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Understanding Neuroplasticity Induced by TrYptamines (UNITy): the effects of dimethyltryptamine (DMT) on drinking

Submission date 01/08/2024	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 01/08/2024	**Overall study status** Ongoing	
Last Edited 09/08/2024	**Condition category** Mental and Behavioural Disorders	

Plain English summary of protocol

Background and study aims

Excessive drinking and alcohol use disorder (AUD) represents a global and highly costly healthcare burden. Current treatments are not effective for a large portion of people and there are relatively few treatment options to help people reduce their drinking when first-line options fail. Recently, there has been significant interest in the potential of psychedelic drugs in various mental health disorders, including alcohol and substance use disorders. Despite some promising findings, we still have very little rigorous experimental data on exactly how psychedelic drugs might produce positive changes in mental health and behaviour. One theory suggests that these drugs might alter the connectivity between key brain regions, better allowing people to modify their memory associations around drinking, drinking-related thoughts and behaviours. Researchers aim to thoroughly assess these and other candidate mechanisms to deepen our understanding of the effects of psychedelic drugs and their potential role in the treatment of substance use disorders. They will do this in a randomised experimental study with a short-acting psychedelic drug called dimethyltryptamine (DMT). They will use questionnaires, cognitive tests and different types of brain imaging to comprehensively understand the impact of DMT on the brain and drinking behaviour. The results of this study may, in the future, lead to improved therapies for mental health disorders such as addiction.

Who can participate?

Healthy adults aged 21-65 years. For this study, the researchers are specifically seeking hazardous and harmful alcohol drinkers who would like to reduce their drinking but are not currently seeking treatment, undergoing treatment, or using NHS services to manage their drinking. Hazardous and harmful drinking refers to alcohol consumption that is regularly in excess of recommended ‘low risk’ limits on intake (one to two or more drinks per day in the UK). Due to the potent effects of the drugs used in the study, the researchers are not recruiting patients or people with current diagnoses of mental health or neurological disorders. Participants will be generally healthy and all potential participants will undergo a thorough screening process. There are strict eligibility criteria that must be met to ensure participants' comfort and safety during the study. These criteria are essential to confirm eligibility and suitability for participation in the study.

What does the study involve?
The study consists of three in-person visits over 2 weeks, followed by several remote follow-up sessions over 9 months.

Visit 1:
Participants will attend the brain scanning unit at UCL, where they will undergo a breathalyzer and drug use screening, and basic health measures will be taken. The researchers will also collect a finger prick blood spot to assess markers of drug and alcohol use over the past month. Participants will then complete a series of questionnaires on mood, attitudes, drinking levels, and drug consumption, along with computer tasks. They will then have an informal conversational 'interview' with the experimenters about their hopes and expectancies for the studies and strategies to help reduce alcohol consumption. Participants will then watch a full-length movie in the MRI scanner while we measure brain activity. Between study sessions, participants will then use a custom-designed study app on their phones to periodically prompt short journal entries and mood questionnaires. Between Visits 1 and 2, participants must complete an online 'psychedelics preparation' course to ensure they are prepared for the infusion on visit 2.

Visit 2:
Participants must fast for four hours and avoid liquids for two hours before attending the study centre. After a breathalyser test, finger-prick blood alcohol/drug test, questionnaires and computer tasks, participants will be fitted with an EEG cap to monitor brain activity while they receive an intravenous infusion of one of the study drugs. The session will last up to 4 hours and participants will be monitored closely during and after the infusion. After the infusion, another informal conversational interview will ask about participants' experiences current mood and expectations going forward, followed by some final questionnaires. Participants must arrange for transportation home, as driving or cycling is not allowed and must not drink or take any drugs for the next 24 hours. Participants will continue to complete daily notes via the study app until visit 3.

Visit 3:
Participants will return to UCL 1 week after Visit 2 to repeat the tests from Visit 1, including finger-prick blood test, questionnaires and watching a different movie in the scanner. This final session concludes the in-person portion of the study, and participants will be reimbursed for their time.

Follow-ups:
Online surveys will be conducted at 1, 3, 6, and 9 months to assess long-term changes in wellbeing. Each follow-up takes 20-30 minutes, and participants will be compensated for their time. These follow-ups will also include additional active weeks for the app.

What are the possible benefits and risks of taking part?
Possible benefits:
Participation in this study may contribute to the development of improved therapies for drug addictions and other mental health disorders. By taking part, participants are directly aiding the advancement of neuroscience and our understanding of the human mind. Participants may find the tasks enjoyable and gain personal insights. While no guarantees can be made, typically individuals taking part in studies like substantially reduce their drinking, and may experience increased self-awareness of drinking patterns, improved mood and other health benefits that come from reduced drinking. Additionally, participants will be reimbursed at the standard UCL rate.

