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Regional brain perfusion in a model of acute stress: a functional and arterial spin labelling magnetic resonance study

Submission date	Recruitment status	[ ] Prospectively registered
28/09/2007	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
28/09/2007	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
16/12/2013	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers

N0264187042

Study information

Scientific Title

Study objectives
The principal research objective is to use magnetic resonance imaging to determine the brain networks activated by an acute and large increase in stress hormones as observed in an intense stress response.

We predict that the activated brain network will comprise the caudate, putamen and anterior cingulate as well as dorsolateral and orbitofrontal prefrontal cortex. Some of these brain areas are in circuits that are essential for emotional responses.

The study is placebo controlled and randomised in order to minimise confounds.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Acute stress

Interventions
We aim to understand how the brain is activated by acute stress. Acute stress has a number of effects that modulate body and brain function in health and disease; these effects have positive and negative consequences that impact on personal well being. For instance the acute stress response facilitates the body's ability to deal with unexpected and extraordinary demands; however, if prolonged, it can also precipitate disease processes in predisposed individuals.

Understanding the changes in brain activity induced by increases in corticosteroids will underpin knowledge on how to modify stress responses. Currently, however, there are no data that link acute changes in human cortisol levels with changes in regional brain activity.

Increased cortisol (a corticosteroid) release by the adