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The effect of serotonin receptor 4 on cognition in unusual experiences

Submission date
17/09/2025

Recruitment status
Recruiting

Registration date
19/09/2025

Overall study status
Ongoing

Last Edited
19/09/2025

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol
Background and study aims
Studying non-impactful psychotic-like experiences (PLEs) is a well-established method for exploring mechanisms underlying the more severe psychosis. PLEs are subclinical, not associated with distress or the problems with thinking seen in psychosis, and affect around 5-10% of the healthy population. However, compared to those without, individuals with PLEs often have subtle thinking differences, making them a useful non-clinical model for screening potential early psychosis treatments. Preclinical data suggest that selectively targeting the fourth serotonin receptor (5-HT4R) could improve thinking by enhancing neurotransmitters and boosting neurotrophic factors. Earlier pilot work in healthy humans shows that 5-HT4R activation (also known as agonism), using prucalopride, is associated with improved performance on thinking tasks. The effect of 5-HT4R agonism has never been assessed in those with psychosis-related symptoms. However, using electronic health records, it was found that prucalopride treatment (a 5-HT4R agonist used as a laxative) was associated with a >70% lower risk of psychosis compared to other anti-constipation treatments.
Experimental medicine models allow rapid assessment of medications that probe specific targets (i.e. prucalopride on 5-HT4Rs) using proxy measures (i.e. effect on thinking patterns) to establish proof-of-concept in a model of the clinical population of interest (i.e. PLE population as a model of early psychosis). These are not Clinical Trials of Investigational Medicinal Products (CTIMPs) as they occur after clinical trials evaluating safety and before assessing clinical efficacy.

Who can participate:
Community healthy volunteers (aged 18 - 40 inclusive) with psychotic-like experiences in the last 12 months

What does the study involve:
Half of the study population will be randomly allocated to receive a highly-selective 5-HT4 R agonist (prucalopride) and half will receive a placebo for 7 days. Baseline and follow-up measures will include neurocognitive tasks and resting state fMRI and MRS; changes in mood, anxiety, subjective cognition, and blood biomarkers and prucalopride levels will also be assessed.

What are the possible benefits and risks of participating?
The results of this research project will be used for research purposes and will not provide

participants with any direct benefit, nor are they intended to be used as part of clinical examinations. Results will not be used to help diagnose, treat or manage a particular condition. However, a clinician or appropriately trained individual will review all blood and structural MRI results. If any relevant clinical findings are identified, the participant and their GP will be informed, if the participant agrees. They or an appropriately qualified (medically trained) study team member will contact the participant to let them know that a potential clinically relevant finding has been identified. They will ask whether the participant would like to know about the results. If they do, the clinical team and/or study team will discuss the results with them and assist them in organising any follow-up assessments that may be required.

The interview materials and the types of questions asked in this project have been used in projects in the past without causing undue distress. Participants can choose not to answer any questions that make them feel uncomfortable, and can request the interviewer to stop at any time. Any support needed will be provided by staff who are not members of the research team.

An MRI or MRS scan does not produce or expose participants to radiation. However, as the imaging machine produces a magnetic field (like a 'giant magnet'), there are certain conditions or situations where an MRI would not be suitable. Before the scan, participants will complete a medical history form, which radiographers will review.

The space inside the MRI scanner is small and can be quite noisy. Feelings of mild anxiety or claustrophobia are normal in the first few minutes. If these feelings persist or become distressing, testing will stop.

The risks of the blood sample collection are the same as those of ordinary blood tests, and there may be some small discomfort, pain and/or bruising. Infection, swelling, excess bleeding, clotting or fainting are also possible, although less common. If this happens, it can be easily treated.

Where is the study run from?
University of Birmingham, UK

When is the study starting?
The study runs from February 2024 to October 2027. Enrolment will commence from September 2025. It is expected to run for 18 months to 2 years.

Who is funding the study?
The NIHR Mental Health Translational Research Collaboration – Mental Health Mission, UK

Who is the main contact?
Dr Angharad de Cates, Principal Investigator and Clinical Lecturer, a.n.decates@bham.ac.uk

Contact information

Type(s)
Public, Scientific, Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Does 5-HT4 receptor agonism have an acute procognitive effect in young adults with psychotic-like experiences: proof-of-concept study: The SERENE study: SErotonin Receptor 4 Effect on NEurocognition

Acronym
SERENE

Study objectives
Primary aim: To determine if pharmacologically activating the 5-HT4R compared to placebo has an effect on acute neurocognition in healthy volunteers with psychotic-like experiences (PLEs) as a proof-of-concept meriting further investigation.

