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Reward emotion learning and ketamine study

Submission date
20/04/2023

Recruitment status
No longer recruiting

Registration date
26/04/2023

Overall study status
Completed

Last Edited
16/07/2024

Condition category
Other

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Ketamine is a licensed drug which is shown to have a rapid antidepressant effect. However, the cognitive mechanisms of ketamine action are not well understood. Ketamine may work on brain areas involved in learning and memory. This study investigates how ketamine influences learning and memory and their underlying brain mechanisms. This study will help the researchers to understand how ketamine influences brain activity while people are engaged with learning and decision-making tasks that involve remembering affective memories.

Who can participate?
Healthy volunteers who do not have a history of psychiatric or neurological disorders or addiction

What does the study involve?
Participants will undergo medical and psychiatric health screening, questionnaires and computer tasks before and after the administration of the study drug (a single infusion of ketamine or saline), and an MRI scan a day after the administration of the drug/placebo. MRI is a type of brain scan that allows us to see how the brain responds during, for example, decision-making between two available options.

What are the possible benefits and risks of participating?
The study will not be of direct benefit to the participants but it is hoped that the results will help improve our understanding of how novel antidepressants like ketamine work in the human brain. Possible risks from taking part involve answering questionnaires and completing memory and computer-based tasks, undergoing an MRI scan and receiving ketamine/placebo. These risks will be discussed with the participants before their enrollment in the study. To minimise any harms or risks, participants will be carefully supervised and we will ensure that any risks are minimised by conducting a detailed medical and psychiatric screening and having 24-hour on-call availability for participants in the study.

Where is the study run from?
The University of Oxford (UK)

When is the study starting and how long it is expected to run?
April 2021 to August 2023

Who is funding the study?
1. Medical Research Council (UK)
2. Janssen Pharmaceuticals (USA)

Who is the main contact?
Prof. Catherine Harmer, catherine.harmer@psych.ox.ac.uk

Contact information

Type(s)
Principal investigator

Contact name
Prof Catherine Harmer

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
NCT04850911

Protocol serial number
MR/S035591/1

Study information

Scientific Title
An experimental medicine model for fast acting antidepressant drug treatment in treatment resistant depression

Acronym
RELAKS

Study objectives

Ketamine's efficacy as an antidepressant is now well established yet the mechanisms underlying its antidepressant effect are yet to be fully described. Work in the animal literature and research in humans is suggestive of specific effects on anhedonia and memory reconsolidation. In this study, the investigators will further explore the effects of ketamine on learning and memory as well as measure the associated changes at the neural level in a sample of healthy volunteers. Participants will be assigned to receive ketamine or a placebo and complete a set of tasks which will allow the investigators to quantify the effect of ketamine on learning about reward and punishment and memory for learned reward associations 24 hours after ketamine infusion. This study will help the investigators to understand the basis of ketamine's antidepressant effects and aid the development of new treatments for depression.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/04/2021, Oxford Central University Research Ethics Committee (CUREC; Research Services, Research Governance, Ethics & Assurance Team, University of Oxford, Boundary Brook House, Churchill Drive, Headington, Oxford, OX3 7GB, UK; +44 (0)1865 616575; ethics@medsci.ox.ac.uk), ref: R73654/RE007

Study design
Double-blind placebo-controlled between-subjects interventional study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Cognitive effects of ketamine on healthy volunteers

Interventions
Participants are randomized in a 1:1 ratio (double-blind) to ketamine infusion at 0.05 mg/kg or saline intravenously via a drug pump over 40 minutes.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Ketamine hydrochloride

Primary outcome(s)
1. Activation of the habenula during the Pavlovian conditioning task in response to the conditioned stimulus associated with pain stimuli and in response to the receipt of shock, measured using the Blood Oxygen Level Dependent (BOLD) signal in the habenula at the time of the shock-associated conditioned stimulus presentation and at the time of shock delivery
2. Habenula response to the absence of expected reward and the receipt of an unexpected loss

(i.e. a negative prediction error signal) in both the reward maximisation and loss minimisation tasks, measured using the BOLD signal in the habenula at the time of outcome presentation in both the reward maximisation and loss minimisation tasks
3. Preference for high-reward probability shapes learned after winning money (in the Wheel of Fortune draw) during the preference test. The proportion of choices where high-reward probability shapes are selected. This will be based on the difference between the perceived reward probability of shapes learned after the winning and losing of money (an area under the curve measure).

Key secondary outcome(s))

