted 3 months following participants' completion of the treatment. This qualitative follow-up study was approved by the John F. Kennedy University Institutional Review Board and the Western Copernicus Group Institutional Review Board of the parent clinical trial.

The parent clinical trial utilized a randomized, double-blind, placebo-controlled design with an open-label crossover protocol to assess the safety, efficacy, and feasibility of MDMA-AT in 18 individuals suffering from anxiety associated with LTI (5, 18). Participants were recruited through referrals from healthcare professionals, word-of-mouth, and internet advertisements (18).

The study design of the clinical trial consisted of two stages: the experimental stage and the open-label crossover stage. First, the experimental stage of treatment provided identically structured courses of treatment to two groups of participants that included two blinded 8-h experimental sessions with participants randomly assigned to receive either MDMA ($n = 13$) or an inactive placebo of lactose ($n = 5$), scheduled 2–4 weeks apart. In addition, participants received nine 60 to 90-min non-drug psychotherapy sessions; three preparing participants for the first experimental session and three for integration after each experimental session (5, 18). Experimental sessions involved 8-h sessions of manualized MDMA-AT with a male and female co-therapy team, regardless of if participants received MDMA or placebo. Participants' status of being in the randomly assigned MDMA or placebo groups was blinded to both the participant and the therapists. The therapeutic process is described in detail in the treatment manual (5).

Following the experimental stage and the primary endpoint of gathering data from the treatment course, the open-label crossover stage of the clinical trial began. Here, participants in the placebo control group were crossed over to an open-label MDMA-AT protocol where they could receive three MDMA-AT sessions. Participants in the MDMA group were offered one additional open-label MDMA-AT session. At the end of the trial, one participant dropped out due to progression of their illness, leaving 17 participants to receive three full MDMA-AT sessions. The five participants in the placebo group received two additional 8-h placebo sessions and nine additional integration sessions of 60–90 mins over those in the MDMA group. All MDMA sessions included the dose of 125 mg MDMA with an optional supplemental dose of 62.5 mg 90–150 min after the initial dose (5, 18).

## Data collection

A subsample of 10 participants from this quantitative study was selected to be interviewed based on the date of their final drug administration session. The first 10 participants (of 17 remaining) to complete the clinical trial were recruited to participate in qualitative interviews; all 10 agreed and completed these interviews 3 months following study completion. An interval of 3 months was chosen so participants would both have a recent connection to their experience in the trial as well as perspective on outcomes. Participants were informed that this interview was optional and would not affect their involvement in the quantitative study. No financial compensation was offered, and there were no penalties for declining to participate. All volunteers gave their informed consent prior to participation. Of these 10 interviews, two were excluded for technical complications (one recording was unusable due to taking place on a poor internet connection and another interview failed to record). Data collection followed standard practices highlighted in both the literature and in similar studies (19–21, 23, 24). Interviews were conducted through Zoom (an online platform for video conferencing) by a qualitative researcher not associated with the clinical trial, lasted between 1 and 2 h, and were video recorded to later be transcribed and de-identified before being provided to the research team.

Interviews followed the Semi-Structured Interview Guide (Appendix B) developed for this study, which included a number of semi-structured, open-ended questions designed to address the general nature of participants' experiences from before, during, and after the treatment, and allowed space to explore any topics that emerged during the interview. This ensured key topics were addressed while allowing participants to share the unique aspects of their individual experience. Questions included inquiries into participants' lives prior to the study to understand their lived experience with LTI related difficulties, explorations of the phenomenology of the MDMA sessions themselves, and how those experiences were integrated in the following 3 months. Examples of questions include "Can you give me a sense of what life was like prior to the treatment sessions," "Can you describe in detail your experiences during (this/these) treatment session(s)," and "In what ways do you feel the study has affected your life since the sessions?" (Appendix B). The interview format was designed to allow participants to reflect on the nature and meaning of their experiences in a safe and supportive environment within the convenience of their homes.

## Coding and analysis

Of the eight usable interviews, six were chosen at random using a web-based randomization system, transcribed, de-identified, and sent to the qualitative research team for coding

and analysis. Using a model for assessing qualitative study sample size in Interpretative Phenomenological Analysis (IPA) studies (23), as well as the concept of Information Power for developing a qualitative study sample (25), it was determined that a sample size of six would be most appropriate for this analysis. This sample size allows for a balance between providing an in-depth examination of the phenomena from each participant's perspective while also comparing and contrasting between participants.

These interviews underwent coding and thematic analysis by the five-member research team. The research team developed an initial codebook based on their review of the first available transcript. Codes were derived both top-down from interview questions and a model codebook developed for a similar study (19), as well as bottom-up from patterns and themes found in the interviews. Codes were purposely designed to be broad rather than narrow categories. For example, a code of *Psychological Symptoms (Psx)* was used that can capture a wide range of symptom types, rather than having individual codes for specific symptoms of each diagnosis. Using broad codes allows for themes and categories to come directly out of the data, rather than data being pre-categorized by the code structure.

The research team individually coded the first interview, then met to discuss any additions or alterations to the codebook. The research team then finalized the codebook (Appendix C) and developed a model of inter-rater agreement before coding further interviews. The codebook was applied to each interview transcript by a minimum of two researchers using standard practices (19, 23, 26), with the two raters coming to consensus on a unified set of codes before being submitted. Codes and themes were discussed among the team at weekly research meetings to maintain continuity among coders and discuss complicated coding examples. The final codes from each transcript were developed into themes designed to capture the nuances of phenomenological experience from the text of each participant. Themes were then clustered into groups based on commonality and patterns of convergence and divergence. Patterns and connections in themes were analyzed across cases, resulting in a master list of themes for the group. Themes were assembled into multiple categories across time frames of before treatment, during treatment, and treatment outcomes.

A computer-assisted qualitative data analysis software package, MAXQDA 18.2.0, was used to assist in data analysis of the interview transcripts (27). This program helped organize data to identify emerging themes, assess interrater reliability, develop tables of co-occurring codes, and provide an opportunity to easily search through large amounts of data.

## Methodology

This study utilized an Interpretative Phenomenological Analysis (IPA) approach, which was informed by previous qualitative studies of psilocybin-assisted therapy (psilocybin-AT) for anxiety associated with LTI (20, 21) as well as MDMA-AT for PTSD (19). The IPA framework is ideal for characterizing participants' experiences and perceptions of their treatment as it focuses on a *double hermeneutic*: the researcher making sense of how participants make sense of their own experience (23). IPA has been called a "qualitative methodology of choice in healthcare research" and has shown to be useful in analysis of novel treatments such as MDMA-AT as it illuminates the meaning participants make of their experiences in the trial [(22), p.214].

## Participants

The six participants who took part in this qualitative study completed the phase 2 clinical trial of MDMA-AT for anxiety associated with LTI within the previous 3 months and completed both the experimental and open-label crossover stages of the trial. All participants met inclusion criteria for the clinical trial, including having a diagnosis of life-threatening cancer or non-dementing neurological illness that could be ongoing or in remission with a possibility of recurrence, and a prognosis of at least 9 months life expectancy (Appendix A). Seventeen participants had a diagnosis of neoplasms and one participant had a diagnosis categorized as a musculoskeletal and connective tissue disorder. Participants also all scored above 45 (of 80) on the the State Trait Anxiety Inventory (STAI) Trait Subscale, indicating moderate to severe anxiety, which was determined to be secondary to their LTI through a structured clinical interview. The 18 who participated in this clinical trial had a mean age of 54.9 years, 14 were women, and four were men. Upon entering the trial, medical histories indicated that many of the participants were previously diagnosed with anxiety (83.3%), major depression (77.8%), PTSD (72.2%), or insomnia (61.1%).

Of the six participants included in this qualitative study, 100% had a cancer diagnosis in various stages of treatment, and all experienced significant psychological distress related to their LTI. Five of these participants had been in the MDMA group of the trial and one had been in the placebo group, with all of them ultimately receiving three MDMA-AT sessions. All of these participants identified as women, with five identifying as White/Caucasian and one identifying as non-White/Armenian. Participant data for the interviews were de-identified before being sent to the research team, and as such, further demographics were unable to be obtained.

# Results

In their qualitative follow-up interviews, participants explored their experience from before, during, and after their treatment in the clinical trial. All participants ($n$ =

6) in this sample described improvements in their mental health symptoms, quality of life, and general functioning, and unanimously credited this treatment process with helping them achieve lasting improvements. Qualitative analysis illuminated what participants felt were important factors relating to psychological symptoms stemming from their LTI diagnosis, the process of treatment with MDMA-AT, and their perceived outcomes of the treatment.

While our complete qualitative analysis explored a range of experiential themes, the following categories were chosen to demonstrate the most frequent, essential elements of participants' experience of the treatment and outcomes reported. Some quotes have been edited to remove filler words, and participants are listed by a de-identified participant number.

## Participant experiences with LTI prior to MDMA-AT

During the interviews, participants recounted their experience of challenges relating to multiple aspects of their LTI prior to participating in the MDMA-AT trial. All participants ($n = 6$) reported that their primary psychological symptoms were a direct result of their experiences with their LTI diagnosis, treatment, and/or remission, and that these symptoms caused substantial impacts to their functioning and quality of life.

### Psychological symptoms associated with LTI prior to MDMA-AT

All participants ($n = 6$) described negative impacts to their mental health immediately upon LTI diagnosis and pointed to the process of LTI treatment as a cause of increased severity of psychological symptoms. In particular, four of six participants described experiencing anxiety and trauma associated with the medical treatment process, and five participants described depressive symptoms secondary to their LTI diagnosis. Three participants described additionally having previous trauma or anxiety related mental health symptoms.

Participant 2 illustrated the sudden impact of being diagnosed with leukemia, recounting that "it felt like someone had kidnapped my life… I felt pretty stopped in my tracks and just in survival mode." Participant 1 had a similar experience of feeling a sudden and drastic change in her life and immediately struggled shifting roles from being an oncologist herself to being a patient. She remembered, "I went from doing grand rounds two nights before my operation to my whole life changed… It's just having the rug pulled out from under you."

Four participants recounted how their experiences with ongoing treatments, difficult physical symptoms, and feelings of hopelessness within the medical system led to symptoms of PTSD. Many participants described classic PTSD symptoms of avoidance, re-experiencing, and hypervigilance around their illness. Participant 3 recounted the impact of the initial process of diagnosis and how this had led to ongoing challenges:

> There is also PTSD around having a doctor tell me something horrible has happened to me. I mean I had horrible anxiety when I had to go see this neurologist. I just was like "I can't do this, I can't go." I was convinced I was gonna be told–it seems like I was believing that was all happening to me again.

Participant 1 shared how the process of scans and procedures in her medical treatment led to anxiety and trauma related symptoms: "Just in the anticipation of things I would become extremely, extremely anxious, and just kind of paralyzed, and really avoidant."

Participant 2 expressed feeling that the trauma symptoms from her medical issues and surgeries could have impacted her prognosis, explaining, "I feel like the compounded trauma had just become stuck and fragmented. That wasn't allowing my body to do the work it wanted to do."

Four of the six participants were in the remission stage of illness at the time of their interviews, and three described how even this phase of their experience sometimes led to more pronounced anxiety than they had previously in their life or course of treatment. For instance, two participants articulated the experience of feeling stuck in limbo, ambiguity, and a constant state of anxiety around returning illness following their cancer treatments. Participant 3 explained feeling stuck after remission, remembering, "I had these visuals of me being in this kind of purgatory. Like where am I? I don't know if I have cancer or if I had cancer." She described the impact of this experience:

> To have to carry around this demon of death that might strike at any minute. And the thing with breast cancer is it typically comes back in your brain, lung, liver or bones. That means if you have a headache, if you have knee pain, if you have a cough, those could be potential signs of metastasis… I had my first two or three terrible scares, where I got a headache and I rushed to the hospital. And I was like "it's gone to my brain." I had a couple of those happen to me and I was just like, "I don't know how to do this." Like I don't know how to move forward from this and just go back into my life.

### Impacts to quality of life

All participants ($n = 6$) described how their LTI experience significantly impacted overall functioning and quality of life. In particular, participants described notable impacts to their relationships, ability to work, and engagement in meaningful activities. Participant 2 reported, "it affects every area. Like obviously the pain, but your life and how much you're able to work and then your income, my availability as a friend and relationships. The vicarious trauma for my family."

Participant 6 expressed how deeply she was impacted by her LTI:

> I was merely going through the motions of life. And sometimes not even doing that. I mean there was this period where I wasn't even getting out of bed. I couldn't think of a reason to get out of bed.

Participant 3 recounted a similar experience, remembering that the LTI and treatment process felt paralyzing: "I was paralyzed, I couldn't see through it, and I couldn't live my life… I couldn't parent my kids, I couldn't focus on anything. I mean I had a real mental illness, acute, short-term mental illness."

### Motivation for participating in MDMA-AT

Participants described coming to the study by varying routes. Multiple participants explained that they needed a different kind of support than what they had previously been offered, feeling that the unique type of existential distress and trauma related to LTI needed a special type of treatment. Participant 3 explained,

> I didn't really feel like going to a therapist and like once a week talking about my cancer. That just felt droney and it didn't feel appropriate. To me that feels like how you can deal with normal issues, but this is not a normal issue. This is a big, big thing. And (MDMA-AT) to me felt like a really big, big way to respond to a really big, big thing.

Some participants had read about MDMA being used for PTSD and considered how it could heal emotional wounds. Participant 2 described the need to address her trauma associated with the medical issues and surgeries:

> My first intention with going into this study… I needed to disrupt this trauma loop. Because the trauma on top of trauma on top of trauma, you know my nervous system just felt like a five alarm fire happening.

Participant 1 reported hearing accounts of the effects of MDMA and considered how they could benefit from the medication:

> What motivated me at that point was this idea I was gonna die not being able to feel or be comforted or trust or heal, like when you have that kind of diagnosis you don't expect to be healed, but there's something in me that wanted to be more whole.

## Experience during MDMA-AT

During their interviews, participants described their experiences during each MDMA-AT session and recounted elements of the experience they felt were pertinent to their process. Participants highlighted themes including the importance of the MDMA experience ($n = 6$), relationship to their illness ($n = 6$), processing trauma ($n = 5$), reconciliation with life and death ($n = 6$), mystical experiences ($n = 5$), reclaiming of presence ($n = 6$), and their relationship with the therapists and study design ($n = 6$).

### The MDMA experience

When considering her experience with the MDMA-AT in relation to other therapies she had been through, Participant 5 recounted, "Even though I'd been to therapy in the past for different reasons and I'd gone to these support groups and gotten a lot of really great help and insights… this particular experience basically just blew open the walls."

Thinking about the role of the MDMA in the treatment process, Participant 6 considered,

> I think it gets us out of the way. It gets our personality, our story out of the way, so that we can remember what is essentially so. That the oneness of everything is just so. There's nothing that can interrupt that. And we're already whole, as broken as we may be. That wholeness is always accessible. But it's all the stuff, the trauma and the wounding and all the fear and the angst and all of these things that are responses to events, that get in the way. So it helps us to be able to access the truth that's already there.

Participant 1, who had described feeling emotionally isolated through much of her life and having a hard time connecting to or sharing emotions, recounted that during the MDMA-AT sessions, "It's just like it all came out. One story after another, patients, kids, and dying. All the things that had ever stuck to me were there for me to talk about. So, it was a really profound experience." She explored what it felt like to help get to that place:

> Fear was gone. Just the constant fear of the whatever must be, the overdrive, or the abnormal. That sense of fear being triggered or taking over. And that was gone. It was like I was looking around, like not outside, but I was looking around in my brain, in what's created out of the brain, you know, like the physical sense of it. So not just like how trauma works, but how everything works, like I had a feeling or an experience that I could see how everything works. Everything I've ever studied, or know about, or been exposed to, I could see everything worked and how it all fit together. It was an incredibly expansive experience, and I can't say it was an intellectual experience, it was like a mind experience. But the vehicle was my body. People ask me if it's spiritual. How could it not be, right? But it was also coherent and it was logical.

Participant 2 described that coming into the MDMA-AT sessions, she could sometimes see her "East Coast Work Ethic" come in, feeling that she had to work hard to get the absolute most out of the sessions. She remembered telling herself, "Okay, now you have to get to work and run each of those traumas through. Like we're gonna heal each one of them individually." She remembered that in response to this, "The medicine kept saying, 'No you don't, it doesn't matter. It doesn't matter.' And I felt such relief in that. This is the healing. Just allowing yourself to be here." She remembered, "this was a big theme to the worker bee in me, there's nothing to figure out. The words that kept coming through all the sessions were trust and allow, just trust and allow it to happen."

Participants also described going into the MDMA-AT sessions feeling that they were supposed to focus completely on their illness, death, and existential issues, given the focus of the study. However, while portions of the sessions did focus on those issues, the non-directive style of the treatment also allowed for other important content to arise during the sessions. All participants ($n = 6$) reported that allowing for focus on other issues from non-LTI trauma to attachment issues was also integral to their healing process. Participant 3 illustrated this:

> I've had all these other things that came out of it that I didn't have any intention around addressing at all. I didn't even know they were issues. I feel like I've just gotten so much from it. It's such a gift, such an extraordinary gift.

## Relationship to illness

While the interviews showed that participants' relationship with their LTI shifted in the long term, all participants ($n = 6$) also described that relationship evolving in real time during their MDMA-AT sessions. A notable example of this process occurred for Participant 2, who expressed an important realization in one of her MDMA sessions that her LTI was not the entirety of her identity. She recounted a feeling that "It was really clear. My health challenges were not defining me." Participant 3, remembered having an illustrative vision during an MDMA session and said, "Behind me is the cancer and it's this thing in the past. It's contained back there. If I look and turn around, I can see it. But it's almost fortified because it ended. It's a thing that's stopped."

Participant 5 also had a momentous realization during an MDMA-AT session about how she could relate to her cancer:

> The biggest thing that came up, and it was huge… my big epiphany was that I wasn't going to die from cancer. Something that wasn't going to kill me anymore. Like all along I was like "what have I done?" and "what am I doing?" Like I made this happen. And just being afraid of eating a little cookie or something, because sugar feeds cancer, right? Or having a drink, you know, not taking that pill that I had to take everyday and stuff. I got a real sense of my body and where it's weak and what I need to work on. But I just knew that the cancer wasn't going to kill me. It wasn't going to come back and kill me.

Participant 3, who was actively in remission but experienced considerable anxiety about cancer recurrence, talked through how she sensed her body during an MDMA session that led to a positive change in perspective:

> The first thing that happened was I did this body scan. So I went into my body and I traveled through it and started at the tip of my toes and circled around each of my little foot bones and in and out of the tendons and the tissues… I could see it so clearly. And I could see the colors so brightly. They were just like bright blue and red. I traveled all the way up through my legs, like through the area where my ovaries used to be… through my liver and my lung and stomach… and it was all so healthy and vibrant and my life force was just like sparkling. Literally there were sparkles… I finally went up to my beautiful brain and it was so clear. There was no cancer anywhere and there was just health.

## Processing trauma

With the clinical trial focusing on anxiety associated with LTI, many participants expressed surprise at how much of their sessions ended up naturally focusing on trauma processing. All participants ($n = 6$) described traumatic experiences related to their LTI diagnosis, treatment process, and/or experience of remission, and three participants also shared past traumas that were unresolved at the start of the study. Each participant described how the study allowed them to process compounding emotional wounds in their lives from their LTI and beyond. For example, Participant 4, who experienced many traumas throughout her life as well as from her LTI, described how accessing traumatic memories was more achievable with this treatment than her attempts with regular talk therapy:

> The connection I felt with previous traumas and health things was also palpable. Which is something that you don't get in talk therapy. It just doesn't happen. Very, very uni-dimensional compared to the multi-dimensional aspects of the MDMA therapy… I was able to talk about traumas that I had experienced earlier in my life, that I had not been able to talk about at all before…What happened as a result of the second session is that I said to Therapist 1, "I think you wrecked my [trauma] story," which is not a bad thing because it wasn't a good story, it wasn't one I wanted… I knew at the end of the third [session] that I no longer had PTSD and it was gone. It was just gone… A huge, huge burden had been released. I had been carrying that around.

> It had just been so awful to hold that inside. Letting go of that story just freed up a lot of energy. It was truly amazing, truly amazing, and completely unanticipated.

Participants described how MDMA-AT allowed them to confront and make meaning of their traumas in a new way. For example, Participant 1 discussed how during her MDMA experience, she was able to confront memories and emotions related to a near-fatal sexual assault which occured over 20 years prior. She was explicit in exploring how her early traumas contributed to the anxiety she felt when diagnosed with an LTI, and was able to differentiate them:

> We went right into my past, childhood, early adulthood, a big trauma I lived through. And then it started to become way more clear why I had made all these connections and the puzzle of my anxiety became very clear, like the origins of it. And it quite separated itself from the cancer experience.

She continued,

> I had never had that experience before, where I could just sustain, trust, and listen and tell the whole truth or emotional truth or say exactly how I was feeling. That was MDMA, for sure. I would not have ever been able to do that. I had never really told the story [of my assault] to anyone–I didn't have access to those memories. They were more like a distant story. Like I knew the content, but I had never really had access to how I actually felt when it was happening. So, the second session was a big breakthrough.

Referring to her process of facing the trauma of battling cancer during her MDMA-AT sessions, Participant 2 considered, "It's not like [MDMA] erases a memory, but it takes the claws out so it doesn't own you anymore." Explaining her experience of how the MDMA contributed to her ability to process this trauma, she remembered the medicine "allowing the body to have experience that contradicts anxiety and trauma. That's really what I had… these affirming experiences are deep and visceral."

Arguably the most important factor of trauma-informed psychotherapy is for patients to feel a sense of safety (28, 29). Participants in this study pointed to feelings of emotional security during the treatment as an aspect of MDMA-AT that helped them come to important insights and process trauma. For instance, Participant 5 described the treatment: "like Heaven in a way. It was like, I felt so safe. In such a safe environment that I realized how unsafe I felt most of my life." Participant 2 recounted this importance of safety in her process, remembering, "that was kind of a big theme for me, feeling safe in my body. That's what I experienced with the medicine. For the first time in years and years and years." Participant 1, who had described considerable challenges with being vulnerable and trusting others through her life, looked back on her sessions and reported,

> I took the MDMA and that trust, I can even feel it now, that feeling that the fear is gone and the trust and the desire to connect with people just came online. And then the rest of it is like working out the details, pretty much.

## Reconciliations with life and death

All six participants said that during the MDMA sessions they were able to interact with and consider the concept of their own death without the fear, anxiety, and dissociation that they had previously experienced. In one example, Participant 3 was able to utilize the feelings of emotional safety occasioned by MDMA to fully confront her fear toward and accept the reality of death, reporting:

> While I was in [the MDMA session], I realized that I could consider my death. Like I could go in there and consider it. So as soon as I had that idea, I was like, "Okay, I want to talk to them about this." So I sat right up and I was like, "Okay, let's talk about this. What would happen if this cancer came back and I died?" And we just had this whole conversation about it. And we got to the fear, like what was the worst thing about that scenario?... "Okay, my kids, I'm giving them so much. I've given them so much, and they are really gonna be okay."... I realized I didn't have a ton of fear about me not living anymore… not that I want to die, I love life.

Participant 1 also described coming to a deeper understanding and comfort with the concept of death from the expanded and non-reactive perspective offered by MDMA:

> It wasn't drama. It was just the human condition, and illness, death. I was seeing my life-long inquiry into life and death from this very expanded place. And it's as if I had these invisible lines of architecture of how consciousness works.

Participant 2 described feeling a deep acceptance with the potential of death: "I remember feeling after the last session if I died tomorrow, which I'm not invoking at all, but like I would feel happy and complete in this." She considered a notable feeling from the sessions that contributed to this sense. She remembered, "there was a real, real sweetness. The messages I was getting were like a Mother Goddess thing, like, 'I got you, you're okay, you're gonna be okay.' I remember just saying, 'I'm okay, I'm gonna be okay."' The authentic acceptance of death she experienced in the trial led her to feeling alive again: "I just felt like in a lot of ways I was feeling more hopeful and excited and I guess had a reset button on life. Just feeling alive after not is pretty amazing."

## Mystical experience

While research on psilocybin-AT shows that having a mystical experience (ME) during the session is correlated with producing positive outcomes (21, 30, 31), previous MDMA-AT studies for PTSD suggested that ME was not correlated with symptom reduction (19, 32). ME also appears to be less prevalent in the use of MDMA than in psilocybin or other classic psychedelics (33–35). However, all but one participant ($n = 5$) in this study reported that some dimensions of ME were present in their sessions and felt these experiences may have played a role in the process of healing. Prominent ME descriptors from the study data include feelings of unity and interconnectedness with all people and things ($n = 5$), a sense of peace and joy ($n = 4$), a sense of sacredness ($n = 5$), ineffability ($n = 5$), an intuitive belief that the experience is a source of objective truth about the nature of reality ($n = 5$), and a sense of transcending normal time and space ($n = 5$).

For example, Participant 2 described a sense of unity while experiencing the medicine, feeling she was "being fueled by everything. The whole interconnectedness piece. I know that people talk about meeting a divine more with psilocybin, but this was absolutely like a million percent me being reconnected." Participant 5 also described a sense of universal merging, remembering, "My body became, it was almost like it was part of everything. It's like to become, like I am the stars and the sun and the trees." Similarly, Participant 6 explained, "I became the earth, giving in this really abundant way that the earth gives us.… All these different people and things that I was. I was a hummingbird and I was the orchid." She considered the connectedness she felt from this experience, "it was a huge exercise in walking in someone's shoes. And really taking that to heart."

Participant 1 described her experience of altered perception and awareness:

> I was aware I was in a state of consciousness very much grounded in the witness. And I saw all the dimensions of the transpersonal state and different states and stages of consciousness. And I wasn't traveling through them but it almost expanded to fill the whole house and it was my mind. And I retained my autonomy.

While not commonly expressed in a previous qualitative study of MDMA-AT for PTSD, multiple participants in this study described transcending space and time in their MDMA sessions (19). Participant 1 vividly recalled an illustrative experience during her second MDMA session,

> I went through a sense of breaking through into a very warm feeling in my chest. And that was quickly an entry into the very cavernous, spiritual state. And then it was just a series of traveling. It was a physical experience. It just was like I was passing through gateway after gateway. It had the sense of going down, like sort of feeling everything deeper, but it was all centered here. And then I would enter into different realms, and I decided to call them that. Very visual, very vivid. And it's like you could spend lifetimes there, it was incredibly beautiful.

While ego boundaries seem to be loosened, the concept of self did not appear to be entirely absent in the MDMA experience. For instance, Participant 1 explained, "So I was 'I' throughout the whole thing. I could see myself, I could hear myself. They ask lots of questions about experiences of oneness. I mean it was definitely an experience of oneness and connectedness."

## Reclaiming of presence

When describing their experiences prior to the clinical trial, many participants ($n = 5$) described various aspects of feeling separated from the present moment, either through dissociation, avoidance, or perseveration on the past or the future. Participant 3 illustrated this experience in remembering "feeling caught in the past and the fear of the future, and not living in my present moment" before MDMA-AT. During treatment, all six participants reported feeling a reclamation of the present moment and a reconnection to self and life.

For example, in recounting a moment during an MDMA session, Participant 2 shared that she was able to connect mindfully to the present, remembering the feeling of "finally feeling what it feels like to be in the present and not the past or the future… I felt like all of me is here, if that makes sense. Whereas I felt like I was so fragmented before."

Similarly, Participant 5 described how the MDMA helped her to come into presence with herself:

> Just trying to love, or be compassionate right now instead of worrying and thinking about what might happen. Being everywhere else but right here. And that's what the MDMA helped me with, was to bring me right back to myself.

Participant 3 felt the spiritual nature of having the ability to truly engage in the present:

> The being present piece was just, the emotion that I have with that, is sort of like euphoria. Like I feel so much awe. You know, it feels divine to me. It feels very spiritual and divine, more than emotional. Under the MDMA, I went to

> this visual place of–and this is so clear for me, this very clear and open plain. With light pouring down on it, which is my present space. And it's just, it's me and I'm healthy.

## Experience of the study design and therapists

In their interviews, participants also considered how the treatment design contributed to a process of healing. All participants ($n = 6$) expressed an understanding that the MDMA is only one part of the system, and that without the other parts of the treatment, it may not be as beneficial. Other important aspects of the treatment process that participants described were the trusting relationship with the treatment providers ($n = 6$) and the container of the study design ($n = 6$).

Participant 4 highlighted the importance of the treatment design and therapists, explaining, "the intensive 6 h with two therapists, that was a tremendous opportunity to go very deeply as well." She added, "I know MDMA created that safety, that was so essential. I loved the way the study was set up. I thought it was so perfect, that there was time to process in between, and to establish a relationship initially."

In describing the deep emotional connection Participant 4 felt with the therapy team, she expressed,

> The connection I felt was a significant part of why I think it was effective. The connection I was able to establish with [the therapists] and them with me, was very deep and very spiritual and very loving and palpable.

Participant 1 also reflected on the importance of the factors beyond just the medicine, explaining,

> It's a triad that was critical for me. The very tight container. A very controlled environment. And then the second part was the skill of the therapists and the devotion. And then the third piece was the medicine. And I would say that the connectivity with the people was as important if not more important than the medicine.

Continuing to describe the importance of the therapeutic relationship and the impact this had on her experience, Participant 1 recalled of the study therapists, "I felt their dedication and I could see it, and obviously I benefited from it and we developed a very close bond. I think for someone like me, they were the perfect guides."

Participant 3 felt the therapist team emulated parental roles that she felt were important to her healing process:

> They were very Mom-Dad for me. Like she's very nurturing and kind of holds space for me emotionally. And then [he] would kind of have this ridiculous sharpness and he would come out with these things, and I would be like, "Oh my God you just blew my mind," like over and over.

# Treatment outcomes

Qualitative analysis of these participant interviews illuminated a range of outcomes from the treatment that complement and expand upon the results of the small pilot clinical trial. As was displayed in previous qualitative explorations in the psychedelic sciences, many important outcomes can be difficult to discern from quantitative symptom scores alone, as these treatments involve complex processes of growth and change that can expand beyond symptom reduction (19). Exemplifying this is that the entire sample of participants ($n = 6$) credited this treatment with significant positive changes to their life, while the quantitative outcomes indicate mixed results on outcome measures (18).

Participant 2 illustrated this change by telling, "I can gush on for a long time about the depth of my gratitude… and how much it's given me back my life. But not the same life as before, but in probably a deeper way, even." Participant 6 also reflected an experience of feeling the MDMA-AT allowed her to get her life back and feel like herself again:

> There's no way I would be where I am right now without this medicine. I would not be. So it feels like it's given me back my life. Not that old life, because that old life is gone, but it's given me back, me.

Participants described qualitative improvement in their Management of Medical Symptoms and Relationship to Illness ($n = 6$), Psychological Symptoms ($n = 6$), Vitality and Quality of Life ($n = 6$), and Self-Awareness ($n = 6$). Preparatory and integrative therapy sessions, strong rapport with the therapy team, and the beneficial effects of MDMA in the treatment process were perceived as factors in aiding long-term benefit.

## Management of medical symptoms and relationship to illness

All participants ($n = 6$) reported that they experienced considerable challenges in coping with medical symptoms and their illness trajectory prior to MDMA-AT. Each participant described an ever-present awareness of their illness that impacted their mental health, identity, and functioning. These participants explained how they witnessed the ways in which they related to their illness evolve throughout their experience of the trial. Regardless of the trajectory of their illness, each participant described improvements to how they managed their medical symptoms and related to the illness following the trial.

Five participants described that prior to the clinical trial they became hypervigilant to medical symptoms, with physical discomforts such as headaches sometimes triggering panic attacks or hospital visits. Participant 3 described a change in her emotional response to physical symptoms that were unlikely to be caused by cancer:

> I think in a different time I would've been anxious about that. And I just really—I really wasn't. I was like, it should pass, like it usually does. If it doesn't pass, then again, that's something I will have to face when it doesn't pass. Which is something that would be in my future, which is not happening right now. So I just was able to kind of like, really put the re—not even reframe it, just frame it.

This was echoed by Participant 1, who noted a shift in her response to medical symptoms and treatments as well as a reduction of anxious perseveration on health issues:

> I still have to handle the neuropathy and the pain at night and stuff like that, and I've got issues, of course radiation. But it's just not taking up a lot of real estate. I'm not so focused on those problems. I think the anxiety was making me glom onto them before. So now I think I'm just a little healthier about my attitude to it.

At the time of her interview, Participant 2 continued to face challenging medical symptoms and treatments related to her cancer. She noticed how she was managing these events differently following the MDMA-AT trial:

> I feel really strongly that even though I'm having some [cancer] symptoms, and they have to do treatment, that the healing from the [MDMA] sessions is still happening. I can't emphasize that enough. Like I can feel it. Even in the midst of symptoms that are causing me pain or discomfort, or make me scared or whatever, I feel very resourced. The healing is still happening.

Prior to the trial, many participants described how their medical issues became a large part of their identity. They felt that much of their world revolved around dealing with symptoms, going through treatments, or focusing on the challenging psychological and existential aspects of the experience. Participant 6 described that even amidst continued medical treatment, she noticed a very different relationship with her illness:

> It feels like the cancer is something that happened to me… I'm not paying a whole lot of attention to it. I'm just not. I'm still on hormone therapy and I'm supposed to be on hormone therapy for 5 years. I'm living my life. I just don't pay a whole lot of attention to it… [it's] no longer consuming me or defining me.

Participant 4 talked about how the change in relationship with her illness allowed her to have hope about living that was previously impacted by fear. She felt this changed her intentions in life altogether:

> The hope that I have, and the lack of fear about living. My intention now is to live, and to live a good life. And I feel confident that I can do that. Whereas before I didn't believe that at all. And I think it would have affected my physical health.

## Reduction in psychological symptoms

In addition to meeting criteria for moderate to severe anxiety as inclusion criteria for the clinical trial, participants described a range of psychological symptoms that stemmed from their illness and process of treatment (18). Four participants shared they were also struggling with mental health issues that pre-date their LTI when the study began. All participants ($n = 6$) described that through the course of this study they experienced a noticeable reduction in psychological symptoms related to their LTI as well as other issues.

In considering her experience of change in this treatment, Participant 1 reflected, "the focus on the cancer anxiety and that whole thing is completely resolved, and even more than I would have hoped for." After previously having debilitating anxiety and trauma symptoms related to medical issues, she felt her nervous system was no longer overactive:

> I don't have an internal reaction where I'm clenching and just super uncomfortable and all that autonomic activity going on, or shame, or limbic hijack, or however you guys say it, is not happening anymore. That's definitely MDMA, because that's a big shift.

Participant 3 described a very similar experience, recounting, "I feel like when I hit moments where I used to struggle, I'm able to navigate them without getting anxious, so I really do feel strong." She spoke about noticing a change in her anxiety response to having a cancer scare:

> It just didn't bring me any feeling of chest tightening at all. So I feel like that chest tightening, adrenaline rush pattern is just not—I just don't feel it happening. I feel like I stay in a calm place while I kind of frame it. And then it's framed, so I don't need to accelerate…Reframe, stay here, not happening right now, if it happens, that would be down there, not now. And then I just stay down here.

Five participants described debilitating issues with depression either before their LTI or as a result of it and saw changes to their symptoms of depression in moving through this treatment. Participant 6, who said that she was previously "merely going through the motions of life, and sometimes not even doing that," explained her current experience of depression:

> Gone. It's gone. It's gone. The depression is gone. And that doesn't mean that I don't have stuff going on in my life that troubles me, but it feels like the normal way that I've always been with stuff. Sitting here now, it felt like some alien energy invaded my life and came in and took over my life. And those aliens are gone.

Participant 4 also considered how she could be impacted if her depression did not improve:

> Had I gone on to be as depressed as I was, if I hadn't actually taken my own life, it wouldn't surprise me if the cancer came back. Whereas I think the chances of that happening are lessened significantly by the change within me.

Many participants expressed a clear recognition that while these improvements are present, that in most cases continued work on these long-standing psychological issues needs to be done. Participant 1 expressed this around the long-standing trauma work that was uncovered and worked on in the MDMA-AT sessions:

> Uncovering that earlier trauma, I think I have work left to do with that. And that I can see how it shows up, it's a lot of digesting for decades of the effects of it. So, that is not finished, but I wouldn't have had that as an expectation, that it's finished. But I feel it's very workable now. In a way that wouldn't have been possible before.

Participant 6 described her experience of ongoing anxiety and panic, but how her response to these symptoms has dramatically changed following this trial:

> The anxiety, I did actually have a little panic attack at one time. It's the only one that's come up since. And I was removed from it, I watched it. I said, "Oh, it looks like I'm having a panic attack right now." And then right after I said that outloud, "No, I don't think that's gonna happen." And then I just watched the whole thing, I felt the whole physical manifestation of it. And then watched it go.

## Improved vitality and quality of life

All participants ($n = 6$) described the ways in which their LTI was a detriment to their quality of life, impacting social relationships, mental health, energy, passion, and vitality. They all report improving their overall quality of life and feeling more able to embrace life once again as a benefit of this treatment. Participant 1, for example, shared, "the knowledge that I was alive was very solid. And I wanted to be alive and I had this big life-force in me." She felt more connected with people and the intrinsic vitality within her:

> I took the MDMA and that trust, I can even feel it now, like that feeling of the fear is gone and the trust and the desire to connect with people just came online. And then the rest of it is like working out the details.

Participant 2 also felt more connected with the people in her life and reported that they took notice in her sense of passion and engagement with life following MDMA-AT:

> I mean my family and friends after that, like I felt better after that session than I had felt in years and years and years. And everybody noticed. Energetically, what I had said, my level of engagement, my level of aliveness and passion. And, yeah, everybody noticed.

She realized that MDMA-AT helped her gain access to an aliveness she has not felt since before her LTI diagnosis, recalling: "I'm feeling more alive than I have for years and my experience with the medicine is helping me access my bright spirit and the wild mind that came through me as so much bigger than the pain."

Similarly, Participant 4 noticed feeling much more able to engage in relationships as well:

> I feel so much more social. I have had a lot of great conversations with my friends and family and my relationships with them have gone much deeper. And I've felt absolutely like a different person in terms of my ability to get in touch with how I feel and communicate that. It was something I just could not do before, I didn't know how I felt.

Participant 4 continued on to share how she feels a renewed sense of energy and happiness following MDMA-AT:

> I felt physically lighter. I had so much energy I don't know what to do with it. I'm so happy. I mean I used to be involved in all kinds of things. And I'm back to that again, after all those years when I was incapable. So, it's real clear. I'm even able to sleep well. And I had not been able to sleep well for 20 some years.

## Feeling more resourced

Inspired by feelings of safety and clarity occasioned by their MDMA sessions, all participants ($n = 6$) describe palpable ways they have incorporated new strategies of coping into their daily lives. For instance, Participant 1 gained a deeper understanding of her defenses and ways she can utilize new capacities for coping:

> It was like hitting at the very core body memory, and through that process, and now through these new capacities I have because of the MDMA, I can kind of do it on my own, figure out the different components of why I have so much anticipatory anxiety and why I will avoid.

Participant 3 also spoke to this improved ability to manage anxiety as it connects to an in depth understanding of her psyche, expressing, "I feel like when I hit moments where I used to struggle, I'm able to navigate them without getting anxious, so I really do feel strong. But, I also didn't know all the layers that were there before." She also felt she learned the important skill of acknowledging her health in the present moment following the treatment:

> When I get stuck thinking about the cancer that happened, I'm like "I'm not there, I'm here." Or if I think about a fear of recurrence, I'm like, "it's not happening, it's not happening right now." And so, yeah, so that was the big takeaway.

Many participants expressed understanding that the treatment did not change their life circumstances or challenges, but rather gave them new ways to move through those things. Participant 4 explained feeling,

> …the ability to address my problems so much more effectively. Yeah it wasn't magic—the pill didn't make my life circumstances go away, but it enabled me to access all of the resources that I have. And just deal with the ups and the downs and see a way through for positive outcomes in every area of my life.

Participant 2 reiterated this as well, remembering how overwhelming her trauma symptoms could be and how much more able to cope with life's difficulties she feels now. She explained, "there's still stuff I'm dealing with and having to deal with, but like I said I'm feeling so much more resourced compared to when I was in the trauma loop I would get flooded pretty quickly."

### Improvements in presence and self-awareness

All participants ($n = 6$) reported challenges in feeling separated from the present moment and many aspects of themselves through their LTI journey. MDMA-AT appears to have broadened participant perspectives and allow them to look at their life and situation with increased self-compassion and self-awareness. For instance, Participant 2 remarked on the wholeness she felt following MDMA-AT:

> I felt like all of me is here, if that makes sense. Whereas I felt like I was so fragmented before. And another thing that's more recent, because I mean I still feel the healing happening on so many levels.

Participant 4 also felt a deep sense of integrity that evolved with each MDMA-AT session:

> It was like the guilt and the shame lifted, you know, this huge weight. I have to say, after each session, even the second one, I felt relieved, very relieved, excited and thrilled. Each time even more so. And at the end of the third session I thought I felt complete.

Participant 4 continued on to share about how her trauma no longer defined her sense of self, remembering, "I would take in traumas and difficult circumstances before and make them part of my definition of self, you know. I'm not doing that at all [now]. I'm really clear about who I am."

Participant 3 also noticed how becoming more aware of her internal process in the moment has changed the way she interacts with herself and the world:

> It's not happening right now. It seems hard to understand, you know, now that I'm saying it. But it just became so clear. It became so true. And that truth changed me. You know, it changed the way I am in the world and the way I orient myself from the thing that had happened and the things that might happen. Cancer or no cancer, that is such a gift. To really be able to be in the present moment is just such a gift.

## Discussion

In the first clinical trial of MDMA-AT for treating anxiety and psychological distress associated with LTI, results indicated that many participants showed improvement on a range of primary and secondary outcome measures, the treatment was well tolerated, and no Serious Adverse Events (SAE) were reported (18). In this pilot study however, not all participants showed significant improvement on outcome measures and the small size of the study lacked the power to find statistically significant results (18). In this qualitative follow-up study, a subset of participants from this trial all described experiencing considerable changes in their relationship to LTI, improvements to functioning and quality of life, and reduction in mental health symptoms. The lessons from this qualitative study are important to further understand the experience and outcomes of participants within this trial, as well as to explore the possible

mechanisms of MDMA-AT for this indication and how they relate to similar psychedelic-assisted treatments.

## Possible psychological mechanisms of action

Multiple participants described that while the intention of this treatment was to focus on anxiety around LTI, they spent much of their sessions focusing on other topics altogether. Some participants expressed feeling concerned at some points that they were not focusing on topics of illness or death as they expected they would, but experienced reassurance both from the therapists and the medicine to follow the process where it goes and trust in their *inner healing intelligence*. In this subset of participants, processing trauma was a particular focus throughout their treatment. This included processing trauma around their health journey, but also focused on old wounds that continued to cause issues in their lives. Additional psychological mechanisms included mystical-type experiences and existential exploration, engaging with the present moment, and facing the illness with an objective and compassionate perspective.

### Processing trauma

Five of six participants in this study described that an important factor of their healing was processing the traumas that arose throughout their process with LTI, as well as their life before. MDMA-AT has shown to be particularly well suited to aiding trauma-focused therapy, leading to posttraumatic growth (13, 14, 36, 37). Potential biological mechanisms for MDMA to decrease PTSD symptoms have been explored and include MDMA's effects of reducing amygdala activity and increasing activity in the Ventromedial Prefrontal Cortex (VMPFC), which reduce common symptoms of PTSD during the treatment and can allow for exploring the traumatic memories without the associated physiological response that can impact the process (37–39). These and other neurobiological effects in combination with a trusting therapeutic relationship and safe container appear to allow participants to feel emotionally safe enough to process traumatic material that is otherwise difficult to access (19, 39–41). When trauma is emotionally tolerable to confront in therapy, it may become possible to deal with traumatic elements following diagnosis and treatment of an LTI. This mechanism of action indicates one major difference in how MDMA-AT treats anxiety associated with LTI differently than psilocybin-AT.

### Mystical experience

Research shows that other psychedelic medicines, such as psilocybin and ketamine, tend to evoke a wide range of ME. These can include a *sense of unity with all in existence*, *a sense of sacredness*, *deep feelings of peace and joy*, *and ineffability* (3, 21, 42). Studies of psilocybin-AT have also found the level of ME to be a key indicator of positive outcomes in the treatment (43). While a previous qualitative study of MDMA-AT for PTSD showed participants experienced a limited range of ME and that there was no correlation between level of ME and outcomes, multiple participants in this study described significant experiences that qualified as ME beyond what is commonly seen in MDMA experiences (19, 32). The most prominent ME descriptors outlined by participants in this study were *interconnectedness* and *transcending of normal time and space*. For these participants MDMA-AT decreased intense feelings of isolation and existential loneliness, which can be common experiences associated with LTI. Temporarily feeling connected to all things and loosening one's orientation to time and space may help those living with LTI or in remission feel able to be more engaged in the present and value connection with others in a deeper way. Participants also described feeling that in MDMA-AT their MEs remained grounded and connected to self, rather than dissociated or characterized by ego dissolution. This may have supported these important experiences in feeling grounded and real, potentially aiding in their ability to be integrated into a long-term understanding beyond the sessions themselves.

### Engaging with the present moment

A common experience in depression and anxiety disorders is difficulty engaging with the present moment (44). In these conditions, focus is often directed to either the past, where things may have taken place that can no longer be changed, or into the future where there exists the unknown and feelings of lacking control (45). For people experiencing challenging situations in life including illness and pain, spending time in the present moment could be especially difficult. Multiple participants in this study described how their relationship to the present moment evolved through the treatment process, and how this played an important role in how they went on to cope with their situation more effectively. While engaging with the present moment, participants described deeply understanding that they were not currently dealing with the unknowns that led to anxiety, namely recurrence/worsening of illness or death. This was often paired with increased confidence that they could deal with those things when/if they did arise in the future. Participants described the importance of both the MDMA and the therapeutic container in supporting their process of engaging with the present moment. In the optimal arousal zone occasioned by this treatment, participants can practice dealing with the discomfort that may exist in the present, and relearn their capability of managing what they find there.

### Facing illness and existential fears

Participants described altering their relationship with illness and the life/death process as another integral part of this treatment. Participants described that MDMA-AT allowed them

to re-identify with being their own person separate from the illness, and also gaining perspective on their feelings about living and dying. Having an altered perspective, increased compassion, and decreased fear and anxiety during MDMA sessions allowed participants to calmly and objectively address these challenging topics and identify their feelings beneath the fear and anxiety, which led to lasting changes in these perspectives.

### Comparisons to psilocybin-AT for LTI

While psychedelic treatments for psychological issues associated with terminal illness have for decades focused on psilocybin and LSD, the parent clinical trial was the first exploring MDMA-AT for this indication (3, 8–11, 18). This provides a unique situation where the phenomenological similarities and differences of psilocybin-AT and MDMA-AT can be explored for the same indication. Despite their differences, there were remarkable similarities in the phenomenological descriptions of healing outcomes between MDMA and psilocybin, including reconciliations with death and dying, acceptance of cancer in one's life, reduction of psychological symptoms, and improvement in quality of life.

While there are similarities in the treatment structures, each of these medicines appear to reach their outcomes in quite different ways. For example, psilocybin sessions commonly include long periods of internal processing where a participant may experience vivid visualizations, alterations in their sense of self (sometimes including complete ego dissolution), and/or wide ranges of emotional experiences (20, 21). These experiences can be rich with relational, autobiographical, spiritual, epistemological, and ontological material that aid in exploring factors of their life and the concepts of life and death (20, 21). Some studies have found that more than 50% of participants experiencing these profoundly altered states of consciousness occasioned by psilocybin can develop acute reactions of fear, confusion, panic, or paranoia at some point during the session; however, they also report that with the support of the therapeutic milieu these states are generally transient and have been described by participants and therapists as a necessary and ultimately beneficial process (20).

Alternatively, while the MDMA-AT protocol also includes participants spending some periods in an internal process, more of the session tends to be engaging in a process of embodied self-exploration with the therapists. Some participants described vivid mystical-type visions in their MDMA sessions but largely still felt cohesive in their sense of self during those visionary states. Overall, participants described MEs as playing a less prominent role in their healing process as opposed to a more connected processing of trauma, grief, and exploring their situation with increased self-awareness, compassion, and reduced physiological activation. Rather than providing deep lessons through a profoundly altered state of consciousness, it seems in many cases that MDMA allows participants to engage in a deep process of self-exploration and psychotherapy that they may normally be blocked from. In MDMA-AT qualitative studies, participants have regularly expressed the feeling that it is the process of psychotherapy and self-exploration that leads to change, and the MDMA just allows this to happen in a more successful way (19).

## Limitations

Study limitations included the small sample size and the exploratory nature of the parent study (18). Due to the small sample size and limited diversity in the parent study, the subset of participants in this analysis was largely homogeneous demographically: 100% were female identified, 100% had a cancer diagnosis, and five of six participants identified as White/Caucasian. In order to better assess the effectiveness of this treatment, future studies need to prioritize diversity with regards to race, socioeconomic status, gender, ability, and other biopsychosocial identities. Demographic information such as religious affiliation, spiritual beliefs, or attachment history was also omitted from the data collection due to this analysis taking place with de-identified data. One participant expressed interest in becoming an MDMA-AT therapist, which could have contributed to a positive bias with regards to outcomes and experience of the treatment. Additionally, the experimental nature of this treatment and the increase in popular excitement around it could potentially lead to a positive bias among participants or a desire to minimize negative feelings; steps were taken in the interview structure and questions to minimize these effects. Interviewing 10 of 17 available participants and analyzing only six of the eight available interviews may have contributed to selection bias in the study results; however, measures were taken to reduce this possibility including interviewing the first 10 participants to complete the trial and using randomization to choose those interviews to be used for analysis. The subset of interviews only includes one of the five participants who were in the placebo arm of the trial, and represents only 33% of the complete sample; as such, these results cannot be generalized to portray experiences from the entire sample or be attributed to a wider population. This type of study is not designed to be generalized to a wider population or make predictions about how the treatment will perform in larger studies; rather, this qualitative methodology uses in-depth exploration of specific participant experiences to create a starting point of understanding and a basis for further study.

## Conclusion

This study used qualitative methods to explore the subjective experiences of a subset of participants in the first clinical trial of MDMA-AT for treating anxiety related to LTI. Systematic

evaluations of semi-structured qualitative interviews revealed major narrative themes in participants' experiences of their treatment and outcomes. All participants in this study described deeply meaningful experiences and new existential perspectives occasioned by MDMA-AT that they feel have led to considerable improvement in mental health symptoms and quality of life. These interviews also highlight possible psychological mechanisms of action for this treatment, and provide a starting point for exploring the similarities and differences among similar treatments for this indication.

The experiences of these six participants provide evidence that MDMA-AT can be beneficial for people experiencing mental health challenges secondary to LTI, even when they have been resistant to traditional treatments. Larger studies will be necessary to determine the success of MDMA-AT across a wider and more diverse population.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors at request. Some data access requests may require approval of the study sponsor.

## Ethics statement

The studies involving human participants were reviewed and approved by John F. Kennedy University IRB. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

WB and MM-W conceived of and wrote the bulk of this report, with input from the other authors. PP and LB created the list of references. TS coordinated with clinical trial and completed the qualitative interviews. All authors contributed to coding, data interpretation, editing, and approved the report before submission.

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## Conflict of interest

Author WB has worked as a consultant for the study sponsor for different clinical trials, including as an Adherence Rater. Author PP began working with MAPS Public Benefit Corp., on different clinical trials after the core work on this study was completed. Measures were taken to reduce any conflicts these relationships may have presented. Authors do not have any steak financial or otherwise in the outcomes of this study or the parent clinical trial.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.944849/full#supplementary-material

## References

1. Grunfeld E, Coyle D, Whelan T, Clinch J, Reyno L, Earle CC, et al. Family caregiver burden: results of a longitudinal study of breast cancer patients and their principal caregivers. *Can Med Assoc J.* (2004) 170:1795–801. doi: 10.1503/cmaj.1031205

2. Arrieta O, Angulo LP, Nunez-Valencia C, Macedo EO, Martínez-Lopez D, Alvarado S, et al. Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol.* (2013) 20:1941–48. doi: 10.1245/s10434-012-2793-5

3. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol.* (2016) 30:1181–97. doi: 10.1177/0269881116675513

4. Stark D, Kiely M, Smith A, Velikova G, House A, Selby P. Anxiety disorders in cancer patients: their nature, associations, and relation to quality of life. *J Clin Oncol.* (2002) 20:3137–48. doi: 10.1200/JCO.2002.08.549

5. Multidisciplinary Association for Psychedelic Studies [Internet]. Santa Cruz: MAPS. In: *Study protocol MDA-1: A randomized, double-blind, placebo-controlled phase 2 pilot study of MDMA-assisted psychotherapy for anxiety associated with a life-threatening illness.* (2015). p. 74. Available online at: https://maps.org/

research-archive/mdma/MDA-1_FINAL_Protocol_Amend%201_29Apr15_web.pdf (accessed May 5, 2022).

6. Grob CS, Grigsby J. *Handbook of Medical Hallucinogens*. New York, NY: Guilford Publications (2021). p. 582.

7. Sessa B. *The Psychedelic Renaissance: Reassessing the Role of Psychedelic Drugs in 21st Century Psychiatry and Society*. Poole: Muswell Hill Press (2013). p. 250.

8. Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt MR, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry*. (2011). 68:71–8. doi: 10.1001/archgenpsychiatry.2010.116

9. Gasser P, Holstein D, Michel Y, Doblin R, Yazar-Klosinski B, Passie T, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *J Nerv Ment Dis*. (2014) 202:513–20. doi: 10.1097/NMD.0000000000000113

10. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol*. (2016) 30:1165–80. doi: 10.1177/0269881116675512

11. McCorvy JD, Olsen RH, Roth BL. Psilocybin for depression and anxiety associated with life-threatening illnesses. *J Psychopharmacol*. (2016) 30:1209–10. doi: 10.1177/0269881116675771

12. Danforth AL, Grob CS, Struble C, Feduccia AA, Walker N, Jerome L, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacol*. (2018) 235:3137–48. doi: 10.1007/s00213-018-5010-9

13. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*. (2018) 5:486–97. doi: 10.1016/S2215-0366(18)30135-4

14. Jerome L, Feduccia AA, Wang JB, Hamilton S, Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacol*. (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

15. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

16. Ching TH, Williams MT, Reed SJ, Kisicki MD, Wang JB, Yazar-Klosinski B, et al. MDMA-assisted therapy for posttraumatic stress disorder: a mixed-methods case study of a participant of color from an open-label trial. *J Humanist Psychol [Internet]*. (2022) 5:93 doi: 10.1177/00221678221076993

17. Sessa B, Higbed L, Nutt D. A review of 3, 4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. *Front Psychiatr*. (2019) 10:138. doi: 10.3389/fpsyt.2019.00138

18. Wolfson PE, Andries J, Feduccia AA, Jerome L, Wang J, Williams E, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Sci Rep*. (2020) 10:20442. doi: 10.1038/s41598-020-75706-1

19. Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived benefits of MDMA-assisted psychotherapy beyond symptom reduction: qualitative follow-up study of a clinical trial for individuals with treatment-resistant PTSD. *J Psychoactive Drugs*. (2019) 51:199–208. doi: 10.1080/02791072.2019.1580805

20. Belser AB, Agin-Liebes G, Swift TC, Terrana S, Devenot N, Friedman H, et al. Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomenological analysis. *J Humanist Psychol*. (2017) 57:354–88. doi: 10.1177/0022167817706884

21. Swift TC, Belser AB, Agin-Liebes G, Devenot N, Terrana S, Friedman HL, et al. Cancer at the dinner table: experiences of psilocybin-assisted psychotherapy for the treatment of cancer-related distress. *J Humanist Psychol*. (2017) 57:488–519. doi: 10.1177/0022167817715966

22. Biggerstaff D, Thompson AR. Interpretative phenomenological analysis (IPA): a qualitative methodology of choice in healthcare research. *Qual Res Psychol*. (2008) 5:214–24. doi: 10.1080/14780880802314304

23. Pietkiewicz I, Smith J. A practical guide to using interpretative phenomenological analysis in qualitative research psychology. *Psychol J*. (2014) 20:7–14. doi: 10.14691/CPPJ.20.1.7

24. Smith JA, Jarman M, Osborn M. Doing interpretative phenomenological analysis. In: Murray M, Chamberlain K, editors. Qu*alitative Health Psychology: Theories and Methods [Internet]*. London: SAGE (1999). p. 218-40. Available online at: http://www.brown.uk.com/teaching/HEST5001/smith.pdf (accessed May 14, 2022).

25. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies. *Qual Health Res*. (2016) 26:1753–60. doi: 10.1177/1049732315617444

26. Berends L, Johnston J. Using multiple coders to enhance qualitative analysis: the case of interviews with consumers of drug treatment. *Addiction Res Theory*. (2005) 13:373–81. doi: 10.1080/16066350500102237

27. VERBI Software. *MAXQDA. [computer software]*. Berlin: VERBI Software; (2020). Available online at: maxqda.com (accessed April 15, 2022).

28. van der Kolk BA. *The Body Keeps the Score: Memory and the Evolving Psychobiology of Posttraumatic Stress*. New York, NY: Penguin Group (2014). p. 464.

29. Levine PA. *Waking the Tiger: Healing Trauma: The Innate Capacity to Transform Overwhelming Experiences*. Berkeley: North Atlantic Books; (1997). p. 288.

30. MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. *J Psychopharmacol*. (2011) 25:1453–61. doi: 10.1177/0269881111420188

31. Griffiths RR, Richards WA, Johnson MW, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol*. (2008) 22:621–32. doi: 10.1177/0269881108094300

32. Mitsunaga-Whitten MA. *A correlative analysis of mystical experiences and lasting symptom improvement from MDMA-assisted psychotherapy for treatment-resistant PTSD: a project based upon an investigation sponsored by Multidisciplinary Association for Psychedelic Studies (MAPS) [Master's thesis]*. Northampton: Smith College (2017). p. 96. Available online at: https://scholarworks.smith.edu/cgi/viewcontent.cgi?article=2985&context=theses (accessed May 2, 2022).

33. Nichols, DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens, identification of a new therapeutic class: entactogens. *J Psychoactive Drugs*. (1986) 18:305–13. doi: 10.1080/02791072.1986.10472362

34. Pahnke N. *Drugs and mysticism: an analysis of the relationship between psychedelic drugs and the mystical consciousness [Thesis]*. Cambridge: Harvard University (1963). p. 34. Available online at: https://maps.org/images/pdf/books/pahnke/walter_pahnke_drugs_and_mysticism.pdf (accessed May 4, 2022).

35. Lyvers M, Meester M. Illicit use of LSD or psilocybin, but not MDMA or nonpsychedelic drugs, is associated with mystical experiences in a dose-dependent manner. *J Psychoactive Drugs*. (2012) 44:410–7. doi: 10.1080/02791072.2012.736842

36. Gorman I, Belser AB, Jerome L, Hennigan C, Shechet B, Hamilton S, et al. Posttraumatic growth after MDMA-assisted psychotherapy for posttraumatic stress disorder. *J Trauma Stress*. (2020) 33:161–70. doi: 10.1002/jts.22479

37. Barone W. *The role of MDMA as an adjunct to therapy for adults with PTSD, as illustrated by participant qualitative data one-year posttreatment [Doctoral dissertation]*. [Pleasant Hill (CA)]: John F. Kennedy University (2017). p. 66. Available online at: https://www.proquest.com/openview/70e4cb8b98e64f8f6fb2f516eb637a29/1?pq-origsite=gscholar&cbl=18750&diss=y

38. Sessa B, MDMA. and PTSD treatment: PTSD: from novel pathophysiology to innovative therapeutics. *Neurosci Lett*. (2017) 649:176–80. doi: 10.1016/j.neulet.2016.07.004

39. Johansen PØ, Krebs TS. How could MDMA (ecstasy) help anxiety disorders? a neurobiological rationale. *J Psychopharmacol*. (2009) 23:389–91. doi: 10.1177/0269881109102787

40. Dumont G, Sweep F, van der Steen R, Hermsen R, Donders A, Touw D, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci*. (2009) 4:359–66. doi: 10.1080/17470910802649470

41. Kamilar-Britt P, Bedi G. The prosocial effects of 3,4-methylenedioxymethamphetamine (MDMA): controlled studies in humans and laboratory animals. *Neurosci Biobehav Rev*. (2015) 57:433–46. doi: 10.1016/j.neubiorev.2015.08.016

42. Rothberg RL, Azhari N, Haug NA, Dakwar E. Mystical-type experiences occasioned by ketamine mediate its impact on at-risk drinking: Results from a randomized, controlled trial. *J Psychopharmacol*. (2021) 35:150–8. doi: 10.1177/0269881120970879

43. Roseman L, Nutt DJ, Carhart-Harris RL. Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. *Front Pharmacol*. (2018) 8:974. doi: 10.3389/fphar.2017.00974

44. Rinaldi L, Locati F, Parolin L, Girelli L. Distancing the present self from the past and the future: Psychological distance in anxiety and depression. *J Exp Psych*. (2017) 70:1106–13. doi: 10.1080/17470218.2016.1271443

45. Eysenck M, Payne S, Santos R. Anxiety and depression: Past, present, and future events. *Cogn Emot*. (2006) 20:274–94. doi: 10.1080/02699930500220066

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EDITED BY
Jennifer Mitchell,
University of California, San Francisco, United States

REVIEWED BY
Collin Reiff,
Grossman School of Medicine, New York University, United States
Anne C. Wagner,
Mental Health Care, Canada

*CORRESPONDENCE
Christopher S. Stauffer
christopher.stauffer@va.gov

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# MDMA-assisted psychotherapy; Inclusion of transgender and gender diverse people in the frontiers of PTSD treatment trials

Christopher S. Stauffer[1,2]*, Melanie R. Brown[3], Dee Adams[4], Marca Cassity[1,2] and Jae Sevelius[5]

[1]Social Neuroscience and Psychotherapy Lab, Oregon Health and Science Institute, Department of Psychiatry, Portland, OR, United States, [2]Portland VA Health Care System, Department of Mental Health, Portland, OR, United States, [3]School of Public Health, Oregon Health and Science University-Portland State University, Portland, OR, United States, [4]Center for Public Health and Human Rights, Department of Epidemiology, John Hopkins University, Baltimore, MD, United States, [5]Center of Excellence for Transgender Health, Department of Medicine, University of California, San Francisco, San Francisco, CA, United States

**Introduction:** Transgender and gender diverse (TGD) people experience stigma, discrimination, trauma, and post-traumatic stress disorder (PTSD) at higher rates compared to the general population; however, TGD people have been underrepresented in PTSD research. Clinical trials of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy demonstrate promising safety and efficacy for the treatment of PTSD. Issues related to equitable access, power imbalances in the therapeutic relationship, and vulnerable states of consciousness occasioned by MDMA are magnified when working with people affected by structural vulnerabilities and health disparities, and community engagement in research planning and implementation is essential. To inform the inclusion and safety of TGD people in future MDMA-assisted psychotherapy research, the aims of the current study were to: characterize TGD experiences with trauma-related mental health care, assess openness of TGD people to participate in experimental PTSD research, and to gather specific feedback on protocol design for conducting MDMA-assisted psychotherapy with TGD people.

**Materials and methods:** We conducted three virtual focus group discussions (FGDs) with 5–6 participants each ($N = 17$). Eligible TGD participants had a history of receiving trauma-related mental health care. Each FGD was facilitated by two licensed clinicians who identified as TGD. Qualitative data analysis was conducted via an iterative process of identification of recurrent patterns and themes.

**Results:** We have identified several key issues TGD people face when seeking and engaging in trauma-related mental health care, including barriers to receiving adequate gender-affirming and trauma-informed mental health care and frustration with providers lacking cultural humility. Suggested amendments to MDMA-assisted psychotherapy protocols include: routine collection of trans-inclusive gender identity data, implementing an explicit gender-affirming treatment approach, ensuring a culturally safe setting, and diversifying co-therapy dyads.

**Discussion:** The inclusion of TGD voices in early conversations about emerging experimental PTSD interventions promotes equitable access, in the context of health and healthcare disparities, and helps researchers understand the needs of the community and tailor research to meet those needs. Through an ongoing conversation with the TGD community, we aim to incorporate a gender-affirming approach into existing research protocols and inform future applications of MDMA-assisted psychotherapy in addressing the effects of minority stress and boosting resilience.

