Trauma Under Psychedelics:
MDMA Shows Protective Effects During the Peritraumatic Period

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Abstract

Traumatic events (TEs) play a causal role in the etiology of psychopathologies such as depression and posttraumatic stress disorder (PTSD). Recent research has highlighted the therapeutic potential of psychoactive substances and especially 3,4-methylenedioxymethamphetamine (MDMA), in alleviating trauma symptoms in chronic patients. However, little is known regarding the consequences of trauma that is acutely experienced under the influence of psychoactive substances. Here we investigated the acute experiences and peritraumatic processing of 657 survivors from the high-casualty terror attack at the Supernova music festival in Israel on October 7th, 2023. Data were collected four to twelve weeks following the TE. Approximately two-thirds of survivors were under the influence of psychoactive substances at the time of the TE, offering a tragic and unique natural experiment on the impact of psychoactive compounds on TE processing. Our findings reveal that individuals who experienced the trauma while under the influence of MDMA demonstrated significantly improved intermediate outcomes compared to those who were under the influence of other substances or no substances at all. Specifically, the MDMA group reported increased feelings of social support, more social interactions and enhanced quality of sleep during the peritraumatic period, yielding reduced levels of mental distress and reduced PTSD symptom severity. These novel findings suggest that the influence of MDMA during the TE may carry protective effects into the peritraumatic period, possibly mediated through the known effects of MDMA in reducing negative emotions and elevating prosociality. These protective effects in turn may mitigate the development of early psychopathology-related symptoms. Current preliminary results underscore the need for further understanding of the cognitive and physiological processes by which psychedelic substances intersect with trauma recovery processes.

Introduction

A traumatic event (TE) is defined as exposure to actual or threatened death, serious injury, or sexual violence[1]. TEs are known to cause acute physiological, cognitive, and emotional responses, and to play a critical causal role in the etiology of psychopathologies such as depression and posttraumatic stress disorder (PTSD). Psychophysiological research revealed pronounced heterogeneity in the processing of TEs and their impact on individuals' overall functioning and mental health. While most individuals show formidable mental resilience even after encountering dramatic TEs, others may develop chronic and debilitating psychopathologies[2–5].

Trauma-related psychopathologies are notoriously difficult to treat and pharmacotherapeutic and psychotherapeutic interventions have shown limited efficacy thus far[6–8]. Recent research has focused on how psychoactive substances such as psychedelics and empathogens may assist in the treatment of PTSD and depression[9–12]. Among these psychoactive compounds, 3,4-methylenedioxymethamphetamine (MDMA) assisted psychotherapy has received substantial attention due to its impressive efficacy in the treatment of chronic PTSD[11,13–17], granting it a "breakthrough therapy" status by the U.S. Food and Drug Administration (FDA). MDMA is a monoamine releaser that induces the release of presynaptic serotonin [5-hydroxytryptamine (5-HT)] as well as dopamine and norepinephrine[18]. Though the exact mechanisms through which its psychopharmacological effects yield increased therapeutic effectiveness are not entirely clear, it was suggested that MDMA facilitates the treatment of PTSD by reducing sensations of fear and threat and inducing prosocial feelings[11,19].

On October 7th 2023, the Supernova music festival was one of the main targets of a surprise large-scale terror attack launched on Israel. Out of 3,500 festival attendees, over 360 participants were slaughtered, and dozens were kidnapped to Gaza as hostages. The survivors, fleeing the festival grounds, experienced and witnessed acute, life-threatening traumatic events for an extended duration (footage of the attack can be viewed here). Critically, many festival attendees were under the influence of mind-altering psychoactive substances during the attack. This is an unprecedented event, in which horrific mass trauma was experienced while in altered states of consciousness. As far as we know, there is no previous knowledge of the immediate or long-term consequences of trauma that is experienced under psychedelics. Studying the survivors

of this tragic natural experiment could provide novel insights on how trauma is acutely experienced under psychedelics, and how this may impact the processing of trauma in the peritraumatic period and determine clinical outcomes.

Here we report first results from an ongoing, large-scale, longitudinal study examining the impact of psychoactive substances on the experience and processing of traumatic events. We investigated a large cohort (n=657) of survivors of the Supernova music festival, assessing their experiences during the trauma itself as well as their processing of the traumatic events during the peritraumatic period four to twelve weeks following the event. Moreover, we collected data regarding mental distress and PTSD symptom severity during the peritraumatic period, as putative predictors of subsequent trauma psychopathology trajectories[20,21].

Methods

Participants: The study cohort consisted of six hundred fifty-seven (n=657) adults (406 males, Mean$\pm$SD Age: 27.03 ± 6.65), who survived the October 7th, 2023, attack at the Supernova music festival. These individuals were identified and recruited through a combination of methods, including a collaboration with "Safeheart" a non-profit organization (NGO) supporting survivors, word-of-mouth among friends who survived the attack together, and via survivor support groups on social media platforms. Prior to data collection, informed consent was obtained from all participants. All procedures were performed in compliance with the institutional guidelines of the University of Haifa and have been approved by the Institutional Ethics Committee (approval no. 374/23).

Data collection: Participant responses were collected from November 2nd, 2023, to January 3rd, 2024, a period extending from 26 to 88 days following the TE. This timeframe was selected to capture the acute and immediate reactions of survivors, thereby providing a snapshot of their initial state. Collecting data in this time window was critical in ensuring the analyses of peritraumatic processes, providing a comprehensive understanding of the survivors' psychological states in the aftermath of the traumatic experience. During this period, eligible participants were contacted via telephone, text message, email, or social media platforms, based on contact information provided by the participants during the initial recruitment stage. The survey instrument

was hosted on the Qualtrics platform, a secure online system that allows for anonymous and confidential submission of responses.