1. Ventral striatum response to the expected reward and the omission of an unexpected loss (i.e. a positive prediction error signal) in both the reward maximisation and loss minimisation tasks. Measured using the BOLD signal in the ventral striatum at the time of outcome presentation in both the reward maximisation and loss minimisation tasks at 24 hours after ketamine administration
2. Pupil dilation (measured by an eye tracker device) in response to decision values in the affective memory preference test. Baseline corrected pupil dilation measured at the time of option presentation during each choice trial of the affective memory preference test at 24 hours after ketamine administration
3. Difference in pupil response to shapes learned after winning versus losing money: between-groups comparison of pupil dilation in response to shapes learned after a loss and shapes learned after a win in a Wheel of Fortune draw that induces an experimental change in negative /positive affect. Measured at 24 hours after ketamine administration
4. Amount of money earned in the learning and memory task: final component completed 24 hours after ketamine administration before scanning.
5. Change in bio-behavioral measures of stress following laboratory-induced stress: between groups comparison of salivary cortisol in response to Oxford Cognition Stress Task at 1 week after ketamine infusion
6. Change in bio-behavioral measures of stress following laboratory-induced stress: between groups comparison of salivary alpha-amylase in response to Oxford Cognition Stress Task at 1 week after ketamine infusion
7. Change in bio-behavioral measures of stress following laboratory-induced stress: between groups comparison of heart rate in response to Oxford Cognition Stress Task at 1 week after ketamine infusion
8. Change in bio-behavioral measures of stress following laboratory-induced stress: between groups comparison of visual analogue scale ratings in response to Oxford Cognition Stress Task at 1 week after ketamine infusion
9. Recognition of positive and negative facial expressions: recognition accuracy for positive and negative facial expressions immediately and 24 hours after ketamine infusion
10. Recognition of positive and negative facial expressions: reaction time to recognise positive and negative facial expressions immediately and 24 hours after ketamine infusion
11. Categorisation of emotional words: accuracy of categorisation for positive and negative descriptor words at 24 hours after ketamine infusion
12. Recognition of emotional words: reaction time to categorise positive and negative descriptor words at 24 hours after ketamine infusion
13. Recall of emotional words: the number of words correctly (hits) and incorrectly (false alarms) recalled at 24 hours after ketamine infusion

Completion date

31/08/2023

Eligibility

Key inclusion criteria
1. BMI between 18 and 30 kg/m²
2. Participant is willing and able to give informed consent for participation in the study
3. Sufficient knowledge of the English language to understand and complete study tasks
4. Willingness to refrain from driving, cycling, or operating heavy machinery, until the following morning or a restful sleep has occurred, whichever is later
5. Willingness to refrain from signing legal documents within 7 days after the infusion visit
6. Willingness to refrain from drinking alcohol for 3 days before the infusion visit and one day before any of the other visits throughout the study

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
70

Key exclusion criteria
1. Any current or past DSM-V significant psychiatric disorder including any psychotic, mood and anxiety and borderline personality disorders
2. History of, or current medical conditions which in the opinion of the investigator may interfere with the safety of the participant or the scientific integrity of the study, including epilepsy /seizures, brain injury, hepatic or renal disease, severe gastrointestinal problems, Central Nervous System (CNS) tumours, neurological conditions
3. First-degree relative with a diagnosis of schizophrenia-spectrum or other psychotic disorder, or bipolar disorder
4. History of unexplained hallucinations or impulse control problems (e.g. pathological gambling)
5. Current or past history of heart rhythm disorders
6. Clinically significant hypertension
7. Increased intraocular pressure/glaucoma
8. Current pregnancy (as determined by urine pregnancy test taken during Screening and Infusion Visits) or breastfeeding
9. Clinically significant abnormal values for clinical chemistry (e.g. liver function tests), urine drug screen, blood pressure measurement and ECG. A participant with a clinical abnormality or parameters outside the reference range for the population being studied may be included only if the Investigator considers that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures

10. Current or previous intake (last 3 months) of any medication that has a significant potential to affect mental functioning (e.g. benzodiazepines, antidepressants, neuroleptics etc)
11. Any intake of recreational drugs in the last 3 months (e.g. marijuana, ecstasy etc)
12. Lifetime recreational use of ketamine or phencyclidine
13. Regular alcohol consumption of more than 14 units a week or excessive alcohol consumption up to three days before any of the in-person study visits
14. Inability to abstain from alcohol for more than 1 week
15. Regular smoker (> 5 cigarettes per day)
16. Excessive caffeine user (> 6 caffeinated drinks per day)
17. History of recurrent rashes or history of allergic reactions to relevant substances (ketamine treatment, placebo treatment)
18. Previous participation in a study using the same or similar tasks
19. Current participation in another study or participation in a similar study within the last 6 months
20. Participant is unlikely to comply with the clinical study protocol or is unsuitable for any other reason, in the opinion of the Investigator
21. Claustrophobia
22. Any implants (including dental implants) or pacemaker
23. Tattoos above the chest
24. Any other MRI contraindications outlined in FMRIB 7 Tesla scanning safety form

Date of first enrolment
20/04/2021

Date of final enrolment
31/08/2023

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Oxford
Warneford Hospital
Oxford
United Kingdom
OX3 7JX

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Janssen Research and Development

Alternative Name(s)
Janssen R&D, Janssen Research & Development, Janssen Research & Development, LLC, Janssen Research & Development LLC, Janssen Pharmaceutical Companies of Johnson & Johnson, Research & Development at Janssen, JRD, J&J PRD

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

To comply with the GDPR and the Data Protection Act 2018, personal data will be deleted as soon as possible after it is no longer needed for the study.

All research data (e.g. MRI scans, behavioural task results, online questionnaire responses) will be stored on the University of Oxford servers and will be downloaded to University-owned computers used by the members of the research team for analysis. Anonymised data will be shared in response to internal and external requests following publication or as part of the publication.

The name and email address of the investigator/body who should be contacted for access to the datasets: Prof. Catherine Harmer (catherine.harmer@psych.ox.ac.uk); erdem.pulcu@psych.ox.ac.uk
The type of data that will be shared: raw behavioural data in .csv and .mat files
Dates of availability: Data will be shared only upon publication of results with corresponding scientific papers
Whether consent from participants was required and obtained: Obtained
Comments on data anonymization: Data will be fully anonymised

IPD sharing plan summary

Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1.1	26/07/2021	24/04/2023	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes