UNIVERSITY OF OXFORD
DEPARTMENT OF PSYCHIATRY

WARNEFORD HOSPITAL
OXFORD
OX3 7JX
TEL: (01865) 226471
FAX: (01865) 251076
andrea.reinecke@psych.ox.ac.uk

PARTICIPANT INFORMATION SHEET
The effect of losartan on emotional processing in healthy volunteers
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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, relatives and your GP if you wish. Take time to decide whether or not you wish to take part.

PART 1: ABOUT THIS STUDY AND PARTICIPATION

What is the purpose of this study?

We are interested in how a single dose of the blood pressure medicine losartan affects accuracy and reaction time in simple computer tasks. Recent studies suggest that this medication might have the potential to improve psychological treatments, and we hope that the knowledge gained from this study will eventually contribute to the improvement of treatment for people who experience emotional problems such as anxiety disorders. We would like to test two groups of people: one who receives a single dose of losartan, and one who receives placebo (a substance not containing any medication). Your allocation to one of these groups will be randomised.

Why have I been chosen?

We would like 40 healthy people aged 18-50 to take part.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you will be given (or can print) this information sheet to keep. You will still be free to withdraw at any time and without giving a reason. The national advisory group INVOLVE (http://www.invo.org.uk) is an independent contact point where potential participants can seek general advice about taking part in research.

What will happen to me if I take part?

If you decide to volunteer, we will initially ask you a few screening questions (for instance, regarding your general health and current medication) via email or phone to make sure you are safe to take part in the study. You can withdraw at any time without giving a reason for doing so. Once we have established your general eligibility, we will invite you to the department for three visits:

<u>1. Screening Visit (Department of Psychiatry/ Warneford Hospital)</u>
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 and complete a routine medical examination

- 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.

During this visit, a medical screening will take place. For this, the doctor will check your heart and lung function using a stethoscope, for which they will ask you to take off any long sleeved jumpers or cardigans. The screening visit will take about 0.5 to 1 hour.

Visit 1: Screening Visit (0.5-1 hour) *Department of Psychiatry/ Warneford* Giving informed consent Medical and psychiatric screening Questionnaires
Visit 2: Testing Visit 1 (3-3.5 hours) *OCMR/ John Radcliffe Hospital* <u>Questionnaires</u> <u>Drug administration</u> Losartan (50mg) vs placebo <u>Fitting of an EEG cap</u> <u>Experimental Testing</u> Computer tasks and fMRI
Visit 3: Next-Day Follow-up Visit(0.5-1 hour) *Department of Psychiatry/ Warneford* Computer tasks Questionnaires

<u>2. Testing Visit (Oxford Centre for Magnetic Resonance Research/ John_Radcliffe Hospital)</u>
We will ask you to <u>have your last meal and caffeinated beverages two hours before</u> this visit. At the beginning of your visit, you will receive a capsule that will either be:

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

Which one of these treatments you will receive will be randomised, and until the end of your study participation, neither you nor the experimenter will be aware which treatment you have received. Losartan has been tested in similar studies before, and it has been shown that single-doses like the one you might be receiving are unlikely to cause any side effects.

One hour after having taken the capsule, during which we will attach the electroencephalography (EEG) cap, you will 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. We will then ask you 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. We will also measure your blood pressure and heart rate throughout the scan, for which with your permission we will place a 3-electrode ECG device to your chest prior to the scan (your ECG will be placed by a female colleague).

The total time of your visit at the John Radcliffe Hospital including the scanning is approximately 3-3.5 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.

3. Follow-up visit (Department of Psychiatry/ Warneford Hospital)
On the day following your long testing visit, we would like you to again work on a series of brief computer tasks similar to the some of the ones run on the previous day. These will only be on a computer in a laboratory, so we will not repeat any EEG or fMRI. Nevertheless, this additional visit will be very important for us to establish the stability of the effects measured on the previous day. This visit will take about 0.5-1 hour.

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. Recent studies have shown that taking such doses is very unlikely to cause side effects. If you nevertheless experience once of these severe side effects, you will be withdrawn from the study.

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. This will give us information about how the drug affects when certain stimuli are processed. 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 study 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. Contrary to EEG measurements, such approaches allow us to find out where in your brain activation changes during information processing after having taking losartan versus placebo. 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. Females might be asked to take off any underwired bras for the duration of the scan, as wearing these might become uncomfortable due the scanner being a strong magnet. Metal jewellery, including body piercing, must also be removed. 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. 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.

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

- are younger than 18 or older than 50 years
- have a Body mass Index below 18 or over 30
- have insufficient English skills
- are smoking more than 5 cigarettes a day
- are pregnant or breast-feeding
- have been on certain medication that influences the central nervous system (e.g. antidepressants, sleeping medication) during the last 6 weeks
- are currently taking blood pressure or other heart medication, especially a drug called aliskiren, or beta blockers
- are currently diagnosed with intravascular fluid depletion
- have ever had a psychological disorder such as depression, bipolar disorder, eating disorder, anxiety disorder, psychotic disorder, alcohol or substance abuse
- have a close family member with a history of a severe psychiatric disease
- have a history of epilepsy or another neurological disorder, or other severe diseases such as kidney, liver, heart or respiratory problems, renal insufficiency, or systemic infection
- participated in another study involving certain medication during the last 6 weeks
- contraindications to MRI scanning, such as pacemakers

Risks and Benefits
There are no direct benefits to participants. 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.

There are no known risks of fMRI for most people. However, the use of magnets means that the scan procedure is not suitable for people with magnetic pacemakers, mechanical heart valves, hip replacements or with other magnetic metal implants in their body. Also, if you have ever sustained an eye injury involving metal or have any history of seizures you should not take part.

You should not take part in this study if you are pregnant, planning to become pregnant, or breast-feeding.

Although we believe this is a very safe study, appropriate resuscitation facilities will be in place.

Expenses and payments
If you take part in this study, you will be paid £50 for participation. If your screening visit indicates you are not eligible for the study, you will receive a pro-rata reimbursement.

PART 2: DATA PROTECTION AND INDEMNITY

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?
We believe that this is a safe study. If a participant in University-sponsored research is ever considered to have suffered harm through their participation, the University has arrangements in place to provide for compensation. If you have a concern about any aspect of this project, please speak to the Principal Investigator, Dr. Andrea Reinecke, who will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how he/she intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, email ctrg@admin.ox.ac.uk, who will inform the chair of the Research Ethics Committee at the University of Oxford. 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.

Will my taking part in this study be kept confidential?
Personal information such as names, email addresses, and phone numbers will be destroyed at the end of the study. All other information that is collected about you during the course of the research will be kept strictly confidential. It will have your name replaced by a code so that you could not be recognised from it. This information must be kept securely in paper or electronic form for at least 5 years following its completion. Responsible members of the University of Oxford may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. With your permission, anonymised data collected during the course of the study may be used in future research.

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. If you are interested in finding out about the results of this research, please let us know and we will make arrangements to inform you once the study is completed.

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

Who has reviewed the study?
All research studies are checked by an Ethics Committee to ensure the research is conducted safely and to the highest standards. This research has been reviewed by and received ethics clearance through the University of Oxford Central University Research Ethics Committee.

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

Dr Andrea Reinecke
Senior Research Fellow/ PI

Prof Catherine Harmer
Professor of Cognitive Neuroscience

Dr Michael Browning
Research Psychiatrist