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PARTICIPANT INFORMATION SHEET
Cognitive-behaviour therapy and losartan
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You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take a moment to read the following information carefully and discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of this study?
Cognitive-behavioural therapy (CBT) is an effective talking treatment for anxiety disorders, but courses are long and difficult to access. However, we have recently shown that even a single session of CBT already has an effect on anxiety. On the other hand, research has shown that a simple blood pressure medication called losartan can improve cognition and memory. In this study, we would like to test whether combining a single-session of CBT with losartan can improve effects on anxiety, and what the underlying brain mechanisms of such an enhancement effect are. We would like to test two groups of people with panic attacks: one who receives CBT after having taken a single capsule of losartan, and one who receives CBT after having taken a placebo capsule. In particular, we would like to monitor your anxiety throughout the study and measure the activity of your brain on the day after treatment, while you are reacting to different types of emotional information. It is hoped that the knowledge gained from this study will contribute to the improvement of treatment for people who experience distressing panic attacks and anxiety disorders.

What is losartan?
Losartan is a medication for high blood pressure which has had UK market authorisation for 20 years. Recent research suggests that this drug can also improve cognition and the effects of learning experiences. As a side effect, some participants experience symptoms such as drowsiness, muscle weakness, low blood sugar, headaches, hypotension or allergic reactions. However, if you are randomised to the losartan condition you will only be asked to take a very low, single dose of 50mg, which is equivalent to what you would be prescribed daily if you had high blood pressure. Recent studies have shown that taking such doses is very unlikely to cause side effects.

Why have I been chosen?
You have been chosen because you have reported to experience panic attacks.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you decide to take part you will be given a paper copy of this information sheet to keep and a consent form to sign. You will still be free to withdraw at any time and without giving a reason. Withdrawal will not affect your clinical care.

What will happen to me if I take part?
If you decide to volunteer, we will establish your general eligibility over the phone or via email. You will then be asked to come to the Warneford Hospital or the John Radcliffe Hospital on five occasions over 6 months (see study flow chart). Before your Treatment Visit, you will be randomised to receiving a capsule before your CBT that will either be:

- a placebo capsule (not containing any medication)
- a 50mg losartan capsule.

Randomisation is a procedure that is often used in these kinds of studies and is comparable to tossing a coin. Until the end of your study participation, neither you nor the experimenter will be aware which treatment you have received.

We will have to ask you to refrain from taking benzodiazepine or beta-blockers 48 hours before your Treatment and Testing visits and your Follow-up visits, as these drugs are known to have an additional impact on the brain and symptom measures we are interested in.

1. Visit 1: Screening (Department of Psychiatry/ Warneford Hospital)

Your first visit will be a screening session where we will make sure that it is safe for you to take part, and that you are suitable for this particular study. We will also give you the chance to ask any questions you might have. This session will involve asking you to:

- sign a consent form
- give us some information about your medical history
- answer some detailed questions about your current and previous psychological well-being
- complete a series of questionnaires asking about symptoms such as anxiety or low mood

The psychiatric interview can raise sensitive or upsetting personal issues. To minimize the chance of distress, these will be carried out by an experienced clinical psychologist in a private room, and you will be given breaks whenever needed.

Previous work has also suggested that normal variations in a particular gene (5HTT polymorphism which affects the chemical messenger serotonin) may influence how the brain responds to emotional information. We would like to measure this using a quick and painless genetic test, which is a cheek swab. This will be optional - you will be asked in the consent form if you agree to the collection and analysis of this sample for this study, and if you agree for your sample to be kept for future use.

The screening visit will take about 1 ½ to 2 hours.

2. Visit 2: Treatment (Department of Psychiatry/ Warneford Hospital)

This visit will take place no later than 1 month after your Screening Visit. At the beginning, we will ask about your mood and will then attach the electroencephalography (EEG) cap. You will then be participating in a testing session lasting about 1.5 hours. During this time, we will measure your speed and accuracy in simple reaction tasks on the computer, including responding to photographs of faces with different expressions, or categorizing words on the screen. Afterwards, you will receive a capsule that will either be a placebo capsule or a 50mg losartan capsule. After 1 hour, during which we will ask you to wait at the department (you will be allowed to read or work during this time), you will receive a single session of CBT. This will involve detailed individual information about the factors maintaining your anxiety and an exercise demonstrating how maintaining versus dropping these factors impacts on your anxiety. For the purpose of quality control, parts of this session might be audio taped but this will be anonymised and will not be published or made available to anyone outside of the research team. The researcher will make you aware of when this is happening and ask for your consent. This session will take 4 hours.

3. Visit 3: Testing (OCMR/ John-Radcliffe Hospital)

On the day following your treatment, we will ask you to come to the scanning centre at the John Radcliffe Hospital. We will ask you to answer some more questions about your mood and to take part in the fMRI scan. The scan will take about 30mins and we will ask you to respond via a button box to simple cognitive tasks displayed on a screen that you can see whilst in the scanner. After the scan, we will ask you to complete some more tasks on a computer laptop. The total time of your Testing Visit including the scanning is approximately 3 hours. **It is essential that you can keep the appointment arranged for you as scanner time is highly sought after and cancellations must be made as soon as possible so that other researchers can use the time on the machine.**

4. Visit 4 and 5: Follow-ups

One month and 6 months after your treatment, we will assess your mood, using questionnaires and a brief interview. Each of these sessions will take about 1 hr.