Survey Design: Several constructs pertinent to the TE and its subsequent processing were collected. These constructs were categorized into three distinct time frames: constructs related to the subjective experiences during the TE itself, constructs relevant to trauma processing in the peritraumatic period following the TE, and current clinical state (Fig. 1A). Participants first provided basic demographic details, including age and sex. They then were queried about their level of exposure to the threat of death, personal injuries sustained, and harm to loved ones. Next, participants were inquired regarding substance use during TE, including the type and quantity of substances used, timing of consumption relative to the TE, and the perceived intensity of the substance's effects at the onset of the attack. Constructs related to the subjective experiences during the TE included feelings of control and isolation, as well as the potential helpfulness of substances taken. Post-event measures relevant to peritraumatic processing encompassed social support, social interactions, guilt feelings, and sleep quality since the TE and up to date. Participants rated these constructs on a scale from 0 to 100, with 100 indicating the most extreme manifestation of the construct (e.g., optimal sleep quality or extreme guilt). Finally, established psychometric instruments were utilized to measure current clinical state. The Kessler Psychological Distress Scale (K6)[22] and the PTSD Checklist for DSM-5 (PCL-5)[23] assessed current levels of mental distress and PTSD symptom severity, respectively. Participants also rated their current level of being overwhelmed (on a scale from 0 to 100). Additional data were collected to control for potential confounding variables. Questions targeted the receipt of psychological aid pre- and post-TE, prior trauma experiences, existing psychiatric or neurological diagnoses, chronic medication usage, return to work status post-TE, and prior experience with psychoactive substances. Supplementary Table S1 provides a detailed account of these questionnaires.

Analytical Approach: Participants were categorized into substance groups based on the substance that they reported being under its influence during the attack: *Hallucinogenic* (e.g., psilocybin and LSD), *MDMA* (i.e., MDMA and Ecstasy), *Stimulants* (e.g., cocaine and amphetamines), light substances (*Light*, i.e., cannabis and/or alcohol), other substances (*Other*, e.g., Ketamine, PCP), and a *No-Use* group

(participants not under the influence of any substance). As the phenomenological and pharmacological effects of the *Other* substances group are highly variable and given that the group was relatively small (2.6% of the entire sample), this group was excluded from the main analyses. Analyzing the peritraumatic processing of the *Hallucinogenic* group is beyond the scope of the current manuscript. One-way ANOVAs were implemented to assess putative differences between groups with respect to (A) the effects of substances during trauma exposure, (B) the effects of substances on peritraumatic processing, and (C) the effects of substances on current clinical state. We focused on the impact of MDMA given its putative efficacy in treatment of PTSD. Therefore, planned contrasts (one-tailed t-tests) were implemented to investigate if participants in the *MDMA* group had improved measures compared to the other substance groups. Partial Chi-square tests were implemented to test for differences in proportions between groups. Multiple comparisons were corrected using False Discovery Rate (FDR) (Benjamini & Hochberg, 1995). Additionally, a Relative Risk (RR) assessment was employed to quantify the impact of substance use during the event on the probability of obtaining favorable outcomes[25]. RR is a measure of the probability ratio of an outcome in the "treatment" group (i.e., *MDMA*) relative to a control group (i.e., *No-Use*). This metric thus elucidates the ratio between the probability of an individual in the *MDMA* group to show a positive outcome compared to that of an individual who did not use any substance during the TE. RR scores above 1 indicate better outcomes in the *MDMA* group and an RR of 1 suggests no difference between groups. Finally, an exploratory correlational analysis was conducted to elucidate the relationships between the study constructs. All correlations reported were statistically significant with p-values below 0.05 before adjusting for multiple comparisons and exceeded a threshold of r=0.3, either positively or negatively.

Results

Trauma exposure across participants: Among the 657 survivors who completed the survey, the magnitude of exposure to trauma was universally high. Specifically, all participants (100%) reported direct exposure to a sequence of life-threatening events during the terror attack, underscoring the severe and immediate threat to their lives. Furthermore, a significant majority (83%) reported witnessing dead or injured individuals during the attack, 79% reported their loved ones were murdered and 68%

reported that loved ones were injured. Critically, all participants met Criterion A for PTSD as in DSM-5[1].

Substance use during trauma exposure: Sixty-eight percent (n=448) of survivors reported consuming at least one substance during the festival. MDMA was the most commonly used substance with 26.8% of individuals reporting consuming it during the party, followed by Hallucinogenic (22.9%), light substances (9.0%), stimulants (6.9%) and other substances (2.6%) (Fig. 1B). Slightly less than a third of the study cohort (31.8%) reported no substance use (*No-Use* group). Multi-substance use was common, most typically with survivors reporting consumption of cannabis or alcohol in addition to Hallucinogenics or MDMA. For a detailed report of all substance combinations see Supplementary Methods. Most individuals (74.2%) consumed the substance within three hours prior to the attack (Fig. 1C), presumably to obtain peak effects of the substances during sunrise. Accordingly, individuals across substance groups reported being strongly under the influence of the different substances when the attack began at 6:29 AM (Mean Rating $\pm$SD: $MDMA = 68.1 \pm 31.4; Stim = 67.9 \pm 26.5; Light = 58.6 \pm 33$). Statistical analysis revealed a significant difference in substance intake time between groups ($F(2,274) = 3.25, p = 0.04, \eta_p^2 = 0.023$), driven by a difference between the *MDMA* (1.72 ± 0.88 hours) and *Stimulants* (1.36 ± 0.57 hours) groups ($p_{adjusted} = 0.04$), with *Stimulants* taken closer in time to the beginning of the attack, in line with the shorter duration of effects of the stimulant substances. Analysis also revealed differences in age among the groups ($F(3,485) = 4.25, p = 0.006, \eta_p^2 = 0.03$), driven by younger ages in the *MDMA* (25.57 ± 5.08) compared to the *Light* (28.24 ± 6.24) and the *No-Use* (27.59 ± 7.83) groups (All $p_{adjusted} < 0.02$), indicating potential variations in substance preference across different age demographics. Furthermore, the analysis revealed a significant difference in sex distribution between groups ($\chi_p^2 = 8.96, p = 0.03$). However, no post-hoc comparisons were significant after correction for multiple comparisons implying that while sex may have played a role in the choice of substance, its impact was not substantial. No differences between groups were found in the time that passed from the TE until the survey completion date ($F(3,485) = 1.41, p = 0.24$, Fig. 1D).