KEYWORDS

gender identity (MeSH), transgender persons (MeSH), N-methyl-3,4-methylenedioxymethamphetamine (MeSH), hallucinogens (MeSH), post-traumatic stress disorder (MeSH), health equity (MeSH), focus groups (MeSH), psychotherapy (MeSH)

## Introduction

Transgender and gender diverse (TGD) people experience violence and trauma exposure—and subsequent post-traumatic stress disorder (PTSD) and suicidality—at higher rates than the general population (1, 2). Transgender and gender diverse people are the target of significant experiences of discrimination, including in healthcare settings by healthcare professionals (3). Transgender and gender diverse identities have historically been pathologized within Western medicine. "Gender identity disorder" was removed from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* in 2013 and replaced with "gender dysphoria." This, and other positive shifts in terminology in the most recent *DSM-5-TR* (e.g., "desired gender" to "experienced gender"), aim to help destigmatize TGD identities while maintaining healthcare access for those who need it (4, 5). Nonetheless, a recent surge in anti-transgender legislation continues to contribute to the structural vulnerability of TGD people (6–8).

Throughout recorded history, hundreds of distinct cultures have recognized third, fourth, fifth, or more genders; while the gender binary that exists in most Western societies is a relatively new construct (9). "Cisgender" people have gender identities that correspond with the sex they were assigned at birth. "Gender diversity" includes individuals who identify as neither a cisgender man nor a cisgender woman (e.g., transgender, two-spirit, non-binary, genderqueer, gender non-conforming, agender, and those who are fluid in their gender identities). Researchers estimate that about 0.5–3% of the U.S. population identify as TGD (10). Due to gender being defined federally as either "male" or "female," government surveys (e.g., U.S. Census) do not ask about TGD identities. Unfortunately, this practice is the norm in clinical research as well. The PTSD Trials Standardized Data Repository (PTSD-Repository) (11)—a resource containing interactive data from over 389 published randomized controlled clinical trials of PTSD treatment—does not include a single TGD clinical trial participant. The PTSD-Repository reports that 69% of trials included both men and women, 13% only men, 12% only women, and 6% of studies did not include gender information for participants. Thus, despite experiencing a disproportionate prevalence of PTSD, TGD people have historically not been explicitly represented in PTSD intervention research.

3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy is an innovative experimental treatment for PTSD with promising results from Phase 2 (12) and Phase 3 clinical trials (13). A recent Phase 3 clinical trial of MDMA-assisted psychotherapy for PTSD included assessment of gender identity beyond binary male and female genders. In the demographics table, Mitchell et al. (13) reported "sex assigned at birth" for the 90 participants in the study (rather than traditionally reporting "gender") and included in a footnote: "Two participants included in the assigned female at birth MDMA group identified their gender as non-binary." It can be assumed that the other 88 participants' identified genders matched their sex assigned at birth (i.e., cisgender vs. transgender), though this is not explicitly stated. The inclusion of measurements that identify TGD people in this trial represents a positive step toward addressing the noted lack of gender diversity among participants in MDMA-assisted psychotherapy clinical research (14) and the broader fields of psychedelic research (15) and PTSD intervention research (11).

As noted by recent psychedelic research focused on the inclusion of people of color (14–16), traditional research protocols and outcomes may not generalize to all cultural groups. Providers of MDMA-assisted psychotherapy must be particularly attentive to the impact of power dynamics; transference and countertransference can be amplified, and participants may be especially open to suggestion, manipulation, and exploitation. Therefore, among people affected by significant structural vulnerabilities and health disparities, there is a unique need for increased attention to

safety and consent, cultural context, trauma themes, symptom manifestation, resilience factors, and culturally adapting protocols (17).

For studies involving participants affected by structural vulnerabilities, the National Bioethics Advisory Commission recommends including the community at various points in the research process—particularly during the study planning phase (18). To achieve this, we have conducted a qualitative study with TGD participants as a formal means of initial inquiry. The aims of this study include: (1) to characterize TGD experiences with trauma-related mental health care, (2) to assess openness of TGD people to participate in experimental trauma-related mental health intervention research, specifically MDMA-assisted psychotherapy, and (3) to gather specific feedback on protocol design and clinical practice of MDMA-assisted psychotherapy for TGD people.

# Methods

## Study participants

We conducted three 90-min virtual focus group discussions (FGDs) in February and March 2021 using WebEx video conferencing. Focus group discussion participants were recruited from a medical university's Transgender Health Program, a Veterans Affairs Sexual Orientation and Gender Identity Advisory Group, and other community organizations focused on providing services and community for TGD individuals. To limit selection bias, we did not mention MDMA or MDMA-assisted psychotherapy in recruitment materials. Participants were compensated $50 upon completion of the FGD. This study was conducted in accordance with the Declaration of Helsinki and was approved jointly by the Oregon Health and Science University and the Veterans Affairs Portland Health Care System Institutional Review Boards.

We enrolled a sample ($N = 17$) consisting of TGD people (defined on recruitment material as "neither exclusively cis-male nor exclusively cis-female"). All had previous experience receiving trauma-related mental health care. Additional inclusion criteria were: (a) age ≥18 years old, (b) currently located within the United States, (c) fluent in English, (d) able to navigate WebEx and provide safety information (e.g., emergency contact information, physical location during the virtual FGD), and (e) available during one of the three scheduled FGDs. See Table 1.

TABLE 1 Demographics.

| | Mean (SD) |
|---|---|
| **Age (years)** | 35.4 (10.9) |
| | ***n* (%)** |
| **Sample size** | 17 (100) |
| **Gender** | |
| Genderqueer | 1 (5.9) |
| Non-binary | 8 (47.1) |
| Trans female | 3 (17.7) |
| Trans male | 4 (23.5) |
| Tumtum | 1 (5.9) |
| **Race** | |
| American Indian | 1 (5.9) |
| Asian | 1 (5.9) |
| Black | 2 (11.8) |
| White | 13 (76.5) |
| **Hispanic ethnicity** | 1 (5.9) |
| **Veteran** | 3 (17.7) |
| **Education** | |
| High school graduate | 5 (29.4) |
| Trade school/Some college | 10 (58.8) |
| Bachelor's degree | 3 (17.7) |
| Masters/Postgraduate degree | 3 (17.7) |
| **Occupation** | |
| Part-time job | 1 (5.9) |
| Self-employed | 3 (17.6) |
| Student | 5 (29.4) |
| Unemployed | 8 (47.1) |
| **Disability** | 5 (29.4) |
| **Living situation** | |
| Alone | 2 (11.8) |
| With parents | 2 (11.8) |
| With partner | 6 (35.3) |
| With roommates | 7 (41.2) |
| **In a primary relationship** | 10 (58.8) |

## Data collection

Participants received an informed consent form via email and discussed this with a researcher virtually. Verbal informed consent was videorecorded in lieu of written consent. After providing informed consent, individual participants completed a structured screening interview over WebEx. Eligible participants were then enrolled, completed a preliminary survey to assess experiences with previous trauma-related mental health care, and were scheduled for a FGD.

Both FGD co-facilitators were TGD-identified and had specialized training in trauma-informed care, gender and sexual minority issues, and MDMA-assisted psychotherapy for PTSD. Facilitators revealed their gender identities and pronouns to participants in the introduction portion of each FGD. The research team developed a semi-structured FGD guide, which started with a description of FGD ground rules and an opportunity for the participants to introduce themselves. The co-facilitators then facilitated discussion around three

main topics: (1) experiences with trauma-related mental health care, (2) existing participant knowledge of MDMA-assisted psychotherapy for PTSD and potential interest in participating in research, and (3) protocol considerations for MDMA-assisted psychotherapy specifically with TGD participants. Between topics 2 and 3, the participants were given a brief, general description of the MDMA-assisted psychotherapy protocol from previous and ongoing clinical trials (13).

The day following each FGD, participants were sent a follow-up questionnaire by email. The questionnaire gathered standardized information related to interest participating in research in general as well as MDMA-assisted psychotherapy research. Lastly, the questionnaire had an open-ended space for any additional feedback that the participant would like to provide on the FGD topics.

## Analysis

Focus group discussions were recorded, transcribed verbatim, and deidentified. Transcripts were uploaded and coded using Taguette. Data analysis was conducted through identification of recurrent patterns and themes following Crabtree and Miller's five steps in qualitative data analysis, or the "interpretive process" (19). These steps are: (i) describing, (ii) organizing, (iii) connecting, (iv) corroborating, and (v) representing. Thematic analysis is an iterative process and requires frequent examination of the goals and aims of the research study. During data immersion, team members read transcripts and noted follow-up probes for later FGDs. A preliminary codebook was developed after the first FGD, which was revised as needed between FGDs to improve code definitions and include any additional themes that emerged. Three independent reviewers identified main and secondary themes.

# Results

## Previous trauma-related mental health treatment

### Quantitative data

All participants had participated in trauma-related psychotherapy. 88.2% of the participants had taken prescribed medication for the treatment of PTSD. See Table 2 for a breakdown of psychotherapy modalities and number of previous PTSD medication trials lasting at least 3 months. Participants were also asked the following questions: 1) "How effective do you feel your previous trauma treatment was?," 2) "How bonded did you feel to your previous trauma treatment provider(s)?," and 3) "How culturally sensitive to gender issues were your previous trauma treatment provider(s)?." Responses were captured using a 0–10 Likert scale (Table 2).

TABLE 2 Previous trauma treatment.

| | *n* (%) |
|---|---|
| **Previous psychotherapy modalities** | |
| Psychodynamic | 17 (100) |
| Cognitive behavioral therapy | 15 (88.2) |
| EMDR | 7 (41.2) |
| Dialectical behavior therapy | 6 (35.3) |
| Group therapy | 6 (35.3) |
| Internal family systems | 3 (17.6) |
| Somatic experiencing | 2 (11.8) |
| Equine therapy | 1 (5.9) |
| Prolonged exposure | 1 (5.9) |
| **Medication trials ≥3 months** | |
| 0 | 2 (11.8) |
| 1 | 5 (29.4) |
| 2 | 4 (23.5) |
| 3+ | 6 (35.3) |
| | **Mean (SD)** |
| Self-reported effectiveness of trauma treatment(s) (0–10) | 6.1 (1.7) |
| Perceived bond to trauma treatment provider(s) (0–10) | 6.4 (2.0) |
| Cultural sensitivity of trauma treatment provider(s) (0–10) | 5.3 (3.4) |

### Qualitative thematic analysis

Several participants reported on positive experiences, particularly with mental health care providers who were TGD themselves or had a lot of experience working with TGD populations. Although one participant noted, *"I don't mean to imply...that it's not okay to want or need a queer and trans therapist because I don't think that that's true. Obviously. But it's not as important to me as it used to be."* (P10). Another participant reported on a positive experience with an empathic provider who had neither lived TGD experience nor particular expertise in TGD health care, distinguishing the provider from systemic issues:

> *It was about someone being an ally to me in the process of moving through systems that were not inclusive. Which is not something that's always thought of as good therapy, but some of the best therapy I ever had. Feeling affirmed at someone standing up for me like that, and me not having to do it. So…and then from that, a lot of trust and a lot of beautiful conversations that helped me to work through things.* (P12).

A primary theme was the general lack of available trauma-related health care with providers who were culturally aware of TGD issues. *"You have to pay out of pocket or have a job with good insurance to get that kind of therapy."* (P4). Often, participants had to utilize whatever trauma-related mental healthcare resources were available to them through their insurance or healthcare plan. Participants mentioned barriers to receiving trauma-related psychotherapies other than cognitive

behavioral therapy (e.g., eye movement desensitization and reprocessing, internal family systems), such as lack of insurance coverage or institutional support for alternative modalities. One participant noted the high turnover within a public psychiatry clinic, *"there needs to be like, a warning, so I can prepare for that, and we can finish out our sessions properly instead of cutting me and taking progress with them."* (P6), and the subsequent dice roll when getting matched with a new provider. Another person commented on a related issue affecting access for TGD people, *"it's a small community, and so when you seek care as a person in that community from people in the community, it's just more awkward. It's more difficult."* (P8). The potential for dual relationships with TGD providers presents an added challenge of navigating issues with confidentiality, communication, and boundaries.

Another theme was negative experiences with trauma-related health care providers. Many participants were frustrated with having to educate providers on basic TGD terminology and concepts. *"I don't like having to explain everything 'cause they could Google things themselves."'* (P4). Some chose to conceal their TGD identities from providers they sensed were unfamiliar with, or even hostile toward, TGD people. Reflecting on a history of TGD people being systemically pathologized within the medical system, one participant noted:

> *It seems to me that, you know, many in the mental health field still regard us as mentally ill. They don't see us as… the diversity of what human beings can be. You know, because they're so binary themselves, so they're seeing the world through a binary lens—which makes it difficult for them to empathize with those of us [who] are outside of that.* (P1).

Another participant in their late 30s described their experiences of mental health treatment during childhood and adolescence:

> *"I just went through the system for a very long time with a lot of like, very cisgender, white, older, male therapists. And they were… very harmful, and sort of like dictated what was wrong with me… there just wasn't like breathing room to kind of know, or have a space in which to, to explore who I was, you know? I feel like I was really told who I was through therapy for years."* (P11).

## MDMA-assisted psychotherapy for PTSD

### Existing knowledge and attitudes

Participant awareness and familiarity prior to the FGD of MDMA-assisted psychotherapy for PTSD was normally distributed. Three participants reported complete unfamiliarity, ten participants reported that they had heard of it or knew a little bit, three said that they knew a lot about this modality, and one did not disclose prior knowledge or lack thereof. Initial impressions ranged from enthusiasm to concern.

One participant stated, *"I'm absolutely obsessed with this. Not just MDMA, but, like, you know, I really love the work that MAPS [Multidisciplinary Association for Psychedelic Studies] is doing. I love the research that's around it."* (P11). A few participants described their own personal experiences with MDMA or other psychedelics, including, *"I've had a lot of my own personal experiences with psychedelics, with MDMA specifically, that have been profoundly moving and life-changing. I've been staying up on the research."* (P8).

Others were more neutral or ambivalent:

> *"So, I was just saying, yeah, after, like, years of treatment-resistance and trying all the different types of therapies, all different kinds of medications, you get to a point where you're pretty much willing to try anything."* (P3).
>
> *"I'm not opposed to it, like, I think it could be really helpful. I think. I'm not sure if it's something I would personally do, but I think I could see it being really beneficial for people."* (P9).

Participants also voiced several initial concerns. Multiple participants asked if current medications would need to be stopped prior to participation in MDMA-assisted psychotherapy. Conversely, a few participants were in addiction recovery and felt this would prevent them from seeking treatment with MDMA-assisted psychotherapy. In the words of one participant:

> *"For me personally, one of the best decisions in recent times is actually to make a choice for sobriety, so I think it would be hard for me to really seriously consider it because I… just don't really engage in any substances for a time already and I would kind of like to keep that going, I guess."* (P7).

Another participant added that they would still support this as an option for others:

> *"I know it's something that I would never do. I'm straight edge.…I do think that there's room for a lot of great and positive stuff to happen there and I want people to have access to it."* (P10).

Lastly, concerns were voiced around vulnerable populations receiving experimental treatments, which is reflective of historical harms and ongoing mistrust in healthcare settings. One participant referenced a series of covert and illegal projects conducted between 1956 and 1971 by the United States Federal Bureau of Investigation targeting groups that were deemed to be subversive:

> *"…using Veterans and at-risk groups as guinea pigs is really triggering for people of color like me, because you have things like COINTELPRO [an abbreviation derived from Counter Intelligence Program] and stuff they did in the past, and I'm like, 'I don't know how I feel about that.'"*(P4).

### MDMA-assisted psychotherapy protocol considerations for TGD participants

Participants offered several recommendations for future protocols of MDMA-assisted psychotherapy for TGD people. One major piece of feedback involved ensuring the screening process utilized gender-inclusive questions and phrasing (20). For example, intake coordinators should ask all potential participants their gender and pronouns. Participants noted the need for providers working with TGD participants to be explicitly gender-affirming and for the physical environment to be intentionally designed to avoid implicit cisnormative and heteronormative messaging or imagery. Overall, participants stressed a desire for a welcoming space, particularly for TGD people, who have a long history of discrimination by providers and healthcare systems. One participant mentioned:

> *"…the super clinical setting is very uncomfortable for a lot of people with medical trauma, which is very common in the queer/trans community. We have all been injured at one point or another by the medical community.…I don't want to be in a hospital room while I'm on MDMA. I just don't."* (P8).

Several comments challenged the historical protocol requirement of male-female therapist dyads. While this practice may have originated to protect patients, FGD participants offered alternative suggestions to avoid harm to TGD people, such as:

> *"I think that it sends a binary message. I think it should be the most qualified people that should be facilitating. It should be—if they're both males, let them be both males. If one's a trans man and one's a cis woman, let them be that. If one's a trans woman and the other one's a trans man, let them be that. You know? Whoever, whoever's qualified to run the show."* (P1).

Another participant acknowledged more recent changes in the male–female therapy dyad:

> *"I know that MAPS has edited their protocol—they used to do one male therapist and one female therapist. And having the option of having whoever you feel comfortable with—a non-binary person, a trans person…is helpful. I know that more folks are getting trained. I know that that's, you know, just been a process, but that I think would be important to me in seeking care…"* (P8).

Participants expressed a mix of interest and hesitancy regarding a group therapy protocol. While some were concerned about possibly becoming overwhelmed in a group setting, others were excited by the possibility of moving through the protocol alongside other TGD people. One participant voiced:

> *"…a lot of people who go through a program like this are going to find it helpful to talk to other people with similar lived experience. And maybe not similar lived experience, but a shared experience of having taken the MDMA. I think it can be really helpful to process the things that come up with a group of people that you feel safe and comfortable with."* (P8).

### Post-FGD quantitative data

In a follow-up email survey, participants were asked to rate "How interested are you in participating in a research study in general (i.e., not just MDMA therapy) in which you would receive an experimental treatment for trauma-related mental health issues?" and "How interested are you in participating in research in which you would specifically receive MDMA-assisted psychotherapy that has been culturally adapted to gender diverse communities" on a scale from 0 to 10. Average respondent ($n$ = 16) ratings revealed a moderate-high interest in "generally participating in trauma-related research," *Mean(SD)*, 7.76(2.82), and similar ratings for "specifically participating in MDMA-assisted psychotherapy research," 7.44(3.41).

## Discussion

In this study, TGD adults shared their previous experiences with trauma-related mental health care, reported their initial thoughts on participating in experimental PTSD research, and offered suggestions for tailoring existing MDMA-assisted psychotherapy protocols for TGD participants. These findings expand the existing literature on TGD peoples' experiences with healthcare providers and systems (21–23) by contributing specific information on trauma-related mental health care. The inclusion of TGD voices in early conversations about research for emerging experimental PTSD interventions allows researchers to understand the needs of the community, tailor research to meet those needs, and promotes equitable and safe access for a population disproportionately affected by trauma and PTSD who have historically been pathologized by the medical system and outwardly excluded from PTSD intervention research (11).

We have identified several key issues TGD people face when seeking and engaging in trauma-related mental health care, including: barriers to receiving adequate gender-affirming, trauma-informed mental health care; frustration with providers lacking cultural humility; and experiences overshadowed by historical medical pathologization of TGD

people. Optimistically, most of the participants also described positive experiences with some providers.

The participants in our FGDs were generally curious about innovative interventions to treat post-traumatic stress, including MDMA-assisted psychotherapy. Participants voiced concerns about potential interactions of MDMA-assisted psychotherapy with other mental health treatments they may be receiving. While the decision to enroll in MDMA-assisted psychotherapy would ultimately lie with the participant, systemic medical or provider distrust may pose a barrier to critical conversations (e.g., a discussion of how to safely taper off current psychotropic regimens before receiving MDMA-assisted psychotherapy, reaching out to be screened for a clinical trial, etc.). Participants engaging in abstinence-based recovery stated that they were not likely to take MDMA—a "mind-altering substance"—as part of their PTSD treatment, despite protocols including only two or three dosing sessions. This is certainly a reasonable approach; although, recent pilot data suggests that MDMA-assisted psychotherapy could also be efficacious for the treatment of alcohol use disorder (24). Synergies between psychedelics and traditionally abstinence-based recovery programs (e.g., 12-step) have been noted for decades, and whether or not to integrate the two is still an active area of debate (25). Reservations were also expressed about vulnerable populations participating in experimental research, particularly in the context of historical harms. Equity-informed approaches recommend that providers explicitly address and invite further discussion around power, structural violence, and everyday injustices experienced by TGD people; tension and disruptions should be expected and, if meaningfully engaged with, can be productive (26).

Historically, research with psychedelics has not been exempt from contributing to medical harms against TGD and sexual minority people. For example, psychedelics have historically been paired with "conversion therapy," based on the assumptions that TGD identities and diverse sexual orientations are mental disorders and should be "repaired" (27). Conversion therapy and other gender identity and sexual orientation change efforts have been explicitly opposed and labeled as harmful by the American Medical Association, the American Psychiatric Association, the American Psychological Association, and other professional medical associations (28–30). Researchers have called for more cultural sensitivity and affinity spaces within psychedelic medicine (15, 26, 27, 31), and organizations have been taking steps to repair historical systemic harms. For example, Multidisciplinary Association for Psychedelic Studies (MAPS)—the primary sponsor to-date for MDMA-assisted psychotherapy research—has provided 38 scholarships to TGD practitioners (and 125 for LGBTQIA + practitioners) to receive training in MDMA-assisted psychotherapy through a Health Equity Scholarship (32, 33), and the Fireside Project—a psychedelic peer support hotline—launched an Equity Initiative that will create a transgender affinity peer integration service (34).

The primary clinical outcome from previous MDMA-assisted psychotherapy studies relied on the Clinician Administered PTSD Scale to diagnose PTSD in accordance with *DSM* criteria, which centers on a single traumatic event. This method has been critiqued for conceptualizing the effects of trauma as individualized pathology as well as for not accounting for repeated or chronic experiences of oppression and violence (3, 35, 36). Recent evidence shows that MDMA and other psychedelics could reduce symptoms associated with racial trauma (14, 37) and demoralization among gay male long-term AIDS survivors (38). Similarly, formal assessment of the effect of MDMA or MDMA-assisted psychotherapy on gender minority stress and resilience is warranted (39). Gender minority stress results from gender-related discrimination, rejection, victimization, and non-affirmation and is associated with internalized transphobia, concealment of identity, negative expectations of future events, isolation, and higher rates of psychiatric comorbidities (39–41). 3,4-Methylenedioxymethamphetamine increases empathy (42), self-compassion (43), and receptivity to positive emotion (44). Increases in the personality domain of Openness were found to moderate the effects of MDMA-assisted psychotherapy on PTSD symptom reduction (45). While access to MDMA-assisted psychotherapy for TGD people does not change ongoing societal stigma and discrimination, MDMA combined with gender-affirming care stands to positively impact aspects of gender minority resilience, such as an increased sense of pride, community connectedness, and other effective coping strategies (2, 3, 39).

The participants in this study suggested several adaptations to the MDMA-assisted psychotherapy protocol for TGD participants, including: gender-inclusive intake procedures (46), gender-affirming providers and physical space (27), diversification of care teams (15), and an option for group therapy with other TGD people (47). When working with TGD people, language is critically important to rapport building (48). Standardized screening for TGD people is a simple initial step in creating an inclusive setting. The American Psychological Association published Guidelines for Psychological Practice with Transgender and Gender Nonconforming People in 2015 (46). Rea and Wallace (26) outline the provision of equity-oriented care in psychedelic medicine, specifically, using the EQUIP Health Care approach. Core dimensions of trauma- and violence-informed care, harm reduction, and culturally safe care need to be tailored to an intervention, population, and context (e.g., MDMA-assisted psychotherapy among TGD people in a medical research setting). These adaptations can be applied to general clinical research or to affinity spaces specifically for TGD people. An ongoing community engagement process will further inform priorities for TGD people and their safety when participating in experimental PTSD research.

## Limitations

Due to timing and the nature of the COVID-19 pandemic, consenting, screening, and FGDs were held virtually. To accommodate this format, inclusion criteria reflected participant ability to adequately access and navigate WebEx, potentially introducing a selection bias toward individuals with more technology fluency and economic resources than would be necessary for an in-person FGD.

In addition to public recruitment efforts, the research team made attempts to recruit Black, Indigenous, and other People of Color by extending specific requests into professional networks; although, recruitment efforts did not extend far enough in order to ensure a racially diverse sample. Racial diversity was not reflected among the research team; thus, potential participants of color may not have seen themselves represented. Furthermore, the intersectionality of race/ethnicity, TGD identity, and PTSD may have compounded to prevent interaction with a medical research group (49). Ultimately, our findings may not adequately reflect the experiences of TGD people of color. In addition to TGD-informed design, future MDMA-assisted psychotherapy research would benefit from incorporating culturally-informed strategies for people of color (50).

Our FGDs highlighted MDMA-assisted psychotherapy, due to its position at the forefront of PTSD intervention research; however, suggestions and feedback from TGD participants may apply to other forms of trauma-related interventions as well (e.g., prolonged exposure therapy, cognitive processing therapy, eye movement desensitization and reprocessing). Further research would be required.

## Conclusion

Due to stigma and systemic discrimination, TGD people experience a disproportionately high burden of trauma and PTSD. Targeted interventions are urgently needed to address health and health care disparities among TGD people, who have historically been excluded from PTSD intervention research. By including TGD people early in the research design and planning phase, this study aims to promote equitable and safe implementation of experimental PTSD intervention research. 3,4-MDMA-assisted psychotherapy is a promising emerging area of PTSD intervention research, and most of our FGD participants expressed a strong interest in participating in such research; while a few were not interested in participating for both personal and structural reasons. Amendments to current protocols for MDMA-assisted psychotherapy—such as an explicit gender-affirming treatment approach, a setting that is inclusive and culturally safe, and diversification of co-therapy dyads—will serve to promote safe and equitable access for TGD people. Future clinical trials that routinely collect trans-inclusive gender identity data and directly recruit TGD people will advance our ability to address health disparities and boost resilience factors.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by the Oregon Health and Science University and the Veterans Affairs Portland Health Care System Institutional Review Boards. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## Author contributions

CS acquired funding and contributed to the conception, design, data acquisition, and data analysis. MB analyzed data. DA contributed to the design and data analysis. MC contributed to the conception, design, and data acquisition. JS contributed to the conception and design. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

Author CS is a paid clinical supervisor and trainer for MDMA-assisted psychotherapy with the MAPS Public Benefit Corporation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor JM declared a shared affiliation with the author JS at the time of review.

## Publisher's note



## References

1. Brown GR, Jones KT. Mental health and medical health disparities in 5135 transgender veterans receiving healthcare in the veterans health administration: a case–control study. *LGBT Health.* (2016) 3:122–31. doi: 10.1089/lgbt.2015.0058

2. Valentine SE, Shipherd JC. A systematic review of social stress and mental health among transgender and gender non-conforming people in the United States. *Clin Psychol Rev.* (2018) 66:24–38. doi: 10.1016/j.cpr.2018.03.003

3. Shipherd JC, Berke D, Livingston NA. Trauma recovery in the transgender and gender diverse community: extensions of the minority stress model for treatment planning. *Cogn Behav Pract.* (2019) 26:629–46. doi: 10.1016/j.cbpra.2019.06.001

4. Beek TF, Cohen-Kettenis PT, Kreukels BPC. Gender incongruence/gender dysphoria and its classification history. *Int Rev Psychiatry.* (2016) 28:5–12. doi: 10.3109/09540261.2015.1091293

5. Vahia VN. Diagnostic and statistical manual of mental disorders 5: a quick glance. *Indian J Psychiatry.* (2013) 55:220–3. doi: 10.4103/0019-5545.117131

6. Bourgois P, Holmes SM, Sue K, Quesada J. Structural vulnerability: operationalizing the concept to address health disparities in clinical care. *Acad Med.* (2017) 92:299–307. doi: 10.1097/ACM.0000000000001294

7. Freedom For All Americans. *Legislative Tracker: Anti-Transgender Legislation. Tracking LGBT-Related Legislation Nationwide.* (2022). Available online at: https://freedomforallamericans.org/legislative-tracker/anti-transgender-legislation/

8. Krishnakumar P. *This Record-Breaking Year for Anti-Transgender Legislation Would Affect Minors the Most.* CNN (2021).

9. PBS. *A Map of Gender-Diverse Cultures [WWW Document].* (2015). Available online at: https://www.pbs.org/independentlens/content/two-spirits_map-html/?msclkid=a0ed6427bc2211ec81392eb0e4276a0d (accessed April 25, 2022).

10. Meerwijk EL, Sevelius JM. Transgender population size in the United States: a meta-regression of population-based probability samples. *Am J Public Health.* (2017) 107:e1–8. doi: 10.2105/AJPH.2016.303578

11. Veterans Affairs. *PTSD-Repository [WWW Document].* (2022). Available online at: https://ptsd-va.data.socrata.com/ (accessed April 25, 2022).

12. Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology (Berl.).* (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

13. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* (2021) 27:1025–33. doi: 10.1038/s,41591-021-01336-3

14. Ching THW, Davis AK, Xin Y, Williams MT. Effects of psychedelic use on racial trauma symptoms and ethnic identity among Asians in North America. *J Psychoactive Drugs.* (2022) 2022:1–11. doi: 10.1080/02791072.2022.2025960

15. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. *BMC Psychiatry.* (2018) 18:245. doi: 10.1186/s12888-018-1824-6

16. Williams MT, Davis AK, Xin Y, Sepeda ND, Grigas PC, Sinnott S, et al. People of color in North America report improvements in racial trauma and mental health symptoms following psychedelic experiences. *Drugs Educ Prev Policy.* (2021) 28:215–26. doi: 10.1080/09687637.2020.1854688

17. MAPS. *MAPS Code of Ethics for Psychedelic Psychotherapy* (2021).

18. Eiseman E. *The National Bioethics Advisory Commission: Contributing to Public Policy.* Santa Monica, CA: RAND Corporation (2003).

19. Crabtree BF, Miller WL. *Doing Qualitative Research. 2nd ed.* Thousand Oaks, CA: Sage (1999).

20. Suen LW, Lunn MR, Katuzny K, Finn S, Duncan L, Sevelius J, et al. What sexual and gender minority people want researchers to know about sexual orientation and gender identity questions: a qualitative study. *Arch Sex Behav.* (2020) 49:2301–18. doi: 10.1007/s10508-020-01810-y

21. Bindman J, Ngo A, Zamudio-Haas S, Sevelius J. Health care experiences of patients with nonbinary gender identities. *Transgend Health.* (2021) 1–7. doi: 10.1089/trgh.2021.0029

22. Cicero EC, Reisner SL, Merwin EI, Humphreys JC, Silva SG. Application of behavioral risk factor surveillance system sampling weights to transgender health measurement. *Nurs Res.* (2020) 69:307–15. doi: 10.1097/NNR.0000000000000428

23. White BP, Fontenot HB. Transgender and non-conforming persons' mental healthcare experiences: an integrative review. *Arch Psychiatr Nurs.* (2019) 33:203–10. doi: 10.1016/j.apnu.2019.01.005

24. Sessa B, Higbed L, O'Brien S, Durant C, Sakal C, Titheradge D, et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J Psychopharmacol. (Oxf.).* (2021) 35:375–83. doi: 10.1177/0269881121991792

25. Yaden DB, Berghella AP, Regier PS, Garcia-Romeu A, Johnson MW, Hendricks PS. Classic psychedelics in the treatment of substance use disorder: potential synergies with twelve-step programs. *Int J Drug Policy.* (2021) 98:103380. doi: 10.1016/j.drugpo.2021.103380

26. Rea K, Wallace B. Enhancing equity-oriented care in psychedelic medicine: utilizing the EQUIP framework. *Int J Drug Policy.* (2021) 98:103429. doi: 10.1016/j.drugpo.2021.103429

27. Belser A. *10 Calls to Action: Toward an LGBTQ-Affirmative Psychedelic Therapy [WWW Document]. Chacruna.* (2019). Available online at: https://chacruna.net/10-calls-to-action-toward-an-lgbtq-affirmative-psychedelic-therapy/?msclkid=bf851eaabb8a11eca233aaafddca4210

28. American Medical Association. *Issue Brief: LGBTQ Change Efforts (So-Called "Conversion Therapy")* (2019).

29. American Psychiatric Association. *Position Statement on Conversion Therapy and LGBTQ Patients* (2018).

30. American Psychological Association. *APA Resolution on Sexual Orientation Change Efforts* (2021).

31. Ching THW. Intersectional insights from an MDMA-assisted psychotherapy training trial: an open letter to racial/ethnic and sexual/gender minorities. *J Psychedelic Stud.* (2019) 4:61–8. doi: 10.1556/2054.2019.017

32. Hale W. *Personal Communication* (2022).

33. MAPS. *MDMA Therapy Training Scholarship [WWW Document].* (2022). Available online at: https://mapspublicbenefit.com/training/scholarship/?msclkid=279bc0b5bc3811eca0edcc4cbfd3ccc9 (accessed April 25, 2022).

34. Wilson L. Fireside Project's New Equity Initiative Expands Psychedelic Support Services [WWW Document]. *Lucid News.* (2022) Available online at: https://www.lucid.news/fireside-projects-new-equity-initiative-expands-psychedelic-support-services/#:$\sim$:text=Only%20months%20after%20their%20launch%2C%20Fireside%E2%80%99s%20team%20began,and%20by%20seeding%20the%20future%20of%20the%20ecosystem.?msclkid$=$be2ed128bc3911ecae35c6b1d884f2a5 (accessed April 25, 2022).

35. Kira IA, Fawzi M, Shuwiekh H, Lewandowski L, Ashby JS, Al Ibraheem B. Do adding attachment, oppression, cumulative and proliferation trauma dynamics to PTSD criterion "a" improve its predictive validity: Toward a paradigm shift? *Curr Psychol.* (2021) 40:2665–79. doi: 10.1007/s12144-019-00206-z

36. Solomon DT, Combs EM, Allen K, Roles S, DiCarlo S, Reed O, et al. The impact of minority stress and gender identity on PTSD outcomes in sexual minority survivors of interpersonal trauma. *Psychol Sex.* (2021) 12:64–78. doi: 10.1080/19419899.2019.1690033

37. Davis AK, Xin Y, Sepeda ND, Garcia-Romeu A, Williams MT. Increases in psychological flexibility mediate relationship between acute psychedelic effects and decreases in racial trauma symptoms among people of color. *Chronic Stress.* (2021) 5:24705470211035610. doi: 10.1177/2470547021 1035607

38. Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, et al. Psilocybin-assisted group therapy for demoralized older long-term AIDS

survivor men: an open-label safety and feasibility pilot study. *eClinicalMedicine*. (2020) 27:100538. doi: 10.1016/j.eclinm.2020.100538

39. Testa RJ, Habarth JM, Peta J, Balsam KF, Bockting WO. Development of the gender minority stress and resilience measure. *Psychol Sex Orientat Gend Divers*. (2015) 2:65–77. doi: 10.1037/sgd0000081

40. Carvalho SA, Guiomar R. Self-compassion and mental health in sexual and gender minority people: a systematic review and meta-analysis. *LGBT Health*. (2022) 9:287–302. doi: 10.1089/lgbt.2021.0434

41. Dyar C, Sarno EL, Newcomb ME, Whitton SW. Longitudinal associations between minority stress, internalizing symptoms, and substance use among sexual and gender minority individuals assigned female at birth. *J Consult Clin Psychol*. (2020) 88:389–401. doi: 10.1037/ccp0000487

42. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci*. (2014) 9:1645–52. doi: 10.1093/scan/nst161

43. Kamboj SK, Walldén YSE, Falconer CJ, Alotaibi MR, Blagbrough IS, Husbands SM, et al. Additive effects of 3,4-methylenedioxymethamphetamine (MDMA) and compassionate imagery on self-compassion in recreational users of ecstasy. *Mindfulness*. (2018) 9:1134–45. doi: 10.1007/s12671-017-0849-0

44. Hysek CM, Domes G, Liechti ME. MDMA enhances "mind reading" of positive emotions and impairs "mind reading" of negative emotions. *Psychopharmacology (Berl.)*. (2012) 222:293–302. doi: 10.1007/s00213-012-2645-9

45. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. Therapeutic effect of increased openness: investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol (Oxf.)*. (2017) 31:967–74. doi: 10.1177/0269881117711712

46. American Psychological Association. Guidelines for psychological practice with transgender and gender nonconforming people. *Am Psychol*. (2015) 70:832–64. doi: 10.1037/a0039906

47. Solness CL, Kivlighan III DM. Queering group therapy: a phenomenological participatory design with transgender and nonbinary individuals. *Prof Psychol Res Pract*. (2022). 53:215–24. doi: 10.1037/pro0000459

48. Sevelius JM. *Psychedelic-Assisted Therapy with Transgender and Gender Diverse Individuals [WWW Document]*. MAPS (2019). Available online at: https://maps.org/news/bulletin/psychedelic-assisted-therapy-with-transgender-and-gender-diverse-individuals-spring-2019/

49. Crenshaw K. Mapping the margins: intersectionality, identity politics, and violence against women of color. *Stanford Law Rev*. (1991) 43:1241–99. doi: 10.2307/1229039

50. Williams MT, Reed S, Aggarwal R. Culturally informed research design issues in a study for MDMA-assisted psychotherapy for posttraumatic stress disorder. *J Psyched Stud*. (2020) 4:40–50. doi: 10.1556/2054.2019.016

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EDITED BY
Gul Dolen,
Johns Hopkins University,
United States

REVIEWED BY
Giovanni Martinotti,
University of Studies G. d'Annunzio
Chieti and Pescara, Italy
Seth Davin Norrholm,
Wayne State University, United States

*CORRESPONDENCE
Lauren Okano
lauren.okano@mapsbcorp.com

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# Therapeutic setting as an essential component of psychedelic research methodology: Reporting recommendations emerging from clinical trials of 3,4-methylenedioxymethamphetamine for post-traumatic stress disorder

Lauren Okano[1]*, Gregory Jones[2], Bri Deyo[3], Alida Brandenburg[4] and Wesley Hale[1]

[1]Department of Training and Supervision, Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA, United States, [2]Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, United States, [3]Department of Data Management, Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA, United States, [4]Department of Research Development and Regulatory Affairs, Multidisciplinary Association for Psychedelic Studies, Santa Cruz, CA, United States

Research of psychedelic assisted therapies is at an all-time high, though few studies highlight extra-pharmacological factors that may affect treatment efficacy. One critical set of attributes includes the therapeutic setting itself, which describe the physical and socio-cultural environments in which the drug-assisted session occurs. Despite enduring consensus of the influence of setting, recommendations for establishing and reporting key setting variables remain sparse across clinical trial protocols and published research methodologies. The purpose of this paper is to: (1) present what is known of the influence and implications of setting to psychedelic-assisted therapies, with a particular focus on 3,4-methylenedioxymethamphetamine (MDMA); and (2) propose a set of reporting guidelines for operationalizing and reporting key setting variables in clinical trials of psychedelic-assisted therapies, based on recommendations emerging from clinical trials of MDMA for PTSD. In fact, recommendations should be expanded to "set" - the subject's mood, expectations, and broader psychological condition - once this is more fully developed in the field. The proposed reporting guidelines offer a means of increasing the volume and

variability of data necessary for future empirical examination of key setting attributes influencing treatment efficacy, while preserving practitioner and patient autonomy to co-construct adaptive therapy settings according to their respective needs and expertise.

KEYWORDS

**psychedelic assisted therapy, MDMA, setting, research methodologies, recommendations**

## Introduction

Research of psychedelic-assisted therapies is at a historical high (1), with 54% of the top-cited 100 psychedelic articles published in the last decade (2). Burgeoning scientific and political interest in psychedelic therapies – in particular for post-traumatic stress disorder (PTSD), addictions, anxiety, and depression – has led to the designation of psilocybin and 3,4-methylenedioxymethamphetamine (MDMA) as breakthrough therapies by the U.S. Food and Drug Administration (3–5). Further evidence of this increasing momentum is the Biden administration's recent call for top officials to prepare for the pending approval and regulation of MDMA and psilocybin-assisted therapies within the next 2 years in the United States (6). Thus, in anticipation of a rapid expansion of psychedelic clinical trials in the near future, there is now an ever urgent need for researchers to reflect on the past, present, and future status of clinical methodology and reporting in this space. Failure to do so could potentially result in the loss of invaluable data that could vitally enhance the long-term safety and efficacy of these medicines.

One such area of particular importance is reporting on the therapeutic setting, a variable which 5 describes as the physical and social contexts in which the psychedelic drug response unfolds, and which is especially relevant to psychedelic-assisted therapies due to the nature of current research protocols. Modern day clinical research protocols for psychedelic therapies involve a rigorous screening process, multiple non-drug preparatory psychotherapy sessions, single or multiple sessions with a psychedelic compound, and additional non-drug integration sessions (7). As the *psychedelic-assisted* moniker implies, rather than exerting solely pharmacological effects, this class of compounds is suggested to enhance psychotherapeutic processes when administered in a supportive setting (8–10). Conversely, lack of consideration for establishing a safe and supportive therapy setting has previously been associated with increased risk of adverse psychological reactions (11).

A recent literature review of 43 psychedelic therapy studies found that authors consistently highlighted the conceptual importance of the physical and social settings, but provided few and inconsistent details on the nature, operationalization, and/or hypothesized mechanisms by which specific setting attributes may affect treatment outcomes (12). Further, accelerating scientific and political interest in the therapeutic use of psychedelics (or perhaps in light of it), guidelines for reporting what constitutes a safe and supportive therapy setting remain sparse across clinical trial protocols and published research methodologies.

As psychedelic research continues to gain scientific and political traction, it is imperative to ensure valid and reliable inferences can be made to advance clinical practice and regulatory policies. Currently, due to the limited sample size of recent clinical trials and the lack of available data characterizing setting, it is not yet feasible to rigorously examine the direct significance of setting attributes to treatment outcomes. However, establishing guidelines for operationalizing and reporting these attributes as essential methodological variables is a prerequisite for future empirical research in order to test these hypotheses directly.

The purpose of this paper is to: (1) present what is known of the influence and implications of setting to psychedelic-assisted therapies, with a particular focus on 3,4-methylenedioxymethamphetamine (MDMA); and (2) propose a set of reporting guidelines for operationalizing and reporting key setting variables in clinical trials of psychedelic assisted therapies, based on recommendations emerging from clinical trials of MDMA for PTSD. While this paper focuses on setting, we acknowledge the importance of "set" – the subject's mood, expectations, and broader psychological condition – and intend to publish a future perspective article to complement this. Lastly, we acknowledge the lack of empirical evidence of key setting attributes specific to MDMA and propose these guidelines as a precursor to future experimental studies examining where settings best for MDMA differ from settings for classic psychedelics.

## Part 1a. What is known about how setting influences the response to psychoactive drugs

Indigenous cultures established the influence of environmental factors shaping the response to psychoactive substances (13) long before "set and setting" became common

parlance among mid twenteeth century researchers (14, 15). Building on this, there now exists a number of natural and experimental studies widely cited as foundational evidence for the influence of physical and social environments on short and long-term responses to psychoactive drugs. This includes Robins et al. (16) and Zinberg (17) studies in which the use of heroin by soldiers serving in Vietnam was, on average, discontinued and did not evolve into addiction once service members returned to their safe and secure home - suggesting that secure and safe environments, or the lack thereof, play an important role in drug responses and addiction. This is further corroborated by Alexander et al. (18) seminal rat park experiment, in which rats housed in "social communities" with "comfortable bedding" were less likely to sustain cocaine use and overdose relative to rats kept solo in cages. Additionally, contemporary evidence involving both recreational MDMA users (19, 20) and clinical trial subjects (12, 21) consistently reinforce the influence of the surrounding environment on both subjective experiences and clinical outcomes of the individuals.

## Part 1b. Neurobiological and preclinical perspectives on the role of setting in MDMA-assisted therapy

The mechanism by which MDMA works synergistically with setting is not yet fully understood. Initial findings suggest it is partly attributable to its distinct synergy of psychostimulant (e.g. catecholaminergic enhancement), oxytocinergic, and classical psychedelic (e.g. 5-HT2A agonism) properties that increase sensitivity to internal (e.g., endogenous processes and pre-existing psychiatric conditions) and external (e.g., setting) attributes (22–24). Additionally, subsequent neurotrophic and neuroplastic downstream responses are thought to impart a "critical period," during which altered awareness, interpretation, and integration of both endogenous (e.g., psychological) and exogenous (e.g., setting) stimuli can facilitate enhanced fear extinction, reward learning, and memory reconsolidation (23–25). Such effects may increase the tolerability of processing traumatic memories when administered in a secure, therapeutic setting designed to enhance and augment the effects of MDMA's pharmacodynamic profile (26–28).

Moreover, factorial analyses of psychometric scales to assess altered states of consciousness provide several clear delineations between MDMA and classical psychedelics that are relevant to setting, and which can inform future research design. Classical psychedelics (LSD and psilocybin), for example, appear far more likely to induce audio-visual, synesthetic, and imagery distortions whereas MDMA appears to impart a heightened state of blissful awareness (10, 22). It is thus plausible that "real" elements in the surroundings (e.g., sounds, artwork, lighting, and color) have distinct importance in the context of MDMA use because these sensory inputs are transmitted in a *heightened* fashion, rather than in a *restructured* fashion as seen with classical psychedelics. Thus, the optimal combination of sensory inputs to impart synesthetic, mystical-type experiences associated with classical psychedelic efficacy may be entirely different from those which can safely foster fear extinction and trauma reprocessing with MDMA.

Though these understandings remain preliminary, such hypotheses are highly testable (even *post-hoc*), if the appropriate data is provided. Such work is already underway with psilocybin (29). Cross-referencing validated experiential questionnaires with individual setting variables in future MDMA trials would appear a necessary preamble to experimentally disentangle drug x environment synergies.

## Part 1c. Setting in modern clinical trials of psychedelic assisted therapies

Despite ample emphasis on the conceptual importance of setting in studies of MDMA and other psychedelics, it is more common to omit, neutralize, or "control" for extra-pharmacological variables within the current model of controlled trials (13). Among the few placebo-controlled clinical studies that do specify key attributes of setting, the following have been documented as important methodological considerations: a quiet, protected environment with a living-room atmosphere, eye shades, headphones with instrumental music, creative imagery, soft lighting, a comfortable temperature, and soothing olfactory cues (8, 30–32). Of course, the concepts of comfort, creativity, and soothingness are all highly subjective, so the ability to adapt these aspects of the setting to each patient's preferences may be essential to maximizing therapeutic effect and minimizing adverse experiences. Baseline personality inventories may be helpful in this regard. Moreover, the social identities – especially visually-apparent aspects like race, gender, voice/language, and stature – of therapists and clinic staff also make up key aspects of the social and cultural context, given their known relation to trauma as well as the framing and interpretation of psychedelic experiences (33, 34). These aspects represent a vital nexus between set and setting which need to be explored.

One noteworthy exception to the dearth of verbiage dedicated to setting methodologies in MDMA trials is a study by Ot'Alora et al. (21), in which the authors cite and make available their treatment manual. The following attributes are specified in the methods section: lamps with "low glow," curtains for privacy that "allowed natural light to come in so that participants could see the sky and tree tops," "a couch that could be transformed into a bed," largely instrumental playlists, plants, fresh flowers, end tables, upholstered chairs for the therapists, colorful rugs, paintings, a small desk and bookcase, and a safe for secure drug storage. This study is exemplary

TABLE 1 Reporting recommendations for documenting physical and socio-cultural setting variables in psychedelic assisted therapy studies.

**Physical setting attributes**

| Attribute | Considerations/Definitions | Variable reporting recommendation |
|---|---|---|
| Facility Location | The physical environment surrounding the treatment room.<br>Describes the general feel of the site. | Facility Location (select one):<br>__ Urban<br>__ Suburban<br>__ Rural<br>Facility Type (select one):<br>__ Hospital (Inpatient)<br>__ Outpatient clinic<br>__ Commercial space<br>__ Residential-type space<br>(Y/N) Do patients have the ability to choose between 2 or more locations? |
| Treatment Room | The room where the drug-assisted treatment session/s occur.<br>Describes the general feel of the room and any built-in resources or features. | __Provide photograph or diagram of room features<br>General Color Tones (select one):<br>__ Mostly cool<br>__ Mostly warm<br>__ Mostly neutral<br>Participant Seating (select all):<br>__ Couch<br>__ Futon (can be converted between couch and bed)<br>__ Chair, recliner<br>__ Chair, not recliner<br>__ Bed<br>Features (select all):<br>__ Window<br>__ Private bathroom<br>__ Space for body motion (yoga, stretching, walking)<br>(Y/N) Do patients have the ability to choose between 2 or more treatment rooms? |
| Accessories | Resources/comforting items available to the patient in the treatment room during the treatment.<br>Describes items that exist in the space for a purpose other than aesthetics or clinical care.<br>Does not include artwork. | Available (select all):<br>__ Bowl or container for drug dispensation<br>__ Eye shades<br>__ Art supplies<br>__ Journaling supplies<br>__ Blanket<br>__ Pillow<br>__ Fan<br>__ Fidget objects<br>__ Musical instruments<br>(Y/N) Do patients have the ability to self-select accessories? |
| Artwork | Treatment room decorations.<br>Describes items that exist for aesthetics. | General Color Tones (select one):<br>__ Mostly Cool<br>__ Mostly Warm<br>__ Mostly Neutral |

*(Continued)*

TABLE 1 (Continued)

| Attribute | Considerations/Definitions | Variable reporting recommendation |
|---|---|---|
| | | Imagery (select all):<br>__ Nature<br>__ Spiritual<br>__ Religious<br>__ Abstract<br>__ Psychedelic<br>Items (select all):<br>__ Wall art, print<br>__ Wall art, objects<br>__ Statues, sculptures, figures<br>(Y/N) Do patients have the ability to change or remove the art pieces that are displayed? |
| Lighting | The natural and created light inside the room.<br>Describes the types and versatility of the light sources that are used during the drug-assisted session/s. | Light sources used (select all):<br>__ Outside window, blackout curtains<br>__ Outside window, light curtains or blinds<br>__ Overhead lights, on/off<br>__ Overhead lights, dimmable<br>__ Floor lamps, on/off<br>__ Floor lamps, dimmable<br>__ Table lamps, on/off<br>__ Table lamps, dimmable<br>__ Nightlight<br>__ String lights<br>Dominant hue of lighting (select one):<br>__ Warm, white-yellow<br>__ Cool, white-blue<br>__ Variable, i.e. LED changeable color bulbs<br>(Y/N) Do patients have the ability to choose the amount and type of lighting used? |
| Sound | The ambient noise that can be heard from outside the treatment room or building, including phones ringing, people talking, dogs barking, and/or traffic noise.<br>Describes unintentional exposure to sounds. | Exposure to sounds from outside the room (select one):<br>__ No sounds<br>__ Faint sounds, easy to miss<br>__ Muffled sounds, able to ignore<br>__ Identifiable sounds, can be disruptive<br>(Y/N) Use of white noise machine |
| Music | Music is an emerging treatment modulator of great interest in psychedelic-assisted therapy research and as a treatment method of its own.<br>Describes recorded songs or sounds that are played during the drug-assisted session/s. | Music delivery system (select all):<br>__ Patient's own headphones<br>__ High quality stereo headphones<br>__ Earbuds<br>__ Speakers<br>__ Built-in surround sound |

*(Continued)*

TABLE 1 (Continued)

| Attribute | Considerations/Definitions | Variable reporting recommendation |
|---|---|---|
| | | Music playlist mostly… (select one):<br>__ Instrumental, no vocals<br>__ Instrumental with vocalizations that are not words<br>__ Songs with words in patient's native language<br>__ Songs with words in language patient does not speak<br>Music playlist, volume, and delivery system are… (select one):<br>__ Fully at patient's discretion during session<br>__ Somewhat at patient's discretion but mostly set<br>__ Fully set ahead of time, no ability to adjust during session |
| Scents | The natural or curated smell of the room. Describes which, if any, artificial scents are used and how air in the room stays feeling fresh. | Aromatic accessories (select all):<br>__ None<br>__ Scented candles<br>__ Incense or herbs<br>__ Essential oils<br>__ Scented sprays<br>(Y/N) Do patients have the ability to choose if or when scent is used? |
| Thermal Conditions | The ambient temperature of the room. Describes air handling and heating/cooling methods. | (Y/N) Central air handling (heating, cooling, circulation)?<br>(Y/N) Temperature measured/kept Consistent?<br>(Y/N) Do patients have the ability to control the thermostat in the room? |
| Food and Drink | The refreshment options that are available to the patient during the drug-assisted session. Describes types of food and drink, as well as storage and preparation options. | Available resources (select all):<br>__ Refrigerator<br>__ Electrolyte beverage<br>__ Fresh fruits and/or vegetables<br>__ Food prep space or counter<br>__ Food prep sink (not in bathroom)<br>__ Dishes/utensils<br>(Y/N) Do patients have the ability to choose what they eat and drink throughout the dosing day? |
| Medical and/or Monitoring Equipment | The equipment that exists in the room for medical or other monitoring. Describes equipment that is present inside the therapy room due to research, safety, and/or other local protocols. | Equipment that is present and plainly visible (select all):<br>__ Blood pressure machine<br>__ ECG machine<br>__ Video camera/s<br>__ Microphone/s<br>__ Automatic External Defibrillator (AED)<br>__ First aid kit<br>(Y/N) Does the participant understand that, while rare, a medical emergency could occur during their drug-assisted session? |
| Risk Minimization | Safeguards put in place to minimize the risk of serious medical adverse events (SMAEs) | (Y/N) Information on how to summon emergency assistance is easily accessible<br>(Y/N) Windows are secured |

*(Continued)*

TABLE 1 (Continued)

| Attribute | Considerations/Definitions | Variable reporting recommendation |
|---|---|---|
| | | (Y/N) Electrical cords are wrapped and out of sight as much as possible<br>(Y/N) Sharp objects (e.g. scissors, knives, etc) are either secured or removed<br>(Y/N) Cleaning supplies are either secured or removed<br>(Y/N) Automated External Defibrillator (AED) is available nearby |
| **Socio-Cultural Setting Variables** | | |
| **Attribute** | **Considerations/Definitions** | **Reporting Guidelines** |
| Places | Describes the arrangement of the facilitators and participants relative to each other and the door | People Placement:<br>__ Line (facilitators sit on either side of patient)<br>__ Triangle (facilitators and participant equal distance from each other)<br>__ Rectangle (facilitators close to each other, farther from patient)<br>__ Backed up (one facilitators sits back from other therapist)<br>Who is closest to the door?<br>__ Patient<br>__ Facilitator<br>(Y/N) Does the participant have the ability to choose where everyone sits? |
| Physical Stature of Facilitator(s) | The physical appearance of a facilitator may be triggering to patients with specific person-related traumas.<br>Describes some key aspects of physical stature that can be triggering. | Facilitator 1 (select all):<br>__ Male<br>__ Tall<br>__ Overweight<br>__ Muscular<br>Facilitator 2 (select all):<br>__ Male<br>__ Tall<br>__ Overweight<br>__ Muscular<br>(Y/N) Does the participant have the ability to choose their therapy pair? |
| Social Identities of Facilitator(s) and Patient | The social identities of the facilitator and the participant may trigger im-/explicit biases, which may impact trust and sense of safety. The process of establishing that trust is beyond the scope of setting.<br>Describes the aspects of the social identities that are mainly visual and impact setting. | Facilitator 1 (select all):<br>__ Gender: mostly masculine<br>__ Gender: mostly feminine<br>__ Gender: non-binary<br>__ LGBTQ+<br>__ White racial/ethnic identity<br>__ Non-white racial/ethnic identity:<br>Please specify _____<br>Therapist 2 (select all):<br>__ Gender: mostly masculine<br>__ Gender: mostly feminine<br>__ Gender: non-binary<br>__ LGBTQ+<br>__ White racial/ethnic identity<br>__ Non-white racial/ethnic identity:<br>Please specify _____<br>Participant (select all):<br>__ Gender: mostly masculine<br>__ Gender: mostly feminine |

*(Continued)*

TABLE 1 (Continued)

| Attribute | Considerations/Definitions | Variable reporting recommendation |
|---|---|---|
| | | __ Gender: non-binary<br>__ LGBTQ+<br>__ White racial/ethnic identity<br>__ Non-White Racial/ethnic Identity:<br>Please specify _____ |
| Presence of Patient's Trusted Contact | The presence of a relative, close friend, or significant other before and/or after the drug-assisted session may increase feelings of safety and trust.<br>Describes whether and when trusted contact was present | (Y/N) Did the patient request the presence of a trusted contact?<br>Presence (select all):<br>__ Before drug-assisted session<br>__ After drug-assisted session (not overnight)<br>__ After drug-assisted session (overnight stay) |

in its transparency and detailed methodologies pertaining to establishing an optimal therapeutic setting. It is clear that elements of setting differentially influence study participants based on their identities and lived experiences, and that efforts to personalize or customize may optimize drug effects, though further research is needed to disentangle the nature and magnitude of their respective influences (12).

## Part 2. Implications for research, policy, and practice

Given historical fallout from adverse events associated with psychedelics, setting optimization with regards to patient safety is particularly paramount. Serious medical adverse events (SMAEs) such as seizures, hyperthermia, hyponatremia, rhabdomyolysis, and serotonin syndrome have been associated with MDMA use, though not observed in clinical trials, and almost exclusively at higher doses in recreational settings (35). In contrast, current research demonstrates that serious medical adverse events (SMAEs) are exceedingly rare in patients taking MDMA in controlled settings [only one episode of ventricular extrasystole in six phase II and one phase III trials ($n = 147$)] (36). It is worth emphasizing that all these SMAE risks can be influenced by setting variables listed in Table 1, such as the quantity (and type) of fluid resuscitation given to patients, ambient temperature, lighting, availability of emergency medical equipment, and provider medical training.

Again, it is critical we understand how to optimize treatment efficacy while mitigating the risk of adverse effects (10). As exclusionary criteria and procedural rigor relax with more widespread use, these types of setting considerations will be of elevated importance. Risk of acute psychiatric complications (increasing depression, suicide, psychosis, and paranoia) seen with MDMA should also inform setting design and reporting (36, 37). In support of this, best practices derived from high-acuity facility design (close supervision, ligature minimization, securing elevated windows, removal of sharp objects, etc.) should be followed and documented in publications. Documenting these variables can not only serve as a checklist for clinicians to reduce short-term risk, but also help to promote widespread adoption of these safeguards by community practitioners through publication.

Detailed reporting of setting variables is also crucial for improving the external validity of psychotherapeutic techniques, study reliability, and comparisons of experimental data across investigations (38). Reliable neurobiological correlates of response remain elusive in psychiatry, in part due to inadequate accounting for extra-pharmacological variables. Psychedelic research presents a promising opportunity in that regard, as such variables are already a central focus of the therapeutic package itself. Emphasis on collection and dissemination of set and setting details, combined with the considerably larger effect sizes seen with psychedelics, may hold significant potential for robust biomarker development and further neuroscientific understanding. Thus, these data are foundational to future studies disentangling MDMA's mechanistic specificity, tracking and predicting therapeutic response, and isolating placebo effects - the basis for understanding how, when, for whom, and under what conditions therapies "work."

Lastly, establishing expectations for transparent documentation of setting is essential in shaping more effective drug policy. In an effort to overcome sensationalism over tentative results, which has derailed prior waves of psychedelic research, scientists are increasingly being called upon to provide rigorous, detailed evidence to inform policy decisions and legalization frameworks (13, 39). Greater use of, and adherence to, reporting guidelines may ensure that findings can be synthesized, reproduced, and applied over time to optimize treatment and care (12). Looking to the future, it is vital that

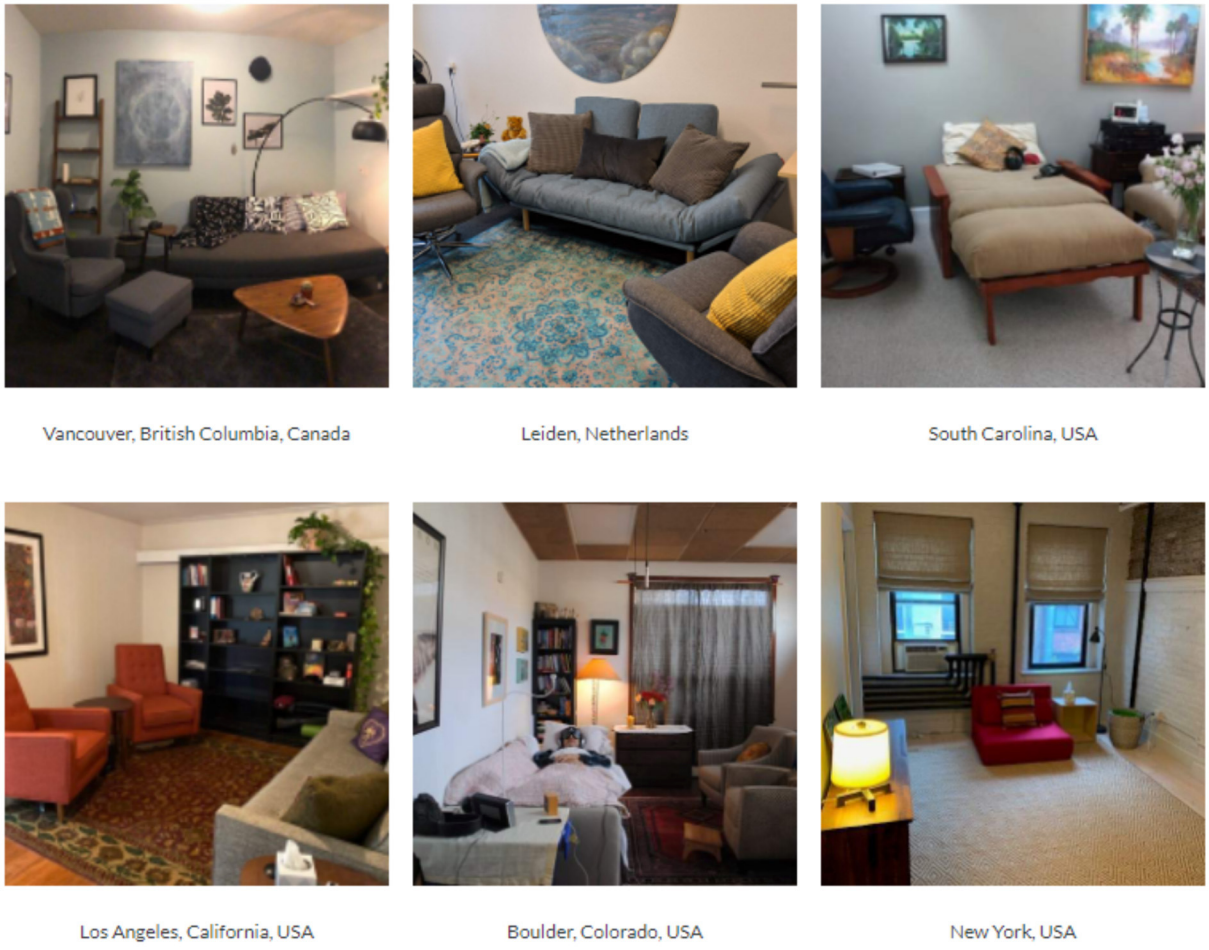


FIGURE 1
Photographs of MDMA-assisted therapy clinical trial settings.

scientists, clinicians, and policymakers embrace this paradigm shift in understanding and utilizing drug x context synergies (8).

## Part 3. Reporting recommendations emerging from clinical trials and expanded access use of MDMA for PTSD

Table 1 presents reporting recommendations for the documentation and future empirical study of key therapeutic setting variables in psychedelic research, with a focus on MDMA therapy. These recommendations are based on the Multidisciplinary Association for Psychedelic Studies (MAPS) MDMA-Assisted Psychotherapy treatment manual (40), which was adopted from approaches to earlier psychedelic treatments (41–43), traditional psychotherapy (44), and modified for use with MDMA (20, 45). Additionally, these recommendations are informed by insights that emerged from semi-structured interviews of seven pioneering MAPS facilitators who refined this therapeutic approach across three phases of clinical trials of MDMA for PTSD and supervised multiple MDMA-assisted therapy training cohorts. These recommendations are primarily intended to guide documentation and reporting rather than suggest standardized protocol for organizing setting in practice; both trained staff and participants must be empowered to collaboratively leverage their respective experiences to construct optimal, adaptive therapy settings.