Study flow-chart:

Visit 1: Screening (1 ½ hours) Information and consent, medical and psychiatric screening, questionnaires
1 day to 1 month later:
Visit 2: Treatment (4 hours) Computer tasks with EEG Randomisation to receive either Losartan (50mg) + CBT Placebo +CBT
24 – 48 hours later:
Visit 3: Testing (3 hours) fMRI scan, computer tasks, questionnaires
28- 40 days after visit 3:
Visit 4: 1-month Follow-up (1/2 hour) Questionnaires
180-200 days after visit 3:
Visit 5: 6-month Follow-up (1/2 hour) Questionnaires

What is Cognitive Behaviour Therapy (CBT)?
CBT is a form of psychotherapy based on the concept that the way we think about things affects how we feel emotionally. Thus, it aims at helping people to modify the way they think and the way they act. The underlying assumption is that learning processes play an important role in overcoming anxiety. Previous research suggests that this type of therapy is very effective in the treatment of anxiety disorders. In this study, we will only be able to offer one session of CBT. Full CBT treatment for panic disorder typically involves around 6-10 sessions, thus we do not expect that you will necessarily be free of all your symptoms after the brief intervention. Nevertheless, our previous work suggests that the majority of people experience a significant improvement in their symptoms at this point.

The EEG recording
During experimental testing, we will use EEG, which will allow us to measure electrical activity of your brain in response to neutral and emotional words and pictures presented on a computer screen. The results from this part of the study are hoped to help us predict who will benefit particularly well from this single-session CBT treatment. EEG recordings are a non-invasive way to indirectly measure your brain's activity. We will provide you with a cap which has several electrodes attached to it. We then need to insert some gel into the hair/onto the skin underneath each electrode in order to get a good connection and be able to measure your brain activity. We'd therefore like to ask you not to use any conditioner, hair gel/wax, or silicone-containing shampoos on the day you are coming in for the Treatment Visit as this might make it more difficult to get a good connection between scalp and electrode. In our lab space, we have facilities for you to wash your hair upon completion of the experimental testing.

The MRI Scan
You will also be asked to take part in an MRI scan. MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). The MRI scanner is a large tube which is open at both ends. You will enter the scanner headfirst and your legs will remain outside the tube. The radiographer and researcher will be able to see you throughout the scan and will provide you with a call button which you can press at any time.

Inclusion Criteria
- Willing to give informed consent for participation in the study and to comply with all study requirements
- Male or Female, aged 18 years or above
- Experience of panic attacks and some life style changes as a results of those attacks

Exclusion Criteria
You will not be able to participate in this study if you:

- have a history of epilepsy or another neurological disorder, or other severe diseases such as kidney, liver, heart or respiratory problems, renal insufficiency, systemic infection, or intravascular fluid depletion
- have a history of a psychotic disorder, bipolar disorder, alcohol or substance abuse
- are pregnant or breast-feeding
- are taking blood pressure or other heart medication, especially a drug called aliskiren, or beta blockers, on a daily basis
- have been on antidepressant medication during the last 6 weeks
- have received the very specific psychological treatment we are using in this study in the last 3 months
- Participated in another study involving certain medication during the last 6 weeks
- will not be able to refrain from benzodiazepines for 48 hours before the sessions

Participants with contraindication to MRI scanning (e.g. metal implant, left-handedness) will be included in the study but will not undergo the MRI scan study component.

Please do not hesitate to contact us if you are unsure as to whether you fulfil criteria for study participation.

Are there any risks in taking part in this study?
For the doses used here, no side effects have been reported in previous studies. However, as a safety measure we will encourage you not to drive or cycle for two hours after study participation on your Testing Visit Day and instead walk or use public transport to get home.

During EEG set up/recordings, we need to fit a cap which has electrodes attached to it. First of all, we will choose the best fitting cap with your help in order to avoid any unnecessary discomfort during the experiment. We then need to insert gel into the cavity of each electrode which we gently rub in to get a good signal. Sometimes, people with very sensitive skin can develop temporary red blotches. If you know your skin to be sensitive, we would kindly ask you to point this out so that we can be extra careful. In order to be able to gain good quality EEG data, we need to record eye movements during the experiment. This is done by attaching electrodes around the eye region. While the electrodes themselves are not painful at all, we need to free the skin of dry skin cells and excessive oil or grease which we do by using a gentle scrub and alcoholic wipes. Again, please tell us if your skin is very sensitive. As alcoholic wipes can make the eyes sting, we will ask you to close your eyes while we fit the electrodes in order to avoid any unnecessary irritation of the eyes.