Effects of substance during trauma exposure: Regarding the perceived influence of the substance during the TE (Fig. 1E), we found a significant difference between groups ($F(2,277) = 4.19, p = 0.016, \eta_p^2 = 0.03$). Specifically, individuals in

the *MDMA* group felt that the substance provided more assistance during the TE (68.12 ± 31.43) compared to the *Light* group (58.64 ± 32.96) ($p_{adjusted} = 0.015$). Contrary to expectations, no significant differences were found between groups in judgments regarding feelings of control ($F(3,485) = 0.57, p = 0.63$) or feelings of isolation ($(3,485) = 0.22, p = 0.88$,) during the TE (Fig. S2).

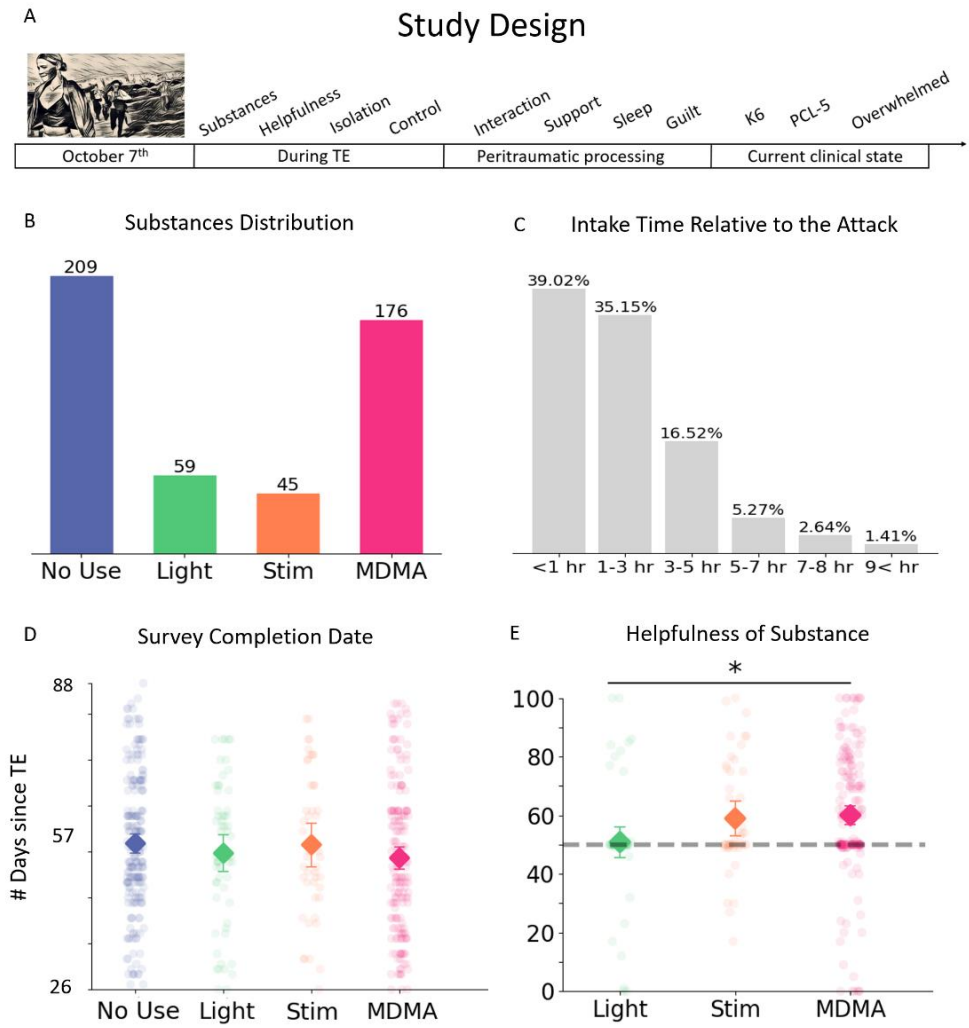

Figure 1: Study design and substance groups distributions. (A) Study design. Study timeline, beginning with the traumatic event on Oct 7th, and questions pertaining to subsequent phases; During TE: substance use during the TE, perceived helpfulness, feelings of isolation, and feelings of control; Peritraumatic processing: social interactions, feelings of support, sleep quality and feelings of guilt; Current clinical state: Distress (K6), PTSD symptoms severity (PCL-5) and feelings of being overwhelmed. All measurements were collected simultaneously but pertain to different epochs of the peritraumatic period. **(B) Substances distribution.** The majority of participants reported no substance use (n=209), followed by those who were under the influence of MDMA (n=176), light substances (n=59), and stimulants (n=45). **(C) Distribution of substance intake times relative to the TE**. Most participants reported consuming substances within the 3 hours prior to the start of the attack (39.02% within 1 hr, 35.15% within 1-3 hrs). **Panels D-E** Individual participants are represented by dots with overlaying mean values (diamonds) and 95% confidence intervals (error bars) for the respective measures in relation to substance groups (*No-Use*, *Light*, *Stim*, and *MDMA*). **(D) Distribution of survey response collection date by substance group.** Dots represent the survey completion date for each participant, measured in days from the TE. No differences were found between groups in the time that passed from the TE until survey completion date. **(E) Participants' perceived helpfulness of the substance during the TE.** Dots represent individual helpfulness ratings on a scale between 0 to 100. Higher scores represent more perceived helpfulness, with the dashed line indicating the threshold for positive judgments. Notably, individuals who consumed MDMA experienced it as significantly more helpful to them during the TE compared to individuals who consumed light substances (*p < .05).

Effects of substance on peritraumatic processing: Regarding constructs related to the processing of trauma following the TE, several significant differences emerged between substance groups. The feeling of support from friends and family was overall high (Fig. 2A) and differed significantly between groups ($F(3,485) = 4.59, p = 0.004, \eta_p^2 = 0.03$). The *MDMA* group reported significantly higher levels of support (83.30 ± 20.29) compared to the *Light* (71.59 ± 24.96) and *No-Use* (77.06 ± 24.56) groups (All $p_{adjusted}$ <0.007). Similarly, the extent of subsequent social interactions (Fig. 2B) differed significantly between groups ($F(3,485) = 2.84, p = 0.04, \eta_p^2 = 0.02$), again with the *MDMA* group reporting higher levels of interactions (75.02 ± 26.17) compared to the *Light* (67.49 ± 27.11) and the *No-Use* (67.59 ± 27.28) groups (All $p_{adjusted}$ <0.046). Sleep quality (Fig. 2C) was generally poor ($Overall\ Mean \pm SD$: 37.10 ± 30.31) and varied significantly between groups ($F(3,485) = 2.72, p = 0.04, \eta_p^2 = 0.02$), with the *MDMA* group reporting improved sleep quality (42.34 ± 31.84) compared to all other groups (Stim $= 32.16 \pm 29.74, Light = 31.64 \pm 26.01, No\ Use = 36.96 \pm 29.64$; All $p_{adjusted} < 0.045$). No significant differences were observed in feelings of guilt ($F(3,485) = 1.32, p = 0.27$), indicating that this aspect of trauma processing was not affected by the type of substance used during the TE (See supplementary Fig. S2).

