

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our [Editorial Policies](#) and the [Editorial Policy Checklist](#).

Please do not complete any field with "not applicable" or n/a. Refer to the help text for what text to use if an item is not relevant to your study.

For final submission: please carefully check your responses for accuracy; you will not be able to make changes later.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- | n/a | Confirmed |
|-------------------------------------|--|
| ☐ | ☒ The exact sample size (<i>n</i>) for each experimental group/condition, given as a discrete number and unit of measurement |
| ☐ | ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly |
| ☐ | ☒ The statistical test(s) used AND whether they are one- or two-sided
<i>Only common tests should be described solely by name; describe more complex techniques in the Methods section.</i> |
| ☐ | ☒ A description of all covariates tested |
| ☐ | ☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons |
| ☐ | ☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals) |
| ☐ | ☒ For null hypothesis testing, the test statistic (e.g. <i>F</i> , <i>t</i> , <i>r</i>) with confidence intervals, effect sizes, degrees of freedom and <i>P</i> value noted
<i>Give P values as exact values whenever suitable.</i> |
| ☒ | ☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings |
| ☒ | ☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes |
| ☐ | ☒ Estimates of effect sizes (e.g. Cohen's <i>d</i> , Pearson's <i>r</i>), indicating how they were calculated |

Our web collection on [statistics for biologists](#) contains articles on many of the points above.

Software and code

Policy information about [availability of computer code](#)

- | | |
|-----------------|--|
| Data collection | Commercially available software was used for data collection through the study including: electronic data capture (EDC) software (Medrio Version 40.5), and interactive web randomization system (IWRS) software (IT Clinical Version 11.0.1). |
| Data analysis | Commercially available software (SAS software version 9.4 (SAS Institute Inc., Cary, N.C.) was used for analyses in keeping with the Statistical Analysis Plan. |

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio [guidelines for submitting code & software](#) for further information.

Data

Policy information about [availability of data](#)

All manuscripts must include a [data availability statement](#). This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our [policy](#)

The data that support the findings of this study are available from the Sponsor beginning one year after completion of the trial. However, 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 from the authors upon reasonable request and with the permission of the Sponsor. All requests for raw and analyzed data are promptly reviewed to verify if the request is subject to any confidentiality obligations. Participant-related data not included in the paper were generated as part of clinical trials and may be subject to participant confidentiality. Any data that can be shared will be released via a data use agreement. Proposals should be directed to maps.org/dataset

Research involving human participants, their data, or biological material

Policy information about studies with [human participants or human data](#). See also policy information about [sex, gender \(identity/presentation\), and sexual orientation](#) and [race, ethnicity and racism](#).

Reporting on sex and gender	This is a human research trial that applies to >1 sex/gender; sex and gender were collected based on self-report.
Reporting on race, ethnicity, or other socially relevant groupings	Race and ethnicity were collected based on self-report. Analyses of primary or secondary outcomes by gender were not planned a priori; some exploratory analyses included sex as a covariate (Supplementary Methods).
Population characteristics	Various demographic and clinical characteristics are reported in Table 1.
Recruitment	Participants were recruited from August 21, 2020, to May 18, 2022 (last participant visit November 2, 2022) through print and internet advertisements, referrals from treatment providers, and by word of mouth. Participants were required to initiate contact with the study sites themselves, even if recommended by a provider.
Ethics oversight	The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonization and with the ethical principles of the Declaration of Helsinki. An independent data monitoring committee ensured the study was conducted safely and had sufficient sample size. The review boards/institutions that approved the study protocol are listed in the Supplementary Methods.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	SAS version 9.4 (SAS Institute) was used for analyses. Sample size was calculated to achieve a power of 90% at an alpha of 0.0499. The statistical analysis plan was guided by the ICH E9 (R1) guidelines ³ , which describe the use of estimands and sensitivity analyses to measure the effects of a drug if taken as directed ('de jure,' assessment of efficacy using an initially randomized treatment estimand) and if taken as assigned, regardless of adherence ('de facto,' assessment of effectiveness using a treatment policy estimand). The de jure dataset did not include outcome measurements taken after treatment discontinuation in the analysis of treatment efficacy, and these were considered missing at random. The de facto estimand, a supportive sensitivity analysis, included CAPS-5 data collected after treatment discontinuations. One participant discontinued after experimental session 1 and declined outcome data collection; this participant was excluded from primary and secondary efficacy analyses per the modified Intent to Treat analysis set, which required exposure to MDMA or placebo and at least one follow-up CAPS-5 assessment.
Replication	This Phase 3 RCT replicates previous findings in a series of previously published controlled Phase 2 trials (Mithoefer 2019) and a previous Phase 3 RCT, MAPP1 (Mitchell 2021).
Randomization	Participants were randomized in a 1:1 allocation and in a blinded fashion to the MDMA-AT and placebo with therapy groups, stratified by clinical site. Randomization was managed via an interactive web randomization system based on a centralized randomization schedule developed by an independent third-party vendor to maintain blinding.
Blinding	This was a double blind study. Additionally, a central pool of blinded independent assessors was used to mitigate the risk of functional unblinding.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing	
Data exclusions	
Non-participation	
Randomization	