We acknowledge the additional time and resources required to report these variables. However, we believe that doing so may ultimately avoid some reproducibility challenges in psychedelic science and ensure time and funding are efficiently expended. When possible, publication of pictures (e.g., room as a whole and individual elements), videos, playlists, or raw data as supplementary files can remove some of the burden from research staff. This may not only capture some unanticipated key

elements, but can also serve as a repository of information to be mined by independent investigators. This may be especially helpful to those who have interest in psychedelic research, but who may not have access to clinical trials at their institutions. In addition to strengthening study validity and reliability, this increased transparency may also attract new investigators interested in conducting secondary data analyses. Figure 1 presents photographs of treatment rooms from MDMA-assisted therapy clinical trials as an exemplar of the significant variability which often goes unreported.

Ultimately, the primary consideration for any psychedelic-assisted therapy setting is to enhance patients' sense of safety and comfort, which makes paramount the documentation of how a setting was customized and adapted. Ensuring that setting attributes are free from connotations with the source of patients' trauma is of particular relevance to MDMA specifically. In the words of one pioneering MDMA therapist, "There isn't a right way. It must be attuned to the client's needs. Introducing and having a conversation about room elements and being curious about how they are received determines whether it is in service to the patient or dissonant with their experience."

This notion is particularly relevant to documenting discernable attributes of the social environment surrounding the psychotherapeutic relationship – race, gender, sexual orientation, and stature of the patients and therapists – which are also inextricably linked to "set." Cultural humility, relevance, and congruence are key to patients' sense of safety and trust within the therapeutic setting and therefore essential considerations to be documented in study protocols and methodologies (46). As another MDMA therapist describes, "If my stature or perceived identity creates anxiety in the room, then the participant's ability to access their authentic self is interfered with, decreasing safety and potential efficacy of the drug." Hence, while further research is needed to disentangle the synergistic effects of both the physical and social attributes of setting, structured reporting of these variables is a seminal step forward.

## Conclusion

The use of reporting guidelines for documenting physical and social setting variables influencing psychedelic therapies may strengthen the rigor and reproducibility of research and treatment efficacy, while also strengthening regulatory efforts and mitigating risks to patients.

Further, future refinement of the recommended variables to report (Table 1) may offer a blueprint for inclusion in central study databases such as RedCap. While not exhaustive, these initial reporting guidelines offer a pragmatic step forward in increasing the volume of data around setting, offering parameters for reporting on study designs, and facilitating future study comparisons. Given the complexity of psychedelic research, these recommendations may not be universally applicable and are likely to evolve as the field progresses. Moreover, they are likely to vary based on the psychedelic drug, practitioner expertise, and patient need. Future research should examine the potential significance and modifying effects of the proposed setting attributes as they relate to treatment efficacy, and refine these reporting recommendations accordingly. We call on scientists to implement and iterate upon these guidelines to advance the medical, legal, and cultural contexts for people to benefit from the careful uses of psychedelics.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

## Conflict of interest

Authors WH, BD, and AB receive full salary support from MAPS-PBC.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note

# References


1. Doblin RE, Christiansen M, Jerome L, Burge B. The past and future of psychedelic science: an introduction to this issue. *J Psychoactive Drugs.* (2019) 51:93–7. doi: 10.1080/02791072.2019.1606472

2. Hadar A, David J, Shalit N, Roseman L, Gross R, Sessa B, et al. The psychedelic renaissance in clinical research: a bibliometric analysis of three decades of human studies with psychedelics. *J Psychoactive Drugs.* (2022) 10–17. doi: 10.1080/02791072.2021.2022254

3. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *J Psychopharmacology.* (2014) 29:57–68. doi: 10.1177/0269881114555249

4. Carhart-Harris RL, Bolstridge M, Rucker J, Day CMJ, Erritzoe D, Kaelen M, et al. Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry.* (2016) 3:619–27. doi: 10.1016/S2215-0366(16)30065-7

5. Palhano-Fontes F, Soares BL, Galvão-Coelho NL, Arcoverde E, Araujo DB. *Ayahuasca for the Treatment of Depression Current Topics in Behavioral Neurosciences*. Berlin: Springer Berlin Heidelberg (2021).

6. Busby, M. (2022). Biden administration plans for legal psychedelic therapies within two years. *The Intercept*. Available online at: https://theintercept.com/2022/07/26/mdma-psilocybin-fda-ptsd/ (accessed July 26, 2022).

7. Aday JS, Heifets BD, Pratscher SD, Bradley E, Rosen R, Woolley JD, et al. Great expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology.* (2022) 1:1–22. doi: 10.1007/s00213-022-06123-7

8. Carhart-Harris RL, Roseman L, Haijen E, Erritzoe D, Watts R, Branchi I, et al. Psychedelics and the essential importance of context. *J Psychopharmacol.* (2018) 32:725–31. doi: 10.1177/0269881118754710

9. Metzner R, Leary T. On programming psychedelic experiences. *Psychedelic Rev.* (1967) 9:5–19.

10. Studerus E, Vizeli P, Harder S, Ley L, Liechti ME. Prediction of MDMA response in healthy humans: a pooled analysis of placebo-controlled studies. *J Psychopharmacol.* (2021) 35:556–65. doi: 10.1177/0269881121998322

11. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. *J Psychopharmacology.* (2008) 22:603–20. doi: 10.1177/0269881108093587

12. Golden TL, Magsamen S, Sandu CC, Lin S, Roebuck GM, Shi KM, et al. *Effects of Setting on Psychedelic Experiences, Therapies, and Outcomes: A Rapid Scoping Review of the Literature. Current Topics in Behavioral Neurosciences*. Berlin: Springer Berlin Heidelberg (2022).

13. Hartogsohn I. Constructing drug effects: A history of set and setting. *Drug Sci Policy Law.* (2017) 3:205032451668332. doi: 10.1177/2050324516683325

14. Von Felsinger JM. Drug-induced mood changes in man. *J Am Med Assoc.* (1955) 157:1113. doi: 10.1001/jama.1955.02950300041009

15. Leary T, Litwin GH, Metzner R. Reactions to psilocybin administered in a supportive environment. *J Nervous Mental Dis.* (1963) 137:561–73. doi: 10.1097/00005053-196312000-00007

16. Robins LN, Helzer JE, Hesselbrock M, Wish E. Vietnam veterans three years after Vietnam: how our study changed our view of heroin. *Am J Addict.* (2010) 19:203–11. doi: 10.1111/j.1521-0391.2010.00046.x

17. Zinberg NE. *The Social Dilemma of the Development of a Policy on Intoxicant Use. Feeling Good and Doing Better*. Totowa, NJ: Humana Press, 27–47 (1984).

18. Alexander B, Peele S, Hadaway P, Morse S, Brodsky A, Beyerstein B, et al. Adult, infant, and animal addiction. *Meaning Addict.* (1985) 77–96.

19. McElrath K, McEvoy K. Negative experiences on ecstasy: the role of drug, set, and setting. *J Psychoactive Drugs.* (2002) 34:199–208. doi: 10.1080/02791072.2002.10399954

20. Greer GR, Tolbert R. A method of conducting therapeutic sessions with MDMA. *J Psychoactive Drugs.* (1998) 30:371–9. doi: 10.1080/02791072.1998.10399713

21. Ot'Alora GM, Grigsby J, Poulter B, Van Derveer JW, Giron SG, Jerome L, et al. 3, 4.-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. *J. Psychopharmacol.* (2018) 32:1295–307. doi: 10.1177/0269881118806297

22. Oeri HE. Beyond ecstasy: alternative entactogens to 3,4-methylenedioxymethamphetamine with potential applications in psychotherapy. *J Psychopharmacol.* (2020) 35:512–36. doi: 10.1177/0269881120920420

23. Carhart-Harris R, Nutt D. Serotonin and brain function: A tale of two receptors. *J Psychopharmacol.* (2017) 31:1091–120. doi: 10.1177/0269881117725915

24. Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature.* (2019) 569:116–20. doi: 10.1038/s41586-019-1075-9

25. Holze F, Vizeli P, Müller F, Ley L, Duerig R, Varghese N, et al. Distinct acute effects of LSD, MDMA, and d-amphetamine in healthy subjects. *Neuropsychopharmacology.* (2019) 45:462–71. doi: 10.1038/s41386-019-0569-3

26. Bershad A. Low-dose MDMA increases responses to psychosocial stress in healthy human volunteers. *Eur Neuropsychopharmacol.* (2016) 2:S695. doi: 10.1016/S0924-977X(16)31826-0

27. Feduccia AA, Holland J, Mithoefer MC. Progress and promise for the MDMA drug development program. *Psychopharmacology.* (2017) 235:561–71. doi: 10.1007/s00213-017-4779-2

28. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. MDMA-assisted psychotherapy may help individuals with treatment-resistant PTSD. *PsycEXTRA Dataset.* (2011) 19:1–7. doi: 10.1037/e717552011-010

29. Strickland JC, Garcia-Romeu A, Johnson MW. Set and setting: A randomized study of different musical genres in supporting psychedelic therapy. *ACS Pharmacol Trans Sci.* (2020) 4:472–8. doi: 10.1021/acsptsci.0c00187

30. Passie T. The early use of MDMA ('Ecstasy') in psychotherapy (1977–1985). *Drug Sci Policy Law.* (2018) 4:205032451876744. doi: 10.1177/2050324518767442

31. Barrett FS, Preller KH, Kaelen M. Psychedelics and music: neuroscience and therapeutic implications. *Int Rev Psychiatry.* (2018) 30:350–62. doi: 10.1080/09540261.2018.1484342

32. Carhart-Harris R. Psilocybin for depression. (2015). Available online at: https://www.isrctn.com/ISRCTN14426797 (accessed October 21, 2022).

33. Neitzke-Spruill L. Race as a component of set and setting: how experiences of race can influence psychedelic experiences. *J Psychedelic Stud.* (2019) 4:51–60. doi: 10.1556/2054.2019.022

34. Buchanan NT. Ensuring the psychedelic renaissance and radical healing reach the Black community: commentary on culture and Psychedelic Psychotherapy. *J Psychedelic Stud.* (2021) 4:142–5. doi: 10.1556/2054.2020.00145

35. Vizeli P, Liechti ME. Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol.* (2017) 31:576–88. doi: 10.1177/0269881117691569

36. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: Study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacolog.* (2019) 236:2735–45. doi: 10.1007/s00213-019-05249-5

37. Cohen RS, Cocores J. Neuropsychiatric manifestations following the use of 3, 4.-methylenedioxymethamphetamine (MDMA; "Ecstasy"). *Prog. Neuro Psychopharmacol. Biol. Psychiatry.* (1997) 21:727–34. doi: 10.1016/S0278-5846(97)00045-6

38. Butler-Struben HM, Kentner AC, Trainor BC. What's wrong with my experiment? The impact of hidden variables on neuropsychopharmacology research. *Neuropsychopharmacology.* (2022) 47:1285–91. doi: 10.1038/s41386-022-01309-1

39. Hartogsohn I. Set and setting, psychedelics and the placebo response: An extra-pharmacological perspective on psychopharmacology. *J. Psychopharmacology.* (2016) 30, 1259–1267. doi: 10.1177/0269881116677852

40. Mithoefer M. *A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder. Version 8.* (2016). Available online at: http://wwwmaps.org/research/mdma/mdma-research-timeline/4887-a-manual-for-mdma-assisted-psychotherapy-in-the-treatment-of-ptsd (accessed October 21, 2022).

41. Grof, S. (2001). *LSD Psychotherapy. 4th Edn*. Ben Lomond, CA: Multidisciplinary Association for Psychedelic Studies.

42. Blewett, D. B. (1959). *Handbook for the therapeutic use of lysergic acid diethylamide-25 individual and group procedures*. OCR by MAPS. Available online at: https://maps.org/wp-content/uploads/2014/02/lsdhandbook.pdf (accessed October 21, 2022).

43. Pahnke WN, Kurland AA, Unger S, Savage C, Grof S. The experimental use of psychedelic (LSD) psychotherapy. *Internationale Zeitschrift fur klinische Pharmakologie, Therapie, und Toxikologie. Int J Clin Pharmacol Ther Toxicol.* (1971) 4:446–54.

44. Pressly PK, Heesacker M. The physical environment and counseling: A review of theory and research. *J Counseling Dev.* (2001) 79:148–60. doi: 10.1002/j.1556-6676.2001.tb01954.x

45. Metzner R, Adamson S. Using MDMA in Healing, Psychotherapy and Spiritual Practice. In: Holland J, editors *Ecstacy, A Complete Guide: A Comprehensive Look at the Risks and Benefits of MDMA* (Rochester VT: Inner Traditions), 182–207 (2001).

46. Williams MT, Reed S, Aggarwal R. Culturally informed research design issues in a study for MDMA-assisted psychotherapy for posttraumatic stress disorder. *J Psychedelic Stud.* (2019) 4:40–50. doi: 10.1556/2054.2019.016

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EDITED BY
Peter Schuyler Hendricks,
University of Alabama at Birmingham,
United States

REVIEWED BY
Yasmin Schmid,
University of California, San Diego,
United States
Natalie Gukasyan,
Johns Hopkins Medicine, United States
Brian Pilecki,
Portland Psychotherapy Clinic,
United States

*CORRESPONDENCE
Elena Argento
bccsu-ea@bccsu.ubc.ca

†These authors share senior authorship

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# MDMA-assisted therapy is associated with a reduction in chronic pain among people with post-traumatic stress disorder

Devon Christie[1], Berra Yazar-Klosinski[2†], Ekaterina Nosova[3], Pam Kryskow[1,4], Will Siu[5], Danielle Lessor[6] and Elena Argento[1,3*†]

[1]Department of Medicine, University of British Columbia, Vancouver, BC, Canada, [2]MAPS Public Benefit Corporation, San Jose, CA, United States, [3]British Columbia Centre on Substance Use, Vancouver, BC, Canada, [4]Department of Health Sciences, Vancouver Island University, Nanaimo, BC, Canada, [5]MD Inc., Los Angeles, CA, United States, [6]Memorial University of Newfoundland, St. John's, NL, Canada

**Introduction:** Increasing evidence demonstrates 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy (MDMA-AT) may be a safe and effective treatment for post-traumatic stress disorder (PTSD). There is growing interest in MDMA-AT to address a range of other health challenges. Chronic pain and PTSD are frequently comorbid, reciprocally interdependent conditions, though the possible role of MDMA-AT in treating chronic pain remains under-investigated. The present analysis examined the impact of manualized MDMA-AT on chronic pain severity among participants with PTSD who were enrolled in a Phase 2 clinical trial investigating MDMA-AT for PTSD (NCT03282123).

**Materials and methods:** Exploratory data from a subset of participants who completed chronic pain measures ($n$ = 32) were drawn from a Phase 2 open-label study sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS). Multivariable analysis of variance (ANOVA) was utilized to compare pre- vs. post-treatment Chronic Pain Grade Scale (CPGS) values, adjusting for demographics (age, sex, and ethnicity). K-means clustering was then used to group the sample into three clusters to denote high ($n$ = 9), medium ($n$ = 11), and low ($n$ = 12) baseline pain severity, and the same analysis was repeated for each cluster.

**Results:** Among the 32 participants included in this analysis, 59% ($n$ = 19) were women, 72% ($n$ = 23) were white, and median age was 38 years [interquartile range (IQR) = 31–47]. Overall, 84% ($n$ = 27) reported having pain, and 75% ($n$ = 24) reported disability associated with their pain. Significant reductions in CPGS subscales for *pain intensity* and *disability score*, and overall CPGS *severity grade* were observed among participants in the highest pain cluster ($n$ = 9, $p < 0.05$), and for *pain intensity* in the medium pain cluster ($n$ = 11, $p < 0.05$) post- vs. pre-treatment.

**Discussion:** Findings demonstrate a high prevalence of chronic pain in this sample of people with severe PTSD and that chronic pain scores among medium and high pain subgroups were significantly lower following MDMA-AT. While these data are preliminary, when considered alongside the frequency of comorbid chronic pain and PTSD and promising efficacy of MDMA-AT for treating PTSD, these findings encourage further research exploring the role of MDMA-AT for chronic pain.

KEYWORDS

**MDMA-assisted therapy, chronic pain, MDMA, post-traumatic stress disorder, mental health**

## Introduction

Increasing evidence demonstrates that MDMA-assisted therapy (MDMA-AT) may be a safe and effective treatment for post-traumatic stress disorder (PTSD) (1–4). To date, 11 blinded randomized, controlled Phase 2 and Phase 3 studies of MDMA-AT for PTSD have been published (1–5), and there is growing interest in MDMA-AT for addressing a range of physical and mental health challenges. For instance, pilot studies have explored the potential for MDMA-AT in end of life anxiety (6), social anxiety in autistic adults (7), and alcohol use disorder (8), and exploratory analysis has generated preliminary data for eating disorders (9, 10). However, the possible effect of MDMA-AT on chronic pain remains under-investigated.

Chronic pain is a common, complex disease affecting approximately one-fifth of Americans (11) and up to 40% of people worldwide according to some studies (12) with far-ranging impacts on individuals and society (13). Chronic pain, defined as consistent pain for at least 3 months (14), is a leading cause of disability and is associated with a reduced life expectancy (12). The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" and clearly denotes that the experience of pain is personal and influenced by biological, psychological, and social factors (15). Whereas opioid medications may be utilized to manage acute and/or severe pain such as postoperative and terminal cancer pain, they are largely inappropriate and ineffective to alleviate chronic non-cancer pain and moreover their use is associated with the development of problematic opioid use disorder (OUD) (16). Innovative approaches to managing chronic pain that reduce long term reliance on pharmaceutical interventions are needed. Current best practice guidelines for chronic pain management recommend multidisciplinary treatments that address biological, psychological and social factors that collectively influence a person's experience of pain (17).

MDMA-AT is a novel intervention under investigation for PTSD that has been granted Breakthrough Therapy status for this indication by the United States' Food and Drug Administration in 2017 (2). PTSD is a complex, difficult to treat, stress-related psychiatric condition with somatization symptoms that has a profound impact on individuals and society and for which novel treatments are needed (1, 18). In well-established protocols, MDMA-AT combines a program of manualized psychotherapy with administration of MDMA on up to three occasions across the course of treatment in a clinically monitored setting for PTSD (1, 5). Long term analysis of pooled data from recent phase 2 studies of MDMA-AT for chronic, treatment-resistant PTSD demonstrated resolution of PTSD diagnosis in 67% of participants at least 12 months later (3), and phase 3 data demonstrated clinically and statistically significant improvement in severe, chronic PTSD in the MDMA-AT group vs. placebo with therapy combined with an acceptable safety profile (5). MDMA-AT has not yet been investigated to treat chronic pain as an indication.

Chronic pain and PTSD are both challenging to treat, and each contributes to significant dysfunction across all aspects of one's life despite current available treatments (19, 20). Chronic pain and PTSD are also frequently comorbid; two systematic reviews found prevalence rates of PTSD in clinical pain populations to range from 11.7 to 19.1% (21, 22), and in people with PTSD, prevalence estimates for chronic pain have been as high as 80%, as seen among military personnel (23–25). Both conditions are independently associated with OUD, yet when comorbid are associated with even higher odds of OUD than either condition alone (26). Those with comorbid pain and PTSD also experience greater pain, PTSD symptoms, depression, anxiety, and disability than those with only one of these conditions (27, 28). Chronic pain and PTSD have been described as reciprocally interdependent conditions, with similar maintenance mechanisms such as fear, avoidance, and catastrophizing (29, 30). One literature review notes, "the tight interdependence of symptoms that can be observed in both PTSD and chronic pain syndromes lends support to the idea that these disorders should be situated on the same level, that of a reactive disorder" (31). It has even been suggested that chronic pain might indeed be interpreted as a version of

PTSD (32). The Mutual Maintenance Model suggests PTSD and chronic pain exacerbate one another through biases of attention and cognition that create heightened expectations, overestimations, and selective and negative interpretations of both pain-evoking and fear-evoking stimuli. Pain may also serve as a traumatic cue, leading to intrusive PTSD symptoms, and vice versa (33). The Shared Vulnerability Model posits that anxiety sensitivity and genetic predispositions related to the stress response increase the likelihood for certain individuals to develop both conditions (24).

Given the relationship and similarities between chronic pain and PTSD, and anticipated efficacy of MDMA-AT in treating PTSD, MDMA-AT may have potential as a treatment for chronic pain. This notion is further supported by evidence suggesting efficacy for psychotherapeutic approaches in chronic pain (34) and the established importance of biopsychosocial interventions for chronic pain, with MDMA-AT being at once a biological *and* psychological treatment, combining the pharmacological effects of MDMA with psychotherapy. However, there remains a lack of research and data on the effect of MDMA-AT on chronic pain conditions. The present study therefore aimed to explore the potential relationship between MDMA-AT and pain outcomes, drawing on exploratory pain data from a Phase 2 trial of MDMA-AT for severe PTSD (35).

## Materials and methods

Data (December 2017 to August 2019) were drawn from a subset of participants enrolled in a multi-site Phase 2 open-label study known as MP16 ($n$ = 33) conducted by MAPS Public Benefit Corporation (MAPS PBC) (35). This study served as a lead-in to Phase 3 studies investigating manualized MDMA-assisted therapy (MDMA-AT) to treat severe PTSD. The researchers designed the study to model the structure of planned Phase 3 trials, and to prepare and supervise sites planning to be part of the Phase 3 studies. The study took place across 12 sites in the United States and followed well-established protocols for MDMA-AT. Details and primary outcomes of the study have been previously described (1).

The primary outcome measure for the MP16 study was the Clinician Administered PTSD Scale according to DSM-5 (CAPS-5), a semi-structured interview addressing PTSD symptom clusters (36). Exploratory data were collected including participants' Adverse Childhood Experiences (ACE) score at Baseline, and the Chronic Pain Grade Scale (CPGS) questionnaire at Baseline and Study Termination, which were of interest for the present analysis. Eligibility required confirmation of severe PTSD, defined as a CAPS-5 total severity score of 35 or greater. Participants could not have a diagnosis of substance use disorder within 60 days of screening, and psychiatric medications were tapered and discontinued prior to commencing study drug sessions. Participants were allowed to continue concomitant analgesic medications including non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, gabapentin, and opiates limited to hydrocodone, morphine and codeine. Participants taking other opiates at enrollment were cross-tapered to an allowable opiate during the preparatory period. Concomitant use of cannabis was prohibited from enrollment to study termination. The protocol for MDMA-AT involved a series of therapy sessions delivered by two clinicians in a "co-therapy" dyad, and participant eligibility and screening were managed by a physician. MDMA administration occurred on three occasions and each session was 8-h in duration in the presence of the co-therapy dyad. These study drug sessions were spaced 3–5 weeks apart and were preceded and/or followed by three non-drug 90-min sessions that served to prepare for and/or facilitate psychotherapeutic integration of each study drug session. According to the flexible dosing schedule, in the first study drug session, all participants received an initial dose of 80 mg MDMA HCl, followed 1.5–2.5 h later by a supplemental dose of 40 mg MDMA HCl. In the second and/or third study drug sessions, participants received an increased dose of 120 mg MDMA HCl followed by a supplemental dose of 60 mg MDMA HCl, 1.5–2.5 h later. All participants followed this dose escalation. The supplemental dose was withheld by the investigator in two instances due to tachycardia and elevated blood pressure following the initial dose, though neither required further medical intervention (35).

The primary outcome for the present analysis was chronic pain, as measured by the CPGS questionnaire, which was administered twice, at Preparatory Session 3 (prior to the first MDMA session), and at study termination which occurred 10–14 weeks after the final MDMA session. Participants were asked to base their responses at study termination on the period since the end of treatment. Secondarily, we looked for associations between chronic pain, childhood adversity and PTSD severity at baseline.

The CPGS questionnaire is a 7-item self-report instrument that measures two dimensions of overall pain severity: pain intensity and pain-related disability, and is valid and reliable for measuring change in severity of chronic pain over time (37). Data encompass current pain, as well as past 6 months pain and pain-related disability and is suitable for use in all chronic pain conditions. *Pain intensity* and *disability score* subscales are combined with *disability points score* to assign a chronic pain *severity grade* (0-IV); individual subscales as well as overall *severity grade* have demonstrated validity and reliability (38) (for definitions of CPGS *severity grade* (0–IV), see **Table 1**). Demographic variables included age, sex, and ethnicity (white vs. other).

### Statistical analysis

Statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

TABLE 1 Pain *severity grade* according to CPG.

| CPG chronic pain severity grade | Classification method | Definition |
|---|---|---|
| 0 | No pain in prior 6 months | No disability, no pain |
| 1 (I) | Pain Intensity < 50, < 3 Disability Points | Low disability, low intensity |
| 2 (II) | Pain Intensity > 50, < 3 Disability Points | Low disability, high intensity |
| 3 (III) | 3–4 Disability Points (regardless of Pain Intensity) | High disability, moderately limiting |
| 4 (IV) | 5–6 Disability Points (regardless of Pain Intensity) | High disability, severely limiting |

*Severity grade* is classified using the two subscales included in the present analysis (*Pain intensity* 0–100, *disability score* 0–100) plus a *disability points* value (number of disability days in the past 6 months converted to a 0–3-point scale plus *disability score* 0–100 converted to a 0–3-point scale).

TABLE 2 Baseline demographic variables among participants receiving MDMA-assisted therapy for PTSD included in this analysis ($n$ = 32).

| Variable | Value | *N* (%) |
|---|---|---|
| Sex assigned at birth | Female | 19(59.38) |
| | Male | 13(40.63) |
| Ethnicity | Indigenous (North America) | 1 (3.13) |
| | Asian | 5 (15.63) |
| | Asian and white | 1 (3.13) |
| | Black or African American | 1 (3.13) |
| | Black or African American and white | 1 (3.13) |
| | White | 23 (71.88) |
| Age (median, IQR) | | 37.5 (30.5 – 46.5) |
| ACE score (median, IQR) | | 4 (3 – 7) |

Bivariate linear and ordinal regression were used to estimate pre-treatment associations between CPGS values, and ACE score, CAPS-5 total severity, and demographic variables.

K-means clustering was used to cluster baseline pain into three groups to denote highest (cluster 1, $n$ = 9), medium (cluster 2, $n$ = 11), and lowest pain (cluster 3, $n$ = 12) within the sample as measured using the CPGS subscale values of *pain intensity*, *disability score*, and the overall pain *severity grade* (39).

To explore the association between MDMA-AT and chronic pain, we compared pre- vs. post-treatment CPGS *pain intensity, disability score*, and composite *severity grade* for all participants ($n$ = 32) using $t$-testing for bivariate association and two-way ANOVA for multivariable analysis, adjusting for demographics (sex, age, and ethnicity: white vs. non-white). We hypothesized that only participants reporting medium or high within-sample chronic pain at baseline would experience significant improvement post-treatment, therefore we repeated the same analysis for each CPGS cluster.

## Results

Of the 33 participants enrolled in study MP16, 32 had pre/post CPGS data and were thus included in this analysis. Overall, 59% ($n$ = 19) were female, 72% ($n$ = 23) were white, and the median age was 38 [interquartile range (IQR) = 31–47] (Table 2). Of this sample, 84% ($n$ = 27) reported having pain, and 75% ($n$ = 24) reported disability associated with their pain. Participants median ACE score was 4 (IQR = 3–7). No strong associations were found between pre-treatment CPGS values and ACE score, CAPS-5 total severity, or demographics (Table 3).

In bivariate $t$-testing and ANOVA, among those in the highest pain cluster mean CPGS values (each of *pain intensity, disability score, and severity grade*) were significantly reduced post-intervention vs. baseline ($n$ = 9, $p < 0.05$) (Tables 4–7). A significant reduction in *pain intensity* was observed in the medium pain cluster using ANOVA ($n$ = 11, $p$ = 0.020; $p$ = 0.095 for $t$-test) and there was a trend to reduction for *disability score* and *severity grade* subscales in both bivariate and multivariable analysis (Tables 4, 8).

## Discussion

The present study found a high prevalence of pain among this sample of individuals with PTSD, in keeping with other published data demonstrating high rates of comorbid pain and PTSD (40). Statistically significant within subjects reductions in CPGS subscales including *pain intensity, disability score, and* composite chronic pain *severity grade* were observed following MDMA-AT among participants in the highest pain cluster ($n$ = 9), and for *pain intensity* only in the medium pain cluster ($n$ = 11), suggesting that MDMA-AT may be associated with reduction in chronic pain and pain-related disability. Significant reductions in pain and pain-related disability among participants in the highest pain cluster may be due to higher baseline pain values allowing greater margin for improvement; there may also be a mechanism related to an amygdala-based threat response to higher levels of pain being positively impacted by MDMA-AT, since overlapping brain areas have been shown to be active in both pain related threat perception, and anxiety and fear-based threat perception as typified by PTSD (32). Interestingly, among this sample baseline pain severity and PTSD severity were not positively correlated (Table 3). We speculate that differences in pain perception among individuals with PTSD symptoms may account for this finding; for example, high PTSD severity may distract from pain symptomatology, and vice versa, but this warrants further investigation. Previous

TABLE 3 Bivariate linear and ordinal regression reveal no strong associations between pre-treatment CPG subscale values and pre-treatment CAPS-5 total severity, ACE score, or demographic variables.

| **Pain intensity** | **Bivariate linear regression** | ***P*-value** | **Adjusted R squared** |
|---|---|---|---|
| | **Estimate (95% CI)** | | |
| CAPS-5 total severity | 0.803 (−0.59, 2.195) | 0.249 | 0.01 |
| ACE score | 3.019 (−0.961, 6.999) | 0.132 | 0.04 |
| Sex–male | 1.105 (−18.751, 20.961) | 0.91 | −0.03 |
| Age | −0.654 (−1.518, 0.21) | 0.132 | 0.04 |
| Ethnicity – white | −17.68 (−38.349, 2.988) | 0.091 | 0.06 |
| **Disability score** | | | |
| CAPS-5 total severity | −0.078 (−1.747, 1.59) | 0.924 | −0.03 |
| ACE score | 1.438 (−3.378, 6.253) | 0.547 | −0.02 |
| Sex–male | −2.873 (−26.114, 20.367) | 0.802 | −0.03 |
| Age | −0.241 (−1.288, 0.807) | 0.642 | −0.03 |
| Ethnicity – white | −17.249 (−41.835, 7.338) | 0.162 | 0.03 |
| **Severity grade** | **Bivariate ordinal regression estimate** | | **Odds ratio (95% CI)** |
| CAPS-5 total severity | 0.02 | 0.661 | 1.02 (0.93-1.12) |
| ACE score | 0.127 | 0.4 | 1.14 (0.85-1.54) |
| Sex–male | 0.014 | 0.983 | 1.01 (0.28-3.72) |
| Age | −0.027 | 0.413 | 0.97 (0.91-1.04) |
| Ethnicity – white | −0.092 | 0.199 | 0.40 (0.09-1.61) |

research has demonstrated a unique and paradoxical pain perception pattern (hypo-responsiveness and hyper-sensitivity) in experimental and chronic pain among people with PTSD: PTSD-related dissociation was associated with higher pain threshold, whereas supra-threshold pain stimulus ratings were higher in those with PTSD in comparison to controls. Pain hyper-responsiveness was positively associated with anxiety sensitivity, but negatively correlated with dissociation levels (41). Anxiety and dissociation are intercorrelated in PTSD (41) yet their relationship to pain perception among people with PTSD has not been systematically studied and warrants further investigation. To our knowledge, this is the first study to demonstrate an association between MDMA-AT and reduced pain among individuals with PTSD.

Chronic pain is an international public health emergency for which new treatments are desperately needed (42, 43). While chronic pain is frequently comorbid with PTSD, few studies have examined treatments designed to effectively address both conditions concurrently (40), yet when outcomes are assessed related to psychological interventions for both disorders in individual studies, moderate effects for PTSD and small effects for pain emerge, suggesting transdiagnostic effects (44). International best practice recommendations involve understanding and addressing chronic pain within a biopsychosocial model, with personalized multidisciplinary treatment approaches that include both physical and psychological interventions (42, 43). Many chronic pain conditions, such as fibromyalgia, tension headache, and non-specific low back pain, involve alterations in central nervous system pain pathways leading to abnormal processing of pain signals, and are known collectively as "nociplastic" type pain. History of psychological, emotional, sexual, or physical abuse or a combination of these predispose to nociplastic pain (45). These conditions tend to respond poorly to physical treatment (medication or procedural interventions), and more readily to non-pharmacological

TABLE 4 Bivariate pre-treatment and post-treatment mean and *p*-values using *t*-testing for CPG *pain intensity*, *disability score* and the *severity grade* according to cluster groups (1-high *n* = 9, 2-medium *n* = 11, 3-low *n* = 12), and for the total sample (*n* = 32).

| **Cluster** | **Value** | **Pre-treatment mean** | **Post-treatment mean** | ***P*-value** |
|---|---|---|---|---|
| 1-High (*n* = 9) | Intensity (0–100) | 67 | 51.9 | 0.034 |
| | Disability (0–100) | 73 | 38.9 | 0.004 |
| | Severity grade (0–5) | 3.2 | 2.1 | 0.019 |
| 2-Medium (*n* = 11) | Intensity (0–100) | 44.3 | 31 | 0.095 |
| | Disability (0–100) | 18.7 | 13.3 | 0.391 |
| | Severity grade (0–5) | 1.3 | 1.1 | 0.408 |
| 3-Low (*n* = 12) | Intensity (0–100) | 9.2 | 7.2 | 0.618 |
| | Disability (0–100) | 1.4 | 0.8 | 0.534 |
| | Severity grade (0–5) | 0.6 | 0.4 | 0.436 |
| Total sample (*n* = 32) | Intensity (0–100) | 37.3 | 27.8 | 0.146 |
| | Disability (0–100) | 27.7 | 15.9 | 0.096 |
| | Severity grade (0–5) | 1.6 | 1.1 | 0.0117 |

TABLE 5 Multivariable ANOVA, adjusted for demographics (sex male vs. female, age, ethnicity white vs. non-white) for the total sample ($n$ = 32).

| | Coeff | Sum Sq | *F*-value | *P*-value |
|---|---|---|---|---|
| **Total sample ($n$ = 32)** | | | | |
| **Intensity** | | | | |
| Post vs. pre | −9.463 | 1, 387.877 | 2.333 | 0.132 |
| Sex male | −1.594 | 10.997 | 0.018 | 0.892 |
| Age | −0.149 | 1, 567.046 | 2.635 | 0.110 |
| Ethnicity white | −17.074 | 2, 894.353 | 4.866 | 0.031 |
| **Disability** | | | | |
| Post vs. pre | −11.828 | 2, 168.380 | 2.898 | 0.094 |
| Sex male | −4.445 | 20.358 | 0.027 | 0.870 |
| Age | 0.311 | 2.969 | 0.004 | 0.950 |
| Ethnicity white | −16.046 | 2, 556.382 | 3.417 | 0.070 |
| **Severity grade** | | | | |
| Post vs. pre | −0.452 | 3.161 | 2.600 | 0.112 |
| Sex male | −0.400 | 1.183 | 0.973 | 0.328 |
| Age | 0.006 | 0.239 | 0.196 | 0.659 |
| Ethnicity white | −0.658 | 4.301 | 3.537 | 0.065 |

TABLE 6 Multivariable ANOVA, adjusted for demographics (sex male vs. female, age, ethnicity white vs. non-white) for cluster 3-low ($n$ = 12).

| | Coeff | Sum Sq | *F*-value | *P*-value |
|---|---|---|---|---|
| **Cluster 3–low ($n$ = 12)** | | | | |
| **Intensity** | | | | |
| Post vs. pre | −1.945 | 22.698 | 0.254 | 0.620 |
| Sex male | 0.895 | 4.779 | 0.053 | 0.820 |
| Age | −0.193 | 186.798 | 2.087 | 0.165 |
| Ethnicity white | −4.104 | 62.434 | 0.697 | 0.414 |
| **Disability** | | | | |
| Post vs. pre | −0.555 | 1.848 | 0.454 | 0.509 |
| Sex male | 0.651 | 0.846 | 0.208 | 0.654 |
| Age | −0.011 | 6.078 | 1.492 | 0.237 |
| Ethnicity white | −2.174 | 17.526 | 4.301 | 0.052 |
| **Severity grade** | | | | |
| Post vs. pre | −0.167 | 0.167 | 0.639 | 0.434 |
| Sex male | −0.054 | 0.171 | 0.657 | 0.428 |
| Age | −0.015 | 0.693 | 2.655 | 0.120 |
| Ethnicity white | −0.052 | 0.010 | 0.039 | 0.846 |

TABLE 7 Multivariable ANOVA, adjusted for demographics (sex male vs. female, age, Ethnicity white vs. non-white) for cluster 1-high ($n$ = 9).

| | Coeff | Sum Sq | *F*-value | *P*-value |
|---|---|---|---|---|
| **Cluster 1-high ($n$ = 9)** | | | | |
| **Intensity** | | | | |
| Post vs. pre | −15.187 | 1, 037.857 | 7.279 | 0.018 |
| Sex male | −7.589 | 100.067 | 0.702 | 0.417 |
| Age | −0.755 | 1, 123.557 | 7.880 | 0.015 |
| Ethnicity white | 0.919 | 1.972 | 0.014 | 0.908 |
| **Disability** | | | | |
| Post vs. pre | −34.073 | 5, 224.464 | 10.396 | 0.007 |
| Sex male | −4.300 | 123.432 | 0.246 | 0.628 |
| Age | 0.120 | 74.018 | 0.147 | 0.707 |
| Ethnicity white | 2.383 | 13.259 | 0.026 | 0.873 |
| **Severity grade** | | | | |
| Post vs. pre | −1.111 | 5.556 | 8.867 | 0.011 |
| Sex male | −0.910 | 4.000 | 6.385 | 0.025 |
| Age | −0.006 | 0.023 | 0.037 | 0.850 |
| Ethnicity white | 0.344 | 0.277 | 0.441 | 0.518 |

TABLE 8 Multivariable ANOVA, adjusted for demographics (sex male vs. female, age, ethnicity white vs. non-white) for the cluster 2-medium ($n$ = 11).

| | Coeff | Sum Sq | *F*-value | *P*-value |
|---|---|---|---|---|
| **Cluster 2-medium ($n$ = 11)** | | | | |
| **Intensity** | | | | |
| Post vs. pre | −13.332 | 888.711 | 6.810 | 0.020 |
| Sex male | −0.345 | 979.720 | 7.507 | 0.015 |
| Age | 0.762 | 126.519 | 0.969 | 0.340 |
| Ethnicity white | −31.285 | 1, 938.220 | 14.851 | 0.002 |
| **Disability** | | | | |
| Post vs. pre | −5.334 | 142.258 | 0.953 | 0.344 |
| Sex male | 7.906 | 802.138 | 5.375 | 0.035 |
| Age | 0.273 | 21.379 | 0.143 | 0.710 |
| Ethnicity white | −10.265 | 208.663 | 1.398 | 0.255 |
| **Severity grade** | | | | |
| Post vs. pre | −0.200 | 0.200 | 2.763 | 0.117 |
| Sex male | 0.144 | 1.800 | 24.863 | 0.000 |
| Age | 0.018 | 0.005 | 0.063 | 0.805 |
| Ethnicity white | −1.032 | 2.109 | 29.138 | 0.000 |

approaches, such as educational, behavioral and psychotherapy interventions (46).

MDMA is a psychoactive compound that promotes serotonin release, and may exert therapeutic effects by enhancing fear memory extinction (47), promoting greater self-compassion (48), reducing self-criticism (48), reducing PTSD-related shame and anger (49) and causing acute prosocial and interpersonal effects that support the quality of the therapeutic alliance in psychotherapy (50). MDMA promotes oxytocin release, which helps increase interpersonal focus, feelings of interpersonal trust and social affiliation (51–53), and has been shown to reduce pain associated with social rejection (54). MDMA-AT has been associated with changes in personality persisting at two-month follow-up, notably increased personality trait Openness and reduction in Neuroticism (55). It has been suggested that MDMA may serve to acutely widen a "window of tolerance" in autonomic regulatory capacity which, combined with therapy,

enables participants to approach and reprocess highly charged traumatic content without becoming overwhelmed or limited by hyperarousal or dissociative processes (5). MDMA may also re-open oxytocin-dependent "critical period" neuroplasticity in social learning that may also function to enhance or accelerate therapeutic change (56).

Given the high comorbidity of PTSD and chronic pain reflected in the present analysis, and the growing literature suggesting shared mechanisms both predisposing to and maintaining both conditions, it is conceivable that some of these proposed mechanisms explaining the efficacy of MDMA-AT for PTSD may be relevant for treating chronic pain. In particular, MDMA-AT effects related to enhanced fear extinction and approaching rather than avoiding negatively charged content may be relevant to fear and avoidance phenomena that are known to intensify and perpetuate chronic pain (32). Self-compassion, enhanced through MDMA, has also been linked with improved pain outcomes (57). Treatment with an existential focus may play an important role in chronic pain recovery (42, 58) particularly when combined with other psychological and pharmacological approaches (40) and has been shown to be effective in decreasing pain-related disability (59). MDMA-related improvements in intrapersonal attitudes including reduced self-criticism may impart benefit to chronic pain-associated existential challenges to related to identity, social roles, meaning and purpose, which are relevant yet underrepresented areas of treatment focus for chronic pain (40). Interpersonal effects that enhance therapeutic alliance may also be of relevance since psychological interventions for chronic pain require a strong therapeutic relationship to maximize benefit (12). Additionally, MDMA-enhanced perception of social connection and support may target chronic pain-related social isolation, a factor that exacerbates pain symptomatology, and when reduced, is associated with improvements in emotional and physical functioning among chronic pain patients (60). The potential for MDMA-AT to promote change in personality including reduced trait Neuroticism may also be of relevance, since neuroticism predicts poor adjustment to chronic pain (61).

Our data demonstrate a high median ACE score among this sample (4; IQR 3–7) and are consistent with previous research in the intersecting fields of chronic pain and trauma, that indicate an association with adverse childhood experiences (ACE) (13, 62). Stress response psychobiology is of particular relevance to this discussion. While short term stress responses support an individuals' immediate survival, chronic adversity and/or repeated stressors, particularly during vulnerable developmental periods, can lead to long term changes to the structure and function of hormonal, neurological and psychological systems in ways that predispose to poor health outcomes (63–65), such as chronic pain. The capacity to tolerate increased levels of stress and to recover quickly, known as resilience, relies upon optimal environmental conditions whereby interacting psychobiological systems can develop ideal responses, and healthy attachment relationships are of particular importance (66). The potential of MDMA to re-open critical period neuroplasticity related to social reward learning, combined with interpersonal effects such as enhanced empathy and trust, may create optimal conditions within the MDMA-AT therapeutic relationship to improve resilience and thus create more favorable conditions for recovering from chronic pain and other chronic conditions that are negatively impacted by stress.

## Strengths and limitations

K-means clustering provided a simple and efficient method to define groups according to pre-treatment CPGS values representing high, medium, and low within-sample pain values, which allowed for analysis using regression, *t*-testing and ANOVA for the whole sample and then separately for each of these stable clusters. The small sample size ($n$ = 32) limited the power of these analyses, especially for the high pain cluster ($n$ = 9) that demonstrated significant post-treatment reductions in pain values. Analysis was not conducted according to a hierarchical testing strategy, introducing the possibility for Type 1 error. Despite these limitations, participants in this sample were not subject to expectation bias regarding any positive impact of MDMA-AT on pain, since participants were recruited to the original study for experimental treatment of PTSD, whereas CPGS was administered and collected as exploratory data only. These data encourage further research with a larger sample in randomized, controlled trials in which the intervention is specifically investigated as a treatment for chronic pain.

In this sample, MDMA was administered 3 times according to a flexible dosing schedule; however, the analysis was not powered to detect differences in total MDMA dose given that the vast majority of participants received the escalation dose (120 mg HCl for the second and/or third dosing session) and supplemental dose of 40 or 60 mg HCl. Future studies could address exposure-response analyses on change in chronic pain.

While the CPGS is a valid and reliable instrument, recall bias may limit accuracy of self-report responses. Further, the CPGS version administered to participants included one question (#5) that differed from the published version of the measure: on the 10-point scale, 10 was defined for this analysis as *10 = Extreme Change*, rather than *10 = Unable to Carry on Any Activities* in response to the question *In the past 6 months how much has pain interfered with your daily activities rated on 0-10 scale?* Therefore, while participants were aware the 10-point scale asked for a rating of severity of pain interference with daily activities, they might have interpreted *extreme change* as still allowing for minimal activity, rather than absolute inability to carry on any activities. This could theoretically lead to false elevation of baseline and post-intervention *disability score*, which could likewise falsely elevate total *severity score*.

Associations between MDMA-AT and chronic pain may be influenced by confounding variables not examined in the present study, such as concurrent analgesic medications. Furthermore, participants in study MP16 were not selected for experiencing chronic pain, rather they were selected for having PTSD symptoms for at least 6 months, therefore some participants may have completed the questionnaire in reference to pain experienced for a shorter period. This limits generalizability of these exploratory data to true chronic pain conditions that are not comorbid with PTSD. In addition, different etiologies for pain could lead to differing pain or disability perceptions, or different secondary responses to the MDMA-AT for PTSD intervention. Within study population and within cluster distribution of pain by etiology could lead to further information and enhance future research protocols investigating MDMA-AT for chronic pain that include a mixed sample.

This study included predominantly white participants, which limits the generalizability of the findings to other populations. Not all people are affected by chronic pain equally; most data indicate higher prevalence in racialized and marginalized populations including African American and Indigenous people, women, and individuals from lower socioeconomic backgrounds (12). Further research should aim to increase diversity among research participants, as well as consider how chronic pain is experienced across the lifespan and across cultures.

## Conclusion

These findings demonstrate a high prevalence of pain in this sample of participants with severe PTSD, and that pain intensity, disability, and a composite pain severity index grade among those with the highest pain were significantly lower following MDMA-AT. While these data are limited and primarily hypothesis generating, they suggest that MDMA-AT may be associated with reductions in pain and pain-related disability among individuals with PTSD. Despite being derived from an exploratory endpoint, these findings when considered alongside the promising efficacy of MDMA-AT for treating PTSD and the transdiagnostic similarities between PTSD and chronic pain, support advancement of research exploring the role of MDMA-AT as a novel intervention for chronic pain and PTSD/chronic pain co-morbidity.

## Data availability statement

The datasets analyzed for this study were accessed by request to the MAPS Public Benefit Corporation (MAPS PBC). Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available upon reasonable request and with the permission of MAPS at http://maps.org/datause. All requests for raw and analyzed data are promptly reviewed by MAPS PBC to verify if the request is subject to any confidentiality obligations. Patient-related data not included in this publication were generated as part of clinical trials and may be subject to patient confidentiality. Any data that can be shared may be released via a data use agreement.

## Ethics statement

The MP16 clinical trial was reviewed and approved by the Western Copernicus Group Independent IRB (Research Triangle, NC, United States), Western IRB (Puyallup, WA, United States), University of California San Francisco Human Resource Protection Program IRB, University of Washington Human Subjects Division IRB, and University of British Columbia Providence Health Care Research Ethics Board. Participants provided their written and informed consent for participation in MP16.

## Author contributions

BY-K: substantial contributions to the conception and design of study MP16. DC and EA: data analysis, plan conception, and design. DC: initial draft manuscript preparation. EN, DC, and EA: analysis and interpretation of the results. PK, WS, DL, and BY-K: review of data analysis and interpretation. DC, EA, PK, WS, DL, and BY-K: critical and final review of the manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

Author BY-K was employed by the company MAPS Public Benefit Corporation. Author WS was employed by Will Siu, MD Inc. Authors EA and DC were part-time consultants, and PK was a Clinical Advisor, to Numinus Wellness Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References

1. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl).* (2019) 236:2735–45. doi: 10.1007/s00213-019-05249-5

2. Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Front Psychiatry.* (2019) 10:650. doi: 10.3389/fpsyt.2019.00650

3. Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology (Berl).* (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

4. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry.* (2018) 5:486–97. doi: 10.1016/S2215-0366(18)30135-4

5. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

6. Wolfson PE, Andries J, Feduccia AA, Jerome L, Wang JB, Williams E, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Sci Rep.* (2020) 10:20442. doi: 10.1038/s41598-020-75706-1

7. Danforth AL, Grob CS, Struble C, Feduccia AA, Walker N, Jerome L, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology (Berl).* (2018) 235:3137–48. doi: 10.1007/s00213-018-5010-9

8. Sessa B, Sakal C, O'Brien S, Nutt D. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in patients with alcohol use disorder: preliminary data on the first four participants. *BMJ Case Rep.* (2019) 12:e230109. doi: 10.1136/bcr-2019-230109

9. Brewerton TD, Lafrance A, Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. *Med Hypotheses.* (2020) 146:110367. doi: 10.1016/j.mehy.2020.110367

10. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of±3, 4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol.* (2011) 25:439–52. doi: 10.1177/0269881110378371

11. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. *MMWR Morb Mortal Wkly Rep.* (2018) 67:1001–6. doi: 10.15585/mmwr.mm6736a2

12. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet.* (2021) 397:2082–97. doi: 10.1016/S0140-6736(21)00393-7

13. Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. *Br J Anaesth.* (2019) 123:e273–83. doi: 10.1016/j.bja.2019.03.023

14. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. *Pain.* (2015) 156:1003–7. doi: 10.1097/j.pain.0000000000000160

15. IASP. *Terminology. International Association for the Study of Pain.* Washington, DC: IASP (2021).

16. Hunter P. New therapies to relieve pain: the search for more efficient and safer alternatives to opioid pain killers. *EMBO Rep.* (2018) 19:e46925. doi: 10.15252/embr.201846925

17. Gatchel RJ, McGeary DD, McGeary CA, Lippe B. Interdisciplinary chronic pain management: past, present, and future. *Am Psychol.* (2014) 69:119–30. doi: 10.1037/a0035514

18. Andreski P, Chilcoat H, Breslau N. Post-traumatic stress disorder and somatization symptoms: a prospective study. *Psychiatry Res.* (1998) 79:131–8. doi: 10.1016/S0165-1781(98)00026-2

19. Jellestad L, Vital NA, Malamud J, Taeymans J, Mueller-Pfeiffer C. Functional impairment in posttraumatic stress disorder: a systematic review and meta-analysis. *J Psychiatr Res.* (2021) 136:14–22. doi: 10.1016/j.jpsychires.2021.01.039

20. Balayan K, Kahloon M, Tobia G, Postolova A, Peek H, Akopyan A, et al. The impact of posttraumatic stress disorder on the quality of life: a systematic review. *Int Neuropsychiatr Dis J.* (2014) 2:214–33. doi: 10.9734/INDJ/2014/7649

21. Siqveland J, Hussain A, Lindstrøm JC, Ruud T, Hauff E. Prevalence of posttraumatic stress disorder in persons with chronic pain: a meta-analysis. *Front Psychiatry.* (2017) 8:164. doi: 10.3389/fpsyt.2017.00164

22. Fishbain DA, Pulikal A, Lewis JE, Gao J. Chronic pain types differ in their reported prevalence of post –traumatic stress disorder (PTSD) and there is consistent evidence that chronic pain is associated with PTSD: an evidence-based structured systematic review. *Pain Med.* (2017) 18:711–35. doi: 10.1093/pm/pnw065

23. Otis JD, Keane TM, Kerns RD, Monson C, Scioli E. The development of an integrated treatment for veterans with comorbid chronic pain and posttraumatic

stress disorder. *Pain Med.* (2009) 10:1300–11. doi: 10.1111/j.1526-4637.2009.00715.x

24. Asmundson GJ, Coons MJ, Taylor S, Katz J. PTSD and the experience of pain: research and clinical implications of shared vulnerability and mutual maintenance models. *Can J Psychiatry.* (2002) 47:930–7. doi: 10.1177/070674370204701004

25. Otis JD, Keane TM, Kerns RD. An examination of the relationship between chronic pain and post-traumatic stress disorder. *J Rehabil Res Dev.* (2003) 40:397–405. doi: 10.1682/JRRD.2003.09.0397

26. Bilevicius E, Sommer JL, Asmundson GJG, El-Gabalawy R. Posttraumatic stress disorder and chronic pain are associated with opioid use disorder: results from a 2012-2013 American nationally representative survey. *Drug Alcohol Depend.* (2018) 188:119–25. doi: 10.1016/j.drugalcdep.2018.04.005

27. Jenewein J, Wittmann L, Moergeli H, Creutzig J, Schnyder U. Mutual influence of posttraumatic stress disorder symptoms and chronic pain among injured accident survivors: a longitudinal study. *J Trauma Stress.* (2009) 22:540–8. doi: 10.1002/jts.20453

28. Sullivan MJL, Thibault P, Simmonds MJ, Milioto M, Cantin A-P, Velly AM. Pain, perceived injustice and the persistence of post-traumatic stress symptoms during the course of rehabilitation for whiplash injuries. *Pain.* (2009) 145:325–31. doi: 10.1016/j.pain.2009.06.031

29. Kind S, Otis JD. The interaction between chronic pain and PTSD. *Curr Pain Headache Rep.* (2019) 23:91. doi: 10.1007/s11916-019-0828-3

30. Hooten WM. Chronic pain and mental health disorders: shared neural mechanisms, epidemiology, and treatment. *Mayo Clin Proc.* (2016) 91:955–70. doi: 10.1016/j.mayocp.2016.04.029

31. Brennstuhl MJ, Tarquinio C, Montel S. Chronic pain and PTSD: evolving views on their comorbidity. *Perspect Psychiatr Care.* (2015) 51:295–304. doi: 10.1111/ppc.12093

32. Elman I, Borsook D. Threat response system: parallel brain processes in pain vis-à-vis fear and anxiety. *Front Psychiatry.* (2018) 9:29. doi: 10.3389/fpsyt.2018.00029

33. Sharp TJ, Harvey AG. Chronic pain and posttraumatic stress disorder: mutual maintenance? *Clin Psychol Rev.* (2001) 21:857–77. doi: 10.1016/S0272-7358(00)00071-4

34. Majeed MH, Ali AA, Sudak DM. Psychotherapeutic interventions for chronic pain: evidence, rationale, and advantages. *Int J Psychiatry Med.* (2019) 54:140–9. doi: 10.1177/0091217418791447

35. Wang, JB, Lin J, Bedrosian L, Coker A, Jerome I, Feduccia A, et al. Scaling up: multisite open-label clinical trials of MDMA-assisted therapy for severe posttraumatic stress disorder. *J Humanist Psychol.* (2021). doi: 10.1177/00221678211023663 [Epub ahead of print].

36. Weathers FW, Bovin MJ, Lee DJ, Sloan DM, Schnurr PP, Kaloupek DG, et al. The clinician-administered PTSD scale for DSM-5 (CAPS-5): development and initial psychometric evaluation in military veterans. *Psychol Assess.* (2018) 30:383–95. doi: 10.1037/pas0000486

37. Elliott AM, Smith BH, Smith CW, Chambers AW. Changes in chronic pain severity over time: the chronic pain grade as a valid measure. *Pain.* (2000) 88:303–8. doi: 10.1016/S0304-3959(00)00337-7

38. Smith BH, Penny KI, Purves AM, Munro C, Wilson B, Grimshaw J, et al. The chronic pain grade questionnaire: validation and reliability in postal research. *Pain.* (1997) 71:141–7. doi: 10.1016/S0304-3959(97)03347-2

39. Jin X, Han J. K-means clustering. In: Sammut C, Webb GI editors. *Encyclopedia of Machine Learning.* (Boston, MA: Springer) (2010). p. 563–4. doi: 10.1007/978-0-387-30164-8_425

40. Reed DE, Cobos B, Nabity P, Doolin J, McGeary DD. Chapter 15 – comorbid chronic pain and posttraumatic stress disorder: current knowledge, treatments, and future directions. In: Pangarkar S, Pham QG, Eapen BC editors. *Pain Care Essentials and Innovations*. (Amsterdam: Elsevier) (2021). p. 211–27. doi: 10.1016/B978-0-323-72216-2.00015-6

41. Defrin R, Schreiber S, Ginzburg K. Paradoxical pain perception in posttraumatic stress disorder: the unique role of anxiety and dissociation. *J Pain.* (2015) 16:961–70. doi: 10.1016/j.jpain.2015.06.010

42. Canadian Pain Task Force. *Chronic Pain in Canada: laying a Foundation for Action*. Ottawa, ON: Health Canada (2019). p. 190179

43. U. S. Department of Health and Human Services. *Pain Management Best Practices Inter-Agency Task Force Report: updates, Gaps, Inconsistencies, and Recommendations*. Washington, DC: U. S. Department of Health and Human Services (2019).

44. Goldstein E, McDonnell C, Atchley R, Dorado K, Bedford C, Brown RL, et al. The impact of psychological interventions on posttraumatic stress disorder and pain symptoms: a systematic review and meta-analysis. *Clin J Pain.* (2019) 35:703–12. doi: 10.1097/AJP.0000000000000730

45. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Häuser W. Nociplastic pain: towards an understanding of prevalent pain conditions. *Lancet.* (2021) 397:2098–110. doi: 10.1016/S0140-6736(21)00392-5

46. Afari N, Ahumada SM, Wright LJ, Mostoufi S, Golnari G, Reis V, et al. Psychological trauma and functional somatic syndromes: a systematic review and meta-analysis. *Psychosom Med.* (2014) 76:2–11. doi: 10.1097/PSY.0000000000000010

47. Young MB, Andero R, Ressler KJ, Howell LL. 3,4-methylenedioxymethamphetamine facilitates fear extinction learning. *Transl Psychiatry.* (2015) 5:e634. doi: 10.1038/tp.2015.138

48. Kamboj SK, Kilford EJ, Minchin S, Moss A, Lawn W, Das RK, et al. Recreational 3,4-methylenedioxy-N-methylamphetamine (MDMA) or "ecstasy" and self-focused compassion: preliminary steps in the development of a therapeutic psychopharmacology of contemplative practices. *J Psychopharmacol.* (2015) 29:961–70. doi: 10.1177/0269881115587143

49. Dewey D, Schuldberg D, Madathil R. Do peritraumatic emotions differentially predict PTSD symptom clusters? Initial evidence for emotion specificity. *Psychol Rep.* (2014) 115:1–12. doi: 10.2466/16.02.PR0.115c11z7

50. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci.* (2014) 9:1645–52. doi: 10.1093/scan/nst161

51. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature.* (2005) 435:673–6. doi: 10.1038/nature03701

52. Bartz JA, Hollander E. The neuroscience of affiliation: forging links between basic and clinical research on neuropeptides and social behavior. *Horm Behav.* (2006) 50:518–28. doi: 10.1016/j.yhbeh.2006.06.018

53. Wagner AC. Couple therapy with MDMA—proposed pathways of action. *Front Psychol.* (2021) 12:733456. doi: 10.3389/fpsyg.2021.733456

54. Frye CG, Wardle MC, Norman GJ, de Wit H. MDMA decreases the effects of simulated social rejection. *Pharmacol Biochem Behav.* (2014) 117:1–6. doi: 10.1016/j.pbb.2013.11.030

55. Wagner MT, Mithoefer MC, Mithoefer AT, MacAulay RK, Jerome L, Yazar-Klosinski B, et al. Therapeutic effect of increased openness: investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol.* (2017) 31:967–74. doi: 10.1177/0269881117711712

56. Nardou R, Lewis EM, Rothhaas R, Xu R, Yang A, Boyden E, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature.* (2019) 569:116–20. doi: 10.1038/s41586-019-1075-9

57. Edwards KA, Pielech M, Hickman J, Ashworth J, Sowden G, Vowles KE. The relation of self-compassion to functioning among adults with chronic pain. *Eur J Pain.* (2019) 23:1538–47. doi: 10.1002/ejp.1429

58. McCabe R, Murray R, Austin P, Siddall P. Spiritual and existential factors predict pain relief in a pain management program with a meaning-based component. *J Pain Manage.* (2018) 11:163–70.

59. Gebler F, Maercker A. Effects of including an existential perspective in a cognitive-behavioral group program for chronic pain: a clinical trial with 6 months follow-up. *J Humanist Psychol.* (2014) 42:155–71. doi: 10.1080/08873267.2013.865188

60. Bannon S, Greenberg J, Mace RA, Locascio JJ, Vranceanu AM. The role of social isolation in physical and emotional outcomes among patients with chronic pain. *Gen Hosp Psychiatry.* (2021) 69:50–4. doi: 10.1016/j.genhosppsych.2021.01.009

61. Asghari A, Nicholas MK. Personality and pain-related beliefs/coping strategies: a prospective study. *Clin J Pain.* (2006) 22:10–8. doi: 10.1097/01.ajp.0000146218.31780.0b

62. Frewen P, Zhu J, Lanius R. Lifetime traumatic stressors and adverse childhood experiences uniquely predict concurrent PTSD, complex PTSD, and dissociative subtype of PTSD symptoms whereas recent adult non-traumatic stressors do not: results from an online survey study. *Eur J Psychotraumatol.* (2019) 10:1606625. doi: 10.1080/20008198.2019.1606625

63. Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. *Phys Ther.* (2014) 94:1816–25. doi: 10.2522/ptj.20130597

64. McEwen BS. The neurobiology of stress: from serendipity to clinical relevance. *Brain Res.* (2000) 886:172–89. doi: 10.1016/S0006-8993(00)02950-4

65. Bellis MDD, Zisk A. The biological effects of childhood trauma. *Child Adolescent Psychiatric Clin.* (2014) 23:185–222. doi: 10.1016/j.chc.2014.01.002

66. Luecken LJ, Lemery KS. Early caregiving and physiological stress responses. *Clin Psychol Rev.* (2004) 24:171–91. doi: 10.1016/j.cpr.2004.01.003

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EDITED BY
Lisa Jerome,
Multidisciplinary Association for Psychedelic Studies, United States

REVIEWED BY
Mercede Erfanian,
University College London, United Kingdom
Thomas H. Dozier,
Misophonia Treatment Institute, United States

*CORRESPONDENCE
Jadon Webb
Research@BloomMH.com

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# MDMA for the treatment of misophonia, a proposal

Jadon Webb[1]* and Shannon Keane[2]

[1]Bloom Mental Health LLC, Littleton, CO, United States, [2]Yale Child Study Center, New Haven, CT, United States

Misophonia is a disorder characterized by negative physical and emotional reactions to certain trigger sounds, such as chewing food. Up to 50% of population samples endorse some symptoms of misophonia, with about 20% having symptoms that impair normal life functioning. Most misophonia patients exhibit intense negative emotions and autonomic arousal (the fight-flight-freeze response) in response to a trigger, similarly to how someone with post-traumatic stress disorder (PTSD) might respond to a trauma trigger. Curiously, misophonia trigger sounds are often most distressing when coming from a specific person, suggesting the disorder may be responsive to interpersonal relationship factors. Treatment of misophonia is currently limited to the use of hearing modifications (e.g., earplugs or headphones) and psychotherapy, but many patients continue to suffer despite these best efforts. Phase 3 clinical trials suggest that MDMA is efficacious at treating the symptoms of autonomic arousal, negative emotions, and interpersonal suffering found in PTSD. As such, we propose that MDMA may represent an ideal treatment for some suffering from severe misophonia. In this perspective article, we review the symptoms of misophonia, and outline how MDMA may be uniquely suited for treating it, perhaps using a protocol analogous to the MAPS Phase 3 studies for PTSD.

KEYWORDS

**MDMA, PTSD, misophonia, trauma response, psychedelic**

## Introduction

Misophonia is a disorder characterized by exaggerated, negative emotional, and physiological responses to otherwise benign sounds. The response to a trigger activates the autonomic nervous system in a "fight-flight-freeze" response (1), which is distinct from how most other people respond to sounds that annoy them (2).

The term misophonia was first used in 2001 (3), but as of this writing, has not yet been classified as a formal diagnosis in the DSM-V or ICD-11. Limiting issues so far include lack of a consistent definition and coherent diagnostic criteria for misophonia, although this is now being addressed through consensus work groups (2). Misophonia is a worldwide phenomenon that likely has been present in the human population for

millenia, and is surprisingly common—around half of population samples have reported some degree of symptoms (4, 5), with up to 20% reporting symptoms that are clinically significant and may impact quality of life (6). Given how universal and prevalent this distressing phenomenon is, it is surprising that it has taken this long for the clinical and scientific community to identify it as a clinical entity, let alone begin formulating ways to treat it.

Treatments for misophonia are still scarce and mostly involve audiology interventions (e.g., white noise generating hearing aids) or variations of cognitive behavioral therapy (7). There are no controlled studies of medications yet, although case reports suggest that antidepressants (8–11), anxiolytics (12), stimulants (13), antipsychotics (14), and beta blockers (15) may help in some cases.

The biological mechanism of misophonia is slowly being elucidated (16, 17), and there are tantalizing clues that it shares overlap with the emotional and autonomic overreaction observed in other mental health disorders, such as post-traumatic stress disorder (PTSD), panic disorder, and specific phobias. Many so-called "misophones" react to a trigger sound analogously to how, for example, a soldier with PTSD after exposure to a bomb explosion might respond to hearing fireworks during a celebration, or how someone with a phobia of spiders may feel when encountering one. A flood of negative emotions and a surge in "fight-flight-freeze" sympathetic arousal is common to these examples.

An unusual feature of misophonia is that a trigger sound (such as chewing) is often much more distressing when generated by a specific person (7), usually someone emotionally close to the patient such as a parent or spouse. Other types of relationships, such as a new romantic interest, can have the opposite effect, and may reduce perceived distress from a trigger.

Trigger reactions to a sound are also more likely when the sound is felt by the patient to violate a rule or social norm. For example, the sound of loud bass drums at a concert may be perceived as acceptable or even enjoyable, but may become a disabling trigger if a next door neighbor is playing music at night, even if playing it quietly. An adult "rudely" smacking their lips may elicit uncontrollable rage, but this lip smacking may not be noticed when generated by an infant who is perceived as too young to "know any better" (7). This suggests that misophonia is not simply a reaction to the physical qualities of a sound, but that higher-order filters around relationship quality and social norms help modulate the perceived trigger distress, and may help determine whether the brain will activate a full fight-or-flight response.

MDMA is efficacious in treating disorders of autonomic arousal from negative stimuli. Recent Phase III trials (18), for instance, suggest that it might be a efficacious pharmacological treatment we currently have for PTSD. MDMA also increases empathetic, prosocial feelings toward others, and may be fairly unique in addressing negative emotions arising from interactions with others. These effects may address two core problems with misophonia: interpreting an otherwise benign triggering event as being very emotionally negative, and the inappropriate activation of a threat response (fight-or-flight) that typically comes with it.

In this perspective article, we examine the emotional and physiological features of misophonia and highlight the significant symptomatic overlap with other problems and disorders that MDMA appears to be efficacious at treating. We hope this can serve as a framework for future clinical trials for this common, sometimes disabling, and vastly understudied disorder.

## Method of literature review for this perspective article

We searched the literature (PubMed, Google Scholar) for any publication with the term "misophonia". One hundred twenty results were returned, and were independently reviewed by both authors. The term "misophonia" yielded multiple reports that explored the characteristic emotional and physiological symptoms and proposed biological mechanisms underpinning misophonia. Of note, misophonia was not found in association with the terms "MDMA," or any other dissociative or psychedelic treatments such as "ketamine", "psychedelics," or "psilocybin".

To review the effects of MDMA on emotional and physiological symptoms relevant to misophonia, we focused on reports containing the term "misophonia" and any of the following: "anxiety," "post-traumatic stress disorder/PTSD," and "phobia." To review effects on interpersonal relationships, we examined the terms: "empathy," "relationship," "mirror" (for mirror neurons), and "interpersonal." We also examined effects of MDMA on the perception of negative stimuli, especially sound issues commonly associated with misophonia, and by searching the terms "auditory," "phonophobia," "tinnitus," and "hyperacusis."

In addition to search term reviews, references cited in recent reviews and meta-analyses were also examined, as were the "cited by" references in PubMed when examining key papers. We also searched https://clinicaltrials.gov/ for any future trails of misophonia and found four results, but none related to MDMA, psychedelics, or any other medication intervention.

The literature regarding the mechanism and treatment of PTSD and other anxiety disorders is vast, and far beyond the scope of this paper to fully capture. The study of the neurobiology of human relationships is similarly extensive, and beyond the scope of this work. As such, we examined the most recent reviews and meta-analyses on this subject (papers cited in Results section), to ensure an up-to-date accounting of the most recent mechanistic hypotheses, which were then compared to the literature regarding the mechanism of misophonia. Search

limiters included all years, any language appearing in PubMed, and works published in peer-reviewed journals.

## Pathophysiology of misophonia

### Auditory component of misophonia

Misophonia triggers are typically common sounds that do not cause excessive annoyance or distress to most people. They are often repetitive in nature, and most commonly generated by the mouth or nose of others. Chewing noises are prototypic, and are perhaps the most common trigger. That said, a vast number of different trigger sounds have been described, including non-human sounds such as dogs barking, water dripping, or the sound of percussion instruments. Of note, other sensory modalities can also serve as triggers and visual triggers (termed misokinesia) are also quite common. Sound triggers are the most extensively characterized, and are thus the focus for this perspective article.

Trigger sounds can lead to extreme distress, and are often compared to "the sound of nails on a chalkboard," or for some, the feeling of being terrorized or physically assaulted. The distress from triggers can lead to impaired school or job performance, avoidance of certain normal life activities, social isolation, reduced life quality, and in extreme cases, self-harm (19).

Since misophonia involves a reaction to sound, it is often thought of as an auditory disorder, and frequently mentioned with other hearing problems such as tinnitus or hyperacusis (20). However, research now suggests that the peripheral auditory system, such as the tympanic membrane and auditory auditory nerve, is not the source of dysfunction in misophonia and that misophonia may not be related to other peripheral auditory problems. As seen in recent research by (21), misophonia appears to be a higher-order, central nervous system problem, rather than due to pathology of the peripheral auditory pathway.

### Emotional response

Trigger sounds characteristically cause an unpleasant, aversive emotional response. Anger and rage has been the most commonly reported emotion, experienced by up to 90% of respondents in surveys (7, 22). Anxiety, panic, disgust, resentment, and self-loathing are other common emotions that can occur during a trigger.

After an acute trigger response is over, many misophones feel a sense of depression and guilt around how they responded, especially if they had hostile thoughts or actions toward someone. The intensity of these adverse emotions can sometimes lead to extreme feelings of hopelessness and even suicidal ideation. Some also experience repetitive, intrusive thoughts about the trigger and may continue to hear the sound repeat in their head, leading to continued physiological response symptoms. Anticipatory anxiety around future triggers is also common, and can lead to avoidance of situations that might cause a trigger.

In many cases, an adverse reaction to a trigger sound will only occur when produced by certain people (1). Because of this unusual phenomenon, misophonia patients will often develop intense negative thoughts and feelings about this other person. Resentment and hostility toward the trigger person is common, with an internal narrative that the other person must not care about them and is being intentionally rude, or is perhaps unacceptably oblivious to polite social manners that "should have" convinced them not to make the trigger sound. Many misophones recognize that these thoughts are irrational, and can vocalize this in an interview, yet will still find themselves having them during a trigger reaction, and even afterward (23). This dichotomy of caring about another person while still feeling a sense of hostility or avoidance toward them can be very distressing, and often convinces the misophone that something is terribly wrong with them. Many will "joke" about believing that they may have sociopathic traits, or worry that they may become "psychotic" or violent later in life.

In many cases, the hostile or avoidant reaction from the misophone leads to interpersonal relationship troubles. It is characteristically hard for many misophones to explain their symptoms to a partner or family member. The description of symptoms often sounds, to the partner, as an attack on them for something that should be relatively benign, such as the way they eat food. This can lead to anger, confusion, and resentment in both partners, and compensatory activities that further harm the relationship, such as if the patient will no longer eat meals with their partner.

### Physical/autonomic response

Virtually all misophonic reactions to trigger sounds involve an immediate, involuntary autonomic response (1). The specific symptoms vary somewhat from person to person, but generally suggest a surge of sympathetic hormones leading to the so-called "fight-flight-freeze" response normally experienced in response to a dangerous threat. The symptoms also overlap considerably with someone exposed to a phobic threat, or during a panic attack.

Autonomic arousal happens within milliseconds of hearing a trigger sound, and feels like an overwhelming surge of emotion and bodily sensations that cannot be consciously controlled. Common symptoms include: elevated heart rate, increased respiratory rate, increased blood pressure, increased body temperature, sweating, clenched or tense muscles, and a pervasive sense of needing to fight the trigger or flee from it. Many misophones report being unable to think rationally when being triggered, and some will scream at or even hit the trigger source. They often feel as if their body is overtaken by the intense neurophysiological changes, so that their entire focus

shifts to attending to the threat (trigger), to the exclusion of almost everything else around them.

This intense autonomic reaction to triggers is very different from the reaction the average person has to generally annoying sounds (2). Annoying sounds can produce measurable physiological effects in humans, but do not typically elicit a fight-flight-freeze trigger reaction normally seen when someone is intensely afraid or in grave danger.

## Neurobiology of misophonia

Misophonia does not appear to arise from abnormalities in the peripheral auditory system as might be expected from hearing loss or tinnitus. Central auditory processing, on the other hand, was found to be abnormal for misophonia patients as measured by N1 auditory evoked potentials to oddball stimuli (24). Functional neuroimaging has also shown overactivity in the auditory cortex in misophones compared to controls (25, 26).

But these differences in central auditory processing do not fully explain the symptom constellation observed in misophonia, such as why highly specific, complex sounds are triggering, as opposed to types of sound with a certain audiological certain quality such as those that are too loud or high pitched, which we might expect from a peripheral auditory hypersensitivity. Auditory processing issues also do not explain why trigger reactions seem to arise preferentially from certain people or only in certain social or environmental contexts. And as noted, the intensity of the reaction to triggers is unlike the reaction to regular annoying sounds, and more resembles a reaction to life-threatening danger. These symptoms suggest unique abnormalities in brain regions connecting sensory input to higher-order emotional processing and threat recognition centers.

Changes in those with misophonia have indeed been observed in regions that mediate connection between perception of stimuli and emotions, in particular, increased activation of the right anterior insular cortex (AIC), a core part of the salience network (25, 27). Abnormal connections between the AIC and the posteromedial cortex (PMC), ventromedial prefrontal cortex (vmPFC), amygdala, and hippocampus were also observed. The AIC is critical for managing focus and attention, and ensuring someone can devote the needed mental resources to processing a complex task. In line with these observations, many misophones describe trigger sounds as being mentally intrusive (1). Studies similarly show that trigger sounds disrupt attention and focus in misophonia patients, when compared to disruption from simply hearing an annoying sound (28). This suggests that misophonia triggers are not simply "annoying sounds" in the conventional sense, but may be causing a deeper sense of cognitive disruption. Being interrupted while trying to focus is commonly experienced as irritation and anger, which are also emotions commonly experienced in response to a misophonia trigger.

Positron Emission Tomography scans have revealed that MDMA decreases blood flow to the motor and somatosensory cortex (29), which are regions important to the motor sensory integration component of misophonia. Blood decreases were also observed in regions central to negative emotional processing, including temporal lobe, left amygdala, cingulate cortex, right anterior insula and thalamus (29, 30). This may suggest a reduction in activity of these emotional centers involved in overactive threat responses, such as those suffering from PTSD and anxiety (31).

Misophonia seems to involve overlapping brain regions also affected by MDMA, including the left amygdala, anterior insular cortex, and anterior cingulate cortex (25–27, 32). Misophones also seem to exhibit overactivation of their left amygdala and temporal lobe in direct response to auditory triggers (32). Specifically, results showed hyperactivity in the bilateral superior temporal cortex during triggering episodes in misophones. Increased activity in the left amygdala could also explain the hypervigilance that is seen in misophones when exposed to particular triggers (32).

A breakthrough in mechanistic thought about misophonia is that it may be due, at least in part, to excessive activity of the brain's motor system and mirror neurons. Mirror neurons recognize complex behaviors and activity sequences in others (26). This system is thought to be crucial for understanding the actions, intentions, and emotions of others (33–35), and may play a key role in socializing and having empathy for others (36).

At a more basic level, when mirror neurons recognize an activity sequence in someone else (such as chewing food), the motor cortex activates as if the observer was actually doing that activity. It has been proposed that in misophonia, these mirror neurons may be "hyper-responding" to activities associated with a trigger, and that this hyper-response causes distress (26).

The mechanism of misophonia appears to be quite complex, and involves aspects of cortical auditory processing, changes in attention and focus, aberrant negative emotional interpretation of a stimulus, and a corresponding physiological threat response. It will likely take many years before it is completely understood, but attempts to develop symptomatic treatments need not wait this long. Misophonic reactions to triggers share considerable symptom overlap with other disorders that are better understood, and that have already powerfully responded to treatments such as MDMA.

## Similarities of misophonia to post-traumatic stress disorder

The misophonic response to triggers shares considerable symptom overlap with sound trigger responses observed in PTSD. As with misophonia, those suffering from PTSD can experience a very strong emotional and physiological response to specific stimuli (such as sounds) that do not bother most people. For example, someone who was abused may be triggered by the sound of a voice that resembles the attacker.

Post-traumatic stress disorder responses to triggers are mediated in part by a "fight-flight-freeze" autonomic surge, which can cause increased heart rate and blood pressure, sweating, hyper-vigilance, feelings of anger or aggression, and inability to think rationally, outside of an intense focus on fighting or fleeing the situation. Autonomic hyperarousal is a risk factor for developing PTSD symptoms (37), and those suffering from PTSD tend to have increased baseline sympathetic nerve activity (38). These autonomic symptoms bear a striking resemblance to those often observed in misophonia, and notably, PTSD was found to be a common comorbid condition with misophonia (39). This may speak to common underlying neurobiological traits and vulnerabilities for both disorders.

It is important to note that although there are similarities between PTSD and misophonia, there are also many fundamental differences in these two disorders as well. PTSD is specifically defined as having an automatic strong reactivity to a spontaneous, involuntary, and intrusive distressing memory of a terrifying traumatic event (39). While in misophonia, the strong negative emotional reactivity is triggered by seemingly harmless stimuli only. PTSD and misophonia are two very distinct disorders that also happen to share similar symptom profiles and neurobiological mechanisms.

PTSD also features other symptoms not typical of misophonia, such as intrusive recall of the trauma, emotional numbing, an exaggerated startle response, and frequent flashbacks. These differing symptoms clearly highlight how these are different disorders, just as PTSD is also not the same thing as, say, a specific phobia. That said, the strong overlap of inappropriate autonomic activation in both offers clues into what medication treatments might be useful. Medications that reduce autonomic hyperactivity can reduce many of the distressing symptoms of PTSD (40). And intriguingly, there are emerging observations that medications that reduce autonomic response may also be helpful in some cases of misophonia (15).

From a neurobiological perspective, a hyperactive amygdala is observed in PTSD (41), and similarly, an enlarged and overactive amygdala is also observed in misophonia (17). Abnormal connectivity between the insula is also observed in both misophonia and PTSD (42). While there are some general functional central nervous system (CNS) similarities with PTSD and misophonia, the complexities of measuring brain activity in response to stressors is complex and relies on numerous environmental and study population variables particular to each study. As such, a direct comparison under similar experimental circumstances will be needed to more definitively compare CNS activity between PTSD and misophonia.

### Similarities of misophonia to panic and phobias

While anger is the most common emotion experienced during a trigger, anxiety, and panic are also very common. The physiological symptoms of intense anxiety, phobia, and panic attacks are very similar to those experienced in response to a misophonia trigger; and panic disorder and anxiety also frequently co-occur in those suffering from misophonia (43). This may suggest some common mechanisms and vulnerabilities.

It is worth noting that misophones generally do not feel afraid of their triggers (1). As such, the misophonic response is not simply a phobia of sounds, which is a separate disorder termed phonophobia. Phonophobia is more specifically a fear or intolerance to sounds, based on specific physical characteristics of sound such as volume and pitch. It usually arises secondary to an illness or defect in the peripheral auditory pathway that causes an unpleasant sensitization to the sound, resulting in the patient becoming afraid or avoidant of sounds with those qualities (44). This is different from misophonia, which is a highly specific aversion to often quiet, non-threatening sounds that do not appear to be aversive based on their physical qualities.

### Misophonia and other psychiatric disorders

Other psychiatric disorders, such as depression, OCD, and anorexia can co-occur in misophonia, and may moderate the severity of the symptoms (39). The wide variety of disorders that may be associated with, and may affect, the experience of misophonia highlights how much we have yet to learn about it.

## Proposed MDMA effects on relevant misophonia symptoms

There are no formal studies on the use of MDMA to treat misophonia, and so this proposal stems from theoretical observations of how MDMA works.

### MDMA effects on perception of negative external stimuli (e.g., sounds)

The process of being triggered from a sound likely involves, to some extent, abnormal auditory processing. Importantly, MDMA can affect the perception of sound. Animal models show that auditory sensory gating is directly affected during MDMA use (45), and that this action depends on the serotonin receptor 5-HT2A (46). Since auditory gating may also be affected in misophonia (24), it would be of interest to see if MDMA administration could counteract these auditory gating abnormalities, but this remains to be examined.

A study in healthy recreational MDMA users showed that 75 mg reduced autonomic arousal to negative/unpleasant sounds, independent of the overall level of arousal (47). The authors specifically noted that clients "felt less discomfort or more at ease" when exposed to unpleasant sounds. While this

study did not specifically address patients misophonia, this clear reduction both in the subjective feeling *and* autonomic response to sound offers particular hope that MDMA may also be useful for aversive autonomic reaction toward misophonic triggers.

In a broader sense, MDMA is well known to reduce the perception of negative visual and other emotional stimuli, such as the recognition of sad, angry, or fearful facial expressions in others (48, 49). It is particularly effecacious at inhibiting a fearful or avoidant response to such stimuli, while allowing the user to maintain rational cognitive control, such as during a psychotherapy session. The mechanism for this is not clear, but some have noted that since MDMA decreases cortisol levels and amygdala activation, which may allow the patient to better access difficult, emotional material in the session. At the same time, MDMA may increase oxytocin levels (31), allowing for stronger bonding with the therapist and/or partner during the therapy session.

In rodent models, MDMA may also modulate how fearful or unpleasant memories are recalled, again allowing for a calmer, safer approach to processing them during a therapy session (50). It may also improve the extinction of any aversive emotions attached to unpleasant memories when doing exposure-based therapy (51, 52), although the degree to which this happens is disputed (53). This impact on prior learned emotional responses may offer a way to also re-imagine the emotions attached to triggers, and to the people who produce those triggers.

## MDMA effects on disorders of autonomic hyperarousal (PTSD)

Misophonia triggers induce a strong autonomic response that mediates much of the physical symptoms, and can reinforce the emotional perception of the trigger as being aversive, analogous to the strong autonomic symptoms experienced during a phobia reaction, panic attack, or a PTSD trigger. A pharmacological agent that could reduce this strong negative, autonomic response may thus potentially be an effective treatment.

Numerous reviews and meta-analyses consistently support MDMA as efficacious for treating PTSD symptoms, even long after the acute effects of the drug (40, 54–60). These clinical benefits appear to exceed any offered by current first-line pharmacological treatments (61). A recently completed Phase III clinical trial (18) has similarly shown good efficacy for PTSD, and therefore, MDMA may soon be offered as a mainstream treatment for it. MDMA is also showing promise for treating other anxiety-spectrum disorders, particularly social anxiety (62). The effects on other disorders such as phobias and panic are unclear, and need more study.

## MDMA effects on rigidity and internal ruminations

MDMA and other entactogens have a unique ability to promote cognitive flexibility, and help patients get unstuck from negative thinking patterns that trap them in cycles of depression, anxiety, and PTSD. Patients will sometimes report feeling able to see a problem with a brand new perspective and see more helpful ways to reframe it, or perhaps be able to forgive and close a chapter on a painful topic. Indeed, negative memories are rated as less negative by subjects taking MDMA, while positive memories are remembered more vividly (63).

While external stimuli (triggers) are the main immediate source of distress in misophonia, internal negative thoughts and feelings may also reinforce or aggravate the disorder, and perhaps sensitize the patient to have a stronger negative reaction toward future triggers.

The sounds that become triggers also often associate with activities seen as violating a social rule or norm. For instance, a patient may develop a trigger reaction to family members eating with their mouth open, when it has been implied in that family that eating with your mouth open is rude. Hearing thumping music being played late at night violates the generally accepted social norm of not playing loud music after hours. While many people can get annoyed at late night loud music, for the misophone, this dislike may grow over time into an intense, triggering rage even when the music is not overly loud or rude.

Misophonia sufferers have high levels of neuroticism (64), and anecdotally, often report that a more rigid insistence of rules and social norms may make them less tolerant of sounds and behaviors that may seem to violate these. Addressing neurotic personality traits is difficult and usually requires years of therapy, often with incomplete results. MDMA can increase feelings that run counter to a self-critical, neurotic state, namely: self-compassion, empathy, forgiveness, openness, and reduced feelings of conflict (65–67). This may open a window of cognitive flexibility to challenge how "rude" or "inappropriate" a trigger sound really is. If a trigger sound could be reframed as something reasonable and acceptable, the distress around it may be reduced.

## MDMA effects on relationship quality

A very unusual characteristic of misophonia trigger sounds is that they are often localized to specific people. Chewing sounds from friends may elicit no reaction, while the same chewing sounds from a parent may be intolerable. Certain kinds of emotive, new highly desirable relationships (e.g., romantic), are anecdotally reported to be protective against trigger effects. This relationship specificity suggests that the interpersonal, emotional context of a trigger may also play a role in determining its severity. If this is the case, then changing the

emotions a misophone feels toward a trigger person may reduce the trigger distress.

MDMA is one of the few pharmacological agents that can profoundly change the feelings people have toward each other, even long after the acute effects have worn off. Couples who use MDMA often report sustained, reduced conflict, increased empathy for each other, happiness, feelings of closeness, communicativeness, generosity, attachment safety, bonding, and intimacy (65, 68, 69). MDMA significantly increased the perceived pleasantness of human to human slow touch, but did increase perceived pleasantness of fast touch (70, 71).

The prosocial effects of MDMA were found to occur among couples in which one was suffering from prior trauma (69). MDMA thus appears to be a promising pharmacological treatment for couples undergoing therapy (Cognitive Behavioral Conjoint Therapy) when one partner has PTSD, with high overall satisfaction rates for both partners (72).

## The biological mechanism of MDMA effects on misophonia

It has been previously noted that MDMA increases serotonin, norepinephrine, and dopamine activity by stimulating neurotransmitter release and inhibiting neurotransmitter reuptake in the synaptic cleft (73). This is thought to be part of the reason for the positive, euphoric effects. MDMA also directly binds to and stimulates serotonin 2A receptors (5HT2AR) (74), and many of MDMA's effects on anxiety, fear, and processing of emotions appear dependent on normal functioning of this receptor. MDMA also improves the results of exposure-based therapy for PTSD, perhaps due to enhancement of fear memory extinction, although some studies dispute this (50). In animal models, blocking the 5-HT transporter (5-HTT) eliminated fear memory extinction effects (52), again highlighting the importance of the 5-HTT and 5-HT2A receptors.

Of critical importance to misophonia, 5-HT2A receptors appear to also be critical for MDMA's ability to reduce arousal caused by negative sounds (47). However, MDMA also affects numerous other neurotransmitters, hormones, and other gene regulators critical to homeostasis and emotional regulation, such as glutamate, oxytocin, cortisol, vasopressin, adrenocorticotropic hormone (ACTH), prolactin, and brain-derived neurotrophic factor (BDNF) (51, 75–77).

Looking even more broadly, other biological systems related to inflammation and immune regulation may also help mediate the effects of MDMA (78). Whole-genome microarrays in animal models exposed to MDMA show *hundreds* of gene expression changes from a variety of different cellular processes (79). These changes vary depending on location in the brain, concurrent environmental cues, and also no doubt will vary depending on the animal model used (none have yet been done in humans). As such, it is clear that a comprehensive molecular understanding of how MDMA effects change is still some distance away.

Meantime, regardless of how MDMA actually produces its neuropsychiatric effects, we should not lose sight of how beneficial it can be in treating disorders that are otherwise notoriously difficult to help. Thus, the development of treatment protocols should not wait on certain determination of the underlying mechanism.

# Discussion and proposed treatment protocol

MDMA offers a unique constellation of benefits that appears almost custom-fit for the symptoms commonly encountered in misophonia. It directly reduces autonomic reaction to aversive sounds, and shows promise for treating disorders characterized by abnormal autonomic arousal (e.g., PTSD). MDMA reduces the fear and avoidance while promoting openness, acceptance, and empathy, which may open a new window during psychotherapy sessions to retrain the negative response to misophonia triggers.

MDMA also appears to uniquely address neurotic ruminations while also reducing negative feelings that underpin interpersonal conflict. We anticipate some cases in which a patient in assistive therapy will realize that they were subconsciously holding on to social norms, neuroses, or resentments that are aggravating the emotional and autonomic response to triggers. The neuroplastic state induced by MDMA may allow deeper ruminative underpinnings triggers to be consciously identified, and perhaps laid to rest.

The ability of MDMA to facilitate healing in couples in which one member suffers from PTSD may be particularly germane to misophonia. As with PTSD, the patient with misophonia often suffers from abnormal emotional and physiological responses to the partner, and the partner also suffers as a result of these abnormal reactions. The beneficial effect of MDMA on both people may thus offer a unique approach to severe cases of misophonia in which both partners are suffering.

## Risks of using MDMA for misophonia

MDMA is generally safe and well tolerated when used in a therapeutic setting, and most side effects occurred during acute treatment, and were transient. In a large study in healthy volunteers (80), side effects included a temporary increase in blood pressure, tachycardia, and increased body temperature in about 1/3 of participants, with no serious adverse effects. A meta-analysis of MDMA for treating PTSD (54) also found

that therapy was generally safe, but teeth grinding, anxiety, headache, nausea, and feeling "jittery" were common during acute intoxication. One of the most serious theoretical concerns (serotonin syndrome), is based on MDMA's ability to increase serotonergic activity, but so far no cases have been reported in clinical studies (81). Not all experience MDMA as pleasant and instead may feel anxiety and panic during a session (82), and thus it is necessary to counsel clients ahead of time that it is possible they will not enjoy or benefit from the experience. It is also possible that MDMA will not help some cases of misophonia, which could be disappointing, particularly since there are few other pharmacological alternatives at this time.

It is critical to understand that recreational use of MDMA is NOT recommended at all. This is a powerful treatment that must be administered in a safe setting, by a trained medical and psychological professional. The concentration and purity of MDMA used outside of research settings cannot be validated since this still remains a schedule 1 substance. Consuming MDMA recreationally may involve risks such as ingesting impure substances, ingesting excess amounts, and experiencing unpleasant effects in unsafe environments. Before recommending MDMA to people struggling from misophonia, randomized controlled trials with good generalizability are needed for evaluating the effectiveness of this treatment.

## Proposed model for treatment of misophonia with MDMA-assisted therapy

Based on the analogy of misophonia trigger symptoms with PTSD, it seems likely that MDMA is a efficacious pharmacological treatment for PTSD, and may also be of benefit in misophonia, both for individuals suffering, and for couples who are both affected as they often are in PTSD (69). Given the similarity of symptoms, we see no reason to deviate from the protocol used in Multidisciplinary Association for Psychedelic Studies (MAPS) Phase 3 studies.

MAPS is one of the leading organizations investigating the use of MDMA-assisted psychotherapy in treating disorders such as PTSD. Their current Phase 3 PTSD protocol (83) has used 75–125 mg of oral MDMA, given during standardized psychotherapy sessions for PTSD in 2–3 total sessions each spaced about a month apart. Three preparatory psychotherapy sessions without MDMA were administered prior to the dosing sessions to build rapport and set goals, and 3–4 sessions would follow, for a total of 8–10 sessions.

During MDMA treatment, feelings and emotions around triggers could be explored in a manner similar to that done for other unpleasant subjects such as trauma. The therapists could assist the client in examining when and how they react to a trigger, and if they wished to consider examining whether they should be more open and accepting toward those making the trigger sounds. It may also be possible to do real-time exposure work to triggers, since MDMA can reduce the otherwise overpowering aversive response that could interfere with the therapy.

As with the PTSD studies, it will be critically important to have the 3–4 follow up sessions in order to integrate the experience, build skills around what was learned, and help any clients that may not have experienced sufficient benefit from the experience. In many cases, it will likely be appropriate to continue regular psychotherapy and medication management well beyond the 8–10 session series, in order to reinforce new habits and ways of responding to things.

In terms of patient selection and inclusion criteria, we would advise that adult patients be selected who have misophonia according to the 2022 consensus definition (2), and that score in clinically concerning range on a generally accepted misophonia rating scale, so that symptom reduction can be more systematically tracked over the course of treatment. Historically, the most widely used rating scale has been the Misophonia Assessment Questionnaire (Johnson, available online, however this is slowly falling out of favor. Newer rating scales such as the S-Five: Selective Sound Sensitivity Syndrome Study (84), Misophonia Response Scale (85), the A-MISO-S (4), or the now revised version AMISOS-R (7), the Duke Misophonia Questionnaire (86), and MisoQuest (87) have made progress toward having a fully validated, internally consistent misophonia rating instrument, and may also be a good choice for tracking progress.

Exclusions for participation would include all comorbid disorders. To establish promising and accurate results on the effectiveness of MDMA on misophonia, it is important to control for all of the possible confounding factors, including pre-existing comorbid disorders. In future clinical practice, we anticipate that misophonia and PTSD will be frequently treated together and see no reason to oppose this, but for purposes of an initial study, would advise these be kept separate. Other exclusions would be any medical contraindication for receiving MDMA, concurrent Bipolar 1 disorder, borderline personality disorder, eating disorder with active purging, or active substance abuse.

Given the highly relational nature of some misophonia sufferers, it would also be advisable to develop protocols for a separate couples therapy study, similar to the successful couples work in which one member suffers from PTSD (69). Empathy, understanding, and forgiveness related to misophonia triggers between the couple could also be an area of focus.

In terms of risk to participants compared to the current treatment protocol (i.e., for PTSD), we note again that misophonia sufferers have high levels of neuroticism (64), and that neuroticism corresponds to a higher risk (82) of having an unpleasant experience with MDMA. This could mean that a higher proportion of misophones will experience a negative

experience on MDMA compared to the general population, and this may be a limitation to these studies.

## Conclusion

MDMA offers a unique profile of emotional and physiological benefits that may be particularly helpful for treating misophonia, including: reduced arousal from hearing aversive sounds, reduced negative emotions toward an undesirable event, a greater sense of openness, acceptance, and forgiveness, and an increase in emphatic, prosocial feelings between those who may otherwise be in conflict. MDMA has already proven itself safe and efficacious in other similar disorders characterized by aberrant emotional and autonomic responses, and we propose it is ready to also be tested on misophonia symptoms, with a protocol analogous to the MAPS Phase 3 trials for PTSD. A successful outcome would represent a major breakthrough in treating this common and complex disorder, which currently has limited treatment options.

## Data availability statement

The original contributions presented in this study are included in the article, further inquiries can be directed to the corresponding author.

## Author contributions

JW: background research, conceptual development, and writing of the manuscript. SK: background research and writing of the manuscript. Both authors contributed to the article and approved the submitted version.

## Conflict of interest

Author JW was employed by Bloom Mental Health LLC.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## References


1. Edelstein M, Brang D, Rouw R, Ramachandran VS. Misophonia: physiological investigations and case descriptions. *Front Hum Neurosci.* (2013) 7:296. doi: 10.3389/fnhum.2013.00296

2. Swedo SE, Baguley DM, Denys D, Dixon LJ, Erfanian M, Fioretti A, et al. Consensus definition of misophonia: a Delphi study. *Front Neurosci.* (2022) 16:841816. doi: 10.3389/fnins.2022.841816

3. Jastreboff M, Jastreboff P. *Hyperacusis. Audiology Online*. (2001). Available online at: https://www.audiologyonline.com/articles/hyperacusis-1223 (accessed June, 2001).

4. Naylor J, Caimino C, Scutt P, Hoare DJ, Baguley DM. The prevalence and severity of misophonia in a UK undergraduate medical student population and validation of the Amsterdam misophonia scale. *Psychiatr Q.* (2021) 92:609–19. doi: 10.1007/s11126-020-09825-3

5. Jaswal SM, De Bleser AKF, Handy TC. Misokinesia is a sensitivity to seeing others fidget that is prevalent in the general population. *Sci Rep.* (2021) 11:17204. doi: 10.1038/s41598-021-96430-4

6. Wu MS, Lewin AB, Murphy TK, Storch EA. Misophonia: incidence, phenomenology, and clinical correlates in an undergraduate student sample. *J Clin Psychol.* (2014) 70:994–1007. doi: 10.1002/jclp.22098

7. Jager I, de Koning P, Bost T, Denys D, Vulink N. Misophonia: phenomenology, comorbidity and demographics in a large sample. *PLoS One.* (2020) 15:e0231390. doi: 10.1371/journal.pone.0231390

8. Kamody RC, Del Conte GS. Using dialectical behavior therapy to treat misophonia in adolescence. *Prim Care Companion CNS Disord.* (2017) 19:17l02105. doi: 10.4088/PCC.17l02105

9. Alekri J, Al Saif F. Suicidal misophonia: a case report. *Psychiatry Clin Psychopharmacol.* (2019) 29:232–7. doi: 10.1080/24750573.2019.1597585

10. Sarigedik E, Yurteri N. Misophonia successfully treated of with fluoxetine: a case report. *Clin Neuropharmacol.* (2021) 44:191–2. doi: 10.1097/WNF.0000000000000465

11. Zuschlag ZD, Leventhal KC. Rapid and sustained resolution of misophonia-type hyperacusis with the selective serotonin reuptake inhibitor sertraline. *Prim Care Companion CNS Disord.* (2021) 23:20l02731. doi: 10.4088/PCC.20l02731

12. Tunç S, Başbuğ HS. An extreme physical reaction in misophonia: stop smacking your mouth! *Psychiatry Clin Psychopharmacol.* (2017) 27:416–8. doi: 10.1080/24750573.2017.1354656

13. Osuagwu FC, Osuagwu VC, Machoka AM. Methylphenidate ameliorates worsening distractibility symptoms of misophonia in an adolescent male. *Prim Care Companion CNS Disord.* (2020) 22:19l02553. doi: 10.4088/PCC.19l02553

14. Naguy A, Al-Humoud AM, Pridmore S, Abuzeid MY, Singh A, Elsori D. Low-dose risperidone for an autistic child with comorbid ARFID and misophonia. *Psychopharmacol Bull.* (2022) 52:91–4.

15. Webb J. β-blockers for the treatment of misophonia and misokinesia. *Clin Neuropharmacol.* (2022) 45:13–4. doi: 10.1097/WNF.0000000000000492

16. Brout JJ, Edelstein M, Erfanian M, Mannino M, Miller LJ, Rouw R, et al. Investigating misophonia: a review of the empirical literature, clinical implications, and a research agenda. *Front Neurosci.* (2018) 12:36. doi: 10.3389/fnins.2018.00036

17. Eijsker N, Schröder A, Smit DJA, van Wingen G, Denys D. Structural and functional brain abnormalities in misophonia. *Eur Neuropsychopharmacol.* (2021) 52:62–71. doi: 10.1016/j.euroneuro.2021.05.013

18. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

19. Rinaldi LJ, Smees R, Ward J, Simner J. Poorer well-being in children with misophonia: evidence from the Sussex misophonia scale for adolescents. *Front Psychol.* (2022) 13:808379. doi: 10.3389/fpsyg.2022.808379

20. Schwartz P, Leyendecker J, Conlon M. Hyperacusis and misophonia: the lesser-known siblings of tinnitus. *Minn Med.* (2011) 94:42–3.

21. Aazh H, Erfanian M, Danesh AA, Moore BCJ. Audiological and other factors predicting the presence of misophonia symptoms among a clinical population seeking help for tinnitus and/or hyperacusis. *Front Neurosci.* (2022) 16:900065. doi: 10.3389/fnins.2022.900065

22. Kumar S, Hancock O, Cope T, Sedley W, Winston J, Griffiths TD. Misophonia: a disorder of emotion processing of sounds. *J Neurol Neurosurg Psychiatry.* (2014) 85:e3. doi: 10.1136/jnnp-2014-308883.38

23. Schröder A, Vulink N, Denys D. Misophonia: diagnostic criteria for a new psychiatric disorder. *PLoS One.* (2013) 8:e54706. doi: 10.1371/journal.pone.0054706

24. Schröder A, van Diepen R, Mazaheri A, Petropoulos-Petalas D, Soto de Amesti V, Vulink N, et al. Diminished n1 auditory evoked potentials to oddball stimuli in misophonia patients. *Front Behav Neurosci.* (2014) 8:123. doi: 10.3389/fnbeh.2014.00123

25. Schröder A, van Wingen G, Eijsker N, San Giorgi R, Vulink NC, Turbyne C, et al. Misophonia is associated with altered brain activity in the auditory cortex and salience network [published correction appears in Sci Rep. 2020. 10:4066]. *Sci Rep.* (2019) 9:7542. doi: 10.1038/s41598-019-44084-8

26. Kumar S, Dheerendra P, Erfanian M, Benzaquén E, Sedley W, Gander PE, et al. The motor basis for misophonia. *J Neurosci.* (2021) 41:5762–70. doi: 10.1523/JNEUROSCI.0261-21.2021

27. Kumar S, Tansley-Hancock O, Sedley W, Winston JS, Callaghan MF, Allen M, et al. The brain basis for misophonia. *Curr Biol.* (2017) 27:527–33. doi: 10.1016/j.cub.2016.12.048

28. Daniels EC, Rodriguez A, Zabelina DL. Severity of misophonia symptoms is associated with worse cognitive control when exposed to misophonia trigger sounds. *PLoS One.* (2020) 15:e0227118. doi: 10.1371/journal.pone.0227118

29. Gamma A, Buck A, Berthold T, Liechti ME, Vollenweider FX. 3,4-methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [HO]-PET in healthy humans. *Neuropsychopharmacology.* (2000) 23:388–95. doi: 10.1016/S0893-133X00130-5

30. Walpola IC, Nest T, Roseman L, Erritzoe D, Feilding A, Nutt DJ, et al. Altered insula connectivity under MDMA. *Neuropsychopharmacology.* (2017) 42:2152–62. doi: 10.1038/npp.2017.35

31. Johansen PØ, Krebs TS. How could MDMA (ecstasy) help anxiety disorders? A neurobiological rationale. *J Psychopharmacol.* (2009) 23:389–91. doi: 10.1177/0269881109102787

32. San Giorgi R. Hyperactivity in amygdala and auditory cortex in misophonia: preliminary results of a functional magnetic resonance imaging study. *Amsterdam Brain Cogn J.* (2015) 2:21–8.

33. Bastiaansen JA, Thioux M, Keysers C. Evidence for mirror systems in emotions. *Philos Trans R Soc Lond B Biol Sci.* (2009) 364:2391–404. doi: 10.1098/rstb.2009.0058

34. Schmidt SNL, Hass J, Kirsch P, Mier D. The human mirror neuron system-a common neural basis for social cognition? *Psychophysiology.* (2021) 58:e13781. doi: 10.1111/psyp.13781

35. de Waal FBM, Preston SD. Mammalian empathy: behavioural manifestations and neural basis. *Nat Rev Neurosci.* (2017) 18:498–509. doi: 10.1038/nrn.2017.72

36. Bekkali S, Youssef GJ, Donaldson PH, Albein-Urios N, Hyde C, Enticott PG. Is the putative mirror neuron system associated with empathy? A systematic review and meta-analysis. *Neuropsychol Rev.* (2021) 31:14–57. doi: 10.1007/s11065-020-09452-6

37. McFarlane AC. Posttraumatic stress disorder: a model of the longitudinal course and the role of risk factors. *J Clin Psychiatry.* (2000) 61(Suppl. 5):15–20; discussion 21–3.

38. Kim YK, Amidfar M, Won E. A review on inflammatory cytokine-induced alterations of the brain as potential neural biomarkers in post-traumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry.* (2019) 91:103–12. doi: 10.1016/j.pnpbp.2018.06.008

39. Erfanian M, Kartsonaki C, Keshavarz A. Misophonia and comorbid psychiatric symptoms: a preliminary study of clinical findings. *Nord J Psychiatry.* (2019) 73:219–28. doi: 10.1080/08039488.2019.1609086

40. Hoskins MD, Sinnerton R, Nakamura A, Underwood JFG, Slater A, Lewis C, et al. Pharmacological-assisted psychotherapy for post-traumatic stress disorder: a systematic review and meta-analysis. *Eur J Psychotraumatol.* (2021) 12:1853379. doi: 10.1080/20008198.2020.1853379

41. Vedantham K, Brunet A, Neylan TC, Weiss DS, Mannar CR. Neurobiological findings in posttraumatic stress disorder: a review. *Dialog Clin Neurosci.* (2000) 2:23–9. doi: 10.31887/DCNS.2000.2.1/kvedantham

42. Zhang Y, Xie B, Chen H, Li M, Guo X, Chen H. Disrupted resting-state insular subregions functional connectivity in post-traumatic stress disorder. *Medicine.* (2016) 95:e4083. doi: 10.1097/MD.0000000000004083

43. Siepsiak M, Rosenthal MZ, Raj-Koziak D, Dragan W. Psychiatric and audiologic features of misophonia: use of a clinical control group with auditory over-responsivity. *J Psychosom Res.* (2022) 156:110777. doi: 10.1016/j.jpsychores.2022.110777

44. Asha'ari ZA, Mat Zain N, Razali A. Phonophobia and hyperacusis: practical points from a case report. *Malays J Med Sci.* (2010) 17:49–51.

45. Lee J, Thwaites S, Gogos A, van den Buuse M. Pharmacological mechanisms involved in sensory gating disruption induced by (±)-3,4-methylenedioxymethamphetamine (MDMA): relevance to schizophrenia. *Brain Sci.* (2020) 10:44. doi: 10.3390/brainsci10010044

46. Padich RA, McCloskey TC, Kehne JH. 5-HT modulation of auditory and visual sensorimotor gating: II. Effects of the 5-HT2A antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats. *Psychopharmacology.* (1996) 124:107–16. doi: 10.1007/BF02245610

47. Kuypers KPC, de la Torre R, Farre M, Pizarro N, Xicota L, Ramaekers JG. MDMA-induced indifference to negative sounds is mediated by the 5-HT2A receptor. *Psychopharmacology.* (2018) 235:481–90. doi: 10.1007/s00213-017-4699-1

48. Bedi G, Phan KL, Angstadt M, de Wit H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology.* (2009) 207:73–83. doi: 10.1007/s00213-009-1635-z

49. Hysek CM, Schmid Y, Simmler LD, Domes G, Heinrichs M, Eisenegger C, et al. MDMA enhances emotional empathy and prosocial behavior. *Soc Cogn Affect Neurosci.* (2014) 9:1645–52. doi: 10.1093/scan/nst161

50. Hake HS, Davis JKP, Wood RR, Tanner MK, Loetz EC, Sanchez A, et al. 3,4-methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiol Behav.* (2019) 199:343–50. doi: 10.1016/j.physbeh.2018.12.007

51. Young MB, Andero R, Ressler KJ, Howell LL. 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Transl Psychiatry.* (2015) 5:e634. doi: 10.1038/tp.2015.138

52. Young MB, Norrholm SD, Khoury LM, Jovanovic T, Rauch SAM, Reiff CM, et al. Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). *Psychopharmacology.* (2017) 234:2883–95. doi: 10.1007/s00213-017-4684-8

53. Maples-Keller JL, Norrholm SD, Burton M, Reiff C, Coghlan C, Jovanovic T, et al. A randomized controlled trial of 3,4-methylenedioxymethamphetamine (MDMA) and fear extinction retention in healthy adults. *J Psychopharmacol.* (2022) 36:368–77. doi: 10.1177/02698811211069124

54. Smith KW, Sicignano DJ, Hernandez AV, White CM. MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder: a systematic review with meta-analysis. *J Clin Pharmacol.* (2022) 62:463–71. doi: 10.1002/jcph.1995

55. Tedesco S, Gajaram G, Chida S, Ahmad A, Pentak M, Kelada M, et al. The efficacy of MDMA (3,4-Methylenedioxymethamphetamine) for post-traumatic stress disorder in humans: a systematic review and meta-analysis. *Cureus.* (2021) 13:e15070. doi: 10.7759/cureus.15070

56. Illingworth BJ, Lewis DJ, Lambarth AT, Stocking K, Duffy JM, Jelen LA, et al. A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: a systematic review and meta-analysis. *J Psychopharmacol.* (2021) 35:501–11. doi: 10.1177/0269881120965915

57. Reiff CM, Richman EE, Nemeroff CB, Carpenter LL, Widge AS, Rodriguez CI, et al. Psychedelics and psychedelic-assisted psychotherapy. *Am J Psychiatry.* (2020) 177:391–410. doi: 10.1176/appi.ajp.2019.19010035

58. Varker T, Watson L, Gibson K, Forbes D, O'Donnell ML. Efficacy of psychoactive drugs for the treatment of posttraumatic stress disorder: a systematic review of MDMA, ketamine, LSD and psilocybin. *J Psychoactive Drugs.* (2021) 53:85–95. doi: 10.1080/02791072.2020.1817639

59. Bahji A, Forsyth A, Groll D, Hawken ER. Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for

posttraumatic stress disorder: a systematic review and meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry.* (2020) 96:109735. doi: 10.1016/j.pnpbp.2019.109735

60. Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology.* (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

61. Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for trauma treatment: safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline. *Front Psychiatry.* (2019) 10:650. doi: 10.3389/fpsyt.2019.00650

62. Luoma JB, Shahar B, Kati Lear M, Pilecki B, Wagner A. Potential processes of change in MDMA-assisted therapy for social anxiety disorder: enhanced memory reconsolidation, self-transcendence, and therapeutic relationships. *Hum Psychopharmacol.* (2022) 37:e2824. doi: 10.1002/hup.2824

63. Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, De Meer I, et al. The effect of acutely administered MDMA on subjective and BOLD-fMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol.* (2014) 17:527–40. doi: 10.1017/S1461145713001405

64. Cassiello-Robbins C, Anand D, McMahon K, Guetta R, Trumbull J, Kelley L, et al. The mediating role of emotion regulation within the relationship between neuroticism and misophonia: a preliminary investigation. *Front Psychiatry.* (2020) 11:847. doi: 10.3389/fpsyt.2020.00847

65. Dolder PC, Müller F, Schmid Y, Borgwardt SJ, Liechti ME. Direct comparison of the acute subjective, emotional, autonomic, and endocrine effects of MDMA, methylphenidate, and modafinil in healthy subjects. *Psychopharmacology.* (2018) 235:467–79. doi: 10.1007/s00213-017-4650-5

66. Kamboj S, Sarmah B, Gupta S, Dwivedi Y. Examining branding co-creation in brand communities on social media: Applying paradigm of Stimulus-Organism-Response. *Int J Inf Manage.* (2018) 39:169–85. doi: 10.1016/j.ijinfomgt.2017.12.001

67. Regan A, Margolis S, de Wit H, Lyubomirsky S. Does ±3,4-methylenedioxymethamphetamine (ecstasy) induce subjective feelings of social connection in humans? A multilevel meta-analysis. *PLoS One.* (2021) 16:e0258849. doi: 10.1371/journal.pone.0258849

68. Baggott MJ, Kirkpatrick MG, Bedi G, de Wit H. Intimate insight: MDMA changes how people talk about significant others. *J Psychopharmacol.* (2015) 29:669–77. doi: 10.1177/0269881115581962

69. Wagner AC, Liebman RE, Mithoefer AT, Mithoefer MC, Monson CM. Relational and growth outcomes following couples therapy with MDMA for PTSD. *Front Psychiatry.* (2021) 12:702838. doi: 10.3389/fpsyt.2021.702838

70. Bershad AK, Mayo LM, Van Hedger K, McGlone F, Walker SC, de Wit H. Effects of MDMA on attention to positive social cues and pleasantness of affective touch. *Neuropsychopharmacology.* (2019) 44:1698–705. doi: 10.1038/s41386-019-0402-z

71. Wardle MC, de Wit H. MDMA alters emotional processing and facilitates positive social interaction. *Psychopharmacology.* (2014) 231:4219–29. doi: 10.1007/s00213-014-3570-x

72. Monson CM, Wagner AC, Mithoefer AT, Liebman RE, Feduccia AA, Jerome L, et al. MDMA-facilitated cognitive-behavioural conjoint therapy for posttraumatic stress disorder: an uncontrolled trial. *Eur J Psychotraumatol.* (2020) 11:1840123. doi: 10.1080/20008198.2020.1840123

73. Mustafa NS, Bakar NHA, Mohamad N, Adnan LHM, Fauzi NFAM, Thoarlim A, et al. MDMA and the brain: a short review on the role of neurotransmitters in neurotoxicity. *Basic Clin Neurosci.* (2020) 11:381–8. doi: 10.32598/bcn.9.10.485

74. Zhang G, Ásgeirsdóttir HN, Cohen SJ, Munchow AH, Barrera MP, Stackman RW Jr. Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6J mice. *Neuropharmacology.* (2013) 64:403–13. doi: 10.1016/j.neuropharm.2012.06.007

75. Grob CS, Poland RE, Chang L, Ernst T. Psychobiologic effects of 3,4-methylenedioxymethamphetamine in humans: methodological considerations and preliminary observations. *Behav Brain Res.* (1996) 73:103–7. doi: 10.1016/0166-432800078-2

76. Wolff K, Tsapakis EM, Winstock AR, Hartley D, Holt D, Forsling ML, et al. Vasopressin and oxytocin secretion in response to the consumption of ecstasy in a clubbing population. *J Psychopharmacol.* (2006) 20:400–10. doi: 10.1177/0269881106061514

77. Feduccia AA, Mithoefer MC. MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms? *Prog Neuropsychopharmacol Biol Psychiatry.* (2018) 84(Pt A):221–8. doi: 10.1016/j.pnpbp.2018.03.003

78. Fernàndez-Castillo N, Orejarena MJ, Ribasés M, Blanco E, Casas M, Robledo P, et al. Active and passive MDMA ('ecstasy') intake induces differential transcriptional changes in the mouse brain. *Genes Brain Behav.* (2012) 11:38–51. doi: 10.1111/j.1601-183X.2011.00735.x

79. Petschner P, Tamasi V, Adori C, Kirilly E, Ando RD, Tothfalusi L, et al. Gene expression analysis indicates reduced memory and cognitive functions in the hippocampus and increase in synaptic reorganization in the frontal cortex 3 weeks after MDMA administration in Dark Agouti rats. *BMC Genomics.* (2018) 19:580. doi: 10.1186/s12864-018-4929-x

80. Vizeli P, Liechti ME. Safety pharmacology of acute MDMA administration in healthy subjects. *J Psychopharmacol.* (2017) 31:576–88. doi: 10.1177/0269881117691569

81. Makunts T, Jerome L, Abagyan R, de Boer A. Reported cases of serotonin syndrome in MDMA users in FAERS database. *Front Psychiatry.* (2022) 12:824288. doi: 10.3389/fpsyt.2021.824288

82. Studerus E, Vizeli P, Harder S, Ley L, Liechti ME. Prediction of MDMA response in healthy humans: a pooled analysis of placebo-controlled studies. *J Psychopharmacol.* (2021) 35:556–65. doi: 10.1177/0269881121998322

83. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology.* (2019) 236:2735–45. doi: 10.1007/s00213-019-05249-5

84. Vitoratou S, Uglik-Marucha N, Hayes C, Gregory J. Listening to people with misophonia: exploring the multiple dimensions of sound intolerance using a new psychometric tool, the S-five, in a large sample of individuals identifying with the condition. *Psych.* (2021) 3:639–62. doi: 10.3390/psych3040041

85. Dibb B, Golding SE, Dozier TH. The development and validation of the misophonia response scale. *J Psychosom Res.* (2021) 149:110587. doi: 10.1016/j.jpsychores.2021.110587

86. Rosenthal MZ, Anand D, Cassiello-Robbins C, Williams ZJ, Guetta RE, Trumbull J, et al. Development and initial validation of the duke misophonia questionnaire. *Front Psychol.* (2021) 12:709928. doi: 10.3389/fpsyg.2021.709928

87. Siepsiak M, Śliwerski A, Łukasz Dragan W. Development and psychometric properties of MisoQuest-a new self-report questionnaire for misophonia. *Int J Environ Res Public Health.* (2020) 17:1797. doi: 10.3390/ijerph17051797

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EDITED BY
Peter Schuyler Hendricks,
University of Alabama at Birmingham,
United States

REVIEWED BY
Maher Battat,
An-Najah National University, Palestine
Jeremy Weleff,
Yale University, United States
Brian Barnett,
Cleveland Clinic, United States

*CORRESPONDENCE
Elliot Marseille
emarseille1@berkeley.edu

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# The economics of psychedelic-assisted therapies: A research agenda

Elliot Marseille[1,2]*, Stefano Bertozzi[1,2,3] and James G. Kahn[1,2,4]

[1]Global Initiative for Psychedelic Science Economics (GIPSE), University of California, Berkeley, Berkeley, CA, United States, [2]Center for Global Health Delivery Diplomacy and Economics, University of California, San Francisco, San Francisco, CA, United States, [3]School of Public Health, University of California, Berkeley, Berkeley, CA, United States, [4]School of Medicine, Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco, San Francisco, CA, United States

After a long hiatus, psychiatry is undergoing a resurgence of interest in psychedelic drugs as therapy for a wide range of mental health disorders Accumulating clinical evidence suggests substantial potential for psychedelics used in a therapeutic context, as treatment for, among other disorders, depression, post-traumatic stress disorder (PTSD), and addictions to tobacco, opioids and alcohol. As soon as 2024, powerful new therapeutic modalities could become available for individuals with mental health problems refractory to traditional therapies. Yet research has lagged on economic considerations, such as costs and cost-effectiveness, the economic effects of widespread implementation, pricing, and economic appraisal's methodological considerations relevant to psychedelic therapies. These issues are critical if psychedelic therapies are to become widely accessible. We describe six types of economic analyses and their rationale for decisions and planning including the needs of health care payers. We also outline desirable features of this research, including scientific rigor, long horizons, equity, and a global view.

KEYWORDS

**psychedelics, health economics, cost-effectiveness, psychiatry, MDMA, psilocybin**

## Background

Mental health disorders are the fifth leading cause of Disability-Adjusted Life Years (DALYs), (1), affecting 10.7% of the global population in 2017 (2). Depression represents about a third of this burden, as do anxiety disorders and post-traumatic stress disorder (PTSD), followed by alcohol and drug use disorders at 13.1 and 8.4%, respectively. The remaining 10% consists of bipolar disorder, schizophrenia, and eating disorders (2). In the United States 21.0% of adults live with mental illness, including 5.6% with serious mental health conditions (3).

Current therapies help a significant portion of people with mental health disorders. Nevertheless, many patients do not respond adequately (4) or cannot tolerate the side effects of interventions such as, for depression, selective serotonin reuptake inhibitors (SSRIs) and electroconvulsive therapy (5–10). Psychotherapeutic approaches also fail to

help a substantial portion of depressed patients (9, 11, 12). Approximately 50% of PTSD patients do not meaningfully respond to current pharmacological and psychotherapeutic treatments (13–15). A 2000 review of drug dependence and its treatments found that 40–60% of patients treated for alcohol and other substance use disorders reverted to active use within a year following treatment (16). The need for more effective mental health treatments is widely acknowledged (17).

In this context, many clinicians and the public are encouraged by recent favorable clinical reports for novel therapies incorporating psychedelic drugs to treat anxiety and depression including treatment-resistant depression and end-of-life distress (18–26); PTSD (21, 23, 27–29). Preliminary data also suggest potential benefits for addictions such as tobacco (30), opioid (31), and alcohol use disorder (32, 33), as well as eating disorders, social anxiety, cluster headaches, OCD and ADHD (34–36). Some of this evidence indicates that new psychedelic-assisted therapies may be effective not only in managing serious psychiatric conditions, but often in inducing long term remission. Despite these generally encouraging findings, no psychedelic-assisted therapy has yet been adopted into national guidelines; see for example the Canadian Network for Mood and Anxiety Treatments Task Force recommendations (37). Nor have any previously illegal psychedelic drugs been approved by a relevant regulatory agency as a legal medicine. Continued research by non-profits and, increasingly, the private sector, is focused on the safety and efficacy of the new therapies.

The economic implications of the metal health burden are huge. In the U.S., the societal economic burden of PTSD in 2018 was $232 billion (38), and of major depression was $210.5 billion in 2010 (39). Yet little investigation has been conducted on the economics of the new therapies. What do they cost per person and for society? What are the potential savings from averted illness? What are the other economic benefits? What are the net costs and cost-effectiveness, for health care payers and society? Yet these questions must be addressed if new therapies with proven clinical benefit are to be embraced by insurers and thus to become accessible at scale.

In this article, we review the economic evaluation agenda for psychedelic therapies, preceded by a brief review of clinical evidence.

The precise definition of "psychedelic" (from the Greek roots meaning "Mind-manifesting") is somewhat controversial. For our purposes, psychedelic drugs include the "classic" serotonergic hallucinogenic agents such as lysergic acid diethylamide (LSD), psilocybin and 5-methoxy-N,N-dimethyltryptamine (DMT), and compounds such as ibogaine, 3,4-Methylenedioxy methamphetamine (MDMA) and its analogs, and ketamine all of which are profoundly mind-manifesting but have different mechanisms of action from the "classic" psychedelics.

A primer on methods for heath economics evaluation is beyond the scope of this article, though a number of excellent books and articles are available to interested readers (40–42).

## Selective overview of the clinical research

A full description of completed and ongoing clinical research on psychedelic-assisted therapy is described elsewhere (34, 43). We have selected three focus areas where: (1) clinical and economic research is relatively advanced (MDMA-assisted therapy for PTSD); (2) there is the potential to affect a disorder of particularly large public health importance (psilocybin for major depressive disorder); and (3) psychedelic therapy can affect a major non-psychiatric public health issue (psilocybin for tobacco cessation). All psychedelic interventions include major counseling components.

### MDMA to treat PTSD

In May 2021, the first of two phase 3 trials was reported: 67% receiving MDMA no longer met diagnostic criteria for PTSD, vs. 32% with placebo (28). The Food and Drug Administration (FDA) may approve MDMA by 2024.

### Psilocybin for depression

The first trial, with an open-label design, found a large benefit at 6 months (44). In 2020, a wait-list controlled randomized trial found that 71% of participants showed clinically significant response at week 4 (45). A double-blind randomized controlled trial (RCT) published in 2021 comparing psilocybin with escitalopram, a selective serotonin-reuptake inhibitor (SSRI), for patients with chronic major depression found no significant difference in depression scores, though psilocybin was superior on secondary measures of depression and well-being (18).

### Psilocybin for tobacco addiction

An open-label pilot study had promising findings (30). Preliminary results from 25 subjects in a phase 2 trial found that at 12-months, 47% of the psilocybin group had biologically-confirmed abstinence compared with 20% with placebo (46). In October, 2021, the National Institutes of Health (NIH) awarded $4 million to Johns Hopkins to support expanded research into psilocybin to treat smoking, representing the first grant to support psychedelic therapies research in over 50 years (47, 48).

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## The agenda for economic analyses of psychedelic-assisted therapy

To date, three peer-reviewed articles have been published (by us) on the economics of psychedelic therapies, all on MDMA for PTSD. The first, a cost-effectiveness analysis based on the pooled results of phase 2 trials, showed that MDMA-AT was likely to generate net savings to health payers by reducing overall health care costs. The second updated this analysis with the more favorable phase 3 trial results and found correspondingly more favorable economics. The third explored the health benefits and medical cost savings to the U.S. for different scale-up rates (49).

It is unsurprising that economic analyses lag behind clinical research. Until a novel intervention demonstrates safety and efficacy, and thus the possibility of becoming FDA-approved, there is little reason to devote major resources to economic analyses. However, in view of rapid clinical research progress, economics seems more urgent. The anticipated access to decriminalized psychedelics in Oregon and elsewhere adds to this impetus.

We anticipate six distinct areas of economics research that will be useful in shaping policy and programs. These include costing, cost-effectiveness and cost-benefit analyses, scale-up and impact analyses, market and price evaluations, and methods development. Each is described below and in Table 1, and how they relate is shown in Figure 1.

***Cost analysis*** is a linchpin of economic assessment. Costing studies are done by quantifying resources needed (e.g., hours of counselor time) and their unit prices. They answer questions such as, "What does it cost to deliver the psychedelic intervention? What are the general costs of treating the disease? How do overall medical costs change with successful treatment?"

***Cost-effectiveness analysis*** (CEA) is the most frequently-used tool to assess health program or policy choice when considering both cost and health benefits. Health benefits are typically denominated in Quality-Adjusted Life-Years[1] (QALYs), or in "natural" metrics such as deaths or cases of disease averted. Results are expressed as incremental cost-effectiveness ratios, eg cost per QALY gained (50). As with any important new health technology, psychedelic therapies will need credible cost-effectiveness analyses if they are to become mainstream (51–53). Particularly in view of residual stigma from the war on drugs, insurers are unlikely to approve routine use of these treatments without credible estimates of delivery cost, potential downstream medical savings, and associated health benefits. These types of estimates are also needed if psychedelic therapies are to be approved in Europe. The European Medicines Agency collaborates with the Health Technology Assessment (HTA) bodies in respective EU countries. These HTAs, in turn, assess the relative effectiveness and cost-effectiveness of new medicines and their impact on healthcare budgets (54, 55).

CEAs of psychedelic therapies should be conducted from the perspective of insurers, as these are the gatekeepers of access. For example, insurance companies are subject to high rates of patient turnover (56). This means that for many patients, the relatively high up-front cost of psychedelic therapies will not be re-couped by the payer since patients will have exited the plan before those costs are fully recovered in the form of reduced medical care spending. Thus, for gaining a realistic estimate of the effect on cash flow and budgets over time, CEAs, when combined with company-specific knowledge of turnover rates, are indispensable.

But important societal benefits are not captured by those who pay for care, creating a tendency to under-invest in the new therapies. For example, health insurers may be concerned that they bear substantial up-front costs of psychedelic-assisted therapy whereas reductions in health care utilization accrue only over years, after many patients have migrated to other insurers. Other misaligned incentives concern increased productivity by people returning to employment; and reduced absenteeism and "presenteeism" among employed individuals. Still other societal benefits fall outside of health care and employment, such as potential reductions in domestic violence (57), incidence of "driving under the influence," and involvement with the criminal justice system (58, 59). In keeping with recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine (42), the psychedelic therapy economic research agenda should quantify such broader societal benefits. Such analyses can build political acceptance for the clinical use of these formerly illegal and stigmatized drugs.

CEAs can also examine delivery options. For example, our recent CEA of the phase 3 MDMA trial assessed the cost-effectiveness of a regimen with three active MDMA sessions for the treatment of PTSD compared with the two sessions employed in the Phase 2 trials (60). Other examples pertain to the relative costs and benefits of individual vs. group sessions and clinical prioritization: all patients with major depressive disorder (MDD), vs. only those with treatment-resistant MDD.

Assessments of severe adverse events (SAEs) need to be included in cost-effectiveness analyses and other economic appraisals. For example, 12 patients in Compass Pathway's Phase IIb trial (n = 233) of their patented psilocybin formulation to treat treatment-resistant depression experienced one or more SAEs including such issues as suicidal behavior and intentional self-injury [COMPASS (61)]. Both the additional medical care cost, such as ambulance and emergency medical services, and the loss of health and well-being (typically measured in QALYs) due to SAEs need to be included in the overall economic assessment. Because patients with severe depression or other disorders may suffer elevated rates of such events compared with the general population in the absence of psychedelic therapy, it will be

1 Disability-Adjusted Life-Years (DALYs) is a similar metric. QALYs are usually applied in developed world settings; and DALYs are applied in developing country settings.