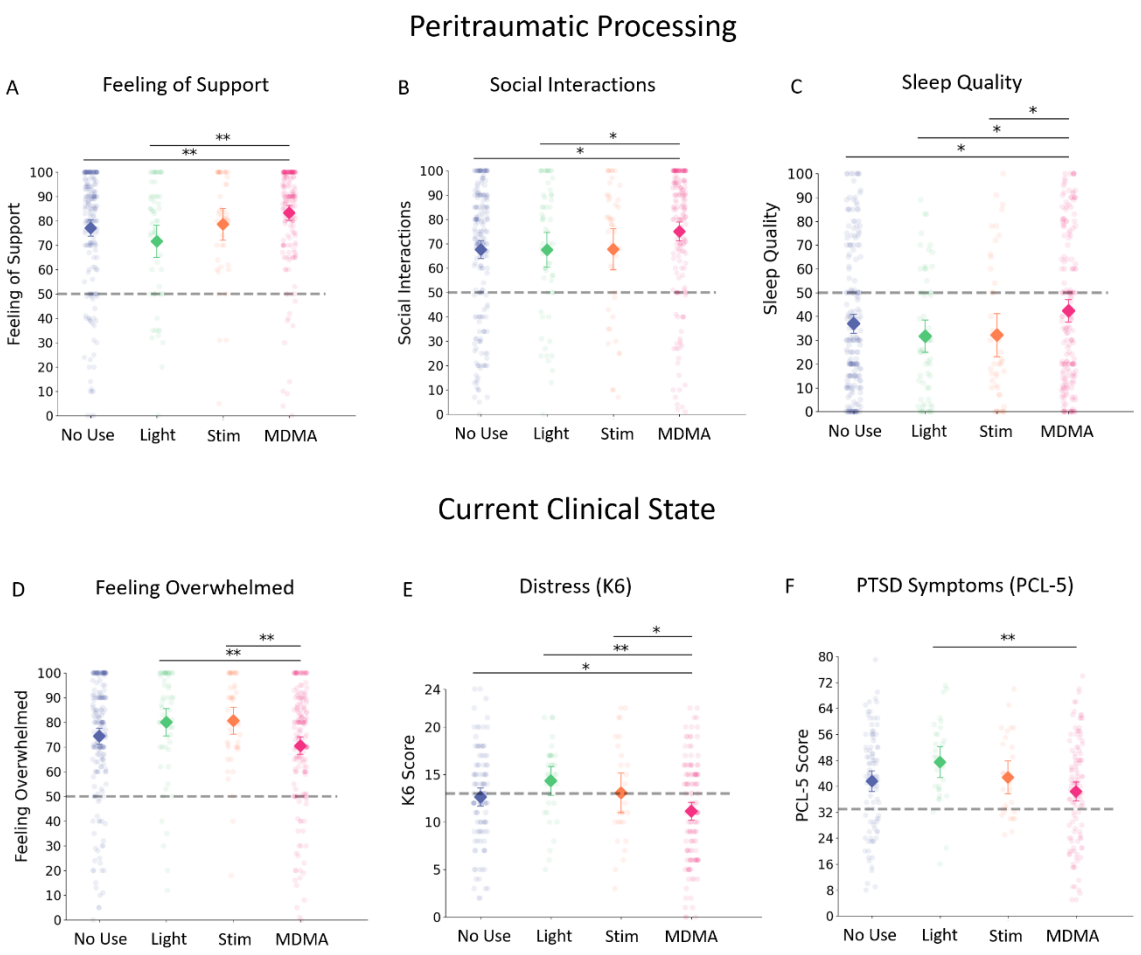

Figure 2: Outcome measures across substance groups. Panels A-F represent dot plots with overlaying mean values (diamonds) and 95% confidence intervals (error bars) for the respective outcome measures in relation to substance groups (*No-Use*, *Light*, *Stim*, and *MDMA*). Statistical significance is denoted by asterisks (*p < 0.05, **p < 0.01) **(A) Feelings of Support**. Mean levels of perceived social support across groups, with the dashed line indicating the threshold for positive judgments, illustrating significantly higher levels of perceived support in the *MDMA* group compared to *No-Use* and *Light* groups. **(B) Social Interactions.** Mean levels of perceived social interactions across groups, with the *MDMA* group demonstrating significantly increased interactions compared to the *No-Use* and *Light* groups. **(C) Sleep Quality.** Aggregate sleep quality scores, where the *MDMA* group showed a significant increase in reported sleep quality compared to the *No-Use*, *Light* and *Stimulants* groups. (**D) Feeling Overwhelmed.** The reported feeling of being overwhelmed, with the *MDMA* group indicating significantly lower levels compared to the *Light* and *Stimulants* groups. **(E) Distress (K6).** The Kessler Psychological Distress Scale (K6) scores, with a dashed line representing the clinical cut-off (=13). The *MDMA* group demonstrated significantly lower distress scores compared to the *No-Use*, *Light* and *Stimulants* groups. **(F) PTSD Symptoms (PCL-5).** Scores from the PTSD Checklist for DSM-5 (PCL-5), with a dashed line representing the clinical cut-off (=33). A significant difference emerged between the *Light* and *MDMA* groups, with the *MDMA* group displaying significantly lower scores compared to the *Light* group, indicative of less severe PTSD symptoms.

Current Clinical State: Assessing the current state of individuals within the 4-12 weeks following the TE revealed a significant difference between groups in the feeling of being overwhelmed ($F(3,485) = 3.95, p = 0.008, \eta_p^2 = 0.02$, Fig. 2D), driven by lower ratings in the *MDMA* group (70.51 ± 23.63) compared to the

