Trauma under psychedelics: how psychoactive substances impact trauma processing

The Hamas-led attack in southern Israel on October 7, 2023 was one of the deadliest terror attacks in history, resulting in 1,182 fatalities, over 4,000 wounded, and 251 taken hostage[1]. The Nova festival, an 18-hour rave held in the Gaza Envelope region, suffered the highest casualties in the attack, with over 370 killed.

For the Nova attendees, the highlight of the all-night party was sunrise, and many of them reported taking psychoactive substances timed to take effect at dawn. Less than half an hour after sunrise, the first rockets came in sight. As a result, survivors endured prolonged exposure to acute, life-threatening traumatic events, many while under the influence of psychoactive substances. These tragic circumstances created an unprecedented opportunity to examine the effect of peritraumatic exposure to psychoactive substances on short- and long-term impact of severe, life-threatening trauma.

From an estimated population of 3,710 Nova survivors (66% male; 76% 18-24 years old), we identified 1,239 eligible individuals. Of these, 923 (74.5%) completed the study questionnaire by February 21, 2024, of whom a total of 107 (11.6%) did not meet the DSM-5 Criterion A for post-traumatic stress disorder (PTSD), as they were not directly exposed, and 44 (4.8%) did not complete all questions, leading to their exclusion. This resulted in an analytic cohort of 772 survivors (487 males; mean age: 26.96±6.55 years). The study was approved by the University of Haifa Ethics Committee, and all participants provided informed consent. We systematically collected data on exposure to psychoactive substances and peritraumatic experiences.

Primary outcome measures included the PTSD Checklist for DSM-5 (PCL-5) with cutoff score set at 33, and the Kessler Psychological Distress Scale (K6) with cutoff score set at 13. Secondary outcomes included a 0-100 metric of perceived substance helpfulness, sense of control, and feelings of isolation during trauma exposure. Post-traumatic processing measures included self-perceived social interactions, social support, feelings of guilt, and sleep quality.

Seventy-two percent (N=556) of survivors reported being under the influence of psychoactive substances during the attack, with most (79.1%) consuming them within the three hours prior to the attack. Due to the prevalence of polysubstance use and in order to isolate the effects of individual substances, analyses focused on participants that were under the influence of a single substance: hallucinogens (psilocybin or lysergic acid, LSD; N=84); 3,4-methylenedioxymethamphetamine (MDMA) (N=99); or cannabis and/or alcohol (N=68). No substance was used by 216 participants. Group differences were analyzed using a linear regression model with substance groups as independent variables, and a multivariate model with age, sex and time from event as covariates. Only models with the lowest Bayesian information criterion (BIC) are presented. Additional results and polysubstance analyses are presented in the supplementary information.

Significant between-groups differences were found on the metric of perceived substance helpfulness during the traumatic event ($F_{2,247}$=6.14, p=0.003, R^2=0.05). Specifically, individuals in the MDMA (62.6±21.7, β=12.4, p=0.001) and hallucinogens (61.5±28.3, β=11.3, p=0.004) groups perceived more substance helpfulness during the traumatic event, as compared to the cannabis/alcohol group (50.2±20.6). This finding is unlikely to be explained by differential scope and impact of the traumatic event, as we found those to be similar across groups (all p values >0.15). Anecdotal reports suggest that survivors who were under the influence of MDMA during the trauma experienced reduced sensations of fear and threat as the event unfolded.

PTSD symptom severity scores differed significantly between groups ($F_{3,229}$=4.8, p=0.003, R^2=0.06), with significantly higher PCL-5 scores in the cannabis/alcohol group (48.3±12.8) compared to the no-use group (39.8±14.9, β=8.5, p=0.006). Notably, mean PCL-5 scores across groups were high (41.3±15.3), with all four groups exceeding the clinical cutoff score of 33 (all p values <0.05).

Mental distress scores also differed significantly between groups ($F_{3,250}$=4.3, p=0.006, R^2=0.05), due to lower K6 scores in the MDMA group (10.5±5.1) compared to the no-use group (12.2±5.1, β=–1.6, p=0.049), and higher scores in the cannabis/alcohol group (14.4±4.1) compared to the no-use group (β=2.3, p=0.031). Mean K6 scores in the cannabis/alcohol group were significantly higher than the clinical cutoff of 13, whereas scores in the MDMA and no-use groups were significantly below this threshold (all p values <0.05).

During the peritraumatic period, substance groups differed significantly in the extent of social interactions ($F_{3,463}$=4.5, p=0.004, R^2=0.03), with the MDMA group reporting significantly higher levels (76.5±26.2) compared to the no-use group (66.5±27.1, β=10.0, p=0.003). Sleep quality also varied significantly across groups ($F_{3,463}$=4.6, p=0.004, R^2=0.03). Compared to the no-use group (37.5±30.0), the MDMA group reported better sleep quality (45.4±30.9, β=7.9, p=0.025), while the cannabis/alcohol group reported worse quality (29.4±25.0, β=–8.1, p=0.046).