MRI is safe and non-invasive and does not involve any ionising radiation (x-rays). However, because they use a large magnet to work, MRI scans are not suitable for everybody. Because of this, you will be asked pre-screening safety questions to help determine if you are able to take part. For example, if you suffer from claustrophobia, you could not be scanned. Normally, MRI scanning for research purposes would not be performed without further investigation if you have a heart pacemaker, mechanical heart valve, mechanical implant such as an aneurysm clip, hip replacement, or if you carry other pieces of metal that have accidentally entered your body. While there is no evidence to suggest that MRI is harmful to unborn babies, as a precaution, the Department of Health advises against scanning pregnant women unless there is a clinical benefit. We do not test for pregnancy as routine so if you think you may be pregnant you should not take part in this study. As some of the scans are noisy, we would give you earplugs, head padding or headphones to make this quieter for you. It is important that these are fitted correctly as they are designed to protect your ears. In preparation for your scan and for your comfort and safety we may ask you to change into pocketless and metal free "pyjama-style" top and trousers, which are available in a range of sizes. You may keep your underwear and socks on, but we would ask ladies to remove underwired bras. If you have a suitable sports type bra you may wear this instead. Metal jewellery, including body piercing, must also be removed. Eye shadow and mascara must also be avoided, since some types contain materials that can interact with the magnetic field. If you wish to wear eye makeup to your scan we can provide makeup removal wipes but you are advised to bring your own makeup to reapply. Lockers are provided to secure your personal belongings and clothing.

It is important to note that we do not carry out scans for diagnostic purposes, and therefore these scans are not a substitute for a doctor's appointment. Our scans are not routinely looked at by a doctor; rather our scans are intended for research purposes only. Occasionally a possible abnormality may be detected. In this case, we would have the scan checked by a doctor. If the doctor felt that the abnormality was medically important, you would be contacted directly and recommended to have a hospital (NHS) diagnostic scan arranged. All information about you is kept strictly confidential.

What are the possible benefits of taking part?
Based on our previous experience it is likely that patients in both treatment groups will experience a decrease in anxiety and panic as well as agoraphobic avoidance. In addition, participants will be given the opportunity to make a contribution to our scientific understanding of how the combination of acute losartan intake in combination with a single session of cognitive–behavioural therapy affects clinical anxiety and emotional processing to help understand the mechanisms underlying successful treatment.

Expenses and payments
If you take part in this study, you will be paid £70 for participation, and we are happy to reimburse reasonable travel expenses. In addition, you will receive one session of CBT for your panic symptoms, and we hope that you will find this useful.

What will happen if I do not want to carry on with the study?
Even after you have signed the consent form, you are absolutely free to withdraw from the study at any point without giving any reason and without medical care/legal rights being affected. Any identifiable data will then be destroyed.

What would happen if there is a problem?
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr. Andrea Reinecke, on (01865) 226471, email: andrea.reinecke@psych.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk. The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact PALS@oxfordhealth.nhs.uk or telephone 0800 328 7971

Will my taking part in this study be kept confidential?
All information that is collected about you during the course of the research will be kept strictly confidential and must be kept securely in paper or electronic form for at least 5 years following its completion. It would have your name and address replaced by a code so that you could not be recognised from it. Responsible members of the University of Oxford, the Oxford Health NHS Foundation Trust or regulatory authority may be given access to anonymised data for monitoring and/or audit of the study to ensure we are complying with regulations. We would also like to have your permission for your anonymised data to be used in future research. This will allow us to re-use your data, for instance if analysis methods become available that might further our understanding of the questions investigated. If your treatment has been audio taped, these will be stored anonymously and will be deleted as soon as quality control has taken place (to confirm that the treatment has been delivered according to protocol). Audio taped information will never be published in direct quotes.

What will happen to the results of the study?
Anonymised results may be published at conferences and in scientific journals. However, no information which could be used to identify any individual participant will be published. Prior to study participation, we will ask for your consent to use your anonymised data in future studies if new research questions emerge. However, you can opt out of agreeing to this, and this will not affect your study participation. At the end of the study, you will receive a lay report of the results if you are interested.

What will happen to my DNA samples?
Should you agree to have DNA samples taken these will be anonymised and stored in the laboratory freezer. We would also like to have your permission to store any remaining DNA. This will allow us to carry out similar work in the future on any genes that are subsequently identified to be potentially involved in anxiety and investigate how people's individual variations in these genes can affect their response to the measures used in this study. Ethical approval will be obtained for all such future projects. If you do not want to provide a DNA sample and/or do not wish us to store it we will note this on your consent form. If you do decide to take part in this part of the study, you can withdraw at any time without giving a reason, up to the point where samples are anonymised. If you withdraw from the study, your samples will be destroyed. The results of our research may eventually allow us to identify functional effects of the different types of brain receptors. However, many other factors are also likely to be involved and individual results will be very difficult to interpret. For this reason, we do not inform individual participants of their results from this part of the study.

Who is organising and funding the research?
The University of Oxford is Sponsor of the research and it is being funded by MQ: Transforming Mental Health.

Who has reviewed the study?
This study has been reviewed and given favourable opinion by South Central – Oxford A Research Ethics Committee.

Contact details
For further information on the study, or if you have any concerns, please contact Dr Andrea Reinecke. Email: andrea.reinecke@psych.ox.ac.uk or telephone: 01865 226471.

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