Stimulants (80.67 ± 18.03) and the *Light* (80.05 ± 21.40) groups (All $p_{adjusted} < 0.007$). Moreover, the *MDMA* group presented better clinical status compared to the other groups. Specifically, mental distress (K6) scores (Fig. 2E) differed significantly between groups ($F(3,287) = 4.19, p = 0.006, \eta_p^2 = 0.04$), due to lower K6 scores in the *MDMA* group (11.15 ± 5.32) compared to all other groups ($Stim = 13.07 \pm 5.27, Light = 14.34 \pm 4.14, No\ Use = 12.64 \pm 4.95; All\ p_{adjusted} < 0.044$). Furthermore, PTSD symptom severity (PCL-5) scores (Fig. 2F) differed significantly between groups ($F(3,267) = 3.16, p = 0.025, \eta_p^2 = 0.03$), driven by lower PCL-5 scores in the *MDMA* group (38.36 ± 15.95) compared to the *Light* group (47.42 ± 12.80) ($p_{adjusted} = 0.006$). Notebly, mean PCL-5 scores across all groups were significantly higher than the clinical cutoff score ($t_{MDMA}(116) = 3.64, t_{Stim}(25) = 3.91, t_{Light}(29) = 6.17, t_{No\ Use}(93) = 5.37, p < 0.0003$ for all; $Clinical\ cutoff = 33$). This was not the case with respect to mental distress ((K6) scores) where *MDMA* was the only group to exhibit significatly lower K6 scores than the clinical cutoff ($t_{MDMA}(122) = -3.87, p = 0.00009$; $Clinical\ cutoff = 13$).

MDMA increases probability of favorable outcomes: The probability of participants in each substance group to achieve a favorable outcome was operationally defined as the ratio of participants in each group depicting a score above the designated threshold for a positive outcome or below the threshold for clinical status. Analysis of the probabilities across these measures revealed that participants who were under the influence of MDMA at the time of the attack had the highest likelihood of obtaining favorable outcomes (Figure 3A). Subsequent RR computations comparing the *MDMA* group to the *No-Use* group yielded the following results: During the TE, participants in the *MDMA* group were more likely to feel in control compared to the *No-Use* group ($RR_{\frac{MDMA}{No\ Use}} = 1.24$), with no difference in feelings of isolation ($RR_{\frac{MDMA}{No\ Use}} = 0.97$). In the peritraumatic processing period, participants in the *MDMA* group were more likely to feel socially supported ($RR_{\frac{MDMA}{No\ Use}} = 1.13$), have social interactions ($RR_{\frac{MDMA}{No\ Use}} = 1.11$) and exhibit improved sleep quality ($RR_{\frac{MDMA}{No\ Use}} = 1.29$) than the *No-Use* group, with no apparent difference in having feelings of guilt ($RR_{\frac{MDMA}{No\ Use}} = 0.98$). In terms of current clinical state, individuals in the *MDMA* group were significantly more likely to exhibit favorable outcomes across all evaluated measures during this phase, including a lower