TABLE 1 Six types of health economic research and their application to the assessment of psychedelic therapies.

| Type of economic research | Application | Examples for psychedelic therapy |
|---|---|---|
| Costing | Characterize resources and costs to deliver intervention and to provide care for persons with relevant disorder. | Cost of delivering MDMA for PTSD adjusted for potential savings in future medical care. |
| Cost-effectiveness analysis | Estimate "health value for money": Divide net costs by health gains, measured in natural units (e.g., depression cases in remission) or composite measures such as Quality-Adjusted Life-Years (QALYs). | 1. Psilocybin for major depression compared with standard of care.<br>2. Care delivery models, e.g., individual vs. group; two vs. one clinician. |
| Cost-benefit analysis | Compare the cost of intervening with the financial value of benefits obtained. | Psilocybin for smoking cessation compared with standard of care: Ratio of dollar valuation of health benefits divided by intervention costs. |
| Scale-up and budget analysis | Estimate the system-wide costs and health benefits of large-scale use, for plausible rates of implementation. | Psilocybin for alcohol use disorder: Aggregate net costs and QALYs gained of implementation at scale. |
| Price analysis | Derive prices for an intervention that maximize an objective such as profit, revenue, or access / social benefit. | Establish appropriate price per unit of MDMA, psilocybin or other psychedelic medicine. |
| Methods development | Identify novel approaches to portrayal of health effects of psychedelic therapies. | 1. Incorporate positive health states into economic analyses.<br>2. Modeling positive and negative health and economic impacts of non-clinical psychedelics use. |

important to isolate the treatment-attributable portion of the reported incidence of SAEs.

Finally, cost-effectiveness analyses of psychedelic therapies to date have been performed for well-resourced and closely-monitored clinical trials. However, trial-derived *efficacy* may exceed observed "real-world" *effectiveness* (62). Thus, as clinics provide decriminalized psychedelic-assisted therapies in Oregon in early 2023, analyses that address real-world use will be needed. Health economists can work with health services researchers to integrate information on costs with assessment of clinical outcomes for operating programs.

## Cost-benefit analysis

(CBA) is another powerful tool for estimating "value for money." By contrast with CEA, in CBA, both health and non-health outcomes are valued in monetary terms. The result of CBA is expressed as a net benefit (benefit minus costs), as a benefit-cost ratio or internal rate of return. CBAs have at least two advantages over CEAs. First, by expressing outcomes in dollars, CBAs come closer to reflecting a societal welfare function (63). CBA thus makes it easier for policy makers to identify investments that have the highest societal returns, and to allocate limited budgets accordingly. Secondly, by eliminating recourse to abstract measures of outcomes such as QALYs, CBAs express results in intuitive language, such as, "For every dollar spent on X the payer will save Y dollars." The choice between CEA or CBA for any given analysis depends on the policy question. If considering the incremental value of a psychedelic vs. a conventional treatment, CEA will suffice. However, if the question pertains to a broader set of options, including a range of outcomes beyond health, CBA is more flexible and robust.

## Scale-up and budget impact analysis

CEAs and CBAs do not quantify the *overall impact* of an intervention on health care budgets, or on the health of populations such as Medicaid beneficiaries or the members of a private health plan. Scale-up and budget impact analyses provide information that insurers and other decision makers need prior to adopting a new therapy. By outlining the nationwide public health and economic impact, they can also help make the case to NIH to fund high-quality research, and to state legislatures and health departments to facilitate access to newly legal therapies.

These models portray the likely trajectory over time of increased access to treatment, the cost of serving those patients, potential net savings in reduced medical care costs, and associated health care benefits such as QALYS gained or deaths averted. In addition, budget impact models can include

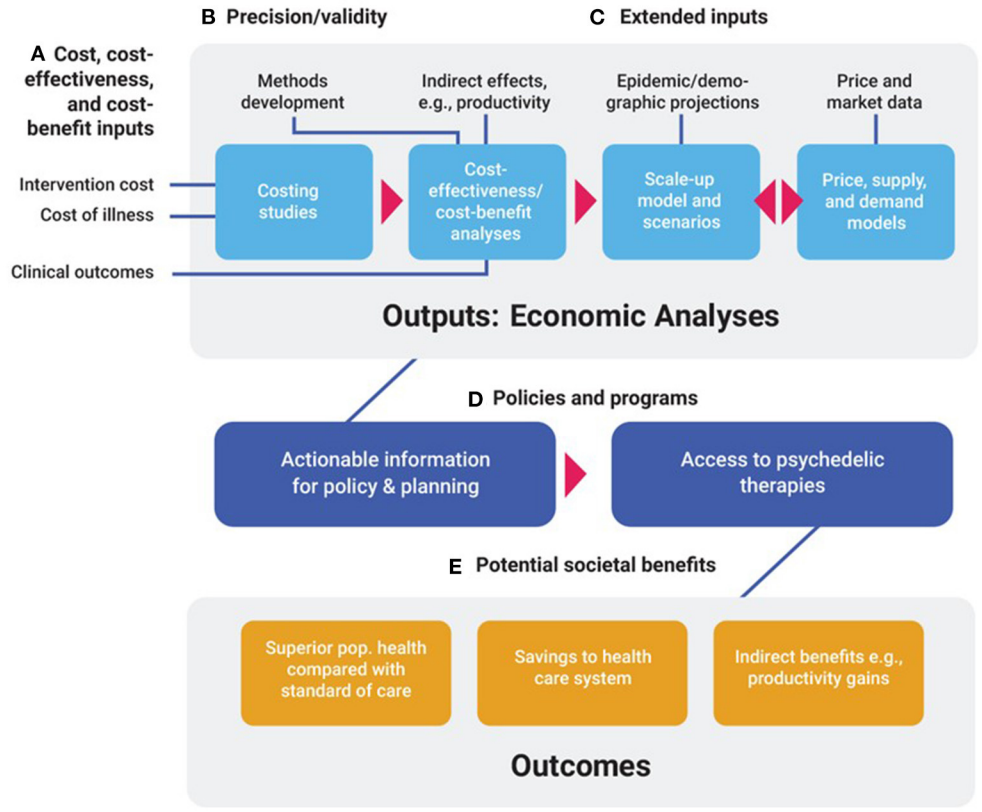


FIGURE 1
Economic evaluations of psychedelic-assisted therapies: Inputs, outputs, outcomes. **(A)** Intervention costs, health care costs (Costs of illness), and clinical outcomes are broad classes of inputs needed for costing studies, and cost-effectiveness and cost-benefit analyses. **(B)** Precision and validity of economic models are enhanced by the development of methods that accurately portray costs and benefits of psychedelic therapies. **(C)** Extended inputs such as indirect economic effects; epidemic and demographic projections; and price and market data are required for cost-effectiveness analyses from a societal perspective, scale-up, and price models, respectively. These four major types of economic analytic outputs can then inform. **(D)** Policies and programs designed to deliver access to psychedelic therapies of demonstrated cost-effectiveness. Access to these therapies generate. **(E)** Societal benefits such as enhanced health outcomes, savings to the health care system, and indirect benefits such as productivity gains.

payer-specific metrics such as percent of annual expenditures represented by the new intervention.

A challenge in developing comprehensive scale-up models is properly portraying supply and demand constraints. On the supply side, a key issue is the rate at which therapists can be certified. As of January 2021, 13 training programs existed across the U.S. The MDMA training program offered by the Multidisciplinary Association for Psychedelic Studies (MAPS), a leading non-profit in the field, had trained or enrolled 1,800 therapists as of November 2021. Scale-up models should include updated estimates of the number of therapists that can be certified within a regulatory and certification environment which is itself rapidly evolving. Scale-up models also need to estimate the percentage of therapists' practice that they are willing to devote to psychedelic therapy. According to a 2021 survey, 75 percent of therapists reported they would be unlikely to provide psychedelic therapy if it meant a reduction in income (64). A modeling effort by the Boston Consulting Group estimated that 22,000–40,000 MDMA-certified therapists would be needed to treat 400,000 PTSD patients by 2031 (64). Considering psychedelic medicine more broadly, this implies that treating one million patients per year by 2031 would require 55,000–100,000 newly-trained therapists in 10 years, approximately 10–17% of the US mental health workforce (64). The rate at which practitioners can be trained and effectively deployed is also a function of the prevalence of skepticism and thus reluctance to participate. This skepticism remains substantial among key clinician groups such as psychiatrists (65) and psychologists (66).

Estimates of effective demand are similarly uncertain. No previously illegal psychedelics have yet been approved as medicines by the FDA or other regulatory agencies. It is unknown which compounds will be approved on what timeline and for which specific psychiatric indications. Although recent

surveys suggest a positive attitude toward psychedelic therapy and research among a majority of Americans affected by mental health issues, especially among the young, (67, 68), little is known about the percent of patients who would be willing to undergo a therapy that entails dramatic alterations in perception, and the possibility of confronting painful emotional content. Residual stigma and cultural associations with psychedelics may also discourage people from seeking treatment. On the other hand, it is reasonable to suppose that if treatments are successful, and thus become increasingly endorsed by mainstream institutions and *via* word-of-mouth, many who were originally reticent will avail themselves of these therapies.

In view of these uncertainties, initial models will need to portray ranges and be updated as the interacting dimensions of clinical effectiveness and legislative, economic, and cultural contexts change over time. Despite these qualifications, models can usefully describe the upper and lower bounds of economic and public health impact for particular medicine-disorder pairs (e.g., MDMA for PTSD) given plausible scale-up scenarios (49). Analyses of the economics of esketamine, an FDA-approved medicine with psychedelic properties, for the treatment of depression, can also inform many aspects of the economic assessment of other psychedelic therapies including scale-up and budget impact models (69).

## Price evaluation

Providers of psychedelic therapies including therapist groups and larger provider networks, as well as insurers, must understand the supply, demand, and price dynamics of these interventions. Appropriate pricing is crucial for patient access, payer adoption, and revenue generation. There are various methods for setting the price of new pharmaceuticals. Value-based approaches seek to develop a societal value estimate as an upper-bound for the price; return on investment (ROI) approaches determine the lower bound. The societal value, in turn, depends on appropriate cost-effectiveness analyses that compare net health care costs with expected health benefits (50, 70). Within plausible price bounds, the profit or revenue-maximizing price is determined by a variety of factors including especially the price elasticity of demand (71). The successful introduction of psychedelic therapies is similar to the rollout of conventional medical therapies. However, an important difference arises from the history of prohibition: Illegal cannabis continues to compete with legal, regulated cannabis products. Similarly, market models for legal psychedelic medicines must account for potential downward pressures on price exerted by well-entrenched informal markets for LSD, MDMA, psilocybin mushrooms, and other psychedelic materials.

With the implementation of Oregon's Propositions 109 and 110 in 2023, psilocybin services will become available to people who are not seeking psychiatric treatment but rather, seek support for other purposes such as personal growth or spiritual development (72). These novel services combine provision of newly-decriminalized and powerful psychoactive materials in a supportive context which is neither traditional psychotherapy nor the mere monitored provision of psychiatric medicines such as SSRIs. Provision of these services might require a lower level of professional certification, and third party payers are unlikely to reimburse for these non-medical services. These factors suggest a different price point from that of potentially reimbursable clinical provision of psychedelic-assisted psychotherapy. There will be a demand for financial analysis to help establish their cost structure and a viable price in a rapidly evolving competitive environment.

Organizations which have adopted public-benefit models for the sale of psychedelics for therapy must balance two competing goals: All else equal, lower prices mean greater access to treatment and greater public health benefit. However, lower prices also mean less revenue to direct back to non-profit research and educational activities. Many of the main actors are concerned with identifying the welfare maximizing price, not the profit-maximizing price. This is a calculation with greater uncertainties.

## Methods development

Current tools of health economic evaluation cannot assess certain issues that arise for psychedelic-assisted therapies. For example, the traditional concept of health state "utility," roughly equivalent to "satisfaction" (73) may underestimate the benefits of psychedelic therapies. Utility ranges from, 0.0 signifying death, to a maximum of 1.0, which signifies the absence of disease. Utility is thus not equipped to reflect sustained, enhanced access to such positive experiences as awe, compassion, self-efficacy, and affinity with nature. These states, which may persist long beyond the acute effects, are reported as a result of ingestion of psychedelic materials in both clinical and naturalistic settings (74–76). Because positive cognitive states are not restricted to exposure to psychedelics, this innovation has implications for health economic evaluation generally. Capitalizing on the work on determinants and measurement of happiness and other positive states that has been developing over the past 20 years (77, 78), it would move the field away from traditional measures of health-state utility and into alignment with broader measures of welfare (79, 80). The methodological problem of developing a validated measure of overall well-being that integrates health-state utility with other measures of well-being that include positive emotional and cognitive states, has not been solved. As a first step, data should be collected from multiple sites on both "utility" and positive states so that the relationship between them can be quantified. Success would be aided by cross-disciplinary collaboration between

health economist's psychologists, happiness researchers, and psychometric experts.

A second issue is standardization and comparability. To ensure both comprehensive analyses and comparability of results, health economists might establish and promulgate best practice guidelines for the conduct of economic analyses of psychedelic therapies. These might focus on the implementation of a subset of the recommendations of the Second Panel and costing guidance from the Global Health Cost Consortium (81, 82). As mentioned above, among these are methods to estimate broad societal benefits such as increased well-being of clients' family members; and important secondary effects such as reductions in domestic violence, substance use disorder; and involvement with the criminal justice system.

Third, unlike standard psychiatric therapies many of which are continuous, economic models for psychedelic therapies need to reflect the incremental costs and benefits of irregular episodic treatment. As long-term outcome data become available, it will be important to construct models that portray changing probabilities of treatment success following relapse.

The increased acceptance of psychedelics for medical use may have externalities, both negative and positive. Recent surveys show a marked increase in the use of psychedelics in the United States. According to the National Survey on Drug Use and Health (NSDUH), between 2015 and 2019 there was an increase in hallucinogen use from 4.69 million to 6.01 million, including a 60% increase in the use of LSD and a 96% increase in the use of other hallucinogens (83). Thus, a fourth area requiring innovative measurement and modeling approaches is quantifying the public health and cost impacts of increased access to psychedelic materials outside of clinical settings.

We are in an era of unprecedented tolerance and perceived legitimacy of psychedelics. This climate of favorable opinion is conferred by reports from FDA-sanctioned clinical trials, the establishment of academic research centers at prestigious institutions, the influx of private investment, decriminalization in some jurisdictions, and the return of NIH funding for psychedelic research. In this environment, it is reasonable to assume that an increasing number of new users will consume psychedelic materials for personal development, celebratory and spiritual purposes, and unadorned recreation. Working with epidemiologists and research methods experts, health economists can help interpret the burgeoning literature on the mental and physical health effects on these new users. Among the key questions: Given the quality of extant research including cross-sectional designs, reliance on self-report and other potential sources of bias in many studies, what does the evidence as a whole suggest about access to psychedelics as an independent cause of positive or negative health effects? Is it possible to model the effects of psychedelic use in naturalistic settings on health care costs and outcomes?

## Principles to guide the health economics research program for psychedelics

We believe that the potentially transformative effects of psychedelics in mental health treatment warrant a proactive economics research agenda. We propose the following characteristics.

### Forward-looking / anticipatory

Cost-effectiveness analyses are often considered only after promising results from clinical trials. There is logic to this: Why devote resources to cost-effectiveness analysis when effectiveness has not yet been established? However, more time than necessary thus elapses between promising clinical findings and the publication of associated economic analyses. The consequence is that the adoption of new therapies and the benefits they confer may be delayed. We advocate a middle ground between premature economic analysis and delaying work until definitive clinical results are available. In addition to more rapid dissemination of important economic findings, by establishing early collaboration with clinical researchers, the quality of the economic analysis stands to benefit since appropriate economic data collection instruments and methods can sometimes be woven into the design of the research. As the clinical research develops over the next several years greater knowledge will be gained on a number of factors that affect both clinical and economic outcomes. For example, as information is gained over time on the long-term durability of benefits and the potential effects of multiple treatment sessions for those who do not respond to the initial regimen, the associated economic analyses will need revision. Thus, the economic analysis of a particular therapy will rarely be final and definitive. Rather, economic assessments will evolve to reflect the increasing refinement of the clinical knowledge.

### Equity

Within the field of economics research on psychedelic therapies, the same efforts to achieve broad representation that are applied to other academic fields are also pertinent. Furthermore, economic research on psychedelics should regularly consider equity issues such as need for mental health treatment, access to psychedelic interventions, and differential clinical and economic effects by economic status. In order to avoid an implementation outcome in which those most in need have the least access, health economists should include analyses of how the realities of health care financing in the United States affect access to psychedelic therapies. Working

with health services researchers to devise reimbursement plans that guarantee equitable access should be high on their agenda. For example, equitable access will require that large private and public payers including, in the U.S., Medicaid, reimburse therapists adequately for psychedelic-assisted therapy sessions. Much depends on Current Procedural Terminology codes and other insurance billing codes that are designated for the new therapies, and the reimbursement associated with those codes. If too low, practitioners will have insufficient incentive to participate. In that case, while formally an insured benefit; psychedelic therapies will remain unavailable to most of the population who could benefit. Health economist has a role to play in generating realistic estimates of the supply of accessible psychedelic therapy available across a range of reimbursement levels.

### Global scope

To date, clinical trials of psychedelic-assisted therapies have been conducted in the USA, Europe, Australia, New Zealand and Israel, yet 84.3% of people affected by mental illness live in low and middle-income countries (84, 85). On the effectiveness side, it will be important to understand if the benefits reported in rich-countries are replicated in different cultural contexts. Some lower-income countries have traditional practices using plant-based psychedelics that long pre-date use in the West. It is not clear whether western-style psychotherapeutic modalities will be appropriate or effective in these contexts. Models developed for rich countries may need to be revised or re-thought entirely for application in low- and middle-income income countries. Delivering psychedelic therapies will cost less in less wealthy countries. However, the potential savings in future medical care costs will also be lower, leaving an unknown effect on net discounted costs.

### Teaching, mentoring, and partnerships

To ensure the emergence of a cadre of researchers prepared to further advance this agenda, health economists should help to develop courses on economics and implementation science for psychedelic therapies. Through partnerships with leading individual researchers and institutions overseas, they can also develop an appropriate psychedelics-related economics research agenda in other countries, including middle and low-income countries.

### Scientific rigor

The last few years have seen a rapid rise of interest in psychedelic-based therapies by the private sector and a concomitant influx of research dollars. Venture capital investments for 2020 and 2021 combined was $31.2 million compared with $49.5 million in the previous 5 years (86, 87). These expenditures eclipse the budgets of the non-profit entities that dominated the early period of the new era of psychedelic science. MAPS, for example, spent $18.6 million in FY 2020 (88). In the decriminalized setting of Oregon, likely to be followed soon in other states, it is easy to imagine how marketing hype could supplant evidence-based practice (89). Thus, patients, practitioners, researchers and health care payers need a countervailing body of objective health services research and economic analysis with a minimum of real or perceived conflicts of interest, and a commitment to Open Science (90). For these reasons, despite the influx of private research investments, there will be an ongoing role for NIH, other government funding, and philanthropic assistance for arms-length support to leading researchers.

## Conclusion

Encouraging results from clinical trials of psychedelic therapies for major mental health disorders suggest that psychiatry may soon expand the range of effective treatments. Findings on effectiveness are now sufficiently advanced that research on the economics of these emerging therapies is timely and needed. Among priority areas for economic analyses are cost-effectiveness and cost-benefit analyses that assess value for money to payers and society at large; scale-up models that portray the cumulative impact of access to psychedelic therapies; and price and market analyses that health care providers and payers need to plan the delivery of care.

## Author contributions

EM: conceptualization, methodology, investigation, formal analysis, project administration, supervision, visualization, writing—original drafts, and writing final draft. JK: conceptualization, methodology, formal analysis, validation, visualization, writing—original drafts, and writing final draft. SB: conceptualization, formal analysis, and writing final draft. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## References

1. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet.* (2013) 382:1575–86. doi: 10.1016/S0140-6736(13)61611-6

2. Saloni D, Hannah R, Roser M. *Mental Health*. Available online at: https://ourworldindata.org/mental-health (accessed October 06, 2022).

3. Substance Abuse and Mental Health Services, Administration. *Key Substance Use and Mental Health Indicators in the United States: Results from the 2020 National Survey on Drug Use and Health (NSDUH Series H-56*. (2021). Available online at: https://www.samhsa.gov/data (accessed September 20, 2022).

4. Harbi KSA. Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Prefer Adherence.* (2012) 6:369–88. doi: 10.2147/PPA.S29716

5. Cartwright C, Gibson K, Read J, Cowan O. Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Prefer Adherence.* (2016) 10:1401–7. doi: 10.2147/PPA.S110632

6. El-Mallakh RS, Gao Y. Tardive dysphoria: the role of long term antidepressant use in-inducing chronic depression. *Med Hypotheses.* (2011) 76:769–73. doi: 10.1016/j.mehy.2011.01.020

7. Mcclintock SM, Choi J, Deng ZD, Appelbaum LG, Krystal AD, Lisanby SH. Multifactorial determinants of the neurocognitive effects of electroconvulsive therapy. *J ECT.* (2014) 30:165–76. doi: 10.1097/YCT.0000000000000137

8. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* (2006) 163:1905–17. doi: 10.1176/ajp.2006.163.11.1905

9. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry.* (2007) 68:1062–70. doi: 10.4088/JCP.v68n0713

10. Verwijk E, Obbels J, Spaans HP, Sienaert P. [Doctor, will I get my memory back? Electroconvulsive therapy and cognitive side-effects in daily practice]. *Tijdschr Psychiatr.* (2017) 59:632–37. doi: 10.1192/bjo.2020.17

11. Berg RC. Effectiveness of psychotherapy for adults with depression: a systematic review of the best available evidence. *Procedia Soc Behav Sci.* (2010) 5:2194–200. doi: 10.1016/j.sbspro.2010.07.435

12. Parker K. Treating depression with the evidence-based psychotherapies: a critique of the evidence. *Acta Psychiatrica Scandinavica.* (2007) 115:352–59. doi: 10.1111/j.1600-0447.2007.01007.x

13. Bisson JI, Roberts NP, Andrew M, Cooper R. Psychological therapies for chronic post-traumatic stress disorder (PTSD) in adults. *Cochrane Database Syst Rev.* (2013) 2013:Cd003388. doi: 10.1002/14651858.CD003388.pub4

14. Gutner CA, Gallagher MW, Baker AS, Sloan DM. Time course of treatment dropout in cognitive-behavioral therapies for posttraumatic stress disorder. *Psychol Trauma.* (2016) 8:115–21. doi: 10.1037/tra0000062

15. Watkins LE, Sprang KR. Treating PTSD: a review of evidence-based psychotherapy interventions. *Front Behav Neurosci.* (2018) 12:258. doi: 10.3389/fnbeh.2018.00258

16. McLellan AT, Lewis DC, O'Brien CP. Drug dependence, a chronic medical illnessimplications for treatment, insurance, and outcomes evaluation. *JAMA.* (2000) 284:1689–95. doi: 10.1001/jama.284.13.1689

17. Lake J. Urgent need for improved mental health care and a more collaborative model of care. *Perm J.* (2017) 21:17–024. doi: 10.7812/TPP/17-024

18. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, et al. Trial of psilocybin versus escitalopram for depression. *N Engl J Med.* (2021) 384:1402–11. doi: 10.1056/NEJMoa2032994

19. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology.* (2017) 235:399–408. doi: 10.1007/s00213-017-4771-x

20. D'Souza DC, Syed SA, Flynn LT, Safi-Aghdam H, Cozzi NV. Exploratory study of the dose-related safety, tolerability, and efficacy of dimethyltryptamine (DMT) in healthy volunteers and major depressive disorder. *Neuropsychopharmacology.* (2022) 47:1854–62. doi: 10.1038/s41386-022-01344-y

21. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li XC, et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry.* (2019) 76:893–903. doi: 10.1001/jamapsychiatry.2019.1189

22. Dos Santos RG, Bouso JC. Serotonergic hallucinogens/psychedelics could be promising treatments for depressive and anxiety disorders in end-stage cancer. *BMC Psychiatry.* (2019) 19:321. doi: 10.1186/s12888-019-2288-z

23. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and safety of fixed-dose esketamine nasal spray combined with a new oral antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study (TRANSFORM-1). *Int J Neuropsychopharmacol.* (2019) 22:616–30. doi: 10.1093/ijnp/pyz039

24. Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. *J Psychopharmacol.* (2016) 30:1181–97. doi: 10.1177/0269881116675513

25. Gukasyan N, Davis AK, Barrett FS, Cosimano MP, Sepeda ND, Johnson MW, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *J Psychopharmacol.* (2022) 36:151–8. doi: 10.1177/02698811211073759

26. Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *J Psychopharmacol.* (2016) 30:1165–80. doi: 10.1177/0269881116675512

27. Jerome L, Feduccia AA, Wang JB, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology* (Berl). (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

28. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nature Med.* (2021) 27:1025–33 doi: 10.1038/s41591-021-01336-3

29. Mithoefer MC, Feduccia AA, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology.* (2019). doi: 10.1007/s00213-019-05249-5

30. Johnson MW, Garcia-Romeu A. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse.* (2017) 43:55–60. doi: 10.3109/00952990.2016.1170135

31. Noller GE, Frampton CM. Ibogaine treatment outcomes for opioid dependence from a twelve-month follow-up observational study. *Am J Drug Alcohol Abuse.* (2018) 44:37–46. doi: 10.1080/00952990.2017.1310218

32. Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs. placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry.* (2022) 79:953–62. doi: 10.1001/jamapsychiatry.2022.2096

33. Sessa B, Higbed L, O'Brien S, Durant C, Sakal C, Titheradge D, et al. First study of safety and tolerability of 3,4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J Psychopharmacol.* (2021) 35:375–83. doi: 10.1177/0269881121991792

34. Andersen KAA, Carhart-Harris R, Nutt DJ. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr Scand.* (2021) 143:101–18. doi: 10.1111/acps.13249

35. Nutt D, Erritzoe D. Psychedelic psychiatry's brave new world. *Cell.* (2020) 181:24–8. doi: 10.1016/j.cell.2020.03.020

36. Schindler EA, Gottschalk CH, Weil MJ, Shapiro RE, Wright DA. Indoleamine hallucinogens in cluster headache: results of the clusterbusters medication use survey. *J Psychoactive Drugs.* (2015) 47:372–81. doi: 10.1080/02791072.2015.1107664

37. Rosenblat JD, Husain MI, Lee Y, McIntyre RS, Mansur RB, Castle D, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force report: serotonergic psychedelic treatments for major depressive disorder. *Can J Psychiatry.* (2022) 0:07067437221111371. doi: 10.1177/07067437221111371

38. Davis LL, Schein J, Cloutier M, Gagnon-Sanschagrin P, Maitland J, Urganus A., et al. The economic burden of posttraumatic stress disorder in the United States From a societal perspective. *J Clin Psychiatry.* (2022) 83:14116. doi: 10.4088/JCP.21m14116

39. Greenberg PE, Fournier AA, Sisitsky T, Pike CT. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry.* (2015) 76:155–62. doi: 10.4088/JCP.14m09298

40. Drummond MF, O'Brien B, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. (Second edition). New York, NY; Oxford: Oxford Medical Publications (1997).

41. Gold MR. *Cost-effectiveness in Health and MEDICINe*. New York, NY: Oxford University Press. (1996).

42. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA.* (2016) 316:1093–103. doi: 10.1001/jama.2016.12195

43. Chi T. A review of emerging therapeutic potential of psychedelic drugs in the treatment of psychiatric illnesses. *J Neurol Sci.* (2020) 411:116715. doi: 10.1016/j.jns.2020.116715

44. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, et al. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology (Berl).* (2018) 235:399–408.

45. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, et al. Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. *JAMA Psychiatry.* (2020) 78:481–9. doi: 10.1001/jamapsychiatry.2020.3285

46. Johnson M. *SYM5-2: Psilocybin-Facilitated Smoking Cessation: Comparative Efficacy vs. Nicotine Patch*. Baltimore, MD: Society for Research on Nicotine and Tobacco (2022).

47. Barnett BS, Parker SE. United States National Institutes of Health grant funding for psychedelic-assisted therapy clinical trials from 2006-2020. *Int J Drug Policy.* (2022) 99:103473. doi: 10.1016/j.drugpo.2021.103473

48. Johns Hopkns Medicine. *Johns Hopkins Medicine Receives First Federal Grant for Psychedelic Treatment Research in 50 years*. (2021). Available online at: https://www.newswise.com/articles/johns-hopkins-medicine-receives-first-federal-grant-for-psychedelic-treatment-research-in-50-years (accessed October 21, 2022).

49. Avancena ALV, Kahn JG. The costs and health benefits of expanded access to MDMA-assisted therapy for chronic and severe PTSD in the USA: a modeling study. *Clin Drug Investig.* (2022). doi: 10.1007/s40261-022-01122-0

50. Drummond M, Sculpher M, Torrance G, O'Brien B. *Methods for the Economic Evaluation of Health Care Programmes (Third Edition)*. Oxford University Press (2005).

51. Hjelmgren J, Berggren F. Health economic guidelines—similarities, differences and some implications. *Value Health.* (2001) 4:225–50. doi: 10.1046/j.1524-4733.2001.43040.x

52. Hoffmann C, Graf von der Schulenburg JM. The influence of economic evaluation studies on decision making. a European survey. The EUROMET group. *Health Policy.* (2000) 52:179–92. doi: 10.1016/S0168-8510(00)00076-2

53. National Institue for Clinical Excellence (NICE). *Guide to Technology Appraisal Process*. NICE (2004).

54. European Medicines Agency. *From Laboratory to Patient: The Journey of a Centrally Authorised Medicine*. (2019). Available online at: https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

55. National Institue for Clinical Excellence (NICE). *Guide to the Methods of Technology Apprisal 2013*. NICE. (2014).

56. Fang H, Frean M, Sylwestrzak G. Trends in disenrollment and reenrollment within US commercial health insurance plans, 2006-2018. *JAMA Network Open.* (2022) 5:e220320–e220320. doi: 10.1001/jamanetworkopen.2022.0320

57. Thiessen MS, Walsh Z, Bird BM. Psychedelic use and intimate partner violence: the role of emotion regulation. *J Psychopharmacol.* (2018) 32:749–55. doi: 10.1177/0269881118771782

58. Hendricks PS, Clark CB, Matthew WJ, Kevin RF. Hallucinogen use predicts reduced recidivism among substance-involved offenders under community corrections supervision. *J Psychopharmacol.* (2014) 28:62–6. doi: 10.1177/0269881113513851

59. Hendricks PS, Michael C, Michael Scott C, Karen LC, Heith C, Sweat NW, et al. The relationships of classic psychedelic use with criminal behavior in the United States adult population. *J Psychopharmacol.* (2018) 32:37–48. doi: 10.1177/0269881117735685

60. Marseille E, Mitchell JM. Updated cost-effectiveness of MDMA-assisted therapy for the treatment of posttraumatic stress disorder in the United States: findings from a phase 3 trial. *PLoS ONE.* (2022) 17:e0263252. doi: 10.1371/journal.pone.0263252

61. Pathways COMPASS. *COMP360 Psilocybin Therapy for Treatment-Resistant Depression: Phase IIb Topline Data*. (2021). Available online at: https://compasspathways.com/wp-content/uploads/2021/11/COMP001_-_topline_data.pdf (accessed October 24, 2022).

62. Depp C. Clinical trials: bridging the gap between efficacy and effectiveness. *Int Rev Psychiatry.* (2007) 19:531–9. doi: 10.1080/09540260701563320

63. Johannesson M. The relationship between cost-effectiveness analysis and cost-benefit analysis. *Soc Sci Med.* (1995) 41:483–9. doi: 10.1016/0277-9536(94)00353-U

64. Psychedelic Science Funders Collaborative. *Psychedelic Landscape Report* (2021).

65. Barnett BS, Beaussant Y, King FT, Doblin,R. Psychedelic knowledge and opinions in psychiatrists at two professional conferences: an exploratory survey. *J Psychoactive Drugs.* (2022) 54:269–277. doi: 10.1080/02791072.2021.1957183

66. Davis AK, Agin-Liebes G, España M, Pilecki B. Attitudes and beliefs about the therapeutic use of psychedelic drugs among psychologists in the United States. *J Psychoactive Drugs.* (2022) 54:309–18. doi: 10.1080/02791072.2021.1971343

67. Corrigan K, Haran M, McCandliss C, McManus R, Cleary S, Trant R, et al. Psychedelic perceptions: mental health service user attitudes to psilocybin therapy. *Ir J Med Sci.* (2022) 191:1385–97. doi: 10.1007/s11845-021-02668-2

68. Newswire CP. *Survey Finds Majority of Affected Americans Approve of Psychedelics as an Alternative Treatment to Address Anxiety, Depression and PTSD*. (2022). Available online at: https://www.prnewswire.com/news-releases/survey-finds-majority-of-affected-americans-approve-of-psychedelics-as-an-alternative-treatment-to-address-anxiety-depression-and-ptsd-301462380.html (accessed October 22, 2022).

69. Voelker J, Sheehan JJ, Le HH, Toro-Diaz H, Li S. US budget impact analysis of esketamine nasal spray in major depressive disorder with acute suicidal ideation/behavior. *J Comp Eff Res.* (2022) 11:319–28. doi: 10.2217/cer-2021-0226

70. Gregson N, Sparrowhawk K, Mauskopf J. Pricing medicines: theory and practice, challenges and opportunities. *Nat Rev Drug Discov.* (2005) 4:121–30. doi: 10.1038/nrd1633

71. Yeung K, Basu A, Hansen RN. Price elasticities of pharmaceuticals in a value based-formulary setting. *Health Econ.* (2018) 27:1788–804. doi: 10.1002/hec.3801

72. Oregon Health Authority. (2022). *Oregon Psilocybin - What are Psilocybin Services*? Available online at: https://www.oregon.gov/oha/PH/PREVENTIONWELLNESS/Pages/What-are-Psilocybin-Services.aspx (accessed September 28, 2022).

73. British Medical Journal. *A Glossary of Health Economics Terms*. (2022). Available online at: https://bestpractice.bmj.com/info/toolkit/ebm-toolbox/a-glossary-of-health-economics-terms/ (accessed October 24, 2022).

74. Aday JS, Mitzkovitz CM, Bloesch EK, Davoli CC. Long-term effects of psychedelic drugs: a systematic review. *Neurosci Biobehav Rev.* (2020) 113:179–89. doi: 10.1016/j.neubiorev.2020.03.017

75. Raison CL, Jain R, Penn AD, Cole SP. Effects of naturalistic psychedelic use on depression, anxiety, and well-being: associations with patterns of use, reported harms, and transformative mental states. *Front Psychiatry.* (2022) 13:831092. doi: 10.3389/fpsyt.2022.831092

76. Teixeira PJ, Johnson MW, Timmermann C, Watts R, Erritzoe D, Douglass H, et al. Psychedelics and health behaviour change. *J Psychopharmacol.* (2022) 36:12–9. doi: 10.1177/02698811211008554

77. Wood AM, Froh JJ. Gratitude and well-being: a review and theoretical integration. *Clin Psychol Rev.* (2010) 30:890–905. doi: 10.1016/j.cpr.2010.03.005

78. Yaden DB. The emotional state assessment tool: a brief, philosophically informed, and cross-culturally sensitive measure. *J Posit Psychol.* (2022) 17:151–65. doi: 10.1080/17439760.2021.2016910

79. Dolan P. Developing methods that really do value the 'Q' in the QALY. *Health Economics, Policy Law.* (2008) 3:69–77. doi: 10.1017/S1744133107004355

80. John F, Helliwell R, Layard JD, Sachs J-EDe, Neve LBA, Shun W. *World Happpiness Report*. (2022). Available online at: https://happiness-report.s3.amazonaws.com/2022/WHR+22.pdf (accessed October 22, 2022).

81. DeCormier Plosky W, Bollinger LA, Alexander L, Cameron DB, Carroll LN, Cunnama L, et al. Developing the global health cost consortium unit cost study repository for HIV and TB: methodology and lessons learned. *Afr J AIDS Res.* (2019) 18:263–76. doi: 10.2989/16085906.2019.1680398

82. Vassall A, Sweeney S, Kahn JG, Gomez GB, Bollinger L, Marseille ELSE, et al. (2017). *Reference Case for Estimating the Costs of Global Health Services and Intervention*. Available online at: https://ghcosting.org/pages/standards/reference_case (accessed August 12, 2022).

83. Substance, Abuse, and Mental Health Services, Administration. *Results from the 2020 National Survey on Drug Use and Health: Detailed Tables*. (2021). Available online at: https://www.samhsa.gov/data/ (accessed September 20, 2022).

84. Steel Z, Marnane C, Iranpour C, Chey T, Jackson JW, Patel V, et al. The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *Int J Epidemiol.* (2014) 43:476–93. doi: 10.1093/ije/dyu038

85. World Bank Open, Data. (2020). *Population, Total*. World Bank. Available online at: https://data.worldbank.org/ (accessed August 05, 2022).

86. Goldhill O. *The 'Shroom Boom': The Meteoric Rise of the Psychedelic Medicine Industry*. (2021). Available online at: https://reports.statnews.com/products/the-shroom-boom?variant=39509576384615 (accessed October 12, 2022).

87. *Psychedelic Landscape Report*. (2021). Available online at: https://psfc.co/landscape-report

88. Multidisciplinary Association for Psychedelic Studies. (2022). *FY 2019-2020 Financial Report*. Available online at: https://maps.org/2021/02/15/fy-2019-2020-financial-report-2/ (accessed August 12, 2022).

89. Smith WR. Two models of legalization of psychedelic substances: reasons for concern. *JAMA*. (2021) 326:697–8. doi: 10.1001/jama.2021.12481

90. Petranker R, Anderson T. Psychedelic research and the need for transparency: polishing alice's looking glass [perspective]. *Front Psychol.* (2020) 11:1681. doi: 10.3389/fpsyg.2020.01681

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EDITED BY
Peter Schuyler Hendricks,
University of Alabama at Birmingham,
United States

REVIEWED BY
Andrew Burke,
Indiana University Bloomington,
United States
Manoj Doss,
Johns Hopkins University,
United States
Haley Dourron,
University of Alabama at Birmingham,
United States

*CORRESPONDENCE
S. Parker Singleton
✉ sps253@cornell.edu

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# Altered brain activity and functional connectivity after MDMA-assisted therapy for post-traumatic stress disorder

S. Parker Singleton[1]*, Julie B. Wang[2], Michael Mithoefer[2,3], Colleen Hanlon[4], Mark S. George[3,5], Annie Mithoefer[2], Oliver Mithoefer[3], Allison R. Coker[2,6], Berra Yazar-Klosinski[7], Amy Emerson[2], Rick Doblin[7] and Amy Kuceyeski[1,8]

[1]Department of Computational Biology, Cornell University, Ithaca, NY, United States, [2]MAPS Public Benefit Corporation, San Jose, CA, United States, [3]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States, [4]Wake Forest School of Medicine, Winston-Salem, NC, United States, [5]Ralph H. Johnson VA Medical Center, Charleston, SC, United States, [6]Department of Neurology, University of California, San Francisco, San Francisco, CA, United States, [7]Multidisciplinary Association for Psychedelic Studies, San Jose, CA, United States, [8]Department of Radiology, Weill Cornell Medicine, New York, NY, United States

**Introduction:** 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) for post-traumatic stress disorder (PTSD) has demonstrated promise in multiple clinical trials. MDMA is hypothesized to facilitate the therapeutic process, in part, by decreasing fear response during fear memory processing while increasing extinction learning. The acute administration of MDMA in healthy controls modifies recruitment of brain regions involved in the hyperactive fear response in PTSD such as the amygdala, hippocampus, and insula. However, to date there have been no neuroimaging studies aimed at directly elucidating the neural impact of MDMA-AT in PTSD patients.

**Methods:** We analyzed brain activity and connectivity via functional MRI during both rest and autobiographical memory (trauma and neutral) response before and two-months after MDMA-AT in nine veterans and first-responders with chronic PTSD of 6 months or more.

**Results:** We hypothesized that MDMA-AT would increase amygdala-hippocampus resting-state functional connectivity, however we only found evidence of a trend in the left amygdala—left hippocampus ($t$ = −2.91, uncorrected $p$ = 0.0225, corrected $p$ = 0.0901). We also found reduced activation contrast (trauma > neutral) after MDMA-AT in the cuneus. Finally, the amount of recovery from PTSD after MDMA-AT correlated with changes in four functional connections during autobiographical memory recall: the left amygdala—left posterior cingulate cortex (PCC), left amygdala—right PCC, left amygdala—left insula, and left isthmus cingulate—left posterior hippocampus.

**Discussion:** Amygdala—insular functional connectivity is reliably implicated in PTSD and anxiety, and both regions are impacted by MDMA administration. These findings compliment previous research indicating that amygdala,

hippocampus, and insula functional connectivity is a potential target of MDMA-AT, and highlights other regions of interest related to memory processes. More research is necessary to determine if these findings are specific to MDMA-AT compared to other types of treatment for PTSD.

**Clinical trial registration:** https://clinicaltrials.gov/ct2/show/NCT02102802, identifier NCT02102802.

KEYWORDS

**PTSD, MDMA, amygdala, hippocampus, insula, fMRI, functional connectivity, autobiographical memory**

## 1. Introduction

Post-traumatic stress disorder (PTSD), which can arise following exposure to a traumatic event or repeated stressful events and is a debilitating social and economic burden on individuals and their families (1, 2). PTSD is associated with an increased fear response (3) and distressing and intrusive re-experiencing of traumatic memories (4) that often serves as a barrier to the therapeutic process. This may explain why individuals with the most severe PTSD symptoms after trauma are more likely to end up with chronic PTSD durations (5, 6). Lifetime occurrence of PTSD in the general population is around 8%, and, prevalence is significantly higher in military personnel (17.1%) and first responders (10–32%), individuals on the front lines of societal trauma (7, 8). A meta-analysis of trials for military-related PTSD found that cognitive behavioral therapy and prolonged exposure therapy delivered clinically meaningful symptom improvements in 49–70% of patients, however 60–72% of veterans receiving these therapies still retained their PTSD diagnosis (9). Adverse outcomes such as increased symptoms and disengagement from treatment cause many current psychological therapies for PTSD to have high dropout rates (10), especially trauma focused therapies (11, 12).

One approach to developing more effective psychotherapies for PTSD is to administer a drug alongside psychotherapy to aid the therapeutic process (13). 3,4-methylenedioxymethamphetamine-assisted therapy (MDMA-AT) is hypothesized to reduce the fear response associated with re-experiencing traumatic memories, and therefore may facilitate tolerable processing of traumatic content in patients with PTSD (14). Phase 2 and 3 trials have demonstrated promise for MDMA-AT as a viable treatment for PTSD (15–18). MDMA, particularly the *R*-enantiomer, increases pro-social behavior and enhances fear extinction in mice and this effect appears to be mediated by serotonergic mechanisms (19, 20). In healthy humans, acute administration of MDMA has been shown to enhance positive and reduce negative affect during the recollection of autobiographical memories, while preserving vividness and emotional intensity (21). In another study, MDMA was found to preserve the memory accuracy when administered during both encoding and retrieval phases, while attenuating the recollection of salient details for both positive and negative memories, suggesting that MDMA alters emotional memory representations (22). Again in healthy controls, MDMA was found to enhance fear extinction learning/retention rates compared to placebo when administered during extinction training phases (23, 24). These findings suggest that MDMA may aid the therapeutic process, in part, by enabling patient access to emotionally challenging material and facilitating memory reconsolidation/fear extinction processes (25).

Functional magnetic resonance imaging (fMRI) measures changes in regional blood oxygenation over time and is thus used as a proxy for fluctuating neuronal activity. In-scanner environments can be absent of stimuli (resting-state fMRI—thought to measure intrinsic brain activity), or tasks or stimuli may be presented to study the regional brain dynamics underlying specific cognitive processes (26). In addition to the study of isolated regional activation changes, functional connectivity (FC) can be assessed to infer interaction between two or more brain regions. FC is defined as the statistical relationship (Pearson correlation in the case of the present study) between two brain regions' activity over time. These tools have been used to study functioning of brain regions and their networks in a wide range of neuropathology and psychiatric disorders (27–29). PTSD patients have shown altered functioning of the precuneus, posterior cingulate cortex (PCC), anterior cingulate cortex (ACC), insula, prefrontal and frontoparietal regions, as well as the hippocampus and amygdala (30–43), suggesting augmented recruitment of brain regions involved in self-referential processing (44), salient autobiographical memory (45–49), and fear and emotion (50).

The specific effects of MDMA-AT on brain function in individuals with PTSD have not been characterized, but several studies suggest the amygdala and hippocampus may play an important role. The amygdala is broadly associated with fear response, and the hippocampus, associated with learning and memory, may provide contextual information necessary for cognitive-affect during memory recall (31, 36, 50). Sripada et al. (43) found combat veterans with PTSD have decreased amygdala-hippocampal resting-state functional connectivity (RSFC) compared to combat veterans without

PTSD, which the authors speculate may represent an inability to contextualize affective information in PTSD. Increased amygdala-hippocampal RSFC following stress/trauma exposure has been shown to correlate with recovery from stress or trauma symptoms (51–53), suggesting a possible adaptive mechanism to threat exposure. In healthy volunteers, the acute administration of MDMA increases amygdala-hippocampal RSFC (54). Intranasal oxytocin also increases amygdala-hippocampal RSFC (53), and this effect appears to be mediated by serotonin system signaling (55)—two neuromodulators that MDMA significantly increases in the extracellular/plasma concentration of, and that play a crucial role in its effects on pro-social behavior and fear extinction (20, 56–61). Despite evidence that RSFC between the amygdala and hippocampus is implicated in PTSD and that this connection may be modulated by MDMA, no study to date has shown relationships between changes in these regions' functional connectivity and the therapeutic effects of MDMA-AT.

Herein, we describe results from a study of combat veterans and first-responders undergoing MDMA-AT for PTSD in a randomized, double-blind, dose-response phase 2 clinical trial (62). The Clinician-Administered PTSD Scale (CAPS-IV) (an hour-long, semi-structured interview centered around an index trauma) (63) was assessed throughout the study to track PTSD severity. Enrolled individuals had moderate-to-severe PTSD with a chronic PTSD duration of 6 months or more. Both resting-state and task-fMRI data, acquired while individuals listened to trauma-related and neutral audio scripts, were collected before and two months after MDMA-AT (follow-up scans were collected after the blind was broken).

Prior to analysis, we hypothesized that MDMA-AT would increase RSFC between the amygdala and hippocampus (43, 52–55, 64). We further hypothesized that, at baseline, brain activity would be higher during the trauma-related listening task compared with the neutral listening task in regions associated with autobiographical memory, fear, and emotion, and that this effect would be reduced post-treatment (30). In a final set of analyses, we assessed pre-to-post treatment change in the FC of several regions of interest contained within the limbic, salience, and default mode networks known to be hyperactive in PTSD (65) during the trauma and neutral autobiographical memory task-fMRI scans. FC changes were then correlated with the pre-to-post treatment recovery in overall PTSD symptomatology—as measured by decreases in CAPS-IV total severity scores.

# 2. Methods

## 2.1. Trial design

The present study analyzed data from a sub-study (NCT02102802) of a Phase 2 randomized, double-blind, dose-response trial of MDMA-AT in veterans and first responders with severe and chronic PTSD (NCT01211405) (62). A detailed study description of the parent study can be found in (62), and we summarize the study design in the **Supplementary material**. Here, we provide a description of the MRI-based sub-study design.

Participants in the parent study were able to opt into the MRI-based sub-study after which they provided written informed consent approved by the Medical University of South Carolina Institutional Review Board. They were screened for additional neuroimaging related eligibility criteria and were excluded for any conditions that could render MRI unsafe. A script-driven autobiographical memory paradigm was used to assess brain activity during symptom provocation (66–68). Following baseline CAPS-IV assessment in the parent study, sub-study participants worked with investigators to create two scripts: one describing a personally traumatic event and one reflecting their typical morning routine at home. Two audio recordings, each six minutes in length, were created from the participant's reading of each script. Each audio recording was divided into two 3-minute blocks for the task-fMRI. All participants, in all arms, were imaged at baseline, prior to therapy, and again at the follow-up visit two months after their final dosing session (**Figure 1**). LD ($N$ = 2) and MD ($N$ = 2) participants were additionally imaged after the primary endpoint visit in Stage 1 (one month following their second dosing session), however the small sample sizes prevented any meaningful analysis with these scans. The present analysis focuses on the pre- and post-therapy effects of MDMA-AT on fMRI biomarkers, and thus uses the scans collected at pre-treatment (baseline) and at least 2 months after the largest dose of MDMA (follow-up).

## 2.2. MRI acquisition

At each scanning session, participants underwent MRI on a 32 channel 3T Siemens system. T1 anatomical scans with TR/TE = 1,900/2.34 ms and 0.9 mm × 0.9 mm × 1.0 mm voxel size were collected, followed by two identical task fMRI (design described below) (TR/TE = 2,200/35 ms, 3.0 mm isotropic voxel size, length of each scan = 14:25 min) and one resting state fMRI (TR/TE = 2,000/30 ms, 3.3 mm × 3.3 mm × 3.0 mm voxel size, length = 5:00 min).

Participants' 6-minute trauma and neutral audio scripts were divided into two three-minute trauma and neutral blocks each (see "2.1 Trial design" for description of audio recordings). During fMRI, participants were presented with the visual cue "allow" and instructed to allow themselves to experience the scripts as their audio recordings were played for both neutral and trauma blocks. Each task scan had an alternating block design (neutral 1, trauma 1, neutral 2, trauma 2) with an 18 second "rest" period at the start of the scan and between each block, and about a minute of

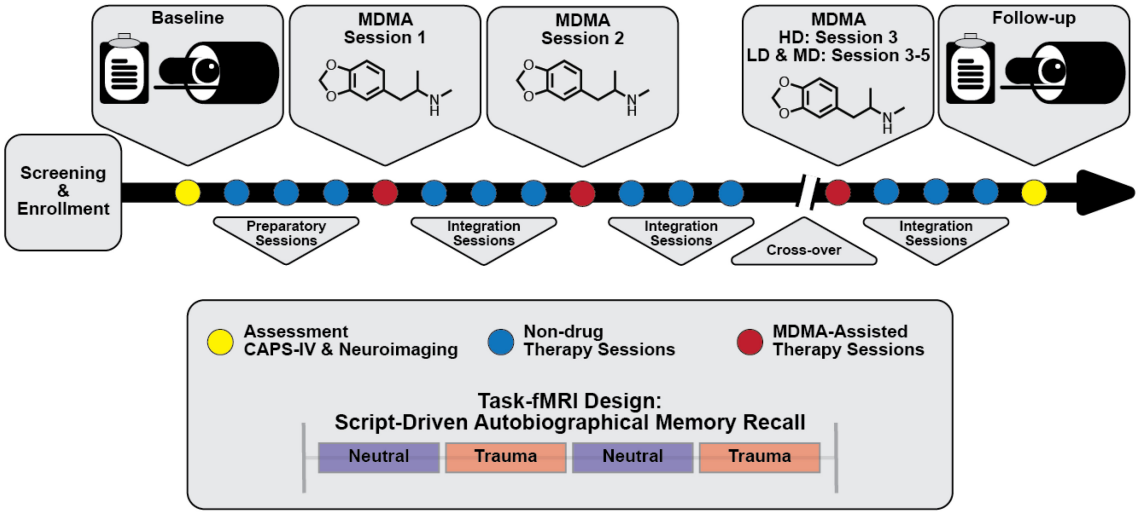


FIGURE 1
Simplified study design. Subjects were assessed and imaged at the start of the study (baseline). All subjects [low dose (LD; 30 mg MDMA), medium dose (MD; 75 mg MDMA), and high dose (HD; 125 mg MDMA)] underwent three non-drug preparatory therapy sessions prior to their first MDMA dosing session. Each MDMA session was followed by three non-drug integration therapy sessions. After MDMA session 2 and the subsequent integration sessions, subjects were assessed and the dosing blind was broken. HD subjects completed their final set of drug and non-drug therapy sessions unblinded, and LD/MD subjects crossed over into the HD arm where they completed three sets of drug and non-drug sessions, now with the higher dose and unblinded. All subjects were assessed and underwent MRI approximately two months following their last HD MDMA session. See "2. Methods" section for a full description of study design and scanning protocols.

rest at the end of the scan. The precise length of each audio block was 2.95 min.

## 2.3. Image preprocessing

FreeSurfer (69) was applied to the T1s to create white matter (WM), gray matter (GM) and cerebrospinal fluid (CSF) segmentations. FMRIB Software Library (FSL) (70) was used for (1) brain extraction, (2) registration between T1s and fMRI's (brain-boundary registration, non-linear, full-search), (3) high-pass filtering (4) slice-time and (5) motion correction.

## 2.4. Motion

High-motion frames [defined as >0.9 mm relative framewise displacement (FD); CONN Toolbox standard parameter (71)] were counted as outlier volumes and scrubbed from functional connectivity and activation analyses. The percentage of scrubbed volumes for resting-state scans ranged from 0 to 6.8% (mean = 2.1%) of total volumes. The percentage of scrubbed volumes for task scans ranged from 0 to 11% (mean = 1.7%) of total volumes. The mean composite FD (72) for each condition (rest and task) was calculated and compared across time-points using two-sided, paired t-tests. Mean FD during resting-state fMRI scans at baseline and follow-up were 0.12 (±0.06 s.d.) mm and 0.12 (±0.07 s.d.) mm, respectively, and were not significantly different from one another ($t$-statistic = −0.02; $p$ = 0.99). Mean FD during task fMRI scans at baseline and follow-up were 0.22 (±0.16 s.d.) mm and 0.17 (±0.09 s.d.) mm, respectively, and were not significantly different from one another ($t$-statistic = 1.23, $p$ = 0.25).

## 2.5. Activation analysis: Brain response to trauma versus neutral audio listening

FSL's fMRI Expert Analysis Tool (FEAT) (73) was used for fitting a general linear model (GLM) to the voxelwise timeseries for each task scan after spatial smoothing using a Gaussian kernel function [6 mm full width at half maximum (FWHM)]. For 1st- level analysis, models were generated for the neutral block, the trauma block, and a contrast of the two (trauma > neutral). Confound explanatory variables (EVs) included the temporal derivative of each block, 5 nuisance regressors each for WM and CSF signal, outlier volumes [spikes in global signal (>5 standard deviations) and motion (>0.9 mm FD); CONN Toolbox standard parameters (71)], and 24 motion confounds (74). Second-level analysis averaged the models from each of the two task scans performed at each time point. Third-level analyses, using a two-sided, one-sample t-test [FSL randomize; (75)] identified group-level response for the contrast model (i) at baseline, and (ii) at

the two-month follow-up. A final third-level analysis (iii) compared the group-level responses to the contrast model at baseline and follow-up using a two-sample, two-sided, paired t-test (FSL randomize; (75)). Third-level results were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE; alpha = 0.05) (76) which identifies significant clusters based on the extent of local support from surrounding voxels.

## 2.6. RSFC analysis

Prior to extraction of RSFC, in addition to the preprocessing steps taken in "2.3 Image preprocessing," fMRI data were further denoised using an in-house pipeline.[1] FMRIs were bandpass filtered and regressed for 24 motion confounds (74), 5 nuisance regressors each for WM and CSF, and one for global GM signal. The first five frames (scanner start-up noise) and confound frames (spikes in global signal and motion) were discarded. RSFC (Fisher Z-transformed Pearson correlation values) between the right and left amygdala and right and left hippocampus (77) was calculated for each resting-state scan. For the supplemental RSFC analysis, each hippocampus was further segmented into head and tail portions using FreeSurfer's hippocampal subregion segmentation tool (78). Two-tailed, paired *t*-tests were used to compare the 4 RSFC measures before and after MDMA-AT. Baseline to follow-up changes in these 4 measures were also correlated (Pearson's) with individual level reductions in CAPS-IV using participant's age and mean FD changes (follow-up—baseline) as covariates of non-interest. All statistical tests were performed at an alpha level of 0.05. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg algorithm (79) where indicated (pFDR).

## 2.7. Task FC analysis

Prior to extraction of task FC, the preprocessed residuals from the task activation analysis (section "2.5 Activation analysis: Brain response to trauma versus neutral audio listening") were further denoised with bandpass filtering and regressed for global GM signal. The first five frames (scanner start-up noise) and confound frames [spikes in global signal (>5 standard deviations) and motion (>0.9 mm FD); CONN Toolbox standard parameters (71)] were ignored. Functional connectivity (Fisher Z-transformed Pearson correlation values) during each task fMRI scan (task FC) was calculated between 18 regions of interest (ROIs): the right and left hippocampus head, hippocampus tail, amygdala, precuneus, caudal anterior cingulate cortex (ACC), rostral ACC, posterior cingulate cortex (PCC), isthmus cingulate, and insula. All ROIs were extracted from the Disikan–Killiany cortical atlas (see **Supplementary Figures 7, 8** for ROI definitions) (77), and head and tail portions of the hippocampus were created using FreeSurfer's hippocampal subregion segmentation tool (78). Two identical task scans were collected at each time point, thus FC values obtained from both scans were averaged to give a single value for each connection per subject. Group-level changes from pre- to post-therapy in the strength of functional connections were assessed using two-tailed, paired *t*-tests. Pearson correlations were calculated between individuals' changes in functional connection strength and change in CAPS-IV total severity scores (follow-up—baseline) using participant age and mean FD changes between baseline and follow-up as covariates of non-interest. All statistical tests were performed at an alpha level of 0.05. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg algorithm (79) where indicated (pFDR).

# 3. Results

## 3.1. CAPS-IV total severity scores significantly decreased after HD MDMA-AT

Ten participants enrolled in the sub-study, and one withdrew consent after baseline due to anxiety in the MRI scanner, leaving nine participants with MRI data at both time points (6 male, 3 female, aged 41.3; standard deviation (SD) = ±10.9 years; 8 veterans and 1 first-responder; see **Supplementary Table 1** for additional demographic information). All participants had chronic PTSD (mean duration = 84 (±45) months). One participant's baseline resting-state fMRI was truncated due to technical issues, leaving eight participants for resting-state analysis and nine for the task fMRI analysis. One participant began the trial with moderate PTSD (CAPS-IV > 39), while the remaining eight presented with severe PTSD (CAPS-IV > 59). Mean (SD) CAPS-IV total severity scores of the nine individuals pre- and post-MDMA-AT were 86 (±16) and 39 (±25), respectively, representing a significant decrease in PTSD symptom severity between the two time points (**Figure 2**; $N = 9$, $t = 6.36$, $p = 0.00022$). The average percent decrease in CAPS was 57 (±26)%. Results on all participants enrolled in the Phase 2 parent trial have been previously reported (62).

## 3.2. Baseline versus two-month follow-up amygdala-hippocampal RSFC

The RSFC was assessed between the amygdala and hippocampus before and after MDMA-AT and the strengths of

1 https://github.com/kjamison/fmriclean

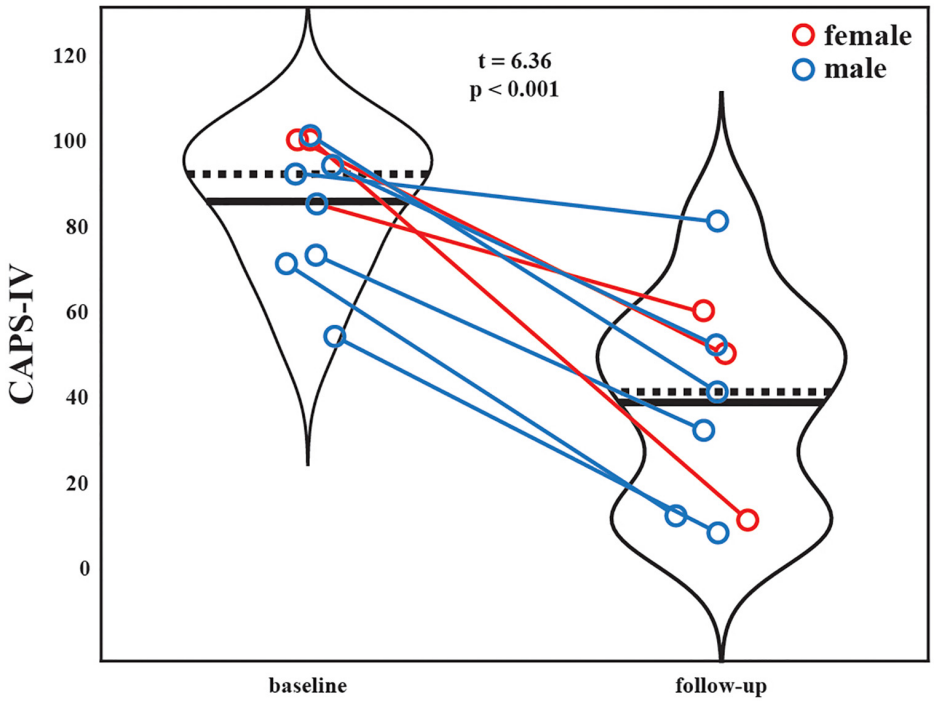


FIGURE 2
Patient CAPS-IV total severity scores at the baseline (pre-therapy) and two-month follow-up (post-therapy) scanning sessions. Black solid and dashed lines indicate group means and medians, respectively. Blue marker = male. Red marker = female. A significant reduction is PTSD severity was observed after MDMA-AT (baseline > follow-up; $N = 9$, $t = 6.36$, $p = 0.00022$).

these connections are illustrated in Figure 3. All connections trended toward increased RSFC after therapy compared to before therapy (using a two-sided paired t-test), with left amygdala to left hippocampus having a significant increase prior to (but not after) corrections for multiple comparisons ($N = 8$, $t = -2.91$, uncorrected $p = 0.0225$, pFDR = 0.0901).

Individual-level pre-to-post-therapy changes between the strength of these functional connections were then correlated (two-sided Pearson's) with changes in CAPS scores (Supplementary Figure 1). Only one of these correlations (right amygdala to left hippocampus FC versus CAPS) was significant before correction ($N = 8$; $R = -0.820$, uncorrected $p = 0.0460$, pFDR = 0.183).

## 3.3. Brain activation during symptom provocation

A script-driven autobiographical memory paradigm was used to assess brain activity during symptom provocation (66–68). We compared whole-brain, script-driven activations (trauma > neutral) at baseline and follow-up (Figure 4). Before therapy (baseline), there tended to be larger magnitude activation in response to the trauma script versus the neutral script, as evidenced by the generally positive t-statistics (Figures 4A–D). After correction using threshold free cluster enhancement (TFCE), there was significantly greater activation during the trauma scripts compared to the neutral scripts in four separate areas (see Figure 4 caption for details of each). After therapy, there were smaller magnitude differences between brain activity in response to the two scripts, with no significant clusters (Figure 4E). Finally, we assessed the differences in the contrast before and after therapy (follow-up > baseline). There was generally greater contrast between the trauma and neutral scripts at baseline compared to at follow-up, with one cluster in the bilateral cuneus and lingual gyrus demonstrating significance after correction using TFCE (Figure 4F).