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	
Research sample	
Sampling strategy	
Data collection	
Timing and spatial scale	
Data exclusions	
Reproducibility	
Randomization	
Blinding	

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	
Location	
Access & import/export	
Disturbance	

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

- | | |
|-------------------------------------|--|
| n/a | Involved in the study |
| ☒ | ☐ Antibodies |
| ☒ | ☐ Eukaryotic cell lines |
| ☒ | ☐ Palaeontology and archaeology |
| ☒ | ☐ Animals and other organisms |
| ☐ | ☒ Clinical data |
| ☒ | ☐ Dual use research of concern |
| ☒ | ☐ Plants |

Methods

- | | |
|-------------------------------------|---|
| n/a | Involved in the study |
| ☒ | ☐ ChIP-seq |
| ☒ | ☐ Flow cytometry |
| ☒ | ☐ MRI-based neuroimaging |

Thirteen study sites (11 in the US and two in Israel; both institutional and private practice sites) participated. Participants were recruited from August 21, 2020, to May 18, 2022 (last participant visit November 2, 2022).

Antibodies

Antibodies used	
Validation	

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	
Authentication	
Mycoplasma contamination	
Commonly misidentified lines (See ICLAC register)	

Palaeontology and Archaeology

Specimen provenance	
Specimen deposition	
Dating methods	
☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.	
Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about [studies involving animals; ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals	
Wild animals	
Reporting on sex	
Field-collected samples	
Ethics oversight	

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov identifier NCT04077437
Study protocol	The study protocol has been provided to and is available via Nature Medicine.
Data collection	Thirteen study sites across the US (11) and Israel (2) participated. These included both institutional and private clinic sites. Participants were recruited from August 21, 2020, to May 18, 2022 (last participant visit November 2, 2022). Eleven US sites: Zen Therapeutic Solutions (Charleston, SC), Aguazul Bluewater, Inc (Boulder, CO), Wholeness Center (Fort Collins, CO), New School Research, LLC (Los Angeles, CA), Ray Worthy Psychiatry, LLC (New Orleans, LA), University of California San Francisco (San Francisco, CA), San Francisco Insight & Integration Center (San Francisco, CA), University of Wisconsin (Madison, WI), New York University (New York, NY), Nautilus Sanctuary (New York, NY), Trauma Research Foundation (Boston, MA). Two Israel sites: Beer Yaakov (Beer Yaakov Mental Health Center), Tel Hashomer (Tel Hashomer Medical Center).
Outcomes	Outcomes: Primary and secondary objectives were mean change in Clinician-Administered PTSD Scale for DSM-5 total severity and Sheehan Disability Scale scores, respectively, for MDMA-AT versus placebo with therapy from baseline to 18 weeks post-baseline. These outcome measures were pre-defined in conjunction with the FDA during a Special Protocol Assessment.

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes
☐	☐ Public health
☐	☐ National security
☐	☐ Crops and/or livestock
☐	☐ Ecosystems
☐	☐ Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes
☐	☐ Demonstrate how to render a vaccine ineffective
☐	☐ Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐ Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐ Increase transmissibility of a pathogen
☐	☐ Alter the host range of a pathogen
☐	☐ Enable evasion of diagnostic/detection modalities
☐	☐ Enable the weaponization of a biological agent or toxin
☐	☐ Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	
Novel plant genotypes	
Authentication	

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links <i>May remain private before publication.</i>	
Files in database submission	
Genome browser session (e.g. UCSC)	

Methodology

Replicates	
Sequencing depth	
Antibodies	
Peak calling parameters	
Data quality	
Software	

Flow Cytometry

Plots

Confirm that:

- ☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	
Instrument	
Software	
Cell population abundance	
Gating strategy	

☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	
Design specifications	
Behavioral performance measures	

Imaging type(s)	
Field strength	
Sequence & imaging parameters	
Area of acquisition	
Diffusion MRI	☐ Used ☐ Not used

Preprocessing

Preprocessing software	
Normalization	
Normalization template	
Noise and artifact removal	
Volume censoring	

Statistical modeling & inference

Model type and settings	
Effect(s) tested	
Specify type of analysis:	☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

(See [Eklund et al. 2016](#))

Correction

Models & analysis

n/a | Involved in the study

- | | | |
|--------------------------|--------------------------|--|
| ☐ | ☐ | Functional and/or effective connectivity |
| ☐ | ☐ | Graph analysis |
| ☐ | ☐ | Multivariate modeling or predictive analysis |

Functional and/or effective connectivity

Graph analysis

Multivariate modeling and predictive analysis