Study objectives:
1. Potentially establish novel proof-of-principle evidence for acute neurocognitive effects of 5-HT4R agonism in people with PLEs
2. Yield an estimate of effect size to aid future design of potential next stage clinical trials where clinical impact on cognition and other outcomes in early psychosis can be explored.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 02/06/2025, Science, Technology, Engineering and Mathematics Committee (University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom; +44 (0)121 414 3344; ADM-researchgov@adf.bham.ac.uk), ref: ERN_3117, amendment approved 03/09/2025

Study design
Experimental medicine (interventional) proof-of-concept randomized double-blinded placebo-controlled study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Healthy volunteer community population with psychotic-like experiences in the last 12 months

Interventions
Intervention arm: Prucalopride (tablets, over-encapsulated in a vegetarian shell and filled with Lactose Monohydrate Ph. Eur. powder or equivalent grade) 1mg for 2 days and then 2x1mg for 5-8 days (max 10 days in total). Taken orally once daily at home. 2 bottles will be dispensed at randomisation by a study clinician: Bottle 1 contains medication for day 1 and day 2; Bottle 2 contains medication for day 3 onwards. A researcher will contact participants by prior agreement on day 2 to confirm that participants have not had side effects and to move from Bottle 1 to Bottle 2. Bottles will be returned to researchers at the end of the study, and the remaining capsules will be counted.

Placebo arm: Placebo (Lactose Monohydrate Ph Eur powder in a hard vegetarian shell to match the active) 1 capsule for 2 days and then 2 capsules for 5-8 days (max 10 days in total). Taken orally once daily at home. 2 bottles will be dispensed at randomisation by a study clinician: Bottle 1 contains medication for day 1 and day 2; Bottle 2 contains medication for day 3 onwards. A researcher will contact participants by prior agreement on day 2 to confirm that participants have not had side effects and to move from Bottle 1 to Bottle 2. Bottles will be returned to researchers at the end of the study, and the remaining capsules will be counted.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Prucalopride

Primary outcome(s)
Pattern of effect across a battery of behavioural neurocognitive measures: the auditory verbal learning task (AVLT), working memory task (N-back), facial expression recognition task (FERT), rewards learning task (PILT) from enrollment to the end of the study (after 7-10 days of medication)

Key secondary outcome(s))
The following secondary outcome measures are assessed at baseline and follow-up, from enrolment to the end of the study (after 7–10 days of medication), unless otherwise stated:
1. Changes in brain network connectivity measured using resting-state functional MRI

2. Brain metabolites, such as choline and glutamate/glutamine, levels in the hippocampus are measured using magnetic resonance spectroscopy (MRS)
3. Blood biomarkers linked to psychotic symptoms and 5-HT4 agonism (IL-1b, IL-6, IL-10, TNFa, IFNg, BDNF, S100B and SuPAR) and prucalopride levels measured using blood tests from enrolment to the end of the study (after 7–10 days of medication). Biomarkers in blood will be quantified by multiplex analysis (Luminex) and ELISA. Prucalopride in the blood will be quantified by chromatography and mass spectrometry.
4. Subjective cognition measured using self-report measures (PDQ-20 (Perceived Deficits Questionnaire))

Completion date
01/10/2027

Eligibility

Key inclusion criteria
1. Aged 18-40 years inclusive
2. Consent to the study
3. Recent psychotic-like experiences (last 12 months)
4. Fluent in English

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
40 years

Sex
All

Key exclusion criteria
1. Current antipsychotic medication
2. Current antidepressant medication
3. Documented history of intellectual disability
4. Past or current clinically relevant central nervous system disorder
5. Current significant medical disorder
6. Current or past treated or untreated psychotic episode
7. Pregnancy, breastfeeding, or actively trying to become pregnant. Participants will be asked to avoid becoming pregnant.
8. Individuals with contraindications for MRI, including those with non-MRI-safe metallic or electronic implants, incompatible medical devices, severe claustrophobia, or exceeding scanner

size limits
9. Recent (in the last 3 months) involvement in a study that uses an experimental drug or device
10. Recent (in the last 6 months) involvement in a study using similar thinking or emotional tasks

Date of first enrolment
25/09/2025

Date of final enrolment
01/09/2027

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository. Analysis code, and pseudoanonymised quantitative raw and MRI data, along with the protocol and analysis plans, will be shared where practicable using repositories such as Open Science Framework (https://osf.io/) and Neurovault (https://neurovault.org/). Personal information will not be shared.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 2	03/08/2025	19/09/2025	No	Yes
Protocol file	version 2	03/09/2025	19/09/2025	No	No