## 3.4. Baseline versus two-month follow-up changes in task FC

We compared the pre- and post-therapy FC strength between 18 brain regions of interest (ROIs) during the task fMRI scans involving neutral and traumatic autobiographical audio recordings (Figure 5A). The ROIs are as follows: the right and left hippocampus head, hippocampus tail, amygdala, precuneus, caudal anterior cingulate cortex (ACC), rostral ACC, posterior cingulate cortex (PCC), isthmus cingulate, and the insula. Only one functional connection was significantly

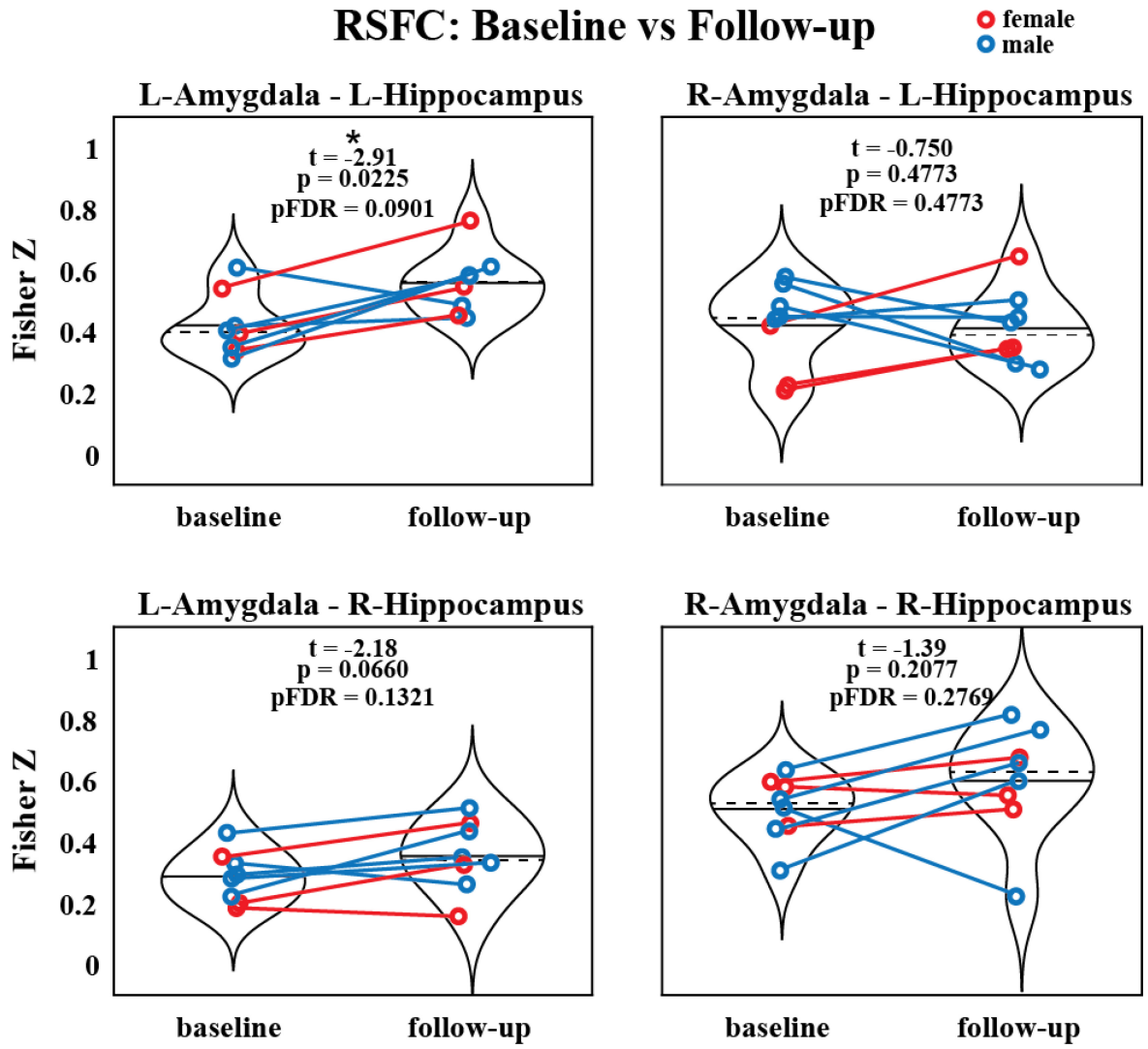


FIGURE 3
Resting-state functional connectivity between the amygdala and hippocampus before and after MDMA-AT. *P*-values from a two-sided, paired t-test. Blue = male. Red = female. Black solid and dashed lines indicate group means and medians, respectively ($N$ = 8; t-statistics indicate baseline > follow-up; *uncorrected $p < 0.05$).

modified at follow-up compared to baseline: the right amygdala to left caudal ACC ($N$ = 9; $t$-statistic = 3.04, $p$ = 0.0148). This finding was no longer significant after corrections for multiple comparisons, however (pFDR = 0.9875).

Individual-level pre-to-post therapy changes in these functional connections were then correlated (two-sided, Pearson's) with the individual-level reductions in CAPS-IV scores (Figure 5B). Most correlations were positive, meaning that larger reductions in connectivity from pre- to post-therapy corresponded to larger improvements in PTSD symptoms. Four correlations between FC and CAPS-IV changes were significant following multiple comparisons correction: the left amygdala and left PCC ($N$ = 9; Pearson's $R$ = 0.951, pFDR = 0.0462), the left amygdala and right PCC ($N$ = 9; Pearson's $R$ = 0.972, pFDR = 0.0197), the left amygdala and left insula ($N$ = 9; Pearson's $R$ = 0.977, pFDR = 0.0197), and the left isthmus cingulate and left hippocampal tail ($N$ = 9; Pearson's $R$ = 0.947, pFDR = 0.0462) (Figure 5C).

## 3.5. Supplemental analyses

Although not the primary focus of our analysis, we also repeated the previous correlations using other secondary outcome measures in place of CAPS-IV total severity scores. Namely, changes between baseline and follow-up in the BDI-II (depression symptoms), the PSQI (sleep quality), the PTGI (perceived growth following trauma), the DES-II

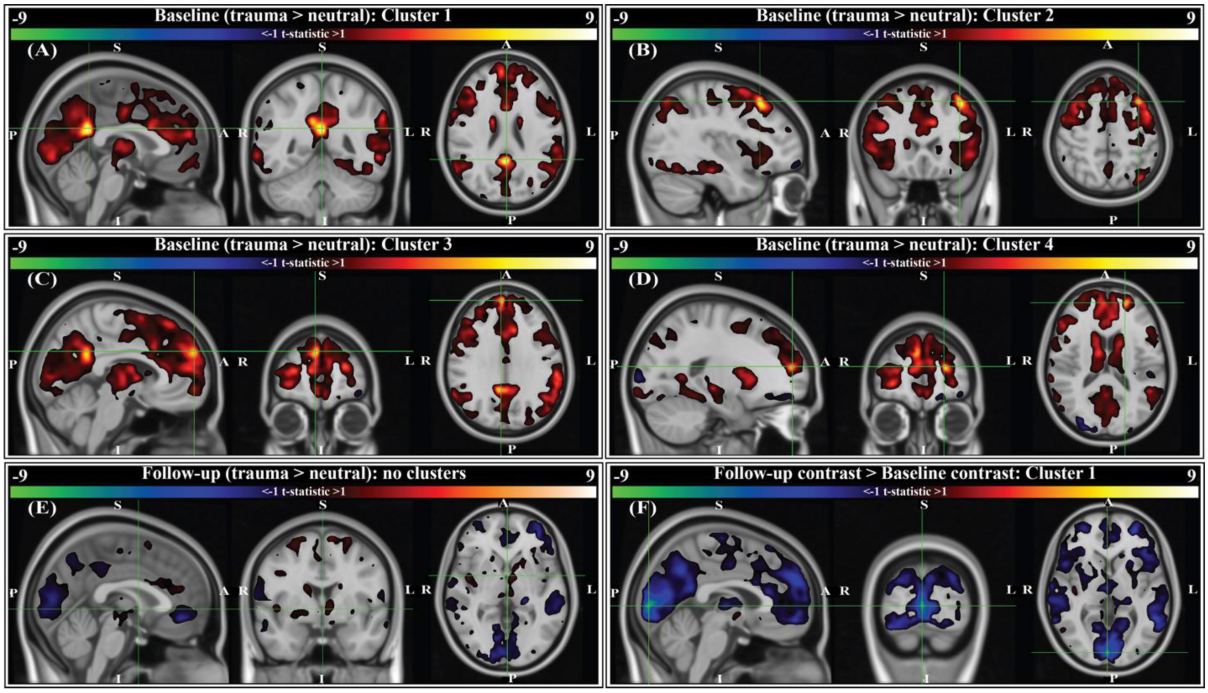


FIGURE 4
Group-level activation contrasts for trauma versus neutral script listening tasks ($N$ = 9). All panels show t-statistics for corresponding contrasts. Analyses were performed in 3 mm MNI standard space, however results here are interpolated into 1 mm MNI standard space and clipped to only show $t$-statistics greater than ± 1 for visualization purposes. Statistics reported below (voxels, volume, t-statistic, corrected $p$-value) were calculated from original 3 mm results. $P$-values were corrected using threshold-free cluster enhancement (TFCE; see section "2. Methods"). For panels **(A–E)**, positive $t$-statistics indicate greater activation to trauma scripts compared to neutral. For panel **(F)**, sign indicates the direction of change in trauma > neutral contrast from baseline (i.e., negative $t$-statistics indicate the contrast between trauma and neutral scripts was decreased at the two-month follow-up compared to baseline). Crosshairs are located on the center of gravity (c.o.g.) of significant clusters. **(A)** Cluster 1 for the baseline contrast is located primarily in the right and left isthmus cingulate, with some overlap into the right and left precuneus (c.o.g. MNI152 [0, −48, 24]; 6 voxels (162 $mm^3$); c.o.g. $t$ = 9.61, $p$(TFCE) = 0.0293). **(B)** Cluster 2 for the baseline contrast is located in the left caudal middle-frontal gyrus (c.o.g. MNI152 [-36, 21, 51]; 3 voxels (81 $mm^3$); c.o.g. $t$ = 9.01, $p$(TFCE) = 0.0234). **(C)** Cluster 3 for the baseline contrast is located in the right medial prefrontal cortex (c.o.g. MNI152 [6, 57, 30]; 2 voxels (54 $mm^3$); c.o.g. $t$ = 7.41, $p$(TFCE) = 0.0488). **(D)** Cluster 4 for the baseline contrast is located in the left rostral middle frontal gyrus (c.o.g. MNI152 [-21, 54, 15]; 1 voxel (27 $mm^3$); c.o.g. $t$ = 9.45, $p$(TFCE) = 0.0312). **(E)** There were no significant activation contrasts at the two-month follow-up (crosshairs shown at MNI152 [0, 0, 0]). **(F)** Comparing the group-level contrasts between time points (follow-up > baseline), there exists one significant cluster located primarily in the right and left cuneus, with some overlap into the right and left lingual gyrus (c.o.g. MNI152 [3, −90, 3]; 47 voxels (1,269 $mm^3$); c.o.g $t$ = −9.31, $p$(TFCE) = 0.0391).

(symptoms of dissociation), and the GAF (general psychological function) were used (Supplementary Figure 2). Following correction for multiple comparisons, none of these correlations were significant.

We also replicated our *a priori* analyses of amygdala-hippocampal RSFC using head (anterior) and tail (posterior) sub-regions of the hippocampus (Supplementary Figure 3). The left hippocampal head to left amygdala RSFC was increased at follow-up compared to baseline ($N$ = 8; $t$ = −2.593, uncorrected $p$ = 0.0358), as was the RSFC between the left hippocampal tail and right amygdala ($N$ = 8; $t$ = −3.00, uncorrected $p$ = 0.0199). Neither of these effects were significant after corrections for multiple comparisons.

Lastly, we replicate our main functional connectivity analyses without the use of global signal regression and find that these results largely show the same trends, however there is less significance in some cases (Supplementary Figures 4–6). The correlation between the left amygdala and left insula task functional connectivity change and CAPS reductions was significant both with and without the use of global signal regression (Supplementary Figure 6; $N$ = 9; $R$ = 0.971, pFDR = 0.0229).

## 4. Discussion

We report signatures of brain response during rest and audio listening task in eight veterans and one first-responder with clinically diagnosed chronic and severe PTSD before and two-months after MDMA-assisted therapy. We found a significant reduction in CAPS-IV total severity scores after therapy (Figure 2), indicating our sub-study participants

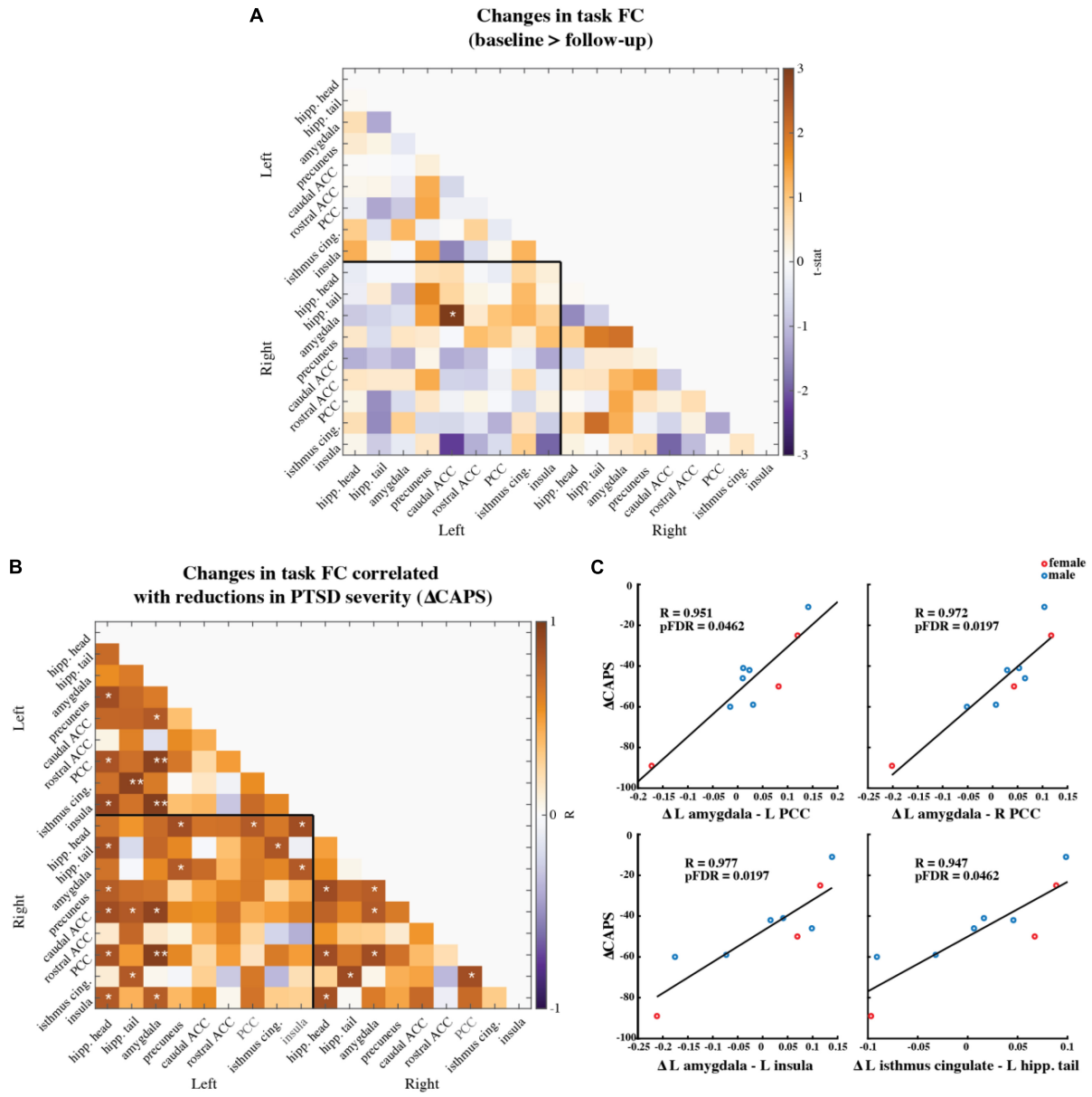


FIGURE 5
**(A)** Paired t-statistics shown for differences in functional connectivity between all brain regions of interest during the task fMRI scan involving neutral and trauma memory audio listening ($N$ = 9; baseline > follow-up; *two-sided uncorrected $p < 0.05$; **pFDR < 0.05, corrected). **(B)** Pearson correlation values between changes in ROI functional connectivity and reduction in CAPS scores. Changes were calculated as follow-up values minus baseline values. ($N$ = 9; *uncorrected $p < 0.05$; **pFDR < 0.05) Age and mean FD difference between baseline and follow-up were included as covariates of non-interest. **(C)** Scatter plots of the three correlations that remained significant after corrections for multiple comparisons (i.e., pFDR < 0.05). Red marker = female. Blue marker = male.

mirrored the results from the parent study (62). We found a trend suggesting that RSFC between the amygdala and hippocampus was strengthened post-therapy, particularly in the left hemisphere (Figure 3). Prior work suggests that modulation of amygdalae-hippocampal RSFC may be an important component of MDMA-AT for PTSD (43, 51–55), thus investigating this connection in future studies is warranted. We also found participants had increased activation in areas involved with self-referential processing and autobiographical memory while listening to traumatic versus neutral memory narrations pre-therapy (Figures 4A–D), and that no significant contrast existed after MDMA-AT (Figure 4E). Comparing trauma versus neutral contrasts between baseline and follow-up revealed a significant decrease in cuneus contrast after MDMA-AT (Figure 4F). Finally, the pre- to post-therapy reductions in FC during the script listening task between the

left amygdala and right PCC, left PCC, and left insula, as well as FC between the left isthmus cingulate and left hippocampal tail strongly and significantly correlated with PTSD symptom improvement (**Figure 5C**). These results begin to shed light on the neurological mechanisms that may drive MDMA-AT for PTSD.

Previous work quantifying functional connectivity in PTSD and in stress exposure (43, 51–53) and acute MDMA administration in controls (54) suggests one mechanism of MDMA-AT may be to increase pathologically lowered amygdala-hippocampal RSFC (25). The amygdala is associated with fear expression, threat recognition, and heightened response to emotional memories and is often dysregulated in patients with PTSD (31, 36, 50, 65, 80, 81). The hippocampus also plays a central role in PTSD as it is thought to provide contextual information important for cognitive-affect during memory recollection (31, 36). Sripada et al. (43) found combat veterans with PTSD had reduced amygdala-hippocampal RSFC compared to combat-exposed controls, leading them to speculate that this may relate to an inability to contextualize affective information in PTSD. Carhart-Harris et al. (54) demonstrated that amygdala-hippocampal RSFC is increased acutely in MDMA administration compared to placebo and this increase occurred in a manner that correlated with the drug's subjective effects at a near-significant level, leading these researchers to propose that this functional connection was a primary target of MDMA-AT. Increased amygdala-hippocampal RSFC has also been linked to intranasal oxytocin administration after stress exposure (53) and this effect was mediated by serotonin signaling (55)—two neuromodulators that play a significant role in the pro-social and fear extinction effects of MDMA (20, 56–61). Prior to our analysis (although after the study was designed and the data collected), we hypothesized that the RSFC between the amygdala and hippocampus would be higher after MDMA-AT compared to pre-therapy levels. Only the RSFC between the left amygdala and left hippocampus was significantly increased (**Figure 3**) however, this finding no longer met thresholds for significance after multiple comparisons correction (pFDR = 0.09). We also found that the amount of increased right amygdala—left hippocampal RSFC after MDMA-AT positively correlated with PTSD symptom improvement at a near-significant level (**Supplementary Figure 1**; $R = -0.820$, uncorrected $p = 0.046$, pFDR = 0.183). Our current findings, though inconclusive, are suggestive of a trend toward moderate increases in amygdala—hippocampal RSFC two-months after MDMA-AT. It is possible that more significant changes would have been observed with a larger sample size, longer resting-state scans, or imaging performed closer to MDMA administration. These findings justify the continued investigation of amygdala-hippocampal RSFC in the therapeutic mechanisms of MDMA-AT in future studies.

We next sought to study brain response during autobiographical memory listening to draw additional conclusions about MDMA-AT's effects in individuals with PTSD. Before therapy, participants had larger activation in four areas during an individualized trauma script listening task compared to neutral script listening: the right and left isthmus cingulate and precuneus, the left caudal middle frontal gyrus, the right medial prefrontal cortex, and the left rostral middle frontal gyrus (**Figures 4A–D**). These regions are broadly involved in self-processing operations (e.g., first-person perspective taking), episodic memory retrieval, visual-spatial imagery, auto-biographical memory recollection, and are included in or interact with the default mode network (44, 46, 49, 82–85). The retrosplenial cortex—located within the isthmus cingulate—is also found to be consistently activated by emotionally salient stimuli, and has been proposed to play a role in the interaction between emotion and memory (48). We conjecture that increased activation in these regions during traumatic compared to neutral audio listening (**Figures 4A–D**) could be related to an increased intensity of the recollection or re-experiencing of traumatic memories compared to neutral ones for patients before therapy. At 2-month follow-up to MDMA-AT, there was no significant difference in the trauma vs neutral script activation (**Figure 4E**). The longitudinal comparison of these two time points indicated that the contrast between trauma and neutral was larger at baseline, particularly in a significant cluster in the right and left cuneus/lingual gyrus (**Figure 4F**). Cuneus activity during autobiographical memory tasks often coincides with activity in the frontal regions highlighted by the baseline contrast, and has been found to correlate with memory recall accuracy (49, 83, 84). Cuneus activity is thought to enhance the visual imagery of autobiographical memory recollection (86), therefore decreased contrast in this area at follow-up suggests that intensity of visual imagery contrast between trauma and neutral memories may be decreased after MDMA-AT. Larger studies may allow more statistical power to identify additional longitudinal differences. Other longitudinal studies of individuals with PTSD have found that decreases in precuneus, isthmus cingulate, and middle frontal gyrus activation during symptom provocation is correlated with reductions in PTSD symptom severity (87, 88).

PTSD is often associated with hyperactivity in the amygdala (36); the acute administration of MDMA in healthy volunteers decreases blood flow to the amygdala during rest (54) and attenuates its response to angry faces (89). We had hypothesized that we would observe hyperactivity of the amygdala to trauma versus neutral scripts at baseline and that MDMA-AT would attenuate this response, however we observed neither. It is important to note inconsistencies in the literature here. Amygdala hyperactivity in PTSD is not always observed, possibly due to differences in subtypes, sex, cultural representations, or choice of paradigm (66, 90–94). Additionally, while MDMA did suppress amygdala activity

during rest and in response to angry faces as previously mentioned, there was no observed impact on its response to autobiographical memories (21). While activation-based analyses deserve continued attention in future studies to rectify these inconsistencies, functional connectivity is a complimentary approach we can use to extract additional information from fMRI.

Functional connectivity analyses in individuals with PTSD have revealed aberrant connectivity between several regions within default mode, limbic, and salience networks, and more broadly, regions involved in emotional and self-referential processing (32–35, 37–41, 43, 67), and, further, the administration of MDMA in healthy volunteers has been shown to disrupt the functional integrity of these networks (54, 95–98). Here, we measured functional connectivity during script-driven autobiographical memory recall between the right and left hippocampus head, hippocampus tail, amygdala, precuneus, caudal ACC, rostral ACC, PCC, isthmus cingulate, and the insula. Our ROIs were defined and labeled based on the Desikan-Killiany (DK) brain atlas (**Supplementary Figures 7**, **8**) (77). We chose to segment the hippocampus into anterior (head) and posterior (tail) ROIs based on recent work showing that the two portions' FC are differentially effected by PTSD (34). We assessed group-level changes in the strength of these functional connections and found no significant differences between baseline and follow-up after corrections for multiple comparisons (**Figure 5A**). However, we did find that greater recovery (larger decreases in CAPS-IV at follow-up) was associated with reductions in FC between the left amygdala and the right and left PCC, as well as the left insula (**Figure 5C**). The acute effects of MDMA in healthy volunteers has been shown to decrease the FC of the PCC (96, 97) and insula (95), and alter amygdala and hippocampus FC (54), highlighting the potential relevance of our current findings. Amygdala to posterior and mid-cingulate cortex FC has been shown to be associated with PTSD severity at different stages of disease progression, although differing patient populations and assessment time-lines lead to conflicting results (40, 99–102). One finding in healthy adults shows increased amygdala—PCC FC following the acute exposure to stress (103), thus the association between recovery and reduced amygdala—PCC task FC at follow-up possibly relates to reduced stress response to trauma memories (although the finding by Veer and colleagues is more posterior to the ROI used here). Amygdala and insula RSFC is increased in PTSD (39, 43) [except in one study which finds the opposite (38)], and reduced amygdala-insula FC during negative image reappraisal is associated with larger improvements in PTSD symptoms (101). The strength of left amygdala-insula FC also positively correlates with the amount of acute anxiety measured in participants just before scanning (104). Attenuated functional connectivity of these two regions at follow-up in the present study possibly suggests a decreased intensity of recalled events, less "re-experiencing," or reduced anxiety during the script-driven memory recall (65). Lastly, we found that reductions in CAPS-IV at follow-up were associated with reduced FC between the left isthmus cingulate and left hippocampal tail (**Figure 5C**). The isthmus cingulate labeled here consists of the most posterior potions of the PCC (**Supplementary Figure 7**). Increased FC between these two regions has previously been reported in PTSD patients compared to trauma-exposed health controls (33, 34), and the present finding is possibly indicative of changes in memory contextualization and reduced threat sensitivity at two-month follow-up to MDMA-AT compared to baseline (100).

PTSD is characterized by decreased fear extinction in response to trauma-related stimuli. One possible mechanism through which MDMA-AT operates is enhanced reconsolidation and/or fear extinction processes (25). Several studies with MDMA implicate reconsolidation or fear extinction processes, and while it is currently unclear whether MDMA acts on only one or both, it is important to note that the two interact (105). Rodent models have demonstrated that the administration of MDMA prior to extinction learning enhances extinction retention (tested 48 h after learning) and this effect is blocked by acute and chronic treatment with a serotonin transporter inhibitor (20, 106). Hake et al. (107) found that MDMA administered during extinction learning phases did not enhance fear extinction memory, while MDMA administration during reconsolidation phases resulted in prolonged reductions in conditioned fear. In addition, MDMA administered prior to trauma-cue exposure (reconsolidation phase) in rodents resulted in reduced stress-related behavioral responses 7 days later (108). Two recent trials in healthy humans found that MDMA (100 and 125 mg, respectively) administered prior to extinction learning resulted in improved extinction learning at extinction recall phases (48 and 24 h later, respectively) compared to the placebo group (23, 24). Doss et al. (22) found that 1 mg/kg of MDMA in healthy humans attenuated the encoding and retrieval of salient details from positive and negative stimuli (but not neutral stimuli), suggesting an ability for MDMA to alter emotional memory representation. Interestingly, a fMRI study in healthy humans found decreased activation in the precuneus/PCC during fear extinction learning (109), regions highlighted by our present study and others in PTSD (87, 88).

## 5. Limitations

The small sample size of the present study and the lack of a control population (e.g., trauma-exposed healthy controls) may decrease the generalizability of these findings. The trial design was placebo-controlled for dose-response (low, medium, and high), however, the follow-up scans used in this study were after the breaking of the blind and dose cross-over (low/medium to high) had occurred. For neuroimaging studies, comparisons with control populations are helpful for contextualizing longitudinal changes in brain response

and provide information about whether changes in patient populations represent an abnormal response being restored to normality or a compensatory mechanism. In addition, multi-point imaging of healthy control or non-treatment (placebo) groups allow for the quantification of test-retest variability. Lastly, had we imaged a cohort that received therapy without MDMA, we would have been able to assess longitudinal brain changes that were unique to or enhanced by MDMA.

Here it must be discussed that PTSD is a disorder exhibiting at least two major sub-types (dissociative and non-dissociative) with characteristically opposing phenomenological and physiological responses to symptom provocation, which may explain inconsistencies in the PTSD neurobiology literature (90). PTSD sub-type information was not collected in the present study. In addition to sub-type heterogeneity, males and females may also differ in their adaptive neural responses to trauma (92). Limited by our sample size, we did not investigate differences between males and females in this study.

The accepted standard for assessing PTSD severity is the Clinician-Administered PTSD Scale (63). Specifically, CAPS-IV was used in this study. CAPS-IV involves an hour-long semi-structured interview with a clinician and, though comprehensive, faces limitations. In their baseline CAPS-IV assessment, and subsequently thereafter, patients were asked to refer to an index trauma that was measured throughout the study. This may present an issue in accurately assessing global PTSD severity if an adjacent or un-related trauma surfaces during therapy and becomes the prominent driver of their symptoms. These issues, combined with difficulty in blinding and expectancy effects, present additional challenges in accurately mapping fMRI metrics to clinical outcomes.

The task design used in this study examined differences in brain response to personalized audio scripts generated from narrations of traumatic and neutral memories. Many different stimuli have been used in fMRI studies of PTSD (30, 42, 110), each providing its own unique advantages and disadvantages. Our present design optimizes personal relevance of the stimuli; however, this has the consequence of presenting each subject with a different set of stimuli, whereby brain responses within each block are not time-locked across participants. Also, it has previously been shown that PTSD survivors take longer to retrieve unrelated autobiographical information when listening to taped imagery scripts of their traumatic memories (111). This suggests the possibility that those with the most severe PTSD will take the longest to cognitively transition to the neutral block from the trauma block. If this is true, then there would perhaps be an inverse-"U" relationship between PTSD severity and contrast between the trauma and neutral conditions, if the blocks are not spaced far enough apart to allow adequate time for patients to return to a baseline level of cognitive functioning. Additionally, because our repeated task fMRI scans were identical (rather than counterbalanced for condition), there could be primacy effects in the neutral condition (which was always first) and/or fatigue effects in the trauma condition (which was always last).

We did not aim to characterize lateralization in our findings, and though most of our significant FC results were found in the left amygdala, we did not test for statistical interaction effects between hemispheres. While lateralization of the amygdala remains debated, it has been suggested by early work that the left amygdala is more strongly related to conscious (versus unconscious) perception and emotional regulation (112).

Finally, the pre-specified aim of this study was to estimate longitudinal (baseline to 2-months after final MDMA session) changes in ROI response to traumatic audio scripts. Between the start of data collection and analysis, new literature emerged (54, 55) implicating amygdala-hippocampus RSFC as a potential target of MDMA-AT, compelling us to expand our analysis beyond the pre-specified aims. Functional connectivity estimates from shorter scans (e.g., five minutes in the case of our resting-state data) can have lower reliability (113) and therefore the trends in increased RSFC between amygdala and hippocampal regions reported here should be considered preliminary.

## 6. Conclusion

We report functional brain changes associated with MDMA-AT in veterans and first responders with moderate-to-severe and chronic PTSD. We had hypothesized that MDMA-AT may act through strengthening the RSFC between the amygdala and hippocampus, a connection which is weaker in PTSD populations (43) and increased acutely by MDMA in healthy volunteers (54). The trends found here are suggestive of such in the left amygdala—left hippocampus, however larger studies are needed. We also provide preliminary evidence that MDMA-AT alters brain response during symptom provocation in regions associated with fear response, anxiety, self-referential processing, and salient autobiographical memory, and are commonly found to be hyperactive in PTSD patients (30, 110). Finally, the reduction of several functional connections during autobiographical memory audio co-varied with symptom reduction in PTSD. Of these connections, the left amygdala—left insula is perhaps the most interesting, due to the role of amygdala-insular FC in anxiety and PTSD symptomatology (39, 43, 101, 104). More research is necessary to confirm these results and to disentangle effects specific to MDMA and its combination with psychotherapy.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Medical University of South Carolina Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

SPS and AK had full access to all the data in the study and take responsibility for the integrity of the data and for the accuracy of the data analysis. BY-K, AE, MM, and RD conceived and designed the clinical trial part of the study. MM and AM carried out experimental treatments and recorded participant scripts. AE carried out sponsor oversight of data collection. CH and MG designed the imaging tasks and acquisition. CH, MG, and OM oversaw the scanning and data collection. SPS, AK, JW, and AC drafted the manuscript. SPS carried out preprocessing, analysis, and interpretation of data. RD obtained funding for the study. All authors contributed to the critical review and final version of the manuscript.

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## Conflict of interest

MM was paid as a contractor by MAPS PBC. AE, AC, and JW received salary support for full-time employment with MAPS PBC. BY-K and RD received salary support for full-time employment with MAPS. MM is on the Clinical Advisory Board of Awakn Life Sciences.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.947622/full#supplementary-material

## References

1. Davidson JRT. Trauma: the impact of post-traumatic stress disorder. *J Psychopharmacol.* (2000) 14:S5–12. doi: 10.1177/0269881100014 2S102

2. Gradus J. Prevalence and prognosis of stress disorders: a review of the epidemiologic literature. *Clin Epidemiol.* (2017) 9:251–60. doi: 10.2147/CLEP. S106250

3. VanElzakker MB, Lindsay K, Bradley S, Lisa MS. The neurocircuitry of fear and PTSD. In: Vermetten E, Germain A, Neylan TC editors. *Sleep and Combat-Related Post Traumatic Stress Disorder*. New York, NY: Springer (2018). p. 111–25. doi: 10.1007/978-1-4939-7148-0_10

4. Ehlers A. Understanding and treating unwanted trauma memories in posttraumatic stress disorder. *Z Psychol.* (2010) 218:141–5.

5. Shalev A, Gevonden M, Ratanatharathorn A, Laska E, van der MW, Qi W, et al. Estimating the risk of PTSD in recent trauma survivors: results of the international consortium to predict PTSD (ICPP). *World Psychiatry.* (2019) 18:77–87. doi: 10.1002/wps.20608

6. van der Mei W, Barbano A, Ratanatharathorn A, Bryant R, Delahanty D, deRoon-Cassini T, et al. Evaluating a screener to quantify PTSD risk using emergency care information: a proof of concept study. *BMC Emerg Med.* (2020) 20:16. doi: 10.1186/s12873-020-00308-z

7. Hoge C, Castro C, Messer S, McGurk D, Cotting D, Koffman R. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med.* (2004) 351:13–22. doi: 10.1056/NEJMoa040603

8. Javidi H, Yadollahie M. Post-traumatic stress disorder. *Int J Occup Environ Med.* (2012) 3:2–9.

9. Steenkamp M, Litz B, Hoge C, Marmar C. Psychotherapy for military-related PTSD: a review of randomized clinical trials. *JAMA.* (2015) 314:489–500. doi: 10.1001/jama.2015.8370

10. Goetter E, Bui E, Ojserkis R, Zakarian R, Brendel R, Simon N. A systematic review of dropout from psychotherapy for posttraumatic stress disorder among iraq and afghanistan combat veterans. *J Trauma Stress.* (2015) 28:401–9. doi: 10.1002/jts.22038

11. Lewis C, Roberts N, Gibson S, Bisson J. Dropout from psychological therapies for post-traumatic stress disorder (PTSD) in adults: systematic review and meta-analysis. *Eur J Psychotraumatol.* (2020) 11:1709709. doi: 10.1080/20008198.2019.1709709

12. Mott J, Mondragon S, Hundt N, Beason-Smith M, Grady R, Teng E. Characteristics of U.S. veterans who begin and complete prolonged exposure and cognitive processing therapy for PTSD. *J Trauma Stress.* (2014) 27:265–73. doi: 10.1002/jts.21927

13. Feduccia A, Mithoefer M, Jerome L, Holland J, Emerson A, Doblin R. Response to the consensus statement of the PTSD psychopharmacology working group. *Biol Psychiatry.* (2018) 84:e21–2. doi: 10.1016/j.biopsych.2017.11.023

14. Mithoefer M, Wagner M, Mithoefer A, Jerome L, Doblin R. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol.* (2011) 25:439–52. doi: 10.1177/0269881110378371

15. Mitchell J, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

16. Mithoefer M, Feduccia A, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology.* (2019) 236:2735–45. doi: 10.1007/s00213-019-05249-5

17. Wang J, Lin J, Bedrosian L, Coker A, Jerome I, Feduccia A, et al. Scaling up: multisite open-label clinical trials of MDMA-assisted therapy for severe posttraumatic stress disorder. *J Humanist Psychol.* (2021). doi: 10.1177/00221678211023663

18. Jerome L, Feduccia A, Wang J, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology.* (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

19. Curry D, Young M, Tran A, Daoud G, Howell L. Separating the agony from ecstasy: R(−)-3,4-methylenedioxymethamphetamine has prosocial and therapeutic-like effects without signs of neurotoxicity in mice. *Neuropharmacology.* (2018) 128:196–206. doi: 10.1016/j.neuropharm.2017.10.003

20. Young M, Norrholm S, Khoury L, Jovanovic T, Rauch S, Reiff C, et al. Inhibition of serotonin transporters disrupts the enhancement of fear memory extinction by 3,4-methylenedioxymethamphetamine (MDMA). *Psychopharmacology.* (2017) 234:2883–95. doi: 10.1007/s00213-017-4684-8

21. Carhart-Harris RL, Wall MB, Erritzoe D, Kaelen M, Ferguson B, Meer ID, et al. The effect of acutely administered MDMA on subjective and BOLD-FMRI responses to favourite and worst autobiographical memories. *Int J Neuropsychopharmacol.* (2014) 17:527–40. doi: 10.1017/S1461145713001405

22. Doss M, Weafer J, Gallo D, de Wit H. MDMA impairs both the encoding and retrieval of emotional recollections. *Neuropsychopharmacology.* (2018) 43:791–800. doi: 10.1038/npp.2017.171

23. Vizeli P, Straumann I, Duthaler U, Varghese N, Eckert A, Paulus M, et al. Effects of 3,4-methylenedioxymethamphetamine on conditioned fear extinction and retention in a crossover study in healthy subjects. *Front Pharmacol.* (2022) 13:906639. doi: 10.3389/fphar.2022.906639

24. Maples-Keller J, Norrholm S, Burton M, Reiff C, Coghlan C, Jovanovic T, et al. A randomized controlled trial of 3,4-methylenedioxymethamphetamine (MDMA) and fear extinction retention in healthy adults. *J Psychopharmacol.* (2022) 36:368–77. doi: 10.1177/02698811211069124

25. Feduccia A, Mithoefer M. MDMA-assisted psychotherapy for PTSD: are memory reconsolidation and fear extinction underlying mechanisms? *Prog Neuropsychopharmacol Biol Psychiatry.* (2018) 84:221–8. doi: 10.1016/J.PNPBP.2018.03.003

26. Glover G. Overview of functional magnetic resonance imaging. *Neurosurg Clin N Am.* (2011) 22:133–9. doi: 10.1016/j.nec.2010.11.001

27. Zhou J, Liu S, Ng K, Wang J. Applications of resting-state functional connectivity to neurodegenerative disease. *Neuroimaging Clin.* (2017) 27:663–83. doi: 10.1016/j.nic.2017.06.007

28. Lucassen P, Pruessner J, Sousa N, Almeida O, Van DA. Neuropathology of stress. *Acta Neuropathol.* (2014) 127:109–35. doi: 10.1007/s00401-013-1223-5

29. Woodward N, Cascio C. Resting-state functional connectivity in psychiatric disorders. *JAMA Psychiatry.* (2015) 72:743–4. doi: 10.1001/jamapsychiatry.2015.0484

30. Sartory G, Cwik J, Knuppertz H, Schürholt B, Lebens M, Seitz R, et al. In search of the trauma memory: a meta-analysis of functional neuroimaging studies of symptom provocation in posttraumatic stress disorder (PTSD). *PLoS One.* (2013) 8:e58150. doi: 10.1371/journal.pone.0058150

31. Harnett N, Goodman A, Knight D. PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Exp Neurol.* (2020) 330:113331. doi: 10.1016/j.expneurol.2020.113331

32. Abdallah CG, Wrocklage KM, Averill CL, Akiki T, Schweinsburg B, Roy A, et al. Anterior hippocampal dysconnectivity in posttraumatic stress disorder: a dimensional and multimodal approach. *Transl Psychiatry.* (2017) 7:e1045. doi: 10.1038/tp.2017.12

33. Lazarov A, Zhu X, Suarez-Jimenez B, Rutherford B, Neria Y. Resting-state functional connectivity of anterior and posterior hippocampus in posttraumatic stress disorder. *J Psychiatr Res.* (2017) 94:15–22. doi: 10.1016/j.jpsychires.2017.06.003

34. Malivoire B, Girard T, Patel R, Monson C. Functional connectivity of hippocampal subregions in PTSD: relations with symptoms. *BMC Psychiatry.* (2018) 18:129. doi: 10.1186/s12888-018-1716-9

35. Brown V, LaBar K, Haswell C, Gold A. Altered resting-state functional connectivity of basolateral and centromedial amygdala complexes in posttraumatic stress disorder. *Neuropsychopharmacology.* (2014) 39:351–9. doi: 10.1038/npp.2013.197

36. Pitman R, Rasmusson A, Koenen K, Shin L, Orr S, Gilbertson M, et al. Biological studies of post-traumatic stress disorder. *Nat Rev Neurosci.* (2012) 13:769–87. doi: 10.1038/nrn3339

37. Gilboa A, Shalev A, Laor L, Lester H, Louzoun Y, Chisin R, et al. Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. *Biol Psychiatry.* (2004) 55:263–72. doi: 10.1016/j.biopsych.2003.08.004

38. Fonzo G, Goodkind M, Oathes D, Zaiko Y, Harvey M, Peng K, et al. Amygdala and insula connectivity changes following psychotherapy for posttraumatic stress disorder: a randomized clinical trial. *Biol Psychiatry.* (2021) 89:857–67. doi: 10.1016/j.biopsych.2020.11.021

39. Rabinak C, Angstadt M, Welsh R, Kenndy A, Lyubkin M, Martis B, et al. Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. *Front Psychiatry.* (2011) 2:62. doi: 10.3389/fpsyt.2011.00062

40. Belleau E, Ehret L, Hanson J, Brasel K, Larson C, deRoon-Cassini T. Amygdala functional connectivity in the acute aftermath of trauma prospectively predicts severity of posttraumatic stress symptoms. *Neurobiol Stress.* (2020) 12:100217. doi: 10.1016/j.ynstr.2020.100217

41. Thome J, Terpou B, McKinnon M, Lanius R. The neural correlates of trauma-related autobiographical memory in posttraumatic stress disorder: a meta-analysis. *Depress Anxiety.* (2020) 37:321–45. doi: 10.1002/da.22977

42. Lanius RA, Bluhm R, Lanius U, Pain C. A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J Psychiatr Res.* (2006) 40:709–29. doi: 10.1016/j.jpsychires.2005.07.007

43. Sripada R, King A, Garfinkel S, Wang X, Sripada C, Welsh R, et al. Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. *J Psychiatry Neurosci.* (2012) 37:241. doi: 10.1503/JPN.110069

44. Cavanna A, Trimble M. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* (2006) 129(Pt 3):564–83. doi: 10.1093/brain/awl004

45. Svoboda E, McKinnon M, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia.* (2006) 44:2189–208. doi: 10.1016/j.neuropsychologia.2006.05.023

46. Spreng R, Mar R, Kim A. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. *J Cogn Neurosci.* (2009) 21:489–510. doi: 10.1162/jocn.2008.21029

47. Sestieri C, Corbetta M, Romani G, Shulman G. Episodic memory retrieval, parietal cortex, and the default mode network: functional and topographic analyses. *J Neurosci.* (2011) 31:4407–20. doi: 10.1523/JNEUROSCI.3335-10.2011

48. Maddock RJ. The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci.* (1999) 22:310–6. doi: 10.1016/S0166-2236(98)01374-5

49. Spreng R, Grady C. Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *J Cogn Neurosci.* (2010) 22:1112–23. doi: 10.1162/jocn.2009.21282

50. LeDoux J. The emotional brain, fear, and the amygdala. *Cell Mol Neurobiol.* (2003) 23:727–38. doi: 10.1023/A:1025048802629

51. Ben-Zion Z, Keynan NJ, Admon R, Sharon H, Halpern P, Liberzon I, et al. Hippocampal-amygdala resting state functional connectivity serves as resilience factor for short- and long-term stress exposure. *Biol Psychiatry.* (2020) 87(Suppl. 9):S88–9. doi: 10.1016/j.biopsych.2020.02.248

52. Vaisvaser S, Lin T, Admon R, Podlipsky I, Greenman Y, Stern N, et al. Neural traces of stress: cortisol related sustained enhancement of amygdala-hippocampal functional connectivity. *Front Hum Neurosci.* (2013) 7:313. doi: 10.3389/fnhum.2013.00313

53. Fan Y, Pestke K, Feeser M, Aust S, Pruessner J, Böker H, et al. Amygdala–hippocampal connectivity changes during acute psychosocial stress: joint effect of early life stress and oxytocin. *Neuropsychopharmacology.* (2015) 40:2736–44. doi: 10.1038/npp.2015.123

54. Carhart-Harris R, Murphy K, Leech R, Erritzoe D, Wall M, Ferguson B, et al. The effects of acutely administered 3,4-methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biol Psychiatry.* (2015) 78:15. doi: 10.1016/J.BIOPSYCH.2013.12.015

55. Lan C, Liu C, Li K, Zhao Z, Yang J, Ma Y, et al. Oxytocinergic modulation of stress-associated amygdala-hippocampus pathways in humans is mediated by serotonergic mechanisms. *Int J Neuropsychopharmacol.* (2022) 25:807–17. doi: 10.1093/ijnp/pyac037

56. Dumont GJH, Sweep FCGJ, van der Steen R, Hermsen R, Donders ART, Touw DJ, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci.* (2009) 4:359–66. doi: 10.1080/17470910802649470

57. Feduccia A, Duvauchelle C. Auditory stimuli enhance MDMA-conditioned reward and MDMA-induced nucleus accumbens dopamine, serotonin and locomotor responses. *Brain Res Bull.* (2008) 77:189–96. doi: 10.1016/j.brainresbull.2008.07.007

58. de la Torre R, Farré M, Roset P, Pizarro N, Abanades S, Segura M, et al. Human pharmacology of MDMA: pharmacokinetics, metabolism, and disposition. *Ther Drug Monit.* (2004) 26:137–44.

59. Green A, Mechan A, Elliott J, O'Shea E, Colado M. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'). *Pharmacol Rev.* (2003) 55:463–508. doi: 10.1124/pr.55.3.3

60. Thompson MR, Callaghan PD, Hunt GE, Cornish JL, McGregor IS. A role for oxytocin and 5-HT1A receptors in the prosocial effects of 3,4 methylenedioxymethamphetamine ('Ecstasy'). *Neuroscience.* (2007) 146:509–14. doi: 10.1016/j.neuroscience.2007.02.032

61. Nardou R, Lewis E, Rothhaas R, Xu R, Yang A, Boyden E, et al. Oxytocin-dependent reopening of a social reward learning critical period with MDMA. *Nature.* (2019) 569:116–20. doi: 10.1038/s41586-019-1075-9

62. Mithoefer M, Mithoefer A, Feduccia A, Jerome L, Wagner M, Wymer J, et al. 3,4-Methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry.* (2018) 5:486–97. doi: 10.1016/S2215-0366(18)30135-4

63. Blake D, Weathers F, Nagy L, Kaloupek G, Charney D, Keane T. A clinician rating scale for assessing current and lifetime PTSD: the CAPS-1. *Behav Ther.* (1990) 18:75–90. doi: 10.1007/BF02105408

64. Ben-Zion Z, Zeevi Y, Keynan N, Admon R, Kozlovski T, Sharon H, et al. Multi-domain potential biomarkers for post-traumatic stress disorder (PTSD) severity in recent trauma survivors. *Transl Psychiatry.* (2020) 10:208. doi: 10.1038/s41398-020-00898-z

65. Etkin A, Wager T. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry.* (2007) 164:1476–88. doi: 10.1176/appi.ajp.2007.07030504

66. Lanius R, Williamson P, Boksman K, Densmore M, Gupta M. Brain activation during script-driven imagery induced dissociative responses in PTSD: a functional magnetic resonance imaging investigation. *Biol Psychiatry.* (2002) 52:305–11. doi: 10.1016/S0006-3223(02)01367-7

67. Lanius R, Williamson P, Densmore M, Boksman K, Neufeld R, Gati J. The nature of traumatic memories: a 4-T FMRI functional connectivity analysis. *Am J Psychiatry.* (2004) 161:36–44. doi: 10.1176/appi.ajp.161.1.36

68. Mertens Y, Manthey A, Sierk A, Walter H, Daniels J. Neural correlates of acute post-traumatic dissociation: a functional neuroimaging script-driven imagery study. *BJPsych Open.* (2022) 8:e109. doi: 10.1192/bjo.2022.65

69. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage.* (1999) 9:179–94. doi: 10.1006/nimg.1998.0395

70. Smith S, Jenkinson M, Woolrich M, Beckmann C, Behrens T, Johansen-Berg H, et al. Advances in functional and structural mr image analysis and implementation as FSL. *Neuroimage.* (2004) 23(Suppl. 1):S208–19. doi: 10.1016/j.neuroimage.2004.07.051

71. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* (2012) 2:125–41. doi: 10.1089/brain.2012.0073

72. Power J, Barnes K, Snyder A, Schlaggar B, Petersen S. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage.* (2012) 59:2142–54. doi: 10.1016/j.neuroimage.2011.10.018

73. Woolrich M, Behrens T, Beckmann C, Jenkinson M, Smith S. Multilevel linear modelling for FMRI group analysis using bayesian inference. *Neuroimage.* (2004) 21:1732–47. doi: 10.1016/j.neuroimage.2003.12.023

74. Friston K, Williams S, Howard R, Frackowiak R, Turner R. Movement-related effects in FMRI time-series. *Magn Reson Med.* (1996) 35:346–55. doi: 10.1002/mrm.1910350312

75. Winkler A, Ridgway G, Webster M, Smith S, Nichols T. Permutation inference for the general linear model. *Neuroimage.* (2014) 92:381–97. doi: 10.1016/j.neuroimage.2014.01.060

76. Smith S, Nichols T. Threshold-free cluster enhancement: addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage.* (2009) 44:83–98. doi: 10.1016/j.neuroimage.2008.03.061

77. Desikan R, Ségonne F, Fischl B, Quinn B, Dickerson B, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage.* (2006) 31:968–80. doi: 10.1016/j.neuroimage.2006.01.021

78. Iglesias J, Augustinack J, Nguyen K, Player C, Player A, Wright M, et al. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. *Neuroimage.* (2015) 115:117–37. doi: 10.1016/j.neuroimage.2015.04.042

79. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B.* (1995) 57:289–300.

80. Liberzon I, Taylor S, Amdur R, Jung T, Chamberlain K, Minoshima S, et al. Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry.* (1999) 45:817–26. doi: 10.1016/S0006-3223(98)00246-7

81. Bremner J, Vermetten E, Schmahl C, Vaccarino V, Vythilingam M, Afzal N, et al. Positron emission tomographic imaging of neural correlates of a fear acquisition and extinction paradigm in women with childhood sexual-abuse-related post-traumatic stress disorder. *Psychol Med.* (2005) 35:791–806. doi: 10.1017/S0033291704003290

82. Cauda F, Geminiani G, D'Agata F, Sacco K, Duca S, Bagshaw A, et al. Functional connectivity of the posteromedial cortex. *PLoS One.* (2010) 5:e13107. doi: 10.1371/journal.pone.0013107

83. Kalenzaga S, Sperduti M, Anssens A, Martinelli P, Devauchelle A, Gallarda T, et al. Episodic memory and self-reference via semantic autobiographical memory: insights from an FMRI study in younger and older adults. *Front Behav Neurosci.* (2015) 8:449. doi: 10.3389/fnbeh.2014.00449

84. Demblon J, Bahri M, D'Argembeau A. Neural correlates of event clusters in past and future thoughts: how the brain integrates specific episodes with autobiographical knowledge. *Neuroimage.* (2016) 127:257–66. doi: 10.1016/j.neuroimage.2015.11.062

85. Raichle ME. The brain's default mode network. *Annu Rev Neurosci.* (2015) 38:433–47. doi: 10.1146/annurev-neuro-071013-014030

86. Cabeza R, St Jacques P. Functional neuroimaging of autobiographical memory. *Trends Cogn Sci.* (2007) 11:219–27. doi: 10.1016/j.tics.2007.02.005

87. Garrett A, Cohen J, Zack S, Carrion V, Jo B, Blader J, et al. Longitudinal changes in brain function associated with symptom improvement in youth with PTSD. *J Psychiatr Res.* (2019) 114:161–9. doi: 10.1016/j.jpsychires.2019.04.021

88. Ke J, Zhang L, Qi R, Li W, Hou C, Zhong Y, et al. A longitudinal FMRI investigation in acute post-traumatic stress disorder (PTSD). *Acta Radiol.* (2016) 57:1387–95. doi: 10.1177/0284185115585848

89. Bedi G, Phan K, Angstadt M, de Wit H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology.* (2009) 207:73–83. doi: 10.1007/s00213-009-1635-z

90. van Huijstee J, Vermetten E. The dissociative subtype of post-traumatic stress disorder: research update on clinical and neurobiological features. *Curr Top Behav Neurosci.* (2018) 38:229–48. doi: 10.1007/7854_2017_33

91. Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, et al. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. *Am J Psychiatry.* (2001) 158:1920–2. doi: 10.1176/appi.ajp.158.11.1920

92. Helpman L, Zhu X, Zilcha-Mano S, Suarez-Jimenez B, Lazarov A, Rutherford B, et al. Reversed patterns of resting state functional connectivity for females vs. males in posttraumatic stress disorder. *Neurobiol Stress.* (2021) 15:100389. doi: 10.1016/J.YNSTR.2021.100389

93. Chiao J, Iidaka T, Gordon H, Nogawa J, Bar M, Aminoff E, et al. Cultural specificity in amygdala response to fear faces. *J Cogn Neurosci.* (2008) 20:2167–74. doi: 10.1162/jocn.2008.20151

94. Liddell B, Jobson L. The impact of cultural differences in self-representation on the neural substrates of posttraumatic stress disorder. *Eur J Psychotraumatol.* (2016) 7:30464. doi: 10.3402/ejpt.v7.30464

95. Walpola I, Nest T, Roseman L, Erritzoe D, Feilding A, Nutt D, et al. Altered insula connectivity under MDMA. *Neuropsychopharmacology.* (2017) 42:2152–62. doi: 10.1038/npp.2017.35

96. Müller F, Holze F, Dolder P, Ley L, Vizeli P, Soltermann A, et al. MDMA-induced changes in within-network connectivity contradict the specificity of these alterations for the effects of serotonergic hallucinogens. *Neuropsychopharmacology.* (2021) 46:545–53. doi: 10.1038/s41386-020-00906-2

97. Dipasquale O, Selvaggi P, Veronese M, Gabay A, Turkheimer F, Mehta M. Receptor-enriched analysis of functional connectivity by targets (REACT): a novel, multimodal analytical approach informed by pet to study the pharmacodynamic response of the brain under MDMA. *Neuroimage.* (2019) 195:252–60. doi: 10.1016/j.neuroimage.2019.04.007

98. Avram M, Müller F, Rogg H, Korda A, Andreou C, Holze F, et al. Characterizing thalamocortical (Dys)connectivity following D-amphetamine, LSD, and MDMA administration. *Biol Psychiatry.* (2022) 7:885–94. doi: 10.1016/j.bpsc.2022.04.003

99. Lanius RA, Bluhm RL, Coupland NJ, Hegadoren KM, Rowe B, Théberge J, et al. Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. *Acta Psychiatr Scand.* (2010) 121:33–40. doi: 10.1111/j.1600-0447.2009.01391.x

100. Bluhm R, Williamson P, Osuch E, Frewen P, Stevens T, Boksman K, et al. Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. *J Psychiatry Neurosci.* (2009) 34:187–94.

101. Cisler JM, Sigel BA, Steele JS, Smitherman S, Vanderzee K, Pemberton J, et al. Changes in functional connectivity of the amygdala during cognitive reappraisal predict symptom reduction during trauma-focused cognitive-behavioral therapy among adolescent girls with post-traumatic stress disorder. *Psychol Med.* (2016) 46:3013–23. doi: 10.1017/S0033291716001847

102. Shou H, Yang Z, Satterthwaite T, Cook P, Bruce S, Shinohara R, et al. Cognitive behavioral therapy increases amygdala connectivity with the cognitive control network in both MDD and PTSD. *Neuroimage.* (2017) 14:464–70. doi: 10.1016/J.NICL.2017.01.030

103. Veer I, Oei N, Spinhoven P, van Buchem M, Elzinga B, Rombouts S. Beyond acute social stress: increased functional connectivity between amygdala and cortical midline structures. *Neuroimage.* (2011) 57:1534–41. doi: 10.1016/j.neuroimage.2011.05.074

104. Baur V, Hänggi J, Langer N, Jäncke L. Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. *Biol Psychiatry.* (2013) 73:85–92. doi: 10.1016/j.biopsych.2012.06.003

105. Suzuki A, Josselyn S, Frankland P, Masushige S, Silva A, Kida S. Memory reconsolidation and extinction have distinct temporal and biochemical signatures. *J Neurosci.* (2004) 24:4787–95. doi: 10.1523/JNEUROSCI.5491-03.2004

106. Young MB, Andero R, Ressler KJ, Howell LL. 3,4-Methylenedioxymethamphetamine facilitates fear extinction learning. *Transl Psychiatry.* (2015) 5:e634. doi: 10.1038/tp.2015.138

107. Hake H, Davis J, Wood R, Tanner M, Loetz E, Sanchez A, et al. 3,4-Methylenedioxymethamphetamine (MDMA) impairs the extinction and reconsolidation of fear memory in rats. *Physiol Behav.* (2019) 199:343–50. doi: 10.1016/j.physbeh.2018.12.007

108. Arluk S, Matar M, Carmi L, Arbel O, Zohar J, Todder D, et al. MDMA treatment paired with a trauma-cue promotes adaptive stress responses in a translational model of PTSD in rats. *Transl Psychiatry.* (2022) 12:181. doi: 10.1038/s41398-022-01952-8

109. Ridderbusch I, Wroblewski A, Yang Y, Richter J, Hollandt M, Hamm A, et al. Neural adaptation of cingulate and insular activity during delayed fear extinction: a replicable pattern across assessment sites and repeated measurements. *Neuroimage.* (2021) 237:118157. doi: 10.1016/j.neuroimage.2021.118157

110. Patel R, Spreng R, Shin L, Girard T. Neurocircuitry models of posttraumatic stress disorder and beyond: a meta-analysis of functional neuroimaging studies. *Neurosci Biobehav Rev.* (2012) 36:2130–42. doi: 10.1016/j.neubiorev.2012.06.003

111. Kleim B, Wallott F, Ehlers A. Are trauma memories disjointed from other autobiographical memories in posttraumatic stress disorder? An experimental investigation. *Behav Cogn Psychother.* (2008) 36:221–34. doi: 10.1017/S1352465807004080

112. Morris JS, Öhman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. *Nature.* (1998) 393:467–70. doi: 10.1038/30976

113. Birn R, Molloy E, Patriat R, Parker T, Meier T, Kirk G, et al. The effect of scan length on the reliability of resting-state FMRI connectivity estimates. *Neuroimage.* (2013) 83:550–8. doi: 10.1016/j.neuroimage.2013.05.099

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EDITED BY
Peter Schuyler Hendricks,
University of Alabama at Birmingham,
United States

REVIEWED BY
Gilles Maussion,
Montreal Neurological Institute, Canada
Shareefa Dalvie,
South African Medical Research Council,
South Africa

*CORRESPONDENCE
Candace R. Lewis
✉ candace.lewis@asu.edu
Baruch Rael Cahn
✉ rael.cahn@usc.edu

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# Pilot study suggests DNA methylation of the glucocorticoid receptor gene (NR3C1) is associated with MDMA-assisted therapy treatment response for severe PTSD

Candace R. Lewis[1,2]*, Joseph Tafur[3], Sophie Spencer[1], Joseph M. Green[1], Charlotte Harrison[4], Benjamin Kelmendi[5], David M. Rabin[6], Rachel Yehuda[7,8], Berra Yazar-Klosinski[4] and Baruch Rael Cahn[9,10]*

[1]School of Life Sciences, Arizona State University, Tempe, AZ, United States, [2]Neurogenomics Division, Translational Genomics Research Institute (TGen), Phoenix, AZ, United States, [3]Modern Spirit, Phoenix, AZ, United States, [4]MAPS Public Benefit Corporation, San Jose, CA, United States, [5]Department of Psychiatry, School of Medicine, Yale University, New Haven, CT, United States, [6]The Board of Medicine, Pittsburgh, PA, United States, [7]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, United States, [8]Department of Psychiatry, James J. Peters VA Medical Center, Bronx, NY, United States, [9]Department of Psychiatry and Behavioral Sciences, University of Southern California, Los Angeles, CA, United States, [10]Brain and Creativity Institute, University of Southern California, Los Angeles, CA, United States

**Background:** Previous research has demonstrated that epigenetic changes in specific hypothalamic-pituitary-adrenal (HPA) genes may predict successful psychotherapy in post-traumatic stress disorder (PTSD). A recent Phase 3 clinical trial reported high efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for treating patients with severe PTSD compared to a therapy with placebo group (NCT03537014). This raises important questions regarding potential mechanisms of MDMA-assisted therapy. In the present study, we examined epigenetic changes in three key HPA axis genes before and after MDMA and placebo with therapy. As a pilot sub-study to the parent clinical trial, we assessed potential HPA epigenetic predictors for treatment response with genomic DNA derived from saliva (MDMA, $n$ = 16; placebo, $n$ = 7). Methylation levels at all 259 CpG sites annotated to three HPA genes (*CRHR1*, *FKBP5*, and *NR3C1*) were assessed in relation to treatment response as measured by the Clinician-Administered PTSD Scale (CAPS-5; Total Severity Score). Second, group (MDMA vs. placebo) differences in methylation change were assessed for sites that predicted treatment response.

**Results:** Methylation change across groups significantly predicted symptom reduction on 37 of 259 CpG sites tested, with two sites surviving false discovery rate (FDR) correction. Further, the MDMA-treatment group showed more methylation change compared to placebo on one site of the *NR3C1* gene.

**Conclusion:** The findings of this study suggest that therapy-related PTSD symptom improvements may be related to DNA methylation changes in HPA genes and

such changes may be greater in those receiving MDMA-assisted therapy. These findings can be used to generate hypothesis driven analyses for future studies with larger cohorts.

KEYWORDS

PTSD, MDMA, MDMA-assisted therapy, HPA, *NR3C1*, glucocorticoid receptor, epigenetics, DNA methylation

## Background

Recent investigations demonstrate significant benefits of MDMA (3,4-methylenedioxymethamphetamine)- vs. placebo with therapy in the treatment of PTSD. A pooled analysis of six Phase 2 trials demonstrated that 54.2% of persons treated with MDMA-assisted therapy no longer met criteria for PTSD at study end compared to 22.6% in the control group, and gains continued to be sustained over time (1, 2). These results were recapitulated in a more recent randomized, double-blind, placebo-controlled Phase 3 study (3). The placebo with therapy also resulted in a rather high rate of PTSD loss of diagnosis, though far less substantial than that observed in the MDMA-assisted therapy arm; 67% of MDMA participants no longer met criteria for PTSD at study end compared to 32% in the placebo group. These findings raise important questions about the biological changes that occur in association with treatment response after MDMA-assisted therapy. To date, however, there have not been molecular studies examining predictors of successful MDMA-assisted therapy for PTSD.

Epigenetic mechanisms, such as DNA methylation, particularly of certain hypothalamic-pituitary-adrenal (HPA) axis-related genes, have been implicated in mediating adaptations to life conditions and may potentially serve as molecular markers of brain-body health (4–9). Importantly, alterations of the HPA axis were one of the earliest findings in PTSD (10) and have been repeatedly replicated. There is now ample support for the idea that epigenetic alterations underlie neuroendocrine abnormalities in PTSD and may be implicated in conferring risk for PTSD following trauma exposure (11–13). Epigenetic marks on HPA axis genes have been associated with the prediction and successful outcome of psychotherapy in PTSD (14–17). These and other genes were recently confirmed in a second study examining epigenome-wide correlates of successful psychotherapy in PTSD (18). As such, epigenetic alterations on HPA axis genes may be markers, or even predictors, of successful psychotherapy in PTSD. Taken together, HPA axis gene methylation appears to be a promising epigenetic mechanism for treatment response in PTSD, motivating the current study focus.

Using a sub-sample from the recent Phase 3 clinical trial, we conducted a pilot study investigating the methylation of three key PTSD-relevant HPA genes in association with MDMA-assisted therapy treatment response (3); *NR3C1, FKBP5,* and *CRHR1*. The gene *NR3C1* encodes for a glucocorticoid receptor (GR) which plays a role in the HPA negative feedback loop. The *FKBP5* gene encodes a molecular co-chaperone that interacts with cortisol-GR complexes to regulate its downstream transcription-factor activity. The *CRHR1* gene encodes corticotropin-releasing hormone (CRH) receptor 1, which is one of two receptors in this gene family. These genes were chosen based on prior studies demonstrating a change in DNA methylation associating with treatment response in PTSD (14, 15, 17). We hypothesized that (1) symptomatic reduction of PTSD after placebo and MDMA-assisted therapy would be predicted by changes in DNA methylation on *NR3C1, FKBP5*, and *CRHR1*; and (2) MDMA-assisted therapy group would exhibit more methylation change compared to placebo, related to the additional efficacy conferred by MDMA relative to placebo conditions.

Abbreviations: HPA, hypothalamic-pituitary-adrenal; PTSD, post-traumatic stress disorder; MDMA, 3,4-methylenedioxymethamphetamine.

## Materials and methods

### Participants

Participants represent a subsample of patients with severe PTSD from a Phase 3 clinical trial (NCT03537014; $N$ = 90 treated) who consented to be in the epigenetic sub-study ($N$ = 33; MDMA $n$ = 16; placebo $n$ = 7) (3). For the parent clinical trial, participants were recruited at 15 study sites through print and internet advertisements, referrals from treatment providers, and by word of mouth. Of the 11 sites located in the USA, seven participated in recruiting for the epigenetic study.

Following an initial phone screening for the clinical trial, participants provided written informed consent and underwent further screening assessments for eligibility in the clinical trial. Eligible participants were enrolled in the trial and began psychiatric medication taper if needed, lasting from 0 days (no taper needed) to 103 days. Only participants who enrolled in the study and met criteria for severe PTSD after the taper period and preparatory therapy were offered the opportunity to proceed with the clinical trial and enroll in the present epigenetics sub-study. A total of $N$ = 33 participants in the parent clinical trial consented to participate in this epigenetics sub-study; however 10 of the 33 did not provide post-treatment salivary samples due to COVID-19 related interruptions to the study, leaving a total of $N$ = 23 (MDMA, $n$ = 16; Placebo, $n$ = 7) participants with both pre- and post-salivary samples for our analysis.

This study was conducted in accordance with the principles of the Declaration of Helsinki–for full information on the larger study, see here (3). Ethics approval for this epigenetics sub-study was obtained from University of Southern California Institutional Review Board.

## Intervention procedures

For full information on the intervention in the parent clinical trial, see Mitchell et al. (3).

Participants were randomized and allocated 1:1 to either the MDMA-assisted therapy group or the placebo with therapy group. Randomization was stratified by site and occurred following enrollment confirmation. The treatment period consisted of three 8-h experimental sessions of either MDMA-assisted therapy or therapy with inactive placebo control, spaced ∼4 weeks apart. In each experimental session the participants received a single divided dose of 80–180 mg MDMA or placebo. Each experimental session was followed by three 90-min integration sessions that were spaced ∼1 week apart to allow the participant to understand and incorporate their experience. The first integration session always occurred on the morning after the experimental session, and the remaining two integration sessions occurred over the following 3–4 weeks.

A blinded and centralized independent rater pool was used to conduct DSM-5 (The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) diagnostic assessments at screening and to administer the primary outcome measure [i.e., Clinician-Administered PTSD Scale (CAPS-5) for DSM-5]. The independent rater measurements were conducted at baseline and ∼3 weeks after each of the first two experimental sessions *via* video interviews. The primary outcome assessment for the clinical trial was the final CAPS-5 conducted ∼8 weeks after the third experimental session (∼18 weeks after the baseline assessment). Saliva samples were collected from participants on days corresponding with the baseline and outcome CAPS-5 assessments to determine epigenetic changes associated with the clinical intervention and primary outcome of PTSD symptoms as measured by CAPS-5.

## DNA methylation

Saliva samples were collected with Oragene-DNA saliva kits (Ottawa, Ontario, Canada) from 33 participants during the baseline visit. Due to COVID-19 related interruptions to the study, 10 participants were unable to provide follow up samples at the final visit, providing a total of 23 participants with both baseline and final saliva samples (MDMA, $n$ = 16; Placebo, $n$ = 7). DNA was extracted with a DNA Genotek isolation kit (PT-L2P; Ottawa, Ontario, Canada). Sample yield and purity were assessed spectrophotometrically using a NanoDrop ND-1000 (Thermo Scientific, Wilmington, DE, United States). Approximately 500 ng of DNA was treated with sodium bisulfite using the EZ-96 DNA Methylation Kit (Zymo Research, Irvine, CA, United States). DNA methylation was quantified using the Infinium MethylationEPIC BeadChip (IlluminaEPICarray) run on an Illumina iScanSystem (Illumina, San Diego, CA, United States). Raw Intensity Data (IDAT) files were exported for preprocessing in R with the minfi package (19). A filter was applied to remove probes located on the sex chromosomes. Data was subjected to quality control analyses, which included quantile normalization, checking for sex mismatches, and excluding low-intensity samples ($p < 0.01$). All samples passed quality control. Using the minfi package, data were normalized and annotated with Illumina CpG site probe names. Using the R package EpiDISH (Epigenetic Dissection of Intra-Sample Heterogeneity, 3.8) Robust Partial Correlation (RPC) method, the proportion of estimated epithelial cells was used as a covariate in our statistical models. M-values were used for methylation analysis as has been recommended, especially for the homoscedasticity (20).

## Statistical analyses

To ensure generalizability of the results, the epigenetics subsample and the parent clinical trial sample were compared on demographic variables and CAPS-5 baseline and outcome scores. Variables were tested for normality using the Shapiro–Wilk's method. A Student's $t$-test was used for normally distributed variables, a non-parametric Kruskal–Wallis rank sum test for non-normally distributed variables, and a $\chi 2$ test for categorical variables. The same procedures were used to compare the MDMA and placebo groups in the sample.

All sites annotated to the genes of interest on the Illumina Infinium MethylationEPIC BeadChip were analyzed. For all sites of interest, a Student's $t$-test was used to compare baseline DNA methylation levels between placebo and MDMA groups. All sites significantly different in DNA methylation between groups pre-treatment were removed from further analyses. Multivariate linear regression modeling was conducted to assess if changes in DNA methylation predicted treatment response across groups (hypothesis 1). CpG change scores were used as an independent variable with CAPS-5 change score (final–baseline) as the dependent variable with sex, age, and proportion of estimated epithelial cells as covariates. Because prior associations between methylation of CpG sites on HPA genes with trauma have mixed directions (either hypermethylation, hypomethylation, mixed findings, or differential effects with no direction specified) [see Figure 4 in Watkeys et al. (21)], we allowed for either an increase or decrease in methylation to predict treatment response by calculating absolute value (abs$\Delta$) methylation changes scores to test in the same regression models. Because this is a small pilot study, we report both non-corrected and false-discovery rate (FDR < 0.1) corrected results (22–24).

Lastly, to determine if there was a group difference in methylation change, we tested if sites that significantly predicted treatment response across groups (FDR corrected) demonstrated significant group differences in methylation change (hypothesis 2). We compared MDMA and placebo groups on methylation change score with analysis of covariance (ANCOVA) models while controlling for sex, age, and proportion of estimated epithelial cells. Analyses were performed using various packages in R (25).

A note on nomenclature relevant to the following description of CpG genomic locations: CpG sites are often assessed in the CpG-rich islands in and around promotor regions of genes, and the methylation of these CpG sites are generally associated with gene silencing (26). If a CpG site occurs at a distance situated within 2 kb from an island, the location is referred to "north shore" or upstream and "south shore" or downstream from the island; if it occurs at a location within 2–4 kb then it is referred to as "north shelf" or "south shelf" and any CpG site located further than 4 kb from an island are referred to as "open sea" (27). This study assessed all sites annotated to the candidate genes on the Infinium MethylationEPIC BeadChip (IlluminaEPICarray). Beta- and M-values for all three analyzed genes can be found in **Supplementary Data Sheets**.

TABLE 1A Full clinical study compared to sub-study.

| | Full M (SD)/% | Sub. M (SD)/% | Test-value | df | *p*-value | Test performed |
|---|---|---|---|---|---|---|
| Age (years) | 41.0 (11.9) | 42.05 (12.87) | 0.18 | 1 | 0.66 | Kruskal |
| Sex (female) | 65.60% | 61% | 0.19 | 1 | 0.66 | Chi Square |
| Baseline CAPS-5 | 44.1 (6.04) | 45.16 (6.54) | 2.09 | 1 | 0.15 | Kruskal |
| Final CAPS-5 | 25.82 (13.7) | 23.32 (14.6) | 0.77 | 62.24 | 0.44 | *t*-test |

TABLE 1B Sub-study sample 3,4-methylenedioxymethamphetamine (MDMA) compared to placebo.

| | MDMA M (SD)/% | Placebo M (SD)/% | Test-value | df | *p*-value | Test performed |
|---|---|---|---|---|---|---|
| Age (years) | 43.4 (13.25) | 39.95 (11.91) | 0.95 | 26.98 | 0.35 | *t*-test |
| Sex (female) | 44% | 71% | 3.58 | 1 | 0.05 | Chi Square |
| Baseline CAPS-5 | 44.2 (6.16) | 46.6 (7.03) | −0.97 | 23.81 | 0.34 | *t*-test |
| Final CAPS-5 | 17.94 (14.28) | 30.77 (11.02) | −2.82 | 28.83 | 0.008 | *t*-test |

# Results

## Epigenetics sub-study participants

The sub-study sample did not differ from the clinical trial sample in age, sex, baseline CAPS-5, or outcome CAPS-5 scores (Table 1A; all $p$'s $> 0.05$). Within the sub-study sample, treatment groups (MDMA vs. placebo) did not significantly differ on age or baseline CAPS-5 score but did differ on sex (Table 1B). Sex is used as a covariate in later analyses to account for any bias due to the different group sex compositions. As expected, treatment groups significantly differed on final CAPS-5 score in favor of MDMA conferring more benefit than placebo (Figure 1). A comparison of DNA methylation levels measured from salivary DNA in this study and publicly available methylation level measured from brain can be found in Supplementary Tables 1–3.

## Relationship between salivary DNA methylation and brain DNA methylation

Beta values (which represent percent methylation at each CpG site) can be visualized for all CpG sites that significantly predicted treatment response (Supplementary Figures 1–3). Correlation between beta values generated from saliva in this study and publicly available beta values generated from brain were compared. *NR3C1* ($r = 0.73$, $p = < 0.00001$), *CRHR1* ($r = 0.88$, $p = < 0.00001$), and *FKBP5* ($r = 0.83$, $p = < 0.00001$) sites all show strong and significant correlations between saliva and brain samples (Supplementary Tables 1–3). Brain DNA methylation values were obtained from the Allen Brain Atlas BrainSpan data.[1]

## Baseline methylation differences between treatment groups

Five *CRHR1* sites, two *FKBP5* sites, and three *NR3C1* sites were significantly different between MDMA and placebo group at baseline thus were removed from further analyses ($p$'s $< 0.05$).

1 http://download.alleninstitute.org/brainspan/Methylation/

## Methylation predicting treatment response across groups

### CRHR1

Methylation change on 20.9% (17 of 81 sites; 7 Δ; 10 absΔ) of sites annotated to *CRHR1* predicted change in CAPS-5 score ($p$'s $< 0.05$; Table 2). Ten of these sites resided in open sea regions, two on south shore regions, two on north shore regions, two on an island, and one on a south shelf. The site with the largest Δ effect size survived FDR correction (open sea: cg08276280; $B = 42.12$, $p = 0.005$–pre-FDR correction) and is depicted in Figures 2A, B.

### FKBP5

Methylation change on 15.8% (9 of 57 sites; 8 Δ; 1 absΔ) of sites annotated to *FKBP5* predicted change in CAPS-5 score [$p$'s $< 0.05$; Table 2]. Seven of these sites resided in open sea regions and two on an island. No sites from this gene survived FDR correction and the site with the largest Δ effect size for this gene (island site: cg16012111; $B = 32.52$, $p = 0.012$) is depicted in Figures 2A, B.

### NR3C1

Methylation change on 10% (11 of 111 sites; 4 Δ; 6 absΔ; 1 Δ and absΔ) of sites annotated to *NR3C1* predicted change in CAPS-5 score ($p$'s $\leq 0.05$; Table 2). Nine of these sites resided in open sea regions, one on north shore regions, one on an island, and one on a north shelf. One site (absΔ; open sea; cg01391283; Figure 3) from this gene survived FDR correction. The site with the largest Δ effect size (open sea: cg6222722; $B = 19.32$, $p = 0.003$) is depicted in Figures 2A, B.

## Group difference in methylation change after treatment

Of the two sites that predicted treatment response across groups after FDR correction (*CRHR1* Δ cg08276280 and *NR3C1* absΔ cg01391283), one site also had a significant difference in methylation change between the MDMA and placebo groups [*NR3C1;* open sea; cg01391283 absΔ; $F(1, 18) = 4.78$, $p = 0.042$]. A figure depicting the absolute change score plotted from pre- to post-treatment can be found in Figure 3.

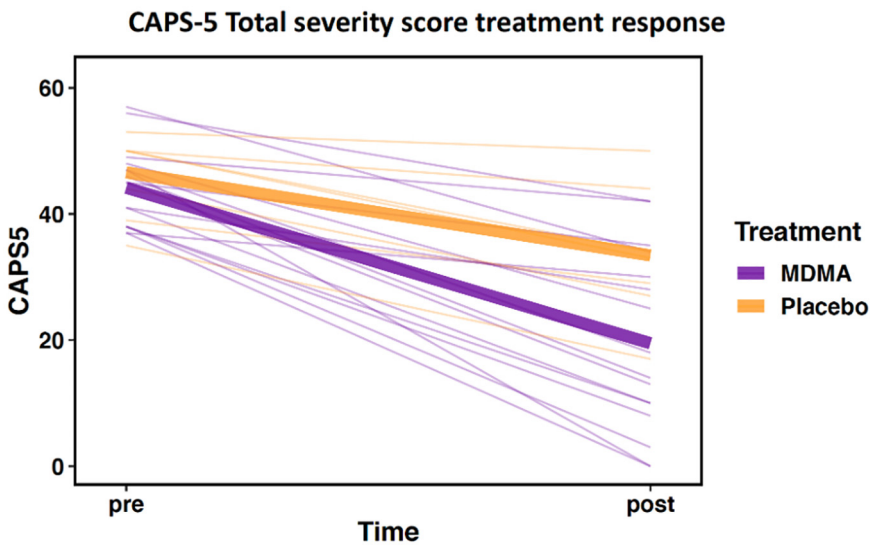


FIGURE 1
Change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total severity score from pre- to post-treatment. Data demonstrate differential treatment response between 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy compared to therapy alone (data represent the subset of the clinical trial included in this study; MDMA, $n$ = 16; placebo, $n$ = 7). Thick lines represent group means, thin lines represent individual scores.

## Discussion

This is the first study to examine DNA methylation relationships with treatment response to MDMA-assisted therapy in patients with severe PTSD. Due to being a small pilot study, we report both non-corrected significant results and FDR-corrected results. Before FDR correction, seventeen *CRHR1*, nine *FKBP5*, and eleven *NR3C1* CpG sites predicted treatment response across groups. After FDR correction, one *CRHR1* (cg08276280) CpG site and one *NR3C1* (cg01391283) CpG remained significant. The results reinforce previous research that symptom reduction after PTSD treatment correlates with DNA methylation changes on the *CRHR1* and *NR3C1* genes (14, 17). Of the two sites that predicted treatment response across groups after FDR correction, *NR3C1* cg01391283 had a significantly larger change in methylation in the MDMA group compared to placebo.

Genes of the HPA axis have been extensively studied in the context of epigenetic response to trauma (8). The most commonly-studied epigenetic candidate gene in the HPA axis is the glucocorticoid receptor gene (nuclear receptor subfamily 3 group C member 1; *NR3C1*) (21). Glucocorticoid binding at this receptor regulates the stress response through a negative feedback loop (28). Much research to date demonstrates that childhood trauma and early stress alter the methylation status of this gene and its expression [for reviews see Watkeys et al. (21), Jiang et al. (29), and Palma-Gudiel et al. (30)]. While the majority of results find early life stress leads to an increase in methylation and a decrease of expression of *NR3C1*, opposing directional findings are reported (21). In addition to trauma-related methylation changes, two seminal papers found *NR3C1* CpG methylation was associated with PTSD symptoms and many have replicated these findings (12, 31, 32). Taking into consideration the dynamic nature of epigenetic marks and their malleability in response to psycho-social experiences, recent research has focused on potential epigenetic changes in response to psychotherapy for stress-related disorders [for review see here (33)]. Our results add to this growing field, suggesting epigenetic change on the *NR3C1* gene may relate to treatment response to MDMA-assisted therapy. Further, this pilot study was intended to inform hypothesis development, these results suggest specific sites to examine on three HPA genes in future studies with a larger sample size.

The *NR3C1* gene consists of nine non-coding first exons and seven of these are located within a CpG island spanning 3 kb along the proximal promoter region of the *NR3C1* gene (30). The majority of studies assessing *NR3C1* methylation in relation to stress, psychopathology, and treatment response have focused on differential methylation primarily in this CpG island. This work has shaped general discussions about the function of experience-dependent DNA methylation changes. There has been much discussion over the notion of epigenetic modifications turning gene regulation "up or down" or "on or off" since methylation in the immediate vicinity of the transcriptional start site inhibits the initiation of transcription. CpG sites with differential methylation are located all along the *NR3C1* gene sequence and the position of methylation across the gene influences its functionality. For example, methylation in the gene body does not block and might even stimulate transcription elongation or have an impact on splicing (34, 35). While the functional implications of upstream methylation is less understood, some data suggests it may increase expression (36). Indeed, others have found methylation of the *NR3C1* promoter region regulates transcript expression and levels (37–39). In this study, the two sites that predicted change in PTSD symptoms are both in open sea regions. To date, little is known about the functional consequences of DNA methylation in open sea positions. Therefore, it is difficult to speculate on the potential downstream effects of open sea DNA methylation changes on the HPA system.

While the majority of research to date has found increased *NR3C1* promotor methylation associated with trauma, the results are not always consistent. A 2018 systematic review summarized results across studies and effectively visualized how CpG sites in the

TABLE 2 Change in methylation predicting change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5).

| Gene (sites tested) | Relation to Island | Genomic location | Change type (post−pre) | Sig. sites ($p < 0.05$) | *B* | Survive FDR |
|---|---|---|---|---|---|---|
| *CRHR1* (86) | | | | | | |
| cg08276280 | os | chr17:43743868 | Δ | 0.005 | 42.12 | Yes |
| cg07657976 | os | chr17:43887205 | Δ | 0.006 | 14.64 | ~ |
| cg13947929 | ssr | chr17:43863356 | Δ | 0.016 | 31.72 | ~ |
| cg03423935 | nsr | chr17:43697902 | Δ | 0.026 | 21.71 | ~ |
| cg18090064 | os | chr17:43716542 | Δ | 0.036 | 12.93 | ~ |
| cg08119837 | os | chr17:43837500 | Δ | 0.038 | 11.87 | ~ |
| cg24394631 | ssr | chr17:43863000 | Δ | 0.046 | −21.22 | ~ |
| cg23420656 | ssf | chr17:43865031 | absΔ | 0.008 | 29.90 | ~ |
| cg14297797 | os | chr17:43867801 | absΔ | 0.011 | −17.73 | ~ |
| cg22046703 | nsr | chr17:43860472 | absΔ | 0.011 | 73.01 | ~ |
| cg13521908 | is | chr17:43861682 | absΔ | 0.012 | −22.14 | ~ |
| cg06537391 | os | chr17:43799898 | absΔ | 0.014 | 38.30 | ~ |
| cg05087823 | os | chr17:43835721 | absΔ | 0.021 | 50.67 | ~ |
| cg10106856 | os | chr17:43880210 | absΔ | 0.024 | 27.08 | ~ |
| cg04194664 | os | chr17:43716617 | absΔ | 0.028 | −15.52 | ~ |
| cg15117716 | os | chr17:43871537 | absΔ | 0.038 | −15.71 | ~ |
| cg12577105 | is | chr17:43860685 | absΔ | 0.042 | 19.27 | ~ |
| *FKBP5* (59) | | | | | | ~ |
| cg16012111 | is | chr6:35656758 | Δ | 0.012 | 32.52 | ~ |
| cg07485685 | is | chr6:35696061 | Δ | 0.024 | 16.92 | ~ |
| cg14339974 | os | chr6:35687310 | Δ | 0.026 | −7.23 | ~ |
| cg04791658 | os | chr6:35611554 | Δ | 0.035 | −31.09 | ~ |
| cg07633853 | os | chr6:35569471 | Δ | 0.036 | 12.64 | ~ |
| cg06409316 | os | chr6:35642470 | Δ | 0.039 | 9.03 | ~ |
| cg09318204 | os | chr6:35511434 | Δ | 0.043 | 20.58 | ~ |
| cg08586216 | os | chr6:35612351 | Δ | 0.049 | 14.08 | ~ |
| cg16005389 | os | chr6:35592694 | absΔ | 0.010 | 23.15 | ~ |
| *NR3C1* (114) | | | | | | ~ |
| cg26222722 | os | chr5:142825390 | Δ | 0.003 | 19.32 | ~ |
| cg07733851 | nsr | chr5:142781498 | Δ | 0.023 | 18.93 | ~ |
| cg14621978 | os | chr5:142735238 | Δ | 0.027 | 11.86 | ~ |
| cg08423118 | os | chr5:142808610 | Δ | 0.034 | −15.39 | ~ |
| cg01751279 | os | chr5:142793924 | Δ | 0.052 | 8.33 | ~ |
| **cg01391283** | **os** | **chr5:142907714** | **absΔ** | **0.002** | **41.88** | **Yes** |
| cg03746860 | os | chr5:142759375 | absΔ | 0.009 | 26.42 | ~ |
| cg06770322 | os | chr5:142851098 | absΔ | 0.013 | −25.25 | ~ |
| cg06613263 | nsf | chr5:142779552 | absΔ | 0.031 | −25.46 | ~ |
| cg11022710 | os | chr5:142820479 | absΔ | 0.036 | 37.00 | ~ |
| cg11152298 | is | chr5:142783383 | absΔ | 0.047 | −49.83 | ~ |
| cg01751279 | os | chr5:142793924 | absΔ | 0.047 | 9.54 | ~ |

os = open sea; is = island; nsr = north shore; ssr = south shore; nsf = north shelf; ssf = south shelf; bold font indicates significantly more methylation change in the MDMA group compared to placebo. A positive direction indicates patients who decrease in symptoms also decrease in methylation; a negative direction indicates patients who decrease in symptoms increase in methylation.

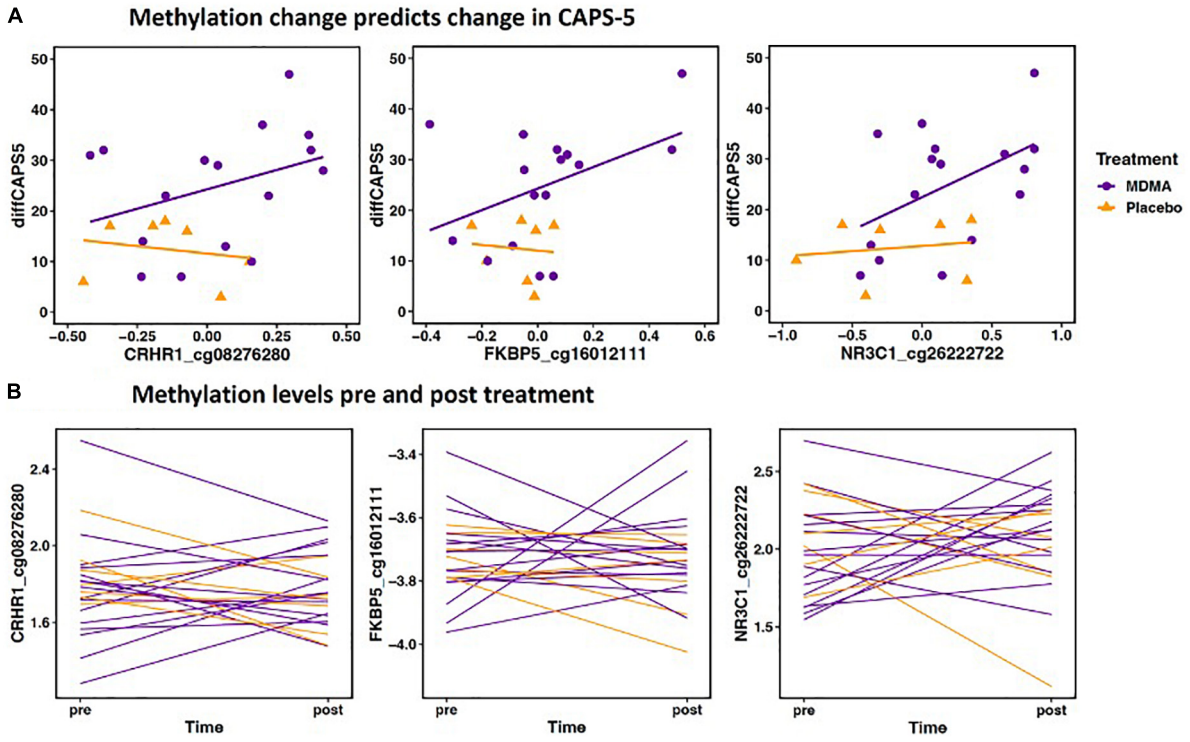


FIGURE 2
**(A)** Methylation change predicts change in Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). The scatterplot depicts the three Δ change scores with the largest effect size from *CRHR1*, *FKBP5*, and *NR3C1* (x axis) plotted with change scores in PTSD symptoms (CAPS-d). All three sites have a significant positive relationship, meaning decreased methylation is associated with decreased PTSD symptoms. The x axis change scores were calculated as post−treatment mVals−pre-treatment M-vals (positive values represent an increase in methylation). The y axis change scores were calculated as baseline−outcome (positive values represent a decrease in symptom severity). *CRHR1* cg08276280 $B = 42.12$, $p = 0.005$; FKBP5 cg16012111 $B = 32.52$, $p = 0.012$; NR3C1 cg26222722 $B = 19.32$, $p = 0.003$. **(B)** Methylation levels from pre and post treatment (mVals). Figures highlight individual variation in methylation change across groups for the same three sites depicted above. M-values are plotted on the Y- axis; positive M-values represent more molecules are methylated than unmethylated, while negative M-values mean the opposite (20).

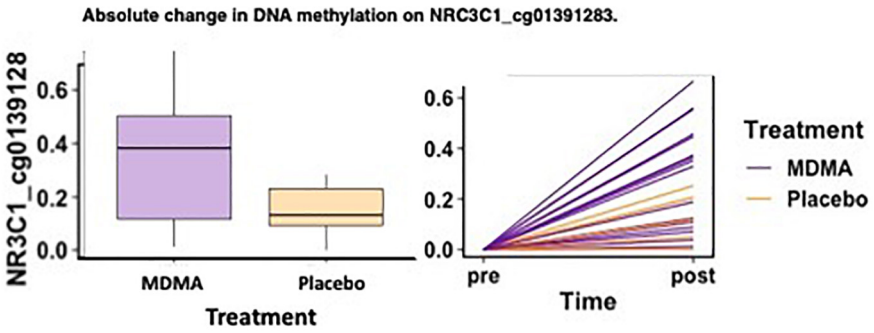


FIGURE 3
MDMA-assisted therapy group had more absolute change in methylation on NRC3C1_cg01391283 compared to the placebo group. Change in DNA methylation (absΔ) at NRC3C1_cg01391283 from pre-treatment to post-treatment [$F(1, 18) = 4.78$, $p = 0.042$].

1F region of *NR3C1* have been associated with hypermethylation, hypomethylation, non-significant findings, mixed findings, or differential effects with no direction specified, in association with both depression and childhood trauma (21). This suggests that trauma may dysregulate the HPA axis through differing routes, i.e., increase or decrease in methylation at various CpG sites, and that both hyper- and hypo-methylation can be maladaptive (30). Therefore, it stands to reason that psychotherapeutic effects mediating treatment response may occur in opposite directions depending on the individual, gene, and CpG site. For this reason, we chose to not only assess raw difference scores as treatment predictors, but also absolute difference scores which allow for a change in either direction. This novel analytic approach highlighted interesting findings such that the CpG methylation absolute difference score was more sensitive at predicting treatment response than the raw difference scores for *NR3C1* and *CRHR1*. Taken together, these results suggest that both trauma-induced dysregulation and psychotherapy-induced changes of the epigenome may entail either hyper- or hypo-methylation dependent on the individual.

MDMA induces a physiological response similar to an activated stress response, such as increased heart rate, blood pressure, oral temperature, and cortisol levels (40). MDMA and acute stress also increase levels of serotonin, dopamine, and norepinephrine (41–44). While the mechanisms behind acute stress induced changes in DNA methylation are not known, it is plausible that the increased monoamine and cortisol exposure induced by psychological stress may be involved in inducing a transient state of *epigenetic-malleability* (45, 46). Especially taken into consideration that the cortisol-bound glucocorticoid receptor directly up- and downregulates thousands of genes as a transcription factor and other mechanisms (47). Further, the glucocorticoid receptor may directly influence DNA methylation through decreasing activity of a transcription factor, p53, known to regulate DNA methyltransferase (DNMT) (48, 49). However, MDMA-induced psychological effects are quite opposite to an acute stressor or traumatic experience. MDMA produces unique subjective properties such as reduced anxiety, acute positive affect, increased insight, accelerated thinking and euphoria, and increased sense of trust and bonding (50–52). Taken together, MDMA may induce a transient *epigenetic-malleable* state similarly to that of stress but a psychological state highly conducive to successful psychotherapy. Therefore, MDMA-assisted therapy may serve as an "inverse trauma experience," such that acute stress and MDMA produce similar physiological states and a highly salient psychological experience. However, trauma has the potential to alter epigenetics underlying symptom formation, whereas MDMA-assisted therapy has the potential to alter epigenetics underlying symptom reduction.

While this study highlights potential biological mechanisms underlying MDMA-assisted therapy for PTSD, there are limitations to address. This initial pilot study was small, intended to assess preliminary evidence to support a larger future investigation. As such, additional studies with more power should be conducted to validate these results, however, these results provide specific loci to be studied in the future which may negate the need for *p*-value correction. The small sample size also necessitated the use of a candidate gene approach; while this study focuses on HPA axis genes, there are other potentially informative genes not assessed here [e.g., immune/inflammatory genes such as IL-12 and IFN-γ, for example see Morrison et al. (53)]. However, our results corroborate a large body of literature associating HPA gene methylation and stress-related disorders. While we accounted for participant age, sex, and cell count in our analyses, we were not powered to control for other factors such as race, smoking, ancestry, or trauma histories. Of note, the Infinium EPIC array probes we utilized do not fully incorporate all CpG sites that have been investigated previously. For example, previous studies have focused on the promoter region in intron seven of the *FKBP5* gene, demonstrating epigenetic changes correlating with trauma exposure and PTSD symptomatology (14, 15, 54). However, these sites were not included in the EPIC array so we cannot ascertain if methylation changes in this region were related to MDMA-assisted therapy efficacy. Finally, it is important to note the limitations of using peripheral samples, which cannot elucidate associations in relevant brain tissue.

More than ever, it has become clear that epigenetic changes in response to trauma or stress co-occur with behavioral and physiological symptoms associated with stress-related disorders. Here, we add to a growing number of studies demonstrating that psychotherapeutic experiences may also lead to alterations in the epigenetic landscape underlying symptom improvement. With the small pilot study sample size, it is difficult to determine if the greater efficacy of MDMA-assisted therapy compared to placebo therapy, is driven by greater changes in epigenetic regulation of HPA genes. However, these findings do suggest potential epigenetic mechanisms of MDMA-assisted therapy and their role in symptom reduction is worthy of continued investigation.

## Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving human participants were reviewed and approved by the University of Southern California Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

BC, JT, DR, BK, CL, RY, and BY-K conceived and planned the experiments. BC organized the data acquisition and IRB approval in collaboration with CH, BY-K, and other MAPS Study Site personnel. BC and CH created the study protocol, instruction manual, trained sites on this sub-study. CL carried out DNA sample preparations, methylation microarrays, conducted all data analyses, and wrote the manuscript. CL and SS processed DNA methylation data. CL and JG created tables and figures. CL, BC, JT, RY, and BY-K contributed to the interpretation of the results. All authors contributed to manuscript revision, read and approved the submitted version.

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## Conflict of interest

BY-K and CH received payment for full-time employment from the MAPS or the MAPS Public Benefit Corporation throughout their work on the parent trial. JT is the Executive Director of Modern Spirit, the non-profit organization that funded this study. BC is on the Board of Directors for Modern Spirit.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.959590/full#supplementary-material

## References


1. Mithoefer M, Feduccia A, Jerome L, Mithoefer A, Wagner M, Walsh Z, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology.* (2019) 236:2735–45. doi: 10.1007/s00213-019-05249-5

2. Jerome L, Feduccia A, Wang J, Hamilton S, Yazar-Klosinski B, Emerson A, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology.* (2020) 237:2485–97. doi: 10.1007/s00213-020-05548-2

3. Mitchell J, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

4. McEwen B. Epigenetic interactions and the brain-body communication. *Psychother Psychosom.* (2017) 86:1–4. doi: 10.1159/000449150

5. Vaiserman A. Epigenetic programming by early-life stress: evidence from human populations. *Dev Dyn.* (2015) 244:254–65. doi: 10.1002/dvdy.24211

6. Matosin N, Cruceanu C, Binder EB. Preclinical and clinical evidence of DNA methylation changes in response to trauma and chronic stress. *Chronic Stress.* (2017) 1:247054701771076. doi: 10.1177/2470547017710764

7. Lewis CR, Olive MF. Early-life stress interactions with the epigenome: potential mechanisms driving vulnerability toward psychiatric illness. *Behav Pharmacol.* (2014) 25:341–51. doi: 10.1097/FBP.0000000000000057

8. Murgatroyd C, Spengler D. Epigenetic programming of the HPA axis: early life decides. *Stress.* (2011) 14:581–9. doi: 10.3109/10253890.2011.602146

9. Lewis C, Breitenstein R, Henderson A, Sowards H, Piras I, Huentelman M, et al. Harsh parenting predicts novel HPA receptor gene methylation and NR3C1 methylation predicts cortisol daily slope in middle childhood. *Cell Mol Neurobiol.* (2021) 41:783–93. doi: 10.1007/s10571-020-00885-4

10. Yehuda R, Giller EL, Southwick SM, Lowy MT, Mason JW. Hypothalamic-pituitary-adrenal dysfunction in posttraumatic stress disorder. *Biol Psychiatry.* (1991) 30:1031–48. doi: 10.1016/0006-3223(91)90123-4

11. Zannas AS, Provençal N, Binder EB. Epigenetics of posttraumatic stress disorder: current evidence, challenges, and future directions. *Biol Psychiatry.* (2015) 78:327–35. doi: 10.1016/j.biopsych.2015.04.003

12. Mehta D, Miller O, Bruenig D, David G, Shakespeare-Finch J. A systematic review of DNA methylation and gene expression studies in posttraumatic stress disorder, posttraumatic growth, and resilience. *J Trauma Stress.* (2020) 33:171–80. doi: 10.1002/jts.22472

13. Fischer S, Schumacher T, Knaevelsrud C, Ehlert U, Schumacher S. Genes and hormones of the hypothalamic-pituitary-adrenal axis in post-traumatic stress disorder. What is their role in symptom expression and treatment response? *J Neural Transm.* (2021) 128:1279–86. doi: 10.1007/s00702-021-02330-2

14. Yehuda R, Daskalakis N, Desarnaud F, Makotkine I, Lehrner A, Koch E, et al. Epigenetic biomarkers as predictors and correlates of symptom improvement following psychotherapy in combat veterans with PTSD. *Front Psychiatry.* (2013) 4:118. doi: 10.3389/fpsyt.2013.00118

15. Bishop J, Lee A, Mills L, Thuras P, Eum S, Clancy D, et al. Methylation of FKBP5 and SLC6A4 in relation to treatment response to mindfulness based stress reduction for posttraumatic stress disorder. *Front Psychiatry.* (2018) 9:418. doi: 10.3389/fpsyt.2018.00418

16. Vinkers C, Geuze E, van Rooij S, Kennis M, Schür R, Nispeling D, et al. Successful treatment of post-traumatic stress disorder reverses DNA methylation marks. *Mol Psychiatry.* (2021) 26:1264–71. doi: 10.1038/s41380-019-0549-3

17. Pape J, Carrillo-Roa T, Rothbaum B, Nemeroff C, Czamara D, Zannas A, et al. DNA methylation levels are associated with CRF1 receptor antagonist treatment outcome in women with post-traumatic stress disorder. *Clin Epigenetics.* (2018) 10:136. doi: 10.1186/s13148-018-0569-x

18. Yang R, Xu C, Bierer L, Flory J, Gautam A, Bader H, et al. Longitudinal genome-wide methylation study of PTSD treatment using prolonged exposure and hydrocortisone. *Transl Psychiatry.* (2021) 11:398. doi: 10.1038/s41398-021-01513-5

19. Aryee M, Jaffe A, Corrada-Bravo H, Ladd-Acosta C, Feinberg A, Hansen K, et al. Minfi: a flexible and comprehensive bioconductor package for the analysis of infinium DNA methylation microarrays. *Bioinformatics.* (2014) 30:1363–9. doi: 10.1093/bioinformatics/btu049

20. Du P, Zhang X, Huang C, Jafari N, Kibbe W, Hou L, et al. Comparison of beta-value and M-value methods for quantifying methylation levels by microarray analysis. *BMC Bioinformatics.* (2010) 11:587. doi: 10.1186/1471-2105-11-587

21. Watkeys OJ, Kremerskothen K, Quidé Y, Fullerton JM, Green MJ. Glucocorticoid receptor gene (NR3C1) DNA methylation in association with trauma, psychopathology, transcript expression, or genotypic variation: a systematic review. *Neurosci Biobehav Rev.* (2018) 95:85–122. doi: 10.1016/j.neubiorev.2018.08.017

22. Guma E, Devenyi G, Malla A, Shah J, Chakravarty M, Pruessner M. Neuroanatomical and symptomatic sex differences in individuals at clinical high risk for psychosis. *Front Psychiatry.* (2017) 8:291. doi: 10.3389/fpsyt.2017.00291

23. Son S, Park B, Choi J, Roh H, Kim N, Sin J, et al. Psychological resilience enhances the orbitofrontal network in the elderly with mild cognitive impairment. *Front Psychiatry.* (2019) 10:615. doi: 10.3389/fpsyt.2019.00615

24. Yuferov V, Zhang Y, Liang Y, Zhao C, Randesi M, Kreek M. Oxycodone self-administration induces alterations in expression of integrin, semaphorin and ephrin genes in the mouse striatum. *Front Psychiatry.* (2018) 9:257. doi: 10.3389/fpsyt.2018.00257

25. R Core Team. *R: a language and environment for statistical computing.* Vienna: R Foundation for Statistical Computing (2020).

26. Suzuki MM, Bird A. DNA methylation landscapes: provocative insights from epigenomics. *Nat Rev Genet.* (2008) 9:465–76. doi: 10.1038/nrg2341

27. Sandoval J, Heyn H, Moran S, Serra-Musach J, Pujana M, Bibikova M, et al. Validation of a DNA methylation microarray for 450,000 CpG sites in the human genome. *Epigenetics.* (2011) 6:692–702. doi: 10.4161/epi.6.6.16196

28. Herman J, McKlveen J, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. *Compr Physiol.* (2016) 6:603–21. doi: 10.1002/cphy.c150015

29. Jiang S, Postovit L, Cattaneo A, Binder EB, Aitchison KJ. Epigenetic modifications in stress response genes associated with childhood trauma. *Front Psychiatry.* (2019) 10:808. doi: 10.3389/fpsyt.2019.00808

30. Palma-Gudiel H, Córdova-Palomera A, Leza J, Fañanás L. Glucocorticoid receptor gene (NR3C1) methylation processes as mediators of early adversity in stress-related disorders causality: a critical review. *Neurosci Biobehav Rev.* (2015) 55:520–35. doi: 10.1016/j.neubiorev.2015.05.016

31. Labonté B, Azoulay N, Yerko V, Turecki G, Brunet A. Epigenetic modulation of glucocorticoid receptors in posttraumatic stress disorder. *Transl Psychiatry.* (2014) 4:e368.

32. Yehuda R, Flory J, Bierer L, Henn-Haase C, Lehrner A, Desarnaud F, et al. Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans with posttraumatic stress disorder. *Biol Psychiatry.* (2015) 77:356–64. doi: 10.1016/j.biopsych.2014.02.006

33. Schiele MA, Gottschalk MG, Domschke K. The applied implications of epigenetics in anxiety, affective and stress-related disorders - A review and synthesis on psychosocial stress, psychotherapy and prevention. *Clin Psychol Rev.* (2020) 77:101830. doi: 10.1016/j.cpr.2020.101830

34. Maunakea AK, Chepelev I, Cui K, Zhao K. Intragenic DNA methylation modulates alternative splicing by recruiting MeCP2 to promote exon recognition. *Cell Res.* (2013) 23:1256–69. doi: 10.1038/cr.2013.110

35. Jones P. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat Rev Genet.* (2012) 13:484–92. doi: 10.1038/nrg3230

36. Rauscher G, Kresovich J, Poulin M, Yan L, Macias V, Mahmoud A, et al. Exploring DNA methylation changes in promoter, intragenic, and intergenic regions as early and late events in breast cancer formation. *BMC Cancer.* (2015) 15:816. doi: 10.1186/s12885-015-1777-9

37. McGowan P, Sasaki A, D'Alessio A, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci.* (2009) 12:342–8. doi: 10.1038/nn.2270

38. Labonte B, Yerko V, Gross J, Mechawar N, Meaney M, Szyf M, et al. Differential glucocorticoid receptor exon 1(B), 1(C), and 1(H) expression and methylation in suicide completers with a history of childhood abuse. *Biol Psychiatry.* (2012) 72:41–8. doi: 10.1016/j.biopsych.2012.01.034

39. Leenen FAD, Muller CP, Turner JD. DNA methylation: conducting the orchestra from exposure to phenotype? *Clin Epigenetics.* (2016) 8:92. doi: 10.1186/s13148-016-0256-8

40. Tancer M, Johanson CE. Reinforcing, subjective, and physiological effects of MDMA in humans: a comparison with d-amphetamine and mCPP. *Drug Alcohol Depend.* (2003) 72:33–44. doi: 10.1016/s0376-8716(03)00172-8

41. Schenk S, Highgate Q. Methylenedioxymethamphetamine (MDMA): serotonergic and dopaminergic mechanisms related to its use and misuse. *J Neurochem.* (2021) 157:1714–24. doi: 10.1111/jnc.15348

42. Morilak D, Barrera G, Echevarria D, Garcia A, Hernandez A, Ma S, et al. Role of brain norepinephrine in the behavioral response to stress. *Prog Neuropsychopharmacol Biol Psychiatry.* (2005) 29:1214–24. doi: 10.1016/j.pnpbp.2005.08.007

43. Vaessen T, Hernaus D, Myin-Germeys I, van Amelsvoort T. The dopaminergic response to acute stress in health and psychopathology: a systematic review. *Neurosci Biobehav Rev.* (2015) 56:241–51. doi: 10.1016/j.neubiorev.2015.07.008

44. Chaouloff F, Berton O, Mormède P. Serotonin and stress. *Neuropsychopharmacology.* (1999) 21:28S–32.

45. Glad C, Andersson-Assarsson J, Berglund P, Bergthorsdottir R, Ragnarsson O, Johannsson G. Reduced DNA methylation and psychopathology following endogenous hypercortisolism - a genome-wide study. *Sci Rep.* (2017) 7:44445. doi: 10.1038/srep44445

46. Müller D, Grevet E, da Silva B, Charão M, Rovaris D, Bau C. The neuroendocrine modulation of global DNA methylation in neuropsychiatric disorders. *Mol Psychiatry.* (2021) 26:66–9. doi: 10.1038/s41380-020-00924-y

47. Weikum ER, Knuesel MT, Ortlund EA, Yamamoto KR. Glucocorticoid receptor control of transcription: precision and plasticity via allostery. *Nat Rev Mol Cell Biol.* (2017) 18:159–74. doi: 10.1038/nrm.2016.152

48. Sengupta S, Vonesch JL, Waltzinger C, Zheng H, Wasylyk B. Negative cross-talk between p53 and the glucocorticoid receptor and its role in neuroblastoma cells. *EMBO J.* (2000) 19:6051–64. doi: 10.1093/emboj/19.22.6051

49. Lara H, Wang Y, Beltran A, Juárez-Moreno K, Yuan X, Kato S, et al. Targeting serous epithelial ovarian cancer with designer zinc finger transcription factors. *J Biol Chem.* (2012) 287:29873–86. doi: 10.1074/jbc.M112.360768

50. Dumont G, Sweep F, van der Steen R, Hermsen R, Donders A, Touw D, et al. Increased oxytocin concentrations and prosocial feelings in humans after ecstasy (3,4-methylenedioxymethamphetamine) administration. *Soc Neurosci.* (2009) 4:359–66. doi: 10.1080/17470910802649470

51. Kirkpatrick M, Delton AW, Robertson TE, De Wit H. Prosocial effects of MDMA: a measure of generosity. *J Psychopharmacol.* (2015) 29:661–8. doi: 10.1177/0269881115573806

52. Liechti ME, Vollenweider FX. Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. *Hum Psychopharmacol.* (2001) 16:589–98. doi: 10.1002/hup.348

53. Morrison FG, Miller MW, Logue MW, Assef M, Wolf EJ. DNA methylation correlates of PTSD: recent findings and technical challenges. *Prog Neuropsychopharmacol Biol Psychiatry.* (2019) 90:223–34. doi: 10.1016/j.pnpbp.2018.11.011

54. Yehuda R, Daskalakis N, Bierer L, Bader H, Klengel T, Holsboer F, et al. Holocaust exposure induced intergenerational effects on FKBP5 methylation. *Biol Psychiatry.* (2016) 80:372–80. doi: 10.1016/j.biopsych.2015.08.005

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EDITED BY
Julie Wang,
Multidisciplinary Association for Psychedelic Studies,
United States

REVIEWED BY
Robert H. Howland,
University of Pittsburgh,
United States
Sara de la Salle,
University of Ottawa,
Canada

*CORRESPONDENCE
Jennifer L. Jones
✉ jonjen@musc.edu

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# Perspectives on the therapeutic potential of MDMA: A nation-wide exploratory survey among substance users

Jennifer L. Jones*

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC, United States

**Background:** Alcohol and other substance use disorders are commonly associated with post-traumatic stress disorder (PTSD), and the presence of these comorbidities is associated with worse treatment outcomes. Additionally, disparities in substance and PTSD prevalence have been associated with minority races and ethnicities, and minorities have been shown to be less likely to engage in treatment. Psychedelic-assisted treatments, including 3,4-methylenedioxymethamphetamine (MDMA), have shown preliminary trans-diagnostic effectiveness, however it is unknown how individuals with substance use disorders view the therapeutic potential of MDMA therapy. Previous studies have also shown that minority races and ethnicities are under-represented in the MDMA trials, leading to concerns about inequitable access to clinical treatment.

**Methods:** To explore demographic characteristics related to patient-level perspectives on the therapeutic potential of MDMA-assisted therapy, this study describes data from a nationwide, cross-sectional survey of 918 individuals self-reporting criteria consistent with alcohol or substance use disorders.

**Results:** Overall, a majority of individuals reported support for medical research of MDMA (68.1%), belief that MDMA-assisted therapy might be a useful treatment (70.1%), and willingness to try MDMA-assisted therapy if it were determined to be an appropriate treatment for them (58.8%). No race or ethnicity differences were found in support for further research or belief in effectiveness, however there were small disparities in terms of willingness to try MDMA-assisted therapy and concerns related to use of this treatment approach.

**Conclusion:** These results provide insights and future directions as the field of psychedelic-assisted therapy seeks to provide equitable access to clinical care and to diversify research participation.

KEYWORDS

**MDMA, PTSD, substance and alcohol use, treatment, race and ethnicity**

## Introduction

Substance use disorders (including alcohol and tobacco) are highly prevalent globally, and commonly occur in the context of other mental health disorders, including post-traumatic stress disorder (PTSD). Substance use varies as a function of legalization status and cultural norms, and prevalence rates of PTSD vary as a function of population exposure to war, regional traumas,

and intra-familial violence as well as cultural values and other influences. A reciprocal relationship between these comorbidities has been noted. Individuals with substance use disorders are more likely to experience traumatic events and to develop PTSD, and individuals with primary PTSD are more likely to develop substance use disorders (hypothetically to self-medicate PTSD symptoms) (1). Previous work has shown individuals with a substance use disorder are 6.5 times more likely to have PTSD (2). Additionally, studies of trauma centers have suggested that between 62 and 79% of individuals with elevated PTSD symptoms have 1 or more concurrent substance use disorders (3). Furthermore, individuals with these comorbid disorders are more likely to experience symptoms that are refractory to treatment (4–6).

The prevalence of PTSD has been noted in some studies to vary as a function of race and ethnicity. Among Vietnam Veterans, individuals identifying as American Indian have been found to be more likely than those identifying as (non-Hispanic) White to report symptoms consistent with PTSD and were shown to have elevated prevalence of lifetime PTSD (7). Other studies of Vietnam Veterans found that individuals identifying as African American or Hispanic were found to be at higher risk of developing PTSD compared to individuals identifying as non-Hispanic White (8). A later study of individuals living nearby during the terrorist attack in New York City on September 11, 2001 also showed that Hispanic individuals were more likely to have symptoms of PTSD (9). Rates of PTSD among American Indian/Alaskan Natives have also been shown to be elevated compared to the general population (10). More recently, lifetime prevalence of PTSD has been estimated to be 8.7% among Blacks, 7.0% among Hispanics, 7.4% among Whites and 4.0% among Asians in a structured diagnostic interview of the U.S. general population (11). Additionally, an increasing body of research supports the development of PTSD symptoms in response to race-based trauma, previously defined as a cumulative traumatic effect of racism on an individual (12).

Notably, rates of both substance use disorder and PTSD treatment have been shown to be significantly lower in all minority race and ethnicities compared to individuals self-reporting as White (11). Compared to White individuals, Blacks and Hispanics have been shown to have significantly lower substance use disorder treatment completion rates (13, 14). Other studies have shown significant differences in treatment location, with Black and Hispanic individuals less likely to receive treatment at a doctor's office compared to Whites, and Black individuals are more likely than Whites to receive treatment through the criminal justice system (15). Additionally, previous work has shown that Black individuals undergoing treatment had worse outcomes compared to White individuals, while Latino individuals had improved treatment outcomes compared Whites and Blacks. (16). Similarly, studies of individuals with PTSD have shown reduced treatment engagement among Blacks, Hispanics, and Asians compared to Whites (11). Furthermore, among individuals seeking integrated treatment for comorbid substance use disorders and PTSD, studies of veterans have shown reduced rates of treatment response in African Americans compared to Whites (17).

Despite the high prevalence of these comorbidities, there are no pharmacologic treatments which have been shown to be effective in improving symptoms of both types of disorders. Within the United States, there are medications approved for alcohol use disorder (disulfuram, naltrexone, and acamprosate) and three medications approved for opioid use disorder treatment (methadone, buprenorphine, and naltrexone). There are currently no approved pharmacotherapies for cocaine, amphetamine, cannabis, or benzodiazepine use disorders. Sertraline and paroxetine, the only two approved medications for PTSD, have shown only modest effects in PTSD (18). Similarly, while multiple behavioral therapies for combined PTSD and substance use disorders have been explored (i.e., cognitive behavioral therapy, mindfulness based therapies, and prolonged exposure therapy), treatment outcomes remain limited (19).

Compounds with psychedelic properties have been explored for their trans-diagnostic effects in the treatment of mental health disorders. Psilocybin and ketamine are among the more well studied compounds with psychedelic effects, and both have shown preliminary effectiveness in multiple types of substance use disorders (including alcohol and tobacco) as well as other mental health disorders including major depressive disorder, PTSD, and anxiety-spectrum disorders (20–28). Further, 3,4-methylenedioxymethamphetamine (MDMA), a compound with non-classical psychedelic effects received breakthrough therapy status designation from the United States Food and Drug Administration in 2017, indicative of its potential therapeutic advantage over existing treatment options. To date, MDMA has been studied in conjunction with therapy in more than 11 Phase 2 and two Phase 3 trials for the treatment of PTSD. Results from the initial Phase 3 trial showed that MDMA-assisted therapy produced a substantial decrease in symptoms associated with severe PTSD (29). In this study, after completing three sessions of MDMA-assisted therapy, 67% of the participants in the MDMA group no longer met diagnostic criteria for PTSD (a certain number of criteria from each of the different PTSD symptom categories), compared to 32% in the placebo-assisted therapy group. Further, 33% of the MDMA-assisted therapy group met criteria for PTSD remission (defined as loss of diagnosis and a CAPS-5 score of less than or equal to 11), compared to 5% in the placebo-assisted therapy group. In this Phase 3 study, subjects were permitted to have mild alcohol or cannabis use disorders, or moderate alcohol or cannabis use disorders (if in early remission); other substance use disorders were excluded. A subsequent secondary analysis of the Phase 3 MDMA-assisted therapy trial data explored changes in assessments of alcohol and drug use severity using the Alcohol and Drug Use Disorders Identification Tests (AUDIT and DUDIT assessments, respectively). The authors found that MDMA-assisted therapy was associated with greater reductions in alcohol use severity, but not drug use severity and did not find a correlation between changes in PTSD severity and AUDIT score reduction (30). Other studies of MDMA-assisted therapy for the treatment of alcohol use disorder have shown preliminary effectiveness in reducing alcohol consumption (31).

Concerningly, demographic analyses of MDMA and other psychedelic-assisted therapy studies have shown that minority races and ethnicities are significantly underrepresented in psychedelic clinical trials. According to the 2021 United States Census, 13.1% of the population identified as Black or American India, 1.3% as American Indian or Alaskan Native, 6.1% as Asian, 0.3% as Native Hawaiian or Pacific Islander, 2.9% as Multi-Racial, and 18.9% as Hispanic or Latino (32). Overall, 40.7% of the population reported being of a race or ethnicity that was not White alone/not Hispanic or Latino. However, a 2018 systematic review of 18 previous psychedelic studies showed that only 17.4% of the aggregated sample identified as Black, Indigenous, or a Person of Color (33). Additionally, in the 2019 analysis of the six Phase 2 MDMA-assisted therapy trials, only 12.4%

of participants self-reported as identifying as Black, Indigenous, or a Person of Color (34). While sub-analyses have supported that psychedelics and MDMA-assisted therapy is equally safe and efficacious in these populations (including in its ability to promote healing from racial trauma), other studies have suggested decreased interest or willingness to participate in psychedelic-assisted therapy (35, 36).

Minority under-representation in clinical trials may occur from a variety of psychosocial concerns. Experienced or perceived barriers to participation include mistrust related to historical abuses of minorities in medical care and research participation (including the racial and ethnic criminal injustices related to the United States "War on Drugs" in the early 1970's), as well as ineffective communication and cultural messaging in the recruitment process, lack of appropriate logistical support such as childcare and transportation to facilitate participation, and overt and subtle racism (37, 38).

Given the preliminary trans-diagnostic effects of MDMA and other psychedelics in previous trials, this study sought to explore patient-level opinions and beliefs on the research and clinical potential of psychedelic-assisted therapies among substance users. Level of support for further research into MDMA-assisted therapy was assessed, as well as beliefs about whether MDMA-assisted therapy might be a beneficial treatment. Additionally, the study assessed subject willingness to try MDMA-assisted therapy if it was deemed an appropriate treatment option for them and whether they had any concerns about trying the treatments. In addition to aggregate data about these patient-level perspectives, this study explored differences in opinions and beliefs as a function of race and ethnicity.

# Methods

## Study design and ethical review

A cross-sectional survey study was designed and administered to assess substance users' perspectives on the use of several psychedelics including MDMA. This study was declared exempt from review by the Medical University of South Carolina's Institutional Review Board (IRB). In order to protect anonymity, written informed consent was not obtained. However, the pre-screening portion of the survey described the study and its purpose, and informed potential participants that submitting their responses constituted consent. Prior to completion of the main survey, potential participants were required to first complete a pre-screener questionnaire to verify inclusion criteria. Internet Protocol (IP) constraints were set up to prevent participants from taking the survey more than once.

## Recruitment

Recruitment was conducted through advertisements placed on the internet (i.e., Craigslist). Online advertisements invited individuals who "struggle with alcohol or drug use" to participate in a short survey about the use of psychedelic substances in addictions treatment. Both pre-screening and the main survey were conducted using the secure web database, REDCap.

## Inclusion criteria

To be eligible for participation in the main survey, participants must have self-reported giving consent to participate in the study, being over the age of 18 and use of a substance of abuse at least once in the past month. Additionally, participants must have self-reported at least two of the following: (1) wanting to cut back on or stop a substance of abuse, (2) previously having been in treatment for alcohol or drug use, or (3) currently being in treatment for alcohol or drug use. Pre-screening questions are shown in Supplementary Figure 1.

## Exclusion criteria

Potential participants were excluded if they (1) did not self-report at least 2 criteria for a substance use disorder, (2) did not report using a substance of abuse at least once per month, (3) denied ever wanting to cut back on or stop using a substance of abuse, or (4) did not give their consent to participate in the study.

## Screening and informed consent

Initial screening eligibility using the inclusion and exclusion criteria was conducted using a pre-screener questionnaire hosted *via* REDCap. Participants were informed that participation in the study was voluntary, and they could discontinue at any time. Participants were provided with an overview of the study procedures in advance on the pre-screening questionnaire.

## Assessment procedures

Following completion of informed consent, and provided that all inclusion and exclusion criteria were satisfied, eligible participants proceeded to take the full survey. The survey took approximately 20 min to complete. The survey was anonymous, but participants were asked basic questions about themselves such as their age, gender, race, and use of alcohol and various substances. Participants were supplied with the following information about MDMA-assisted therapy: "In 2016, the FDA approved MDMA (also known as ecstasy) for Phase 3 clinical trials as a treatment for post-traumatic stress disorder (PTSD), which is a common disorder that occurs with addictions. These studies are one of the final steps before possible approval as a prescription drug. One previous study showed that with 3 doses of MDMA administered under a psychiatrist's guidance, the patients reported a 56% decrease in severity of PTSD symptoms on average. At the end of the study, 2/3 of the study participants (66%) no longer met the criteria for having PTSD. Improvements lasted more than a year after therapy." Participants were subsequently asked (1) "Based on these findings and what you may have known previously, do you support or oppose similar medical trials with MDMA being conducted in the future," (2) "do you think that MDMA could or could not be a beneficial treatment for people suffering from PTSD," and (3) if MDMA is proven to be safe and effective for treatment after further trials, would you or would you not try this treatment if it was appropriate for you?"

## Participant compensation

Participants who completed the full survey were eligible to be compensated for their time with a $15 Amazon gift card. This gift card would be sent to their email address. If the participant did not wish to provide their email address, they could still take the survey, but they would not be able to receive compensation.

## Data analytic procedure

All data from this survey was collected and managed using the secure REDCap (Research Electronic Data Capture) database. Data was analyzed using the SPSS statistical software platform. Baseline demographic characteristics were collected from all participants and descriptive statistics for the sample population were analyzed. Descriptive statistics were analyzed with regard to overall sample with regard to regard to (1) level of support for further clinical trial research into MDMA assisted therapy, (2) subject belief that MDMA might be a beneficial treatment, and (3) subject willingness to try MDMA-assisted therapy. Additionally, Kruskal-Wallis H tests were used to evaluate potential differences between race and ethnicity group differences with regard to these three variables. Descriptive statistics were also analyzed with regard to proportion of the total sample expressing different potential concerns related to use of psychedelics.

# Results

## Demographic profile of respondents

Of the 935 individuals that initiated the survey, 918 (98.2%) individuals completed responses to the full survey and were included in the analysis. The demographic profile of respondents was generally diverse. Of the respondents that completed the full survey, a majority of individuals (70.9%) self-identified as male, while 28.2% of respondents identified as female, 0.4% as transgender or non-binary, and 0.4% as other or responded that they preferred not to gender identify. Survey respondents self-identified as being of one or more of the following race or ethnicity categories: American Indian or Alaska Native (4.4%), Asian (2.4%), Black or African American (20.6%), Hispanic or Latino (13.6), Native Hawaiian or Other Pacific Islander (0.7%), White (56.2%), Multi-racial (1.7%) or Other/Preferred Not to Answer (0.4%).

## Overall level of support for MDMA therapy

A majority of individuals reported either supporting or strongly supporting medical research of MDMA (68.1%). Furthermore, a majority reported either strongly or very strongly believing that MDMA could be useful for the treatment of mental health disorders such as addiction and PTSD (70.1%). Similarly, if MDMA was proven to be a safe and effective treatment of a disorder that they suffered from, a majority stated that they would personally be willing to therapeutically use it (58.8%).

## Racial and ethnic differences

Descriptive analysis of level of support for MDMA trial research, belief that MDMA-assisted therapy could be a beneficial treatment for PTSD, and willingness to try MDMA-assisted therapy (if it were appropriate for them) by race and ethnicity are shown in Figures 1–3. Potential race and ethnicity group differences with regard to level of support for further clinical trial research into MDMA assisted therapy was assessed using a Kruskal-Wallis H test. Distributions of level of support were not similar for all groups, as assessed by visual inspection of a boxplot. The mean rank of level of support scores was not statistically significantly different between groups, $\chi^2(7) = 9.198$, $p = 0.239$.

Similarly, race and ethnicity differences with regard to subject belief that MDMA might be a beneficial treatment for individuals suffering from PTSD were analyzed using a Kruskal-Wallis H test. Distributions of level of belief in benefit were not similar for all groups, as assessed by visual inspection of a boxplot. The mean rank of level of support scores was not statistically significantly different between groups, $\chi^2(7) = 2.763$, $p = 0.906$.

Finally, group differences with regard to subject willingness to try MDMA-assisted therapy were analyzed using a Kruskal-Wallis H test and are shown in Figure 3. Distributions of level of willingness to try MDMA-assisted therapy were not similar for all groups, as assessed by visual inspection of a boxplot. A between group difference in subject willingness to try MDMA-assisted therapy was found, $\chi^2(7) = 24.699$, $p < 0.001$. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. As shown in Figure 3, Asians to were less likely to report willingness to try MDMA-assisted therapy compared to Whites ($p = 0.029$) or Hispanics or Latinos ($p = 0.002$). American Indians and Alaskan Natives were also reported decreased willingness to try MDMA-assisted compared to Hispanics or Latinos ($p = 0.041$). Among Hispanic/Latino respondents, 68.0% reported that they definitely or probably would be willing to try MDMA-assisted therapy, while only 57.5% of White respondents, 47.5% of American Indian and Alaskan Natives, and 40.9% of Asians reported definite or probable willingness to try this treatment. No other significant pairwise comparisons emerged.

## Concerns

Despite overall high levels of support for MDMA research trials, belief that MDMA could be a beneficial treatment, and willingness to try the treatment if it was an appropriate treatment for their condition, a majority (96.2%) of individuals also expressed concerns about psychedelic-assisted therapies. Concerns endorsed included fear of a bad trip (31.8%), fear that it would change [them] (35.4%), fear that it would cause [them] to go crazy (39.9%), fear that [they] would feel guilt during the experience (32.8%), fear of losing [their] sense of self (31.5%), fear that it would affect employment (26.7%), fear that family, friends or neighbors would find out (27.3%), and fear that they would no longer enjoy using substances (35.4%). Survey respondents were also queried about non-listed concerns, and 2.7% indicated that they had additional concerns. Of the 7 concerns that were submitted, 4 related to concerns about becoming addicted to a new substance, 1 expressed concern that they would say something they would regret, 1 was concerned about potential side effects, and 1 expressed concern that because they had previously done psychedelics, that they would not gain benefit from their

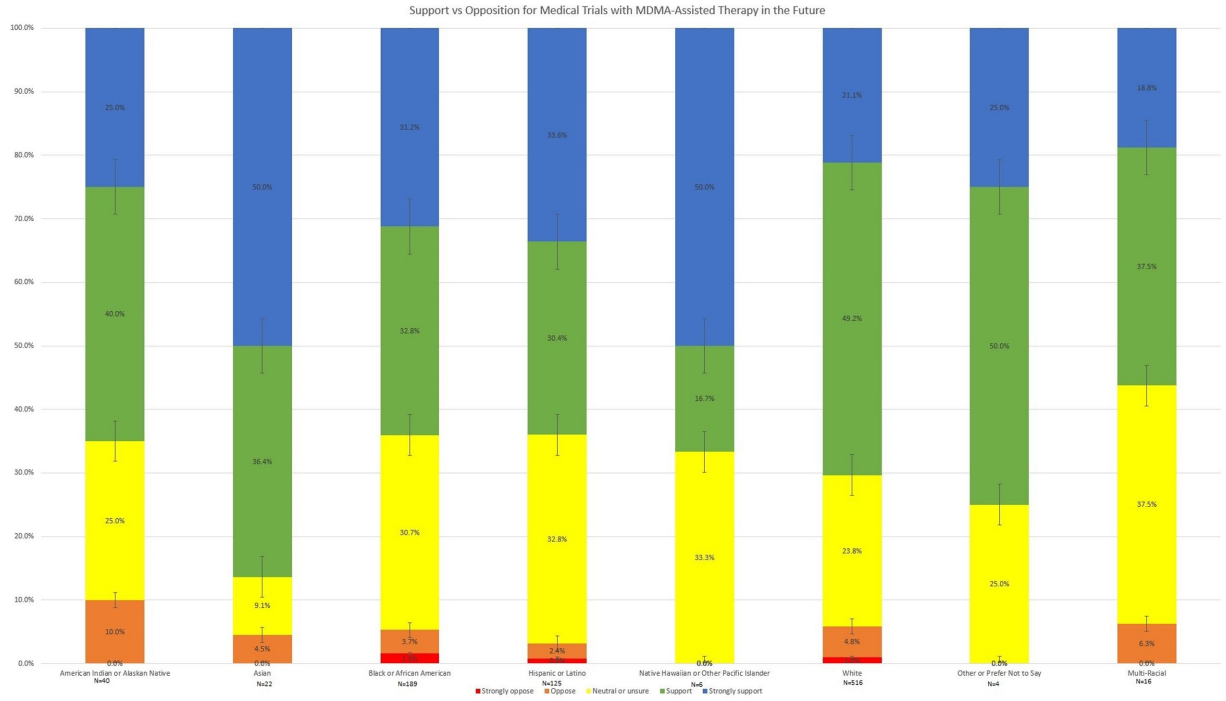


FIGURE 1
Support vs opposition for medical trials with MDMA-assisted therapy in the future.

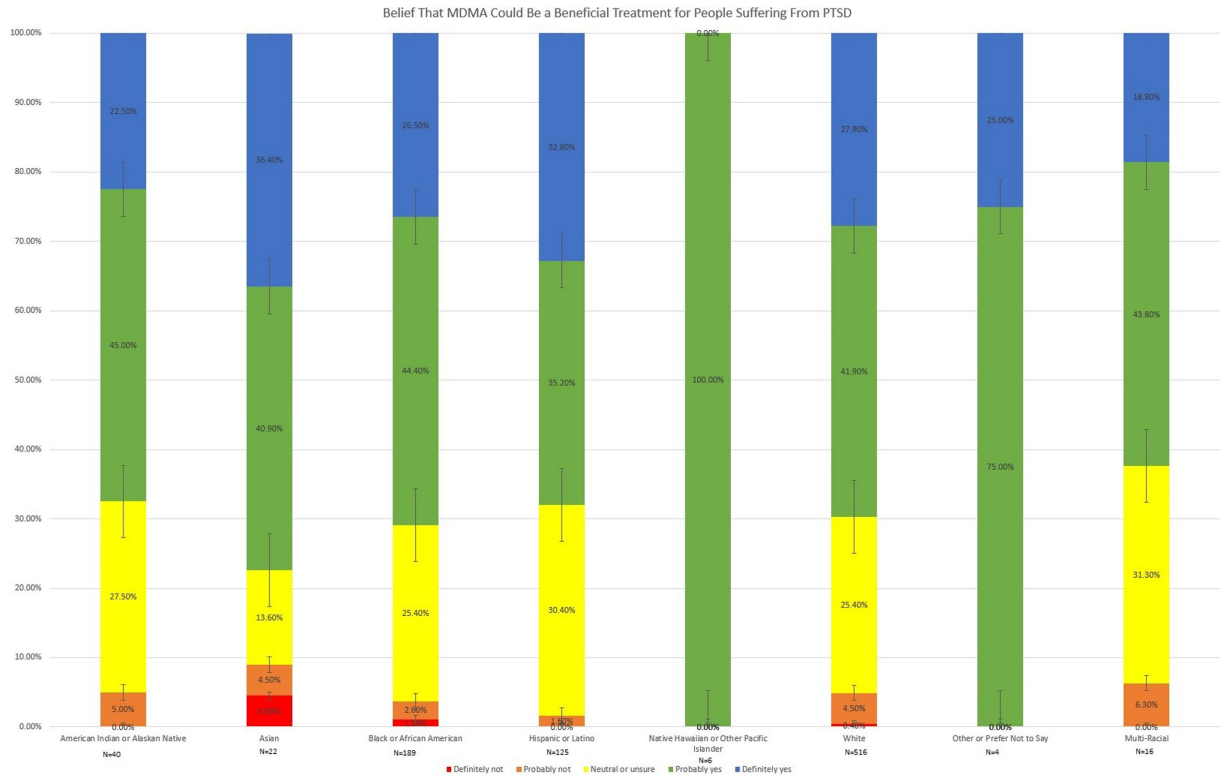


FIGURE 2
Belief that MDMA-assisted therapy could be a beneficial treatment for people suffering from PTSD.

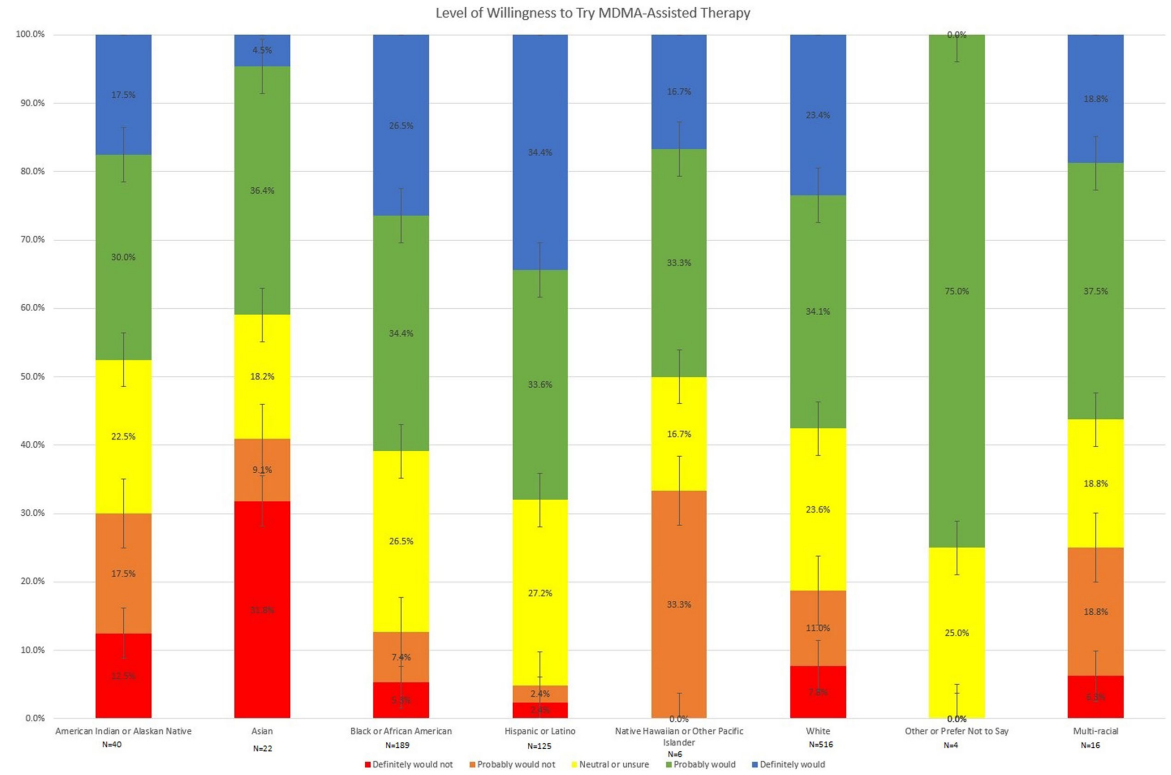


FIGURE 3
Level of willingness to try MDMA-assisted therapy.

**TABLE 1** Total number of concerns by race and ethnicity.

| Total # Concerns | AIAN | Asian | Black /AA | Hisp/Latx | Haw/PI | White | Other /Prefer Not to Say | Multi-racial | Total |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 7.5% | | 2.1% | 5.6% | | 5.6% | | 6.3% | 4.8% |
| 1 | 17.5% | 40.9% | 5.8% | 7.2% | 16.7% | 4.8% | | 6.3% | 6.9% |
| 2 | 30.0% | 22.7% | 10.6% | 6.4% | 33.3% | 15.5% | 25.0% | 37.5% | 14.6% |
| 3 | 30.0% | 22.7% | 59.8% | 72.8% | 50.0% | 51.9% | 50.0% | 18.8% | 54.1% |
| 4 | 12.5% | 13.6% | 10.6% | 4.8% | | 11.8% | | 18.8% | 10.7% |
| 5 | 2.5% | | 4.8% | | | 6.4% | 25.0% | | 4.8% |
| 6 | | | 1.1% | 2.4% | | 1.9% | | 6.3% | 1.7% |
| 7 | | | 4.2% | | | 1.0% | | 6.3% | 1.5% |
| 8 | | | 0.5% | | | 0.4% | | | 0.3% |
| 9 | | | 0.5% | 0.8% | | | | | 0.2% |
| 10 | | | | | | 0.6% | | | 0.3% |
| Mean | 2.30 | 2.09 | 3.17 | 2.79 | 2.33 | 2.98 | 3.25 | 2.94 | 2.94 |

AIAN, American Indian or Alaskan Native; AA, African American; Hisp/Latx, Hispanic or Latinx.

therapeutic use. Survey respondents reported a mean number of 2.94 concerns, with a range of 0–10 of these concerns. Total number of concerns by race and ethnicity is shown in Table 1. Only 4.8% of respondents denied having any concerns about use of psychedelic-assisted therapies, and the independent binomial proportions of respondents with no concerns were not statistically significantly different between race/ethnicities ($p > 0.05$). A Kruskal-Wallis H test was subsequently conducted to determine if there were differences in the mean number of concerns reported between the racial and ethnicity groups. Values are mean ranks unless otherwise stated. Distributions of number of concerns were not similar for all groups, as assessed by visual inspection of a boxplot. The mean ranks of number of concerns were statistically significantly different between groups, $\chi^2(3) = 14.468$, $p = 0.002$. Pairwise comparisons were performed using Dunn's procedure with a Bonferroni correction for multiple comparisons. Asians reported a fewer number of concerns than Whites ($p = 0.018$) or than African American ($p = 0.004$). American Indians/Alaskan Natives also reported a fewer number of concerns than Whites ($p = 0.019$) or African Americans ($p = 0.003$).

## Discussion

Engagement in clinical treatments for PTSD and substance use disorders have been shown to be significantly lower in minority race and ethnicities compared to individuals self-reporting as White, and individuals with alcohol or substance use disorders are more likely to experience symptoms that are refractory to PTSD treatment. MDMA and other psychedelic-assisted therapies represent an exciting new trans-diagnostic treatment approach, however minority races and ethnicities have been significantly under-represented in previous research trials. These disparities in psychedelic research trials have further prompted concern that clinical adoption of these treatments may also be inequitable, although reasons behind the reduced research representation remain largely unstudied. Importantly, no previous studies have directly assessed patient-level perspectives on psychedelic-assisted therapies as a function of race and ethnicity.

The results of this study indicate that an overall majority of individuals self-reporting criteria for substance use disorders (including alcohol) support continued clinical trial research of MDMA-assisted therapy, with no between-group differences in level of support found between the races and ethnicities. Similarly, an overall majority reported either strongly or very strongly believing that MDMA could be useful for the treatment of mental health disorders such as addiction and PTSD, and no between-group differences were found with regard to this belief.

Most germane to clinical treatment adoption, a majority of individuals with substance use disorders reported that they would be willing to try MDMA-assisted therapy if it were determined to be an appropriate treatment for their condition. Pairwise comparisons reported small between group differences. Asians to were less likely to report willingness to try MDMA-assisted therapy compared to Whites, while Hispanics and Latinos were more likely to report willingness to try MDMA-assisted therapies compared to American Indians and Alaskan Natives or Asians. Previous work has suggested that the disproportionate illicit use of MDMA among Asian Americans may relate to feelings of acculturation stress and a desire for social connectedness (39). Willingness to try a treatment modality may be influenced by both cultural and individual perceptions about the potential risks and benefits of the treatment, as well as prior experience with MDMA, which was not assessed in this study. Interestingly, there were no between group differences regarding the belief that MDMA-assisted therapy could be a beneficial treatment in general, which suggests that reduced willingness to try this treatment might be related either to greater assessment of potential risks or reduced belief that it would be of personal benefit. Future research studies and clinical work should examine not only levels of race and ethnicity participation, but concerns related to potential risks or harms that might be addressable with specific education or outreach efforts.

One of the strengths of this survey is the relatively large sample size (918 unique survey completers) which generally represented a diverse demographic profile. Compared to national averages taken from US Census Data, there were higher proportions of all minority races except Asian Americans (4.4% of survey respondents, but 6.1% of the US population); Hispanics/Latinos were also slightly underrepresented compared to national averages (18.9% nationally but only 13.6% of survey respondents) (24). Several important study limitations are to be noted. First, participants self-selected to participate in this online survey, potentially introducing selection bias. Additionally, participants were only eligible for participation if they self-reported 2 criteria consistent with a substance use disorder (including alcohol) as per Supplementary Figure 1, these questions are not validated for formal diagnostic assessment. Additionally, PTSD and other psychiatric symptomatology was not assessed. Given that there has been more limited research into MDMA-assisted therapy for substance use disorders compared to PTSD, this may have influenced subject perception of treatment efficacy or willingness to try MDMA-assisted therapy. Further, while this study evaluated potential concerns specifically about the use of psychedelics, it did not survey general concerns related to research engagement, or what criteria subjects felt was essential for a treatment to "be proven safe and effective." Further level of prior knowledge about the treatment (which could vary by race/ethnicity) was not characterized.

Importantly, this study was not designed to assess the efficacy of MDMA-assisted therapy in the treatment of substance use disorders (either singularly or co-occurring with PTSD), nor was this exploratory study designed to provide conclusive results about patient-level opinions on MDMA-assisted therapy. However, this study does provide a valuable descriptive analysis of substance users' belief in the therapeutic potential of MDMA-assisted therapy and their willingness to use it if they were found to be a clinically appropriate treatment for them. Additionally, this study demonstrated that a majority of individuals had some concerns about psychedelic-assisted therapies, which provide direction into further research, public education and counseling strategies related to these treatments.

MDMA and other psychedelic-assisted therapies offer enormous promise in the treatment of refractory and comorbid mental health disorders. However, much work remains ahead. As MDMA and other psychedelics advance toward becoming clinical treatments, improving research diversity and ensuring equitable access to care are of paramount importance.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board of the Medical University of South Carolina. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

JJ designed and implemented the study design, searched for the references, and drafted the manuscript including figures and tables.

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## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.1096298/full#supplementary-material

## References


1. Gielen N, Havermans R, Tekelenburg M, Jansen A. Prevalence of post-traumatic stress disorder among patients with substance use disorder: it is higher than clinicians think it is. *Eur J Psychotraumatol*. (2012) 3:17734. doi: 10.3402/ejpt.v3i0.17734

2. Mills K, Teeson M, Ross J, Peters L. Trauma, PTSD, and substance use disorders: findings from the Australian National Survey of mental health and well-being. *Am J Psychiatry*. (2006) 163:652–8. doi: 10.1176/ajp.2006.163.4.652

3. Nguyen J, Whiteside LK, Bulger EM, Veach L, Moloney K, Russo J, et al. Post-traumatic stress disorder (PTSD) symptoms and alcohol and drug use comorbidity at 25 US level I trauma centers. *Trauma Surg Acute Care Open*. (2022) 7:e000913. doi: 10.1136/tsaco-2022-000913

4. Bedard-Gilligan M, Garcia N, Zoellner LA, Feeny NC. Alcohol, cannabis, and other drug use: engagement and outcome in PTSD treatment. *Psychol Addict Behav*. (2018) 32:277–88. doi: 10.1037/adb0000355

5. Norman SB, Haller M, Hamblen JL, Southwick SM, Pietrzak RH. The burden of co-occurring alcohol use disorder and PTSD in U.S. military veterans: comorbidities, functioning, and suicidality. *Psychol Addict Behav*. (2018) 32:224–9. doi: 10.1037/adb0000348

6. Tripp JC, Jones JL, Back SE, Norman SB. Dealing with complexity and comorbidity: comorbid PTSD and substance use disorders. *Curr Treat Options Psychiatry*. (2019) 6:188–97. doi: 10.1007/s40501-019-00176-w

7. Beals J, Manson SM, Shore JH, Friedman M, Ashcraft M, Fairbank JA, et al. The prevalence of posttraumatic stress disorder among American Indian Vietnam veterans: disparities and context. *J Traumat Stress*. (2002) 15:89–97. doi: 10.1023/A:1014894506325

8. Kulka RA, Schlenger WE, Fairbank JA, Hough RL, Jordan BK, Marmar CR, et al. *Trauma and the Vietnam war generation*. New York: Brunner/Mazel (1990).

9. Galea S, Ahern J, Resnick H, Kilpatrick D, Bucuvalas M, Gold J, et al. Psychological sequelae of the September 11 terrorist attacks in New York City. *N Engl J Med*. (2002) 346:982–7. doi: 10.1056/NEJMsa013404

10. Bassett D, Buchwald D, Manson S. Posttraumatic stress disorder and symptoms among American Indians and Alaska natives: a review of the literature. *Soc Psychiatry Psychiatr Epidemiol*. (2014) 49:417–33. doi: 10.1007/s00127-013-0759-y

11. Roberts AL, Gilman SE, Breslau J, Breslau N, Koenen KC. Race/ethnic differences in exposure to traumatic events, development of post-traumatic stress disorder, and treatment-seeking for post-traumatic stress disorder in the United States. *Psychol Med*. (2011) 41:71–83. doi: 10.1017/S0033291710000401

12. Williams MT, Haeny A, Holmes S. Posttraumatic stress disorder and racial trauma. *PTSD Res Q*. (2021) 32:1–9.

13. Mennis J, Stahler GJ. Racial and ethnic disparities in outpatient substance use disorder treatment episode completion for different substances. *J Subst Abus Treat*. (2016) 63:25–33. doi: 10.1016/j.jsat.2015.12.007

14. Mennis J, Stahler GJ, Abou El Magd S, Baron DA. How long does it take to complete outpatient substance use disorder treatment? Disparities among blacks, Hispanics, and whites in the US. *Addict Behav*. (2019) 93:158–65. doi: 10.1016/j.addbeh.2019.01.041

15. Archibald ME, Behrman P, Yakoby J. Racial-ethnic disparities across substance use disorder treatment settings: sources of treatment insurance, socioeconomic correlates and clinical features. *J Ethn Subst Abus*. (2022)21:1–25. doi: 10.1080/15332640.2022.2129537

16. Sahker E, Pro G, Sakata M, Furukawa TA. Substance use improvement depends on race/ethnicity: outpatient treatment disparities observed in a large US national sample. *Drug Alcohol Depend*. (2020) 213:108087. doi: 10.1016/j.drugalcdep.2020.108087

17. Brown DG, Flanagan JC, Jarnecke A, Killeen TK, Back SE. Ethnoracial differences in treatment-seeking veterans with substance use disorders and co-occurring PTSD: presenting characteristics and response to integrated exposure-based treatment. *J Ethn Subst Abus*. (2022) 21:1141–64. doi: 10.1080/15332640.2020.1836699

18. Gasparyan A, Navarro D, Navarrete F, Manzanares J. Pharmacological strategies for post-traumatic stress disorder (PTSD): from animal to clinical studies. *Neuropharmacology*. (2022) 218:109211. doi: 10.1016/j.neuropharm.2022.109211

19. Lancaster CL, Teeters JB, Gros DF, Back SE. Posttraumatic stress disorder: overview of evidence-based assessment and treatment. *J Clin Med*. (2016) 5:105. doi: 10.3390/jcm5110105

20. Albott CS, Lim KO, Forbes MK, Erbes C, Tye SJ, Grabowski JG, et al. Efficacy, safety, and durability of repeated ketamine infusions for comorbid posttraumatic stress disorder and treatment-resistant depression. *J Clin Psychiatry*. (2018) 79:17462. doi: 10.4088/JCP.17m11634

21. Jones JL, Mateus CF, Malcolm RJ, Brady KT, Back SE. Efficacy of ketamine in the treatment of substance use disorders: a systematic review. *Front Psych*. (2018) 9:277. doi: 10.3389/fpsyt.2018.00277

22. Dakwar E, Nunes EV, Hart CL, Foltin RW, Mathew SJ, Carpenter KM, et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. *Am J Psychiatr*. (2019) 176:923–30. doi: 10.1176/appi.ajp.2019.18101123

23. Grabski M, McAndrew A, Lawn W, Marsh B, Raymen L, Stevens T, et al. Adjunctive ketamine with relapse prevention–based psychological therapy in the treatment of alcohol use disorder. *Am J Psychiatr*. (2022) 179:152–62. doi: 10.1176/appi.ajp.2021.21030277

24. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. *J Psychopharmacol*. (2015) 29:289–99. doi: 10.1177/0269881114565144

25. Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, et al. Percentage of heavy drinking days following psilocybin-assisted psychotherapy vs placebo in the treatment of adult patients with alcohol use disorder: a randomized clinical trial. *JAMA Psychiatry*. (2022) 79:953–62. doi: 10.1001/jamapsychiatry.2022.2096

26. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. *J Psychopharmacol*. (2014) 28:983–92. doi: 10.1177/0269881114548296

27. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. *Am J Drug Alcohol Abuse*. (2017) 43:55–60. doi: 10.3109/00952990.2016.1170135

28. Feder A, Costi S, Rutter SB, Collins AB, Govindarajulu U, Jha MK, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatr*. (2021) 178:193–202. doi: 10.1176/appi.ajp.2020.20050596

29. Mitchell JM, Bogenschutz M, Lilienstein A, Harrison C, Kleiman S, Parker-Guilbert K, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. (2021) 27:1025–33. doi: 10.1038/s41591-021-01336-3

30. Nicholas CR, Wang JB, Coker A, Mitchell JM, Klaire SS, Yazar-Klosinski B, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug Alcohol Depend*. (2022) 233:109356. doi: 10.1016/j.drugalcdep.2022.109356

31. Sessa B, Higbed L, O'Brien S, Durant C, Sakal C, Titheradge D, et al. First study of safety and tolerability of 3, 4-methylenedioxymethamphetamine-assisted psychotherapy in patients with alcohol use disorder. *J Psychopharmacol*. (2021) 35:375–83. doi: 10.1177/0269881121991792

32. U.S. Census Bureau (2021) Quick facts. Available at: https://www.census.gov/quickfacts/fact/table/US/PST045219 (Accessed November 1, 2022).

33. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: a review of the literature. *BMC Psychiatry*. (2018) 18:245. doi: 10.1186/s12888-018-1824-6

34. Ching TH, Williams MT, Wang JB, Jerome L, Yazar-Klosinski B, Emerson A, et al. MDMA-assisted therapy for posttraumatic stress disorder: a pooled analysis of ethnoracial differences in efficacy and safety from two phase 2 open-label lead-in trials and a phase 3 randomized, blinded placebo-controlled trial. *J Psychopharmacol*. (2022) 36:974–86. doi: 10.1177/02698811221104052

35. Williams MT, Davis AK, Xin Y, Sepeda ND, Grigas PC, Sinnott S, et al. People of color in North America report improvements in racial trauma and mental health symptoms following psychedelic experiences. *Drugs Educ Prev Policy*. (2021) 28:215–26. doi: 10.1080/09687637.2020.1854688

36. George JR, Michaels TI, Sevelius J, Williams MT. The psychedelic renaissance and the limitations of a white-dominant medical framework: a call for indigenous and ethnic minority inclusion. *J Psychedelic Stud*. (2019) 4:4–15. doi: 10.1556/2054.2019.015

37. George S, Duran N, Norris K. A systematic review of barriers and facilitators to minority research participation among African Americans, Latinos, Asian Americans, and Pacific islanders. *Am J Public Health*. (2014) 104:e16–31. doi: 10.2105/AJPH.2013.301706

38. Smith DT, Faber SC, Buchanan NT, Foster D, Green L. The need for psychedelic-assisted therapy in the black community and the burdens of its provision. *Frontiers in Psychiatry*. (2022) 12:774736. doi: 10.3389/fpsyt.2021.774736

39. Chan, Michelle Stephanie (2017). Coping with acculturative stress: MDMA usage among Asian American young adults in the electronic dance music scene. Pomona Senior Theses, 194.

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EDITED BY
Jennifer Mitchell,
University of California, San Francisco,
United States

REVIEWED BY
Sarah Tedesco,
Richmond University Medical Center,
United States
Darko Hren,
University of Split, Croatia
Patrick Vizeli,
University of California, San Diego,
United States

*CORRESPONDENCE
Macha Godes
machagodes@gmail.com

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# Perceived key change phenomena of MDMA-assisted psychotherapy for the treatment of severe PTSD: an interpretative phenomenological analysis of clinical integration sessions

Macha Godes[1]*, Jasper Lucas[2] and Eric Vermetten[3]

[1]Institute of Psychology, Social Science Department, University of Amsterdam, Amsterdam, Netherlands, [2]Institute of Psychology, Social Science Department, Leiden University, Leiden, Netherlands, [3]Department of Psychiatry, Leiden University Medical Center, Leiden, Netherlands

Post-traumatic stress disorder (PTSD) is a prevalent psychiatric condition that significantly impacts daily functioning in patients but lacks adequate treatment options. 3,4-methylenedioxymethamphetamine (MDMA) as an adjunct to psychotherapy for the treatment of PTSD has been studied increasingly for the last two decades and has shown promising results through quantitative data. However, few qualitative studies have been conducted to investigate patients' experiences who participate in these trials. This study intends to complement and clarify the quantitative findings resulting from a Phase-II clinical trial for assessing the safety and efficacy of MDMA-assisted psychotherapy for PTSD by using a qualitative approach based on available material of 4 recorded and transcripted integrative sessions per participant. An Interpretative Phenomenological Analysis (IPA) was conducted for 7 participants who met criteria for severe PTSD to develop a deeper understanding of the treatment and its efficacy. Analysis results provided real-life statements from participants that reflect perceived mechanisms of change and showed to what extent their proposed working mechanisms integrate into daily life.

KEYWORDS

**PTSD, interpretative phenomenological analyses, psychotherapy, MDMA, MDMA-assisted psychotherapy, qualitative research, psychedelics**

## Introduction

Post-traumatic stress disorder (PTSD) is an impairing anxiety disorder marked by re-experiencing phenomena, affect dysregulation, hypervigilance, and, most importantly, fear and avoidance associated with recalling traumatic memories (1). Studies on existing treatments have demonstrated that only 50–60% of individuals no longer meet PTSD criteria in most successful trials, leaving behind nearly half of the studied population with chronic PTSD that gain little to no benefit from current treatments (2–4).

For the last two decades, 3,4-methylenedioxymethamphetamine (MDMA) -assisted psychotherapy (MDMA-AP) has regained interest as a promising therapy for severe

therapy-resistant PTSD (5–8). Multiple of these trials have primarily focused on collecting quantitative data necessary for mapping the safety and efficacy of MDMA-AP (5, 9–11). While quantitative measures successfully address the intensity and frequency of PTSD symptoms, they fail to provide a deeper phenomenological understanding of the treatment process. Consequently, they cannot fully capture the potential benefits that may arise during the treatment. A qualitative research approach may yield a more comprehensive view of the issue being studied and enables exploration of respondents' inner experience (12, 13). To date, relatively little attention has been devoted to qualitative studies on MDMA-AP as a clinical practice to examine how patients perceive the therapy to work and describe key phenomena related to symptom improvement and behavioral change. Previous work includes Barone and colleagues' paper from 2019, which explored long-term follow-up sessions of MDMA-AP for veterans, police officers, and firefighters (14).

This study is the first to explore how participants experience change and processing of trauma after undergoing MDMA-AP by assessment of recorded clinical integration sessions. It is also explored how participants integrate the therapeutic elements of the therapy into their daily life during the course of the treatment.

# Methods

For this study, MAPS provided video material of therapy sessions conducted for the phase 2 open-label clinical trial for assessing the safety and efficacy of MDMA-AP for severe PTSD (15). For a detailed report of quantitative outcomes of this phase 2 trial, see Multidisciplinary Association for Psychedelic Studies (16).

Each participant underwent a recorded treatment consisting of 15 sessions divided over 12 weeks. The treatment protocol embodied three different types of sessions (Figure 1). Three experimental MDMA sessions took place in which either 80 mg or 120 mg is orally administered with an optional supplemental dose of 40 mg or 60 mg. In these 6–8-h long sessions, addressing PTSD symptoms and processing the trauma is an essential part. After each MDMA session, three integration meetings took place. See Figures 1, 2 for the treatment design and procedure. More information on the treatment procedure and protocol is found in the 'Manual for MDMA-AP for the treatment of post-traumatic stress disorder (15).

To explore and understand the content, quality, and meaning of participants' descriptions after undergoing MDMA-AP, transcribed video recordings of the first therapeutic integration sessions right after the experimental sessions and the last of all sessions were analyzed using a qualitative approach (Figure 3). The integration sessions included in this analysis were part of a complete clinical treatment, and no structured qualitative interviews were conducted apart from the therapeutic intervention.

## Coding and analysis

For analysis, Interpretative Phenomenological Analysis (IPA) (17) was used. IPA aims to provide a "detailed examination of personal lived experience, the meaning of experience to participants and how participants make sense of that experience" (18) and, therefore, make sense of the changes they go through in response to the treatment. In essence, the inquirer undertakes several steps to reduce the data and attempts to capture the phenomena that all participants hold in common. IPA typically holds an idiographic component which allows the researcher to look for the meaning behind an individual's experience by interpreting the data through a psychological lens (19). Also, IPA is one of the primary methodologies used in similar clinical trials focusing on MDMA and alternate compounds (14, 20, 21).

After the recorded treatment sessions were transcribed, they underwent thematic analysis by the three-member research team. The coding team (MG and JL) constructed an initial coding frame, which was then reviewed and discussed by the auditor (EV). The encoding process was based on the step-by-step protocol of conducting IPA as proposed by Pietkiewicz and Smith (19).

## Participants

Initially, 308 participants were assessed for eligibility for the open-label pilot study of MDMA-AP for severe PTSD. After screening, 37 participants actually enrolled in the study. From those 37 participants,

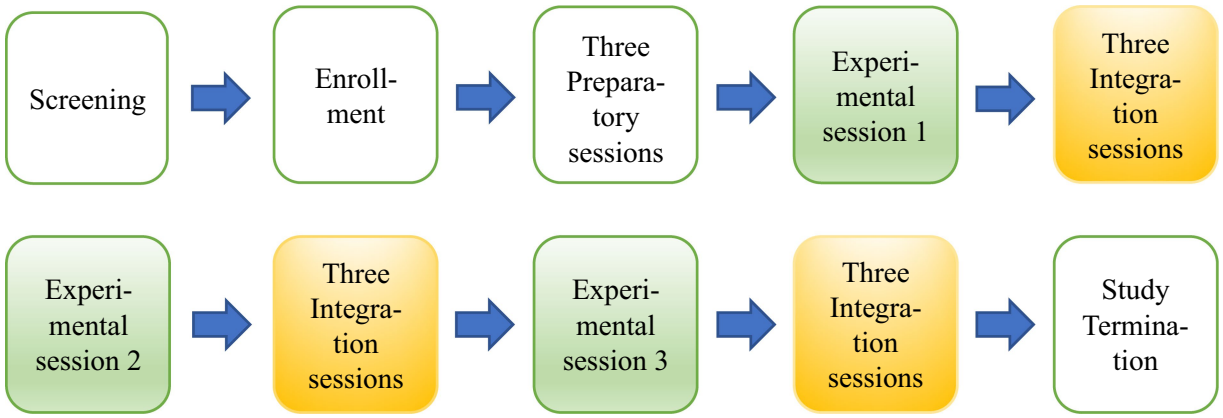


FIGURE 1
Study design of MDMA assisted psychotherapy. Experimental sessions shown in green. Integration sessions shown in yellow.

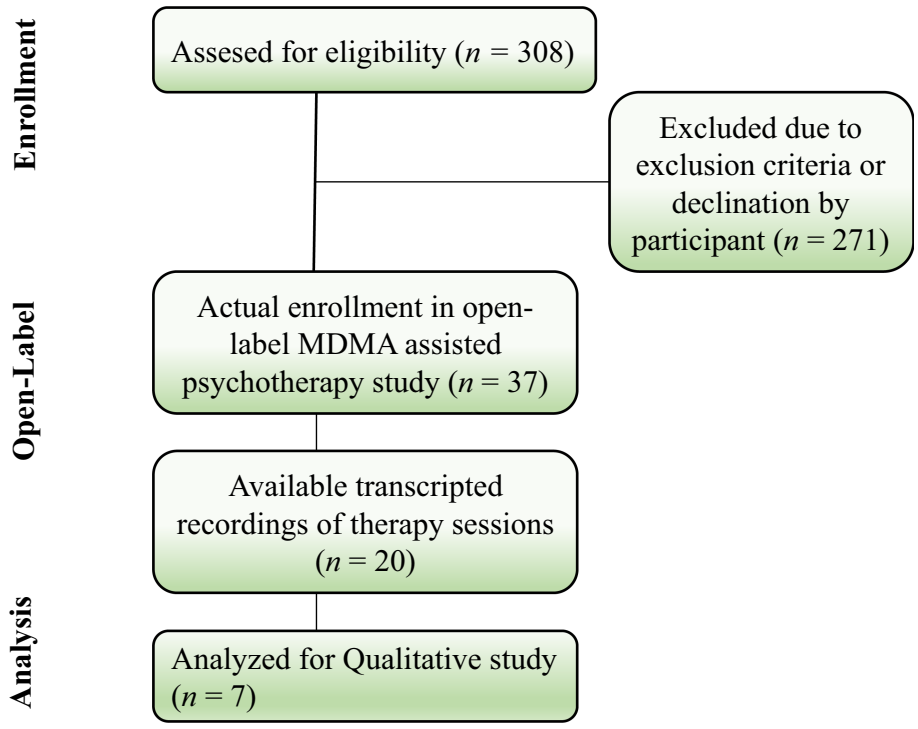


FIGURE 2
Diagram denoting flow of participants throuhout the study.

there were video recordings available from 20 participants. Five participant videos were excluded due to unusable video and sound quality. Given practical matters such as time limitation and taking Robinsons' guidelines for choosing a sample size for a qualitative IPA study into consideration, a subset of 7 participants was chosen by applying stratified sampling (22, 23). In doing so, four women and three men were randomly chosen after dividing the full sample into males and females. An overview of demographic characteristics, initial CAPS-5 scores and CAPS-5 scores after the treatment are shown in Tables 1, 2. A diagram presenting the flow of participants from the phase 2 clinical trial to the current study is shown in Figure 2.

## Results

In total, 2,240 min of recorded video material from seven participants' integration sessions were coded and analyzed. All seven participants reported experiencing a range of benefits during the course and at the end of the treatment. The presented coding schema (Table 3) entails the data's main categories and themes and served as a guiding framework. All quotes illustrating the themes of the coding scheme are found in the supplementary materials. For data to be valid and reportable, it was decided that each theme had to be reported by at least four participants.

## Tolerance of conflict

### Staying with what 'is'

This theme refers to the participants' ability to stay with, observe, and acknowledge a feeling before responding or reacting in the way one usually would do. This may be accompanied by a sense of curiosity concerning the meaning and source of the emotion. Rather than attempting to suppress the feeling through distraction or other methods, participants now take the time to notice the feeling, sit with it for a while, and trust and allow it to dissipate. They recognize the transient and subjective nature of emotional states, resulting in greater flexibility and adaptability. Sophie, for example, strikingly describes the ability to not only tolerate painful memories but actually continue the healing process in those moments:

> "I feel like even with our session on Saturday, even though it was difficult, and there was a lot of pain. I let myself experience that pain again. I don't feel like any progress had been robbed from it. I feel like probably more progress have been made from it. And that's like the same thing with, if any unwanted memories come up, now it's an interesting kind of re-evaluating of an unwanted memory, because I know in this process I'm trying to heal and understand and remember the totality of what has happened."

### Decreased reactivity

In this theme, participants report experiencing diminished reactivity and engagement with aversive thoughts, memories, and daily encounters. Also, experiences relating to increased tolerance towards others, especially towards elements that would previously evoke an aversive reaction and negatively affect the participant, were reported. Some participants described these diminished feelings as 'spontaneous,' while others experienced them as a result of insights or emotional processing during the MDMA sessions.

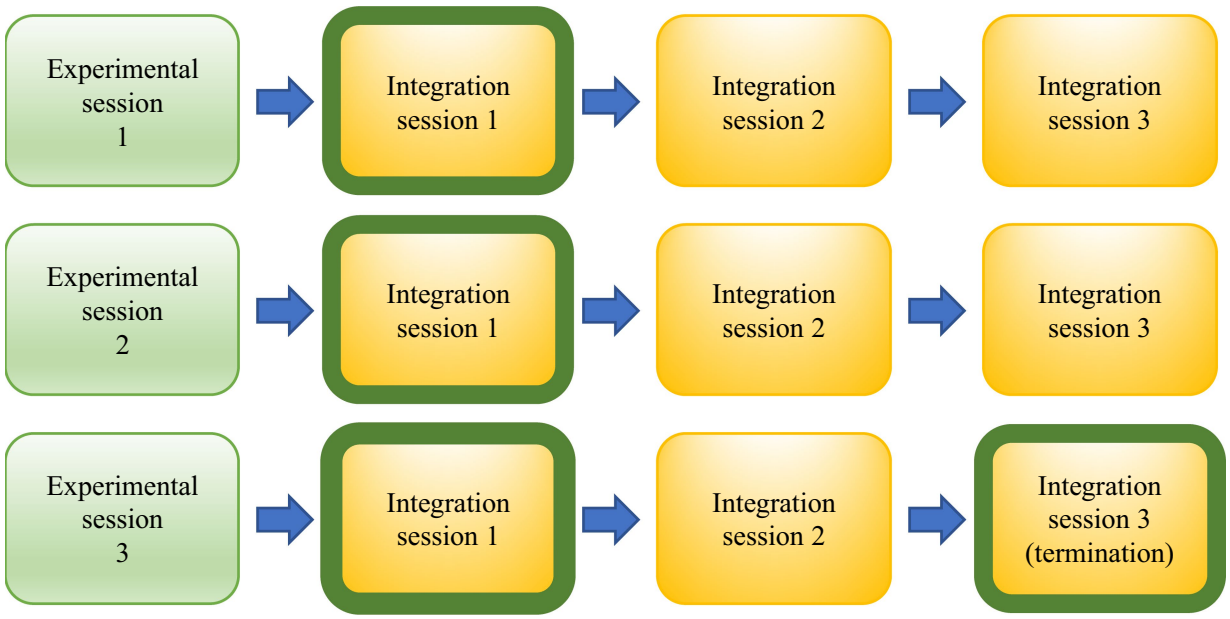


FIGURE 3
Selected integration sessions per participant for qualitative analysis (shown with green border).

TABLE 1 Demographic characteristics for 7 participants in the qualitative analysis.

| Fictive name | Gender | Age | Ethnicity | Cause of PTSD | CAPS-5 baseline | CAPS-5 termination |
|---|---|---|---|---|---|---|
| Sophie | Female | 25 | White | Developmental trauma/multiple trauma | 43 | 23 |
| Isa | Female | 43 | White | Developmental trauma/multiple trauma | 47 | 5 |
| Rose | Female | 23 | White | Developmental trauma/multiple trauma | 55 | 14 |
| Jacky | Female | 40 | White | Developmental trauma/multiple trauma | 38 | 5 |
| Nick | Male | 50 | White | Veteran/combat exposure | 41 | 13 |
| Rico | Male | 32 | Asian | Veteran/combat exposure | 53 | 13 |
| Harry | Male | 41 | White | Developmental trauma | 47 | 10 |

## Processing trauma

### Insight, reflecting

This theme comprehends the degree of reflective thinking or insights gained regarding psychological processes. This reflective thinking may be related to relational or internal patterns, cultural norms, or specific insights about the traumatic encounter and PTSD symptoms. For example, participants' descriptions included pivotal insights about the trauma origin and their behavior in response to the traumatic content. Participants also showed an increased capacity to put formerly ineffable complexities into words. Nick, for example, describes a greater understanding of what the trauma 'took from him'.

> "I was thinking last night that a lot did connect for me and starts to make sense for me that I've never really been able to put together before. (…) I think that part softened for me, knowing what it meant to me. Mentally knowing that that

TABLE 2 Demographic characteristics for initially enrolled participants and subset.

| | Total ($N$ =37) | Subset ($n$ =7) |
|---|---|---|
| Gender, $n$ (%) | | |
| Male | 15 (40.5) | 4 (57.15) |
| Female | 22 (59.5) | 3 (42.85) |
| Age, M (SD) | 35.6 (10.8) | 36.3 (9.19) |
| Min, Max | 18.6, 62.3 | 23, 50 |
| Ethnicity, $n$ (%) | | |
| American Indian | 1 (2.7) | 0 |
| or Alaskan native | | |
| Asian | 6 (16.2) | 1 (14.3) |
| Black | 1 (2.7) | 0 |
| White | 27 (73.0) | 6 (85.7) |
| Multiple | 2 (5.4) | 0 |
| Type of trauma, $n$ (%) | | |
| Developmental trauma | 29 (78.4) | 5 (71.4) |
| Veteran | 5 (15.2) | 2 (28.6) |
| Combat exposure | 3 (9.1) | 2 (28.6) |
| Multiple trauma | 27 (81.8) | 4 (57.1) |
| CAPS-5, baseline ($n$ =37), M (SD) | 45.4 (7.18) | 46.28 (5.72) |
| Change in CAPS-5, baseline to termination ($n$ =36), M (SD) | −29.89 (13.45) | −34 (15.71) |

One participant withdrew from the trial before to the onset of the second MDMA-AP session due to a mild increase of nightmares. This individual was the only one who did not complete the primary endpoint evaluation.

> damage was done to me. That softened, I feel like now that I know what it took from me, I know where to begin to rebuild, and just finding that out almost gave me back a little bit of data that I felt they stole from me. Because now I have a starting point. I think all of this is going to build on my self-confidence and love for myself and love for others and appreciation for life."

### Mental clarity

This theme depicts participants' experiences of a clearer understanding of complex concepts and life situations. Participants showed an increased ability to explore feelings and traumatic memories with a degree of focus and coherence that is usually out of their reach, often leading to new insights. This theme can further be characterized by participants' experiences of a mental 'fog' or 'cloud' disappearing, enabling them to think and reason more clearly.

### Recovery of traumatic memories

This theme refers to participants' ability to retrieve previously inaccessible memories. Participants reported spontaneous recovery of traumatic memories that they had largely or completely forgotten about. This recovery was often accompanied by a critical insight into their trauma history and how it shaped their current behavior.

### Disentangling trauma from self

For this theme, participants described a sense of separation from their trauma and the behavioral patterns it caused them to adopt. They somehow managed to recognize how these patterns may have served them in the past while also recognizing how they cause dysfunction in their current lives. This theme includes quotes from participants reflecting on their trauma as a separate construct from the larger "being" they identify with - almost like an uninvited friend they had to deal with but for whom it is now time to leave. The following quote from Isa showcases her realization that she had internalized her trauma and need not to do so any longer:

> "I really felt like it wasn't part of me or attached to me anymore. And I feel like it made me realize the totality of everything that's happened. I've made it mine and my fault or something. I've made it part of me. You know, and the ugliness and the craziness of it all. I made it mine. Like I'm that monster, evil I'm that, you know. But it wasn't me. It was just something that happened I guess I don't know. It's not me, it just happened to me, it's like some violent thing happens to somebody."

### Reuniting lost parts

This theme describes participants' experiences of remembering or relating to an aspect of the self that had previously been lost, locked-up or split off, rejected, suppressed, controlled, or amputated by the participant, often as a result of the traumatic experience.

> "After that first session there were, in my mind's eye, two individuals. That were the 15-year-old Harry and there was the present-day Harry. They were distinct bodies but at the end of yesterday, they went together and that was really the connection that I was looking for. I felt so good. There was the unification integration."

## Positive emotions

### Self-acceptance

This theme refers to participants' feelings of appreciation, acceptance, compassion, and empathy for themselves. This includes feeling more secure when rejected by others and reduced feelings of guilt and shame. Participants described that these feelings of guilt and shame often arose from the belief that they had played a responsible role in the traumatic event(s). Participants' quotes selected for this theme also include descriptions of forgiveness and care towards oneself.

### Joy, happiness, gratitude

An essential aspect of the increase in positive emotions that participants describe is increased joy and gratitude. They report being enabled to enjoy pleasurable activities again without interference from their anxiety. Also, they report an increased ability to enjoy life or certain aspects of life again. In addition, they express greater gratitude towards their life circumstances and those they share them with. Besides the burden that the symptoms of PTSD have been in their lives, they saw now how these experiences can enrich them as a person.

### Hope and empowerment

This theme reflects participants' experiences of self-confidence, empowerment, and hope. They look forward to continuing the therapeutic process after the trial has finished as they experience a sense of trust, empowerment, and confidence in their ability to defend their boundaries or manage other challenging situations. Participants state feeling in control of one's own life and experiencing the freedom to stay with a feeling or react according to one's preference. Rico expressed his experience of this theme using a metaphor:

> "I kind of had this vision of a traditional brick and mortar stacking, this wall, finally sealing off. And what I saw, it's like more softened and I can just push these bricks out. I can predict the bricks to dismantle the wall at the pace that I need to do it, the wall is still there, but I can take down the pieces of it at my own pace. And I can see what's beyond it again."

### Relaxation, calmness, peace

This theme illustrates participants' enhanced ability to relax and calm down, where they usually would have been alert and tense. Participants also described a sense of relief in their body, particularly in areas of the body that had previously been in pain, tension, or tightness.

## Interpersonal

### Comfort

This theme refers to an increased sense of comfort in accepting help and love from others. Participants report feeling more secure in seeing to it that their emotional needs are met, in addition to increased levels of intimacy. Participants describe a diminishing of obstacles or defenses that previously impeded social closeness. Also, participants noted how trusting and opening up positively add to the deepening of social connections with others, which Rose describes as follows:

> "I was stressing out, and he was trying to give me advice. And never before could I confidently say that somebody could give me advice, and I would sit there and try to listen to what they're saying. Usually I'm just like, no, you're wrong when you don't understand, but like I was actively, believing him and wanting his advice and I was able to see it from that perspective. You know, but like before I was so stuck that I couldn't listen to what they were saying."

### Gratitude, compassion, empathy

Participants' examples of appreciation, gratitude, forgiveness, and compassion for others are illustrated in this theme. Also included are participants' expressions of interest in volunteering or peer counseling. Finally, participants felt that they wanted to share what they have gained throughout the therapy and, in this way, serve others, PTSD sufferers in particular.

## Connection

### Union, wider perspective

This theme refers to an increased sense of union that participants report with the "universe," their surroundings, and others. Also, a sense of 'awe' at the vastness of the world and universe is described. These feelings seemed to provide participants with a broader perspective on their problems. This can involve recognizing the common human plight that they share with others and feeling a sense of belonging in the world.

### Inner healing intelligence

Here, participants' report sensing the presence of an "inner-healing intelligence" or "guide" within themselves, which, once recognized and connected with, can aid in healing and recovery. Participants reported feeling stronger connected to this semi-autonomous part of their psyche. When connecting with this mysterious intelligence, it seems to open up a path to recovery and healing. In the following quote, Sophie emphasizes the 'magical' and 'esoteric' elements of MDMA-AP.

> "When you say, 'the inner healer' I think that the medicine (MDMA) allows something within you to find that awaiting ability to express it, whatever that something is. So, there's definitely a almost esoteric sense to it, for lack of a better term, there's some kind of magic to that, of you getting in that spot and be like, "hey, remember this?" And it's not always a good thing. But it's there. It's being brought up for a reason. And that to me is like, whoa. Yeah, truly It really is. It's like a moment of like, Oh, yeah, there's this memory. That's there for a reason. What is it bringing me? What is it teaching me and why is it still prevalent? What does it mean?"

### Accessibility to emotions, in contact with feelings

This theme illustrates participants' experiences of acknowledging or coping with previously rejected or inaccessible feelings and self-states. These feelings and self-states may reflect vulnerability, tenderness, love, happiness, carefree, playful, and a broader and deeper level of feeling in general.

### Mind–body connection

Participants linked to this theme referred to specific bodily sensations and how they relate to their trauma. This may include connecting a particular bodily state with an emotional state or reconnecting to one's bodily state at the time of a traumatic event. Also, an overall sense of connecting more to the body was repeatedly stated. Experiencing this connection between mind and body allowed for a greater understanding of their trauma, facilitating new ways of adapting to and dealing with its consequences.

# Discussion

This study is the first to explore how participants experience change and relief of symptoms after undergoing MDMA-AP by investigating recorded clinical integration sessions. Results include statements of how patients perceive, experience, explore and process

TABLE 3 Coding scheme denoting all categories and themes for 7 participants.

| Coding scheme | | |
|---|---|---|
| Categories | Themes | Participants per theme |
| Tolerance of conflict | Staying with what 'is' | 7 |
| | Decreased reactivity | 6 |
| Processing trauma | Insight, reflection, linking | 7 |
| | Mental clarity | 4 |
| | Recovery of traumatic memories | 5 |
| | Disentangling trauma from self | 5 |
| | Reuniting lost affects and parts | 4 |
| Positive emotions | Self-acceptance | 7 |
| | Joy, happiness, gratitude | 7 |
| | Hope and Empowerment | 7 |
| | Relaxation, calmness, peace | 7 |
| Interpersonal | Comfort | 5 |
| | Gratitude, empathy, compassion | 4 |
| Connection | Union, wider perspective | 4 |
| | Inner healing intelligence | 6 |
| | Accessibility to emotions | 5 |
| | Mind–body connection | 4 |

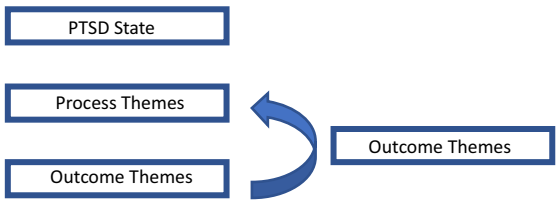


FIGURE 4
Schematic representation denoting the interrelatedness of identified themes.

challenging emotions previously avoided or blocked. It explored how individuals with severe PTSD experience change and relief of symptoms after undergoing MDMA-AP and how the underlying therapeutic elements were integrated into their daily lives. We attempted to portray the participants' integration experience through the lens of psychological growth and therapeutic action and capture which mechanisms of action might have played a role. We will now briefly expand on our views concerning the interrelatedness of the different themes.

At the risk of attempting to organize such complex, subjective material into an overly rigid theoretical framework with heterogeneous and overlapping constructs, we would nonetheless like to categorize the found categories and their subthemes in 'process', 'outcome' and 'growth themes'. The 'process' themes, which include the categories 'Tolerance of conflict' and 'Processing trauma', refer to psychological processes that lead to 'outcome' themes, which include the categories 'Positive emotions' and 'Interpersonal'. For example, in our view, the 'process' subtheme 'Staying with what is' may actually facilitate the outcome subtheme 'Comfort'. We make this distinction in part because of the deep sense that MDMA-AP is by no means a magic bullet: MDMA opens patients up to engage in psychological processes that lead to beneficial outcomes and thereby requires considerable effort from the patients. However, a short-coming of this distinction is that the participants in our study also almost invariably describe the sense that their therapeutic work will continue for a long time following their participation in the trial. To recognize this aspect of our findings, we would like to formulate the third and final category of growth themes, which includes the category 'Connection'. 'Growth' themes refer not to processes that occur as a result of MDMA administration, but to abilities that participants take with them from the experience and continue to apply in daily life. These growth themes seem to allow participants to once again engage in processes similar to those they experienced during their MDMA sessions. For example, participants reported increased ability to connect to their feelings, as described by the subtheme 'Accessibility to emotions'. This might allow participants to once again engage in the process of 'staying with what is' in daily life after the treatment has ended, thereby further facilitating outcome themes. See Figure 4 for a schematic representation of our views on the possible interrelatedness of our identified themes.

The main findings of this research offered several insights that well complement and expand upon the quantitative outcomes of the study it is based on. The Primary Category 'Positive Emotions' in particular shows how the benefits of MDMA-AP may well go beyond symptom reduction, as noted by Barone and colleagues as well (14). Our findings also offer support for existing theoretical models that aimed to explain how MDMA's physiological and psychological effects might mediate the treatment of PTSD. The themes 'mental clarity' and 'staying with what is', for example, correspond well to speculation about the role of down regulation of limbic structures and upregulation of prefrontal areas in the brain in MDMA-AP's therapeutic effects (24).

Furthermore, confronting the painful event and allowing for memory updating and modifying the fear response plays an essential role in most trauma-focused therapies (25, 26). Previous research by Mithoefer et al., (27) found that MDMA-AP provides a desirable state of altered perception in which the psychological root cause of PTSD symptoms may be addressed, and fear extinction and memory reconsolidation of threatening memories may be facilitated. Supporting this theory, the current study found how certain elements of this state may have remained an accessible resource throughout the treatment, even after the physiological effects of MDMA had drawn off. During and after constructing the coding scheme, it became apparent that the participants' increased ability to 'stay with what is' and tolerate whatever came up ran like a thread throughout the relevant data. Participants often stated that feelings of joy, compassion, decreased defenses and improved introspection and communication resulted from an increased ability to endure otherwise painful states. Their increased ability to relax and stay

present in the moment seemed to create space for participants to direct their energy toward other important aspects of life that would previously be inaccessible.

Moreover, this study found how participants may recover from 'moral injury'. Moral injury refers to the violation of moral beliefs that create a deep sense of internal estrangement and conflict (23). The guilt and shame associated with moral injury often form an obstacle in participating in therapies (23). The participants' statements showed an increase in acceptance, self-forgiveness, and self-empathy, which are key in addressing moral injury and the feelings of guilt and shame that tie to it.

Further, the results portray how MDMA-AP impacts daily functioning regardless of the relative change in CAPS-5 scores. The FDA's decision to approve MAPS to proceed forward with phase 3 clinical studies was mainly based on the sustained improvement in CAPS-5 scores seen in phase 2 trials. A change in CAPS-5 scores, however, can only present the frequency and intensity of symptoms and cannot account for other factors that affect daily functioning and quality of life as a result of having PTSD. In our sample, all 7 participants showed clinically significant decreases in PTSD symptoms at trial termination compared to baseline CAPS-5 scores, with an average change in CAPS-5 total scores of 34 ($SD = 8$), ranging from a difference of 20 (Sophie) to 42 (Isa; Figure 1). Although the difference in both scores is relatively high, both participants state that they experienced a range of additional outcomes apart from features addressed by the CAPS-5, including increased self-acceptance and an enhanced capacity to reflect on themselves. Outcomes like these not only contribute by discerning specific features of MDMA-AP that play an essential role in symptom improvement, but also help in better customize future studies and inform and improve therapy effectiveness.

## Limitations

This study presents several limitations that warrant consideration. Firstly, participants reported challenges in articulating their post-therapy experiences, as they were still processing the internal experiential changes. Consequently, the best available spoken language of participants was employed to develop an appropriate coding scheme. Participants may benefit from additional time and distance to gain a more comprehensive understanding of their experiences. Secondly, a larger team conducting the qualitative analysis would have been ideal. The smaller team size may have led to subjective overinterpretation, influenced in part by enthusiasm regarding the method. A more extensive team could have helped mitigate this risk. Thirdly, the varied MDMA dosage per individual might have resulted in substantial differences in response and subsequent experiences. The concentration of MDMA in the body is a critical determinant of its effects (28). Every participant received 80–120 mg initially and had an option to receive an additional dose of 60 mg after 3 h into the session. The research team was unable to access the individual dose range, which constitutes a major limitation to this study.

The findings of this study emphasize the importance of qualitative research in studying MDMA-AP by complementing and clarifying its quantitative outcomes. The themes reflected by participants aid in a better understanding of the known theoretical frameworks that sought to explain this therapy's working mechanism. Future research could use this study's findings in designing better fitting protocols in order to expand psychological mechanisms of action and maximize therapeutic benefit.

## Data availability statement

Raw data can only be requested and granted by obtaining a confidentiality agreement with MAPS, as the data contains highly sensitive and private data of the participants. Further inquires can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by Western Copernicus Group Independent IRB (Research Triangle, NC), University of California San Francisco Human Resource Protection Program IRB, University of Madison Wisconsin Health Sciences IRB, Western IRB (Puyallup, WA), and University of British Columbia Providence Health Care Research Ethics Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

MG wrote and coded and designed the entire material. MG designed the coding scheme together with JL. JL coded the entire material and helped designing the coding scheme. EV held an overview and gave critical feedback during the entire process. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2023.957824/full#supplementary-material

## References


1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 5th* ed. Washington DC: American Psychiatric Association (2013).

2. Resick PA, Nishith P, Weaver TL, Astin MC, Feuer CA. A comparison of cognitive-processing therapy with prolonged exposure and a waiting list condition for the treatment of chronic posttraumatic stress disorder in female rape victims. *J Consult Clin Psychol.* (2002) 70:867–79. doi: 10.1037/0022-006X.70.4.867

3. Foa EB, Hembree EA, Cahill SP, Rauch SA, Riggs DS, Feeny NC, et al. Randomized trial of prolonged exposure for posttraumatic stress disorder with and without cognitive restructuring: outcome at academic and community clinics. *J Consult Clin Psychol.* (2005) 73:953–64. doi: 10.1037/0022-006X.73.5.953

4. Monson CM, Schnurr PP, Resick PA, Friedman MJ, Young-Xu Y, Stevens SP, et al. Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. *J Consult Clin Psychol.* (2006) 74:898–907. doi: 10.1037/0022-006X.74.5.898

5. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {+/−}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *J Psychopharmacol.* (2011) 25:439–52. doi: 10.1177/0269881110378371

6. Mithoefer MC, Mithoefer AT, Feduccia AA, Jerome L, Wagner M, Wymer J, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. The lancet. *Psychiatry.* (2018) 5:486–97. doi: 10.1016/S2215-0366(18)30135-4

7. Schenberg EE. Psychedelic-assisted psychotherapy: a paradigm shift in psychiatric research and development. *Front Pharmacol.* (2018) 9:733. doi: 10.3389/fphar.2018.00733

8. Vermetten E, Yehuda R. MDMA-assisted psychotherapy for posttraumatic stress disorder: a promising novel approach to treatment. *Neuropsychopharmacology.* (2020) 45:231–2. doi: 10.1038/s41386-019-0482-9

9. Multidisciplinary Association for Psychedelic Studies. *In Protocol: A Randomized, Triple-Blind, Phase-2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction with Manualized Psychotherapy in 24 Veterans, Firefighters, and Police Officers with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD). 5th* ed. Santa Cruz, CA: MAPS (2013).

10. Otalora GM, Grigsby J, Poulter B, Van Derveer JW, Giron SG, Jerome L, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: a randomized phase 2 controlled trial. *J Psychopharmacol.* (2018) 32:1295–307. doi: 10.1177/0269881118806297

11. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (± 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic post-traumatic stress disorder (PTSD). *J Psychopharmacol.* (2013) 27:40–52. doi: 10.1177/0269881112464827

12. Creswell JW. *Qualitative Inquiry & Research Design: Choosing among Five Approaches.* Thousand Oaks, CA: Sage Publications (2016).

13. Green J, Thorogood N. *Qualitative Methods for Health Research. 2nd* ed. London: Sage Publications (2009).

14. Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived benefits of MDMA-assisted psychotherapy beyond symptom reduction: qualitative follow-up study of a clinical trial for individuals with treatment-resistant PTSD. *J Psychoactive Drugs.* (2019) 51:199–208. doi: 10.1080/02791072.2019.1580805

15. Wang JB, Lin J, Bedrosian L, Coker A, Jerome I, Feduccia A, et al. Scaling up: multisite open-label clinical trials of MDMA-assisted therapy for severe posttraumatic stress disorder. *J Humanist Psychol.* (2021). doi: 10.1177/00221678211023663

16. Multidisciplinary Association for Psychedelic Studies. A Manual for MDMA-Assisted Psychotherapy in the Treatment of Posttraumatic Stress Disorder; (2022) Available at: https://s3-us-west-1.amazonaws.com/mapscontent/research-archive/mdma/TreatmentManual_MDMAAssistedPsychotherapyVersion+8.1_22+Aug2017.pdf (Accessed March 28, 2022)

17. Smith JA. Evaluating the contribution of interpretative phenomenological analysis. *Health Psychol Rev.* (2011) 5:9–27. doi: 10.1080/17437199.2010.510659

18. Biggerstaff D, Thompson AR. Interpretative phenomenological analysis (IPA): a qualitative methodology of choice in healthcare research. *Qual Res Psychol.* (2008) 5:214–24. doi: 10.1080/14780880802314304

19. Pietkiewicz I, Smith JA. A practical guide to using interpretative phenomenological analysis in qualitative research psychology. *Psychol J.* (2014) 20:7–14. doi: 10.14691/CPPJ.20.1.7

20. Schenberg EE. A phenomenological analysis of the subjective experience elicited by ibogaine in the context of a drug dependence treatment. *J Psychedelic Stud.* (2017) 1:74–83. doi: 10.1556/2054.01.2017.007

21. Belser A, Agin-Liebes G, Swift TC. Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomonological analysis. *J Humanist Psychol.* (2017) 57:354–88. doi: 10.1177/0022167817706884

22. Smith JA, Flower P, Larkin M. *Interpretative Phenomenological Analysis: Theory Method and Research.* London: Sage (2009).

23. Robinson OC. Sampling in interview-based qualitative research: a theoretical and practical guide. *Qual Res Psychol.* (2014) 11:25–41. doi: 10.1080/14780887.2013.801543

24. Carhart-Harris RL, Murphy K, Leech R, Erritzoe D, Wall MB, Ferguson B, et al. The effects of acutely administered 3,4-Methylenedioxymethamphetamine on spontaneous brain function in healthy volunteers measured with arterial spin labeling and blood oxygen level-dependent resting state functional connectivity. *Biol Psychiatry.* (2015) 78:554–62. doi: 10.1016/j.biopsych.2013.12.015

25. Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature.* (2000) 406:722–6. doi: 10.1038/35021052

26. Sessa B. MDMA and PTSD treatment: from novel pathophysiology to innovative therapeutics. *Neurosci Lett.* (2017) 176:649. doi: 10.1016/j.neulet.2016.07.004

27. Litz BT, Stein N, Delaney E, Lebowitz L, Nash WP, Silva C, et al. Moral injury and moral repair in war veterans: a preliminary model and intervention strategy. *Clin Psychol Rev.* (2009) 29:695–706. doi: 10.1016/j.cpr.2009.07.003

28. Studerus E, Kometer M, Hasler F, Vollenweider FX. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. *Front Psych.* (2021) 2:241.

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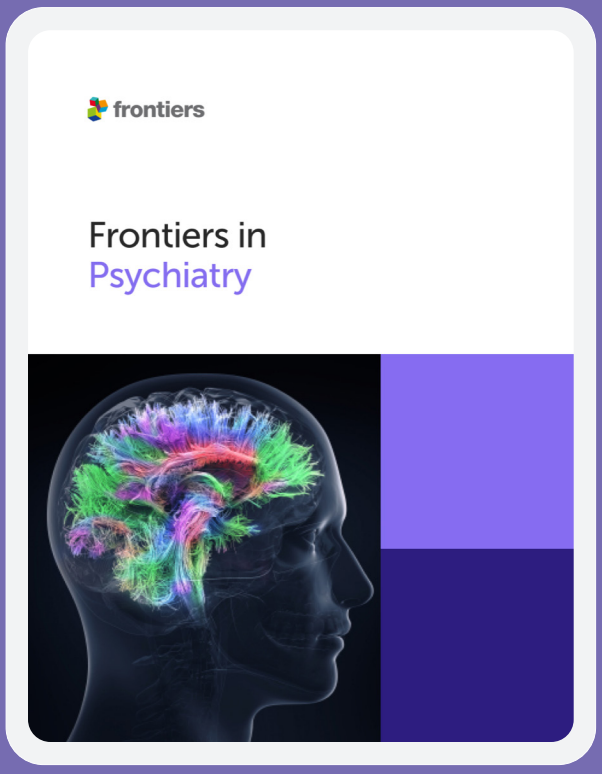


**Frontiers**

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

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