likelihood of feeling overwhelmed ($RR_{\frac{MDMA}{No\ Use}} = 1.34$), reduced mental distress ($RR_{\frac{MDMA}{No\ Use}} = 1.16$) and lower PTSD symptom severity ($RR_{\frac{MDMA}{No\ Use}} = 1.11$). Further examination of the intersection of outcomes across all measures for each temporal epoch (Figure 3B) emphasized the heightened probability of favorable outcomes for the *MDMA* group during the peritraumatic processing period ($RR_{\frac{MDMA}{No\ Use}} = 1.52$) and in the current clinical state ($RR_{\frac{MDMA}{No\ Use}} = 1.14$), yet no difference was evident in RR relating measures during the TE itself ($RR_{\frac{MDMA}{No\ Use}} = 1.03$). In summary, exposure to trauma while under the influence of MDMA consistently yielded an increased probability of favorable outcomes across a range of psychological and social measures, when contrasted with no substance use. We note that the comparison to the *No-Use* group was chosen as a baseline for RR measures as these individuals represent the effect of trauma with no pharmacological modulations. Comparisons of RR measures to other substances revealed even larger favorable outcomes for MDMA (see Supplementary Table S2-S4).

Correlation Analysis: As expected, the clinical measures of K6 and PCL-5 demonstrated a significant positive intercorrelation ($r = 0.81$). These clinical measures were also positively correlated with the subjective feeling of being overwhelmed (K6 with overwhelmed: $r = 0.51$; PCL with overwhelmed: $r = 0.53$). Moreover, as per expectations, the social constructs were highly correlated with each other (Support with Social interaction: $r = 0.47$), affirming the intertwined nature of these social constructs. Interestingly, both social support and social interactions were inversely related to clinical measures (K6 with support: $r = -0.35$; PCL with support: $r = -0.30$; K6 with social interactions: $r = -0.43$; PCL with social interactions: $r = -0.38$), suggesting that higher levels of perceived social support and frequent social interactions may be associated with better clinical outcomes. Sleep quality was also inversely correlated with the aforementioned clinical measures (sleep with K6: $r = -0.43$; sleep with PCL: $r = -0.49$; sleep with feeling overwhelmed: $r = -0.47$), suggesting that better sleep is associated with lower levels of psychological distress, PTSD symptoms severity and feelings of being overwhelmed. Moreover, feelings of guilt were positively correlated with K6 ($r = 0.42$) and PCL scores ($r = 0.43$), which

may imply that guilt is a contributing factor to psychological distress and the development of post-traumatic stress symptoms.

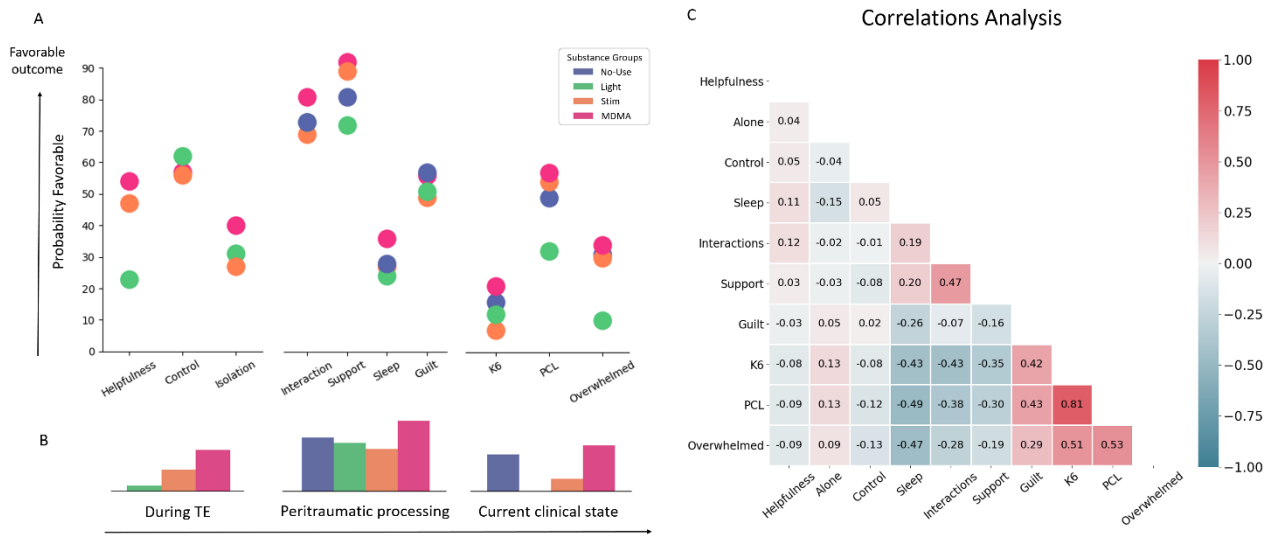

Figure 3: Probability for favorable outcome across substance groups and correlation analysis. (A) Favorable outcome for each trauma related measure. Composite bubble chart depicting the percentage of participants above the cutoff score of each measure in the favorable outcome direction, across different substance groups. Color coding indicates the substance group as per legend. Measures include perceived helpfulness of substance during the TE, feelings of control during the TE, feelings of isolation during the TE, social interaction, support, sleep quality and feelings of guilt during the peritraumatic period, and current levels of mental distress (K6), PTSD symptom severity (PCL-5), and feelings of being overwhelmed. Note that the MDMA group exhibited more favorable outcomes across most measures. **(B) Favorable outcome by time period.** Bar graphs represent the intersection of outcomes across all measures for each temporal epoch, providing a visual comparison of the central tendencies. **(C) Correlation analysis.** Correlation matrix heatmap showing the strength of associations between the different trauma related measures across substance groups. Correlation coefficients range from -1 to 1, with the scale illustrated on the right. Positive correlations are indicated in shades of red, negative correlations in blue, and neutral associations in white. Positive correlations are observed, particularly between clinical measures such as K6 and PCL scores (r = 0.81), as well as between these clinical measures and between feeling overwhelmed and having feelings of guilt. K6 and PCL were found to be negatively correlated with social measures and sleep quality.

Discussion

The attack on Oct 7th, 2023, targeting the Supernova music festival, allowed for the first time ever, to investigate the impact of different psychoactive substances consumed during extreme trauma on the subsequent processing of the trauma and its clinical consequences. Our results show a previously unreported effect by which survivors of a mass trauma event that experienced the trauma under the influence of MDMA exhibit enhanced coping across several clinical and subjective measures. Survivors who consumed MDMA reported that the substance assisted them during the TE compared to survivors who consumed alcohol and cannabis. Anecdotal reports from these survivors suggest that the substance may have endowed them with energy to run further and faster during the attack, in line with the known energizing effects of

MDMA[26]. These reports also suggest beneficial effects of MDMA during the trauma that were expressed by reduced sensations of fear and threat while the event unfolded.

Whether or not directly connected to its immediate effects during the TE, MDMA was also associated with improved processing during the peritraumatic period. Survivors who consumed MDMA during the TE reported feeling more social support, more social interactions, and better sleep quality one to three months subsequent to the event. Interestingly, survivors from the MDMA group exhibited increased social interactions and enhanced feelings of social support not only compared to participants who consumed cannabis and alcohol, but also compared to participants who did not consume any substance during the event. These findings are in line with the well-documented prosocial effects of MDMA in both animals and humans[19,27,28]. Studies investigating MDMA-assisted psychotherapy suggested an important role for the prosocial effects of MDMA in its therapeutic efficacy[15,29]. This in turn may relate to the improved clinical state that participants reported in the peritraumatic period, subsequent to their consumption of MDMA during the TE. Specifically, participants in the MDMA group exhibited reduced feelings of overwhelmingness as well as lower mental distress and less severe PTSD symptoms one to three months following the trauma, compared to participants who did not consume MDMA during the TE. Another construct that may have been impacted by MDMA is sleep. Survivors who consumed MDMA during the TE reported having better subjective sleep quality over the subsequent one to three months compared to all other groups. Sleep quality is known to be impaired in the aftermath of trauma and this impairment is considered to not only represent a symptom of trauma exposure, but to play a causal role in the formation of post-traumatic psychopathologies[30–32]. Hence, improved sleep quality in the peritraumatic period may have contributed to the overall improved clinical state reported by participants in the MDMA group.

Taken together, our results show that psychoactive compounds impact the acute experience of TE as well as their processing during the peritraumatic period. Survivors who experienced this extreme trauma while under the effects of MDMA showed improved trauma processing in the peritraumatic period and a better clinical state. This novel finding, showing a putative protective effect of MDMA, is in line with theoretical and empirical accounts of the therapeutic effect of MDMA for PTSD treatment[11,15]. The current protocols for MDMA-assisted psychotherapy suggest that re-experiencing the traumatic events in a safe setting while experiencing the prosocial and fear-reducing

effects of MDMA may enhance the benefits of psychotherapy for PTSD[11,12,28]. Our results show that experiencing trauma under the influence of MDMA, in a horrific setting, may reduce harmful effects during the peritraumatic period. These preliminary results suggest that the better clinical presentation during the peritraumatic period may stem from enhanced social processing after the events. Participants in the *MDMA* group showed strikingly better social coping measures in the aftermath of the event which in turn were negatively correlated with their clinical ratings. Moreover, no differences in sociality ratings during the event were found, suggesting that this effect may have manifested more strongly after, rather than during the TE. Thus, while MDMA was felt to have assisted participants during the TE through increased levels of alertness and energy similarly to stimulants, the prosocial and fear-reducing aspects of MDMA may drive the improved clinical state of the survivors over time.

While considering these novel insights it is important to acknowledge that, as in all natural experiments, we have no control over numerous additional factors that might have impacted participants' perception during the event and its subsequent processing. Moreover, current results pertain to the peritraumatic period. Hence, while PTSD symptom severity during the peritraumatic period is predictive of post-traumatic psychopathology, results do not reflect the full clinical picture that has yet to stabilize at this moment in time. Finally, we have to consider possible biases in the data. First, a clear survivor bias as we cannot collect data from the many people who did not survive the attack. Second, as in most studies, it is possible that survivors showing more severe symptoms are underrepresented in our sample. We note however that the mean PCL score in our sample across substance groups (40.88 ± 15.42) is well above the clinical cutoff suggesting that our cohort is experiencing substantial PTSD symptoms.

In summary, this tragic natural experiment enabled us to provide the first-ever investigation of how different psychoactive substances impact the processing of trauma during the trauma as well as in the peritraumatic period. Our results show that participants who consumed MDMA during the TE exhibit better processing and improved clinical states compared to participants who consumed other substances or no substances at all during the TE. The current results are a first report from an ongoing longitudinal study that aims to elucidate the cognitive, physiological and neural mechanisms underlying the protective effects of MDMA. We hope that our results will not only enhance our understanding of trauma under psychedelics but will also help the survivors of this harrowing experience.