Possible risks:
While DMT is generally considered a very safe drug, it is important to note that the subjective experience or 'trip' can be intense and emotionally challenging for some individuals. DMT produces profound visual, auditory and bodily hallucinations. Potential effects include confusion, anxiety, rapid heart rate, raised blood pressure, feelings of tightness, agitation, dizziness, rapid eye movements, and dilated pupils. These, and the subjective effects of the drug, should dissipate very rapidly after stopping the infusion.
Individuals with a predisposition to mental health conditions, particularly schizophrenia and psychosis, may experience triggered symptoms due to the rapid and intense changes in brain chemistry caused by DMT. Therefore, individuals with a history of these disorders or with first-degree family members who have these conditions must not participate and we will undergo a thorough screening to minimise this risk.
DMT interacts with the brain's serotonin system and may have dangerous interactions with drugs that affect serotonin levels, such as antidepressants (SSRIs), monoamine oxidase inhibitors (MAOIs), amphetamines, and opioids. Individuals taking any of these medications are not eligible to participate.
To minimize the likelihood of difficult experiences, participants will be thoroughly prepared through a tailor-made course and conversations with experienced research team members. Participants are under no obligation to continue and may withdraw from the study at any point. A safe, calm, and relaxing environment will be provided to reduce the likelihood of challenging experiences. Additionally, participants will have the opportunity to discuss their experiences in detail with the research team immediately afterwards.

Where is the study run from?
Each of the three visits will take place at University College London, near Euston Station. Visit 1 and 3 will be at the brain scanning facility at 26 Bedford Way, WC1H 0AP, and visit 2 will be at the drug infusion facility in the Clinical Psychopharmacology Unit at 1-19 Torrington Place, WC1E 7HB.

When is the study starting and how long is it expected to last?
October 2020 to December 2027

Who is funding the study?
This study is funded by the Wellcome Trust through the Wellcome Leap: Untangling Addiction programme. This is a non-profit organization that funds scientific research and there is no funding from pharmaceutical or private entities.

Who is the main contact?
Prof. Ravi Das, unity-project@ucl.ac.uk

Contact information

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Additional identifiers

Protocol serial number
17715/001

Study information

Scientific Title
A randomised, placebo-controlled experimental study of dimethyltryptamine on alcohol reward memory in non-treatment-seeking excessive drinking: effects on drinking, therapeutic mechanisms and neural biomarkers

Acronym
UNITY

Study objectives
1. N,N-Dimethyltryptamine (DMT) will lead to a greater reduction than placebo in self-reported drinking levels (g EtOH/day via timeline follow-back; TLFB), confirmed by phosphatidylethanol (pEth) levels. The greatest reductions in drinking and pETh will be observed when DMT infusion follows an alcohol memory reactivation procedure designed to destabilise maladaptive drinking memories, consistent with reconsolidation-interference.
2. DMT will reduce cue reactivity (liking/wanting) to alcohol stimuli compared to placebo, with the greatest reductions when DMT is combined with alcohol memory reactivation.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 06/01/2021, UCL Research Ethics Committee (Graduate School, North Cloisters, Wilkins Building UCL, Gower Street, London, WC1E 6BT, United Kingdom; +44 (0)2076798368; ethics@ucl.ac.uk), ref: 17715/001

Primary study design
Interventional

Study design
2 x 2 factorial randomized placebo-controlled mechanistic study

Study type(s)
Other

Health condition(s) or problem(s) studied
Alcohol consumption, cue reactivity, craving and neural connectivity in non-treatment-seeking excessive (hazardous/harmful) alcohol drinking

Interventions
Drugs:
1. Active drug: 25 mg N,N -Dimethyltryptamine fumarate, administered as 10 ml 2.5 mg/ml solution in buffer, intravenously over 10 minutes
2. Placebo: equal volume (10 ml) buffer solution, administered intravenously over 10 minutes

Behavioural:
1. Alcohol memory reactivation procedure involving exposure to preferred alcohol and visual cues
2. Control memory reactivation involving exposure to non-alcohol stimuli and visual cues

Participants are randomised to one combination of drug and behavioural intervention in a 2 x 2 factorial design. Block randomisation using a random code is used to balance group Ns at 40, 80 and 120.

Intervention Type
Mixed

Primary outcome(s)
Current primary outcome measure as of 09/08/2024:
Alcohol consumption (mean g EtOH/day) measured by self-report timeline-follow-back (TLFB) of the prior two weeks' consumption at dosing - 7 days (baseline), + 14 days (post-intervention) and +28 days (1-month post-intervention). Follow-up timepoints are at +12 weeks, +24 weeks and +36 weeks. Timepoints may not be exact due to scheduling constraints but aim to be +/- 2 days from those above.