No significant group differences were found in perceived control ($F_{3,463}$=0.59, p=0.62) or feelings of social isolation ($F_{3,463}$=1.53, p=0.21) during trauma exposure. In the peritraumatic period, feelings of guilt ($F_{3,463}$=0.97, p=0.41) and perceived support from friends and family ($F_{3,463}$=2.5, p=0.056, R^2=0.016) did not differ between groups.

These findings suggest that trauma exposure under the influence of MDMA is associated with reduced psychological distress, higher sociality and improved sleep quality in the post-traumatic period, possibly mediated through MDMA's known effects of reducing negative emotions and elevating prosociality[2,3].

This beneficial effect of MDMA aligns with evidence from MDMA-assisted psychotherapy studies highlighting reduction of negative affect as key to its therapeutic efficacy[4-6]. Clinical protocols for MDMA-assisted psychotherapy suggest that re-experiencing traumatic events in a safe setting, while exposed to MDMA's prosocial and fear-reducing effects, may enhance the benefits of psychotherapy for PTSD[2-4]. The present study extends this idea by demonstrat-

ing that, even outside a structured therapy setting, MDMA may facilitate adaptive post-trauma social behaviors that could support psychological recovery.

Survivors who were under the influence of cannabis and/or alcohol during the attack exhibited worse sleep quality and poorer clinical outcomes, including higher mental distress and post-traumatic symptoms. These findings align with previous research demonstrating the detrimental effects of alcohol on trauma processing, including increased risk of peritraumatic dissociation, anxiety, depression, and acute stress disorder symptoms[7].

Limitations of this study include lack of control over substance choice, dosage, and intake time, as well as potential personality-based selection biases. Exposure to substances was self-reported and is prone to information biases. While the study captures real-world trauma survivors' behavior, its generalizability might be limited. Findings reflect only the initial post-traumatic period, which, though predictive, may not capture long-term clinical outcomes. Additionally, cannabis and alcohol were grouped, due to sample size constraints, limiting substance-specific analyses.

Survivor bias is inherent, and survivors with more severe symptoms may be under-represented in our cohort. However, the mean PCL-5 score in our sample across groups is well above the clinical cutoff, suggesting substantial post-traumatic symptoms. Unmeasured confounders are unavoidable, and causal assumptions should be made with much caution, if at all. Further research should explore the mechanisms linking psychoactive substances to trauma recovery and explain the putative protective role of MDMA and detrimental effect of cannabis and alcohol.

This unprecedented natural experiment offers novel insights into how psychoactive substances influence trauma processing during acute trauma and in the initial post-traumatic period. As part of an ongoing longitudinal study, these findings have important clinical implications for both survivors of this attack and trauma survivors more broadly.

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Prevalence of clinically significant radiological abnormalities in people with first episode psychosis

Magnetic resonance imaging (MRI) can be used to identify secondary psychoses caused by structural brain abnormalities, which may require different treatment from primary psychoses[1]. However, there is no international consensus as to whether MRI should be routinely offered in first episode psychosis[2-5]. We examined MRI radiology reports in a large sample of people with first episode psychosis, drawn from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre Case Register. We determined the clinical significance of MRI scans by assessing the proportion of patients with a scan that was abnormal, and the proportion of scans that led to a change in the clinical management.

The study population comprised all patients who received a first diagnosis of a psychotic disorder within a 14-year period (from January 1, 2007 to June 30, 2021). In those who underwent MRI in an 18-month window around the index diagnosis, we determined the indication for the scan, the results of the scan, and any subsequent change to clinical management. The project was approved by the Oxfordshire Research Ethics Committee (23/SC/0257).

We categorized indication for MRI as: cognitive impairment (including suspected dementia), head injury, neurological features (for example, focal neurological signs or seizures), headaches, suspected encephalitis, suspected space-occupying lesion (including suspected brain metastases), hyperprolactinaemia, other atypical presentation (such as unusual age of onset or rapid onset), routine screening, and not specified. An MRI was coded as "normal" if this was specified in the radiology report, or if the findings were described as "within normal limits", a "normal variant", "no abnormality detected", "normal for age" or words to this effect. When abnormalities were reported, we specified the finding and grouped them following the classification used in the meta-analysis by Blackman et al[6]. The broad categories comprised atrophy, cyst, pituitary abnormality, tumour, vascular abnormality (excluding white matter), ventricular abnormality, white matter abnormality, or other.

We used logistic regression to examine the association of indication for the scan with having an abnormal result. The same approach was used to examine the relationship between indication and a subsequent change in clinical management. Covariates included in these models were age, ethnicity, gender, and primary