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References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5™, 5th Ed.* xliv, 947 (American Psychiatric Publishing, Inc., Arlington, VA, US, 2013). doi:10.1176/appi.books.9780890425596.
2. Admon, R., Milad, M. R. & Hendler, T. A causal model of post-traumatic stress disorder: disentangling predisposed from acquired neural abnormalities. *Trends in Cognitive Sciences* **17**, 337–347 (2013).
3. Rab, S. L. & Admon, R. Parsing inter- and intra-individual variability in key nervous system mechanisms of stress responsivity and across functional domains. *Neurosci Biobehav Rev* **120**, 550–564 (2021).
4. Shalev *et al.* Estimating the risk of PTSD in recent trauma survivors: results of the International Consortium to Predict PTSD (ICPP). *World Psychiatry* **18**, 77–87 (2019).
5. Yehuda, R. *et al.* Post-traumatic stress disorder. *Nat Rev Dis Primers* **1**, 1–22 (2015).
6. Haagen, J. F., Smid, G. E., Knipscheer, J. W. & Kleber, R. J. The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis. *Clinical psychology review* **40**, 184–194 (2015).

7. Kitchiner, N. J., Lewis, C., Roberts, N. P. & Bisson, J. I. Active duty and ex-serving military personnel with post-traumatic stress disorder treated with psychological therapies: systematic review and meta-analysis. *European journal of psychotraumatology* **10**, 1684226 (2019).
8. Krystal, J. H. *et al.* It is time to address the crisis in the pharmacotherapy of posttraumatic stress disorder: a consensus statement of the PTSD psychopharmacology working group. *Biological psychiatry* **82**, e51–e59 (2017).
9. Carhart-Harris, R. *et al.* Trial of psilocybin versus escitalopram for depression. *New England Journal of Medicine* **384**, 1402–1411 (2021).
10. Krediet, E. *et al.* Reviewing the Potential of Psychedelics for the Treatment of PTSD. *International Journal of Neuropsychopharmacology* **23**, 385–400 (2020).
11. Mitchell, J. M. *et al.* MDMA-assisted therapy for moderate to severe PTSD: a randomized, placebo-controlled phase 3 trial. *Nature Medicine* 1–8 (2023).
12. Vermetten, E. & Yehuda, R. MDMA-assisted psychotherapy for posttraumatic stress disorder: A promising novel approach to treatment. *Neuropsychopharmacology* **45**, 231–232 (2020).
13. Bershad, A. K., Miller, M. A., Baggott, M. J. & de Wit, H. The effects of MDMA on socio-emotional processing: Does MDMA differ from other stimulants? *J Psychopharmacol* **30**, 1248–1258 (2016).
14. Jerome, L. *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* **237**, 2485–2497 (2020).
15. Mithoefer, M. C. *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* **5**, 486–497 (2018).

16. Mithoefer, M. C. *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* **236**, 2735–2745 (2019).
17. Nutt, D. J. & de Wit, H. Putting the MD back into MDMA. *Nat Med* **27**, 950–951 (2021).
18. Simmler, L. D. & Liechti, M. E. Pharmacology of MDMA- and Amphetamine-Like New Psychoactive Substances. in *New Psychoactive Substances : Pharmacology, Clinical, Forensic and Analytical Toxicology* (eds. Maurer, H. H. & Brandt, S. D.) 143–164 (Springer International Publishing, Cham, 2018). doi:10.1007/164_2018_113.
19. Bedi, G., Phan, K. L., Angstadt, M. & De Wit, H. Effects of MDMA on sociability and neural response to social threat and social reward. *Psychopharmacology* **207**, 73–83 (2009).
20. Jagodnik, K. M. *et al.* Screening for post-traumatic stress disorder following childbirth using the Peritraumatic Distress Inventory. *Journal of Affective Disorders* **348**, 17–25 (2024).
21. Ozer, E. J., Best, S. R., Lipsey, T. L. & Weiss, D. S. Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin* **129**, 52–73 (2003).
22. Furukawa, T. A., Kessler, R. C., Slade, T. & Andrews, G. The performance of the K6 and K10 screening scales for psychological distress in the Australian National Survey of Mental Health and Well-Being. *Psychological medicine* **33**, 357–362 (2003).
23. Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K. & Domino, J. L. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *Journal of traumatic stress* **28**, 489–498 (2015).
24. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (Methodological)* **57**, 289–300 (1995).
25. McGough, J. J. & Faraone, S. V. Estimating the Size of Treatment Effects. *Psychiatry (Edgmont)* **6**, 21–29 (2009).

26. Holze, F. *et al.* Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. *Neuropsychopharmacol.* **45**, 462–471 (2020).
27. Heifets, B. D. *et al.* Distinct neural mechanisms for the prosocial and rewarding properties of MDMA. *Science translational medicine* **11**, eaaw6435 (2019).
28. Kamilar-Britt, P. & Bedi, G. The prosocial effects of 3, 4-methylenedioxymethamphetamine (MDMA): controlled studies in humans and laboratory animals. *Neuroscience & Biobehavioral Reviews* **57**, 433–446 (2015).
29. Schmid, Y. & Bershad, A. K. Altered states and social bonds: Effects of MDMA and serotonergic psychedelics on social behavior as a mechanism underlying substance-assisted therapy. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* (2024) doi:10.1016/j.bpsc.2024.02.001.
30. Pace-Schott, E. F., Germain, A. & Milad, M. R. Effects of sleep on memory for conditioned fear and fear extinction. *Psychol Bull* **141**, 835–857 (2015).
31. Simon, L. & Admon, R. From childhood adversity to latent stress vulnerability in adulthood: the mediating roles of sleep disturbances and HPA axis dysfunction. *Neuropsychopharmacol.* **48**, 1425–1435 (2023).
32. Weber, F. C. & Wetter, T. C. The Many Faces of Sleep Disorders in Post-Traumatic Stress Disorder: An Update on Clinical Features and Treatment. *Neuropsychobiology* **81**, 85–97 (2022).