Previous primary outcome measure:
Alcohol consumption (mean g EtOH/day) measured by self-report timeline-follow-back (TLFB) at – 7 days (baseline), + 7 days (post-intervention) and +28 days (1-month post-intervention), with follow-up at +12 weeks, +24 weeks and +36 weeks

Key secondary outcome(s)
Current secondary outcome measures as of 09/08/2024:
1. Blood phosphatidylethanol (pEth) levels measured by dried blood spot analysis at baseline, post-intervention (+14 days) and +28 days, with follow-up at + 12 weeks, +24 weeks and +36 weeks
2. Neural alcohol cue reactivity measured via cue reactivity fMRI task at baseline and +14 days
3. Subjective alcohol cue reactivity measured via exposure to in vivo cues at baseline and +14 days
4. Alcohol craving measured with the alcohol craving questionnaire (ACQ) at baseline, +14 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks.
5. Daily alcohol consumption measured via smartphone ecological momentary assessment response (EMA) at -baseline, +14 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks
6. Daily alcohol craving measured via daily smartphone VAS at -baseline, +14 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks
Timepoints may not be exact due to scheduling constraints, but aim to be +/- 2 days from those above.

Previous secondary outcome measures:
1. Phosphatidylethanol (pEth) levels measured by dried blood spot analysis at baseline, +7 days and +28 days, with
follow-up at + 12 weeks, +24 weeks and +36 weeks
2. Neural alcohol cue reactivity measured via cue reactivity fMRI task at baseline and +7 days
3. Subjective alcohol cue reactivity measured via exposure to in vivo cues at baseline and +7 days
4. Alcohol craving measured with the alcohol craving questionnaire (ACQ) at baseline, +7 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks.
5. Daily alcohol consumption measured via smartphone ecological momentary assessment response (EMA) at -baseline, +7 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks
6. Daily alcohol craving measured via daily smartphone VAS at -baseline, +7 days and +28 days with follow-up at + 12 weeks, +24 weeks and +36 weeks

Completion date
30/12/2027

Eligibility

Key inclusion criteria
1. Aged 21 - 65 years
2. Normal or corrected-to-normal vision and hearing
3. Fluent English
4. Scoring >10 on the AUDIT questionnaire
5. Drinking ≥3 times a week
6. Drinking >20 UK units (160g etOH) per week for women or >35 UK units (280g etOH) per week for men; equivalent to ≥ WHO 'moderate risk' criteria
7. Motivated to reduce consumption based on the Motivation to Reduce Alcohol Consumption (MRAC) Scale

Participant type(s)
Healthy volunteer, Other

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
21 Years

Upper age limit
65 Years

Sex
All

Key exclusion criteria
1. Currently seeking or receiving treatment for alcohol use disorder (AUD) or other substance use disorders (SUDs)
2. Any current major mental health, neurological or physical health disorder
3. BMI <18 or >35 kg/m²
4. Severe alcohol dependence as assessed by Severity of Alcohol Dependence Questionnaire (SADQ)
5. Personal or family history of psychosis or schizophrenia
6. Personality disorder (assessed by Structured Assessment of Personality Abbreviated Scale [SAPAS] and clinical psychologist screening)
7. Lifetime trauma exposure (assessed by Stressful Life Events Screening Questionnaire [SLESQ])
8. >3 lifetime uses of DMT
9. Use of psychedelics within the past 6 months / any regular lifetime use
10. Regular use (> 2x /month) of psychoactive drugs other than nicotine, alcohol or caffeine
11. Contraindications to MRI
12. Known contraindication to psychedelic drugs

13. Current participation in other psychedelics or alcohol studies
14. Prior participation in similar studies within the UCL Clinical Psychopharmacology Unit
15. Previous familiarity with movies used in MRI scanning

Date of first enrolment
24/08/2024

Date of final enrolment
30/08/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Clinical Psychopharmacology Unit
University College London
1-19 Torrington Place
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Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Charity

Funder Name
Wellcome Leap

Alternative Name(s)

Leap, Wellcome Leap Inc, Wellcome Leap, Inc.

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The anonymised datasets generated during and/or analysed during the current study will be stored in publicly a available repository (openneuro.org, OSF.io) and on local servers, with access granted to researchers upon reasonable request. Analysis code for neuroimaging data will be made available on openneuro.org to maximise reproducibility.

IPD sharing plan summary
Stored in publicly available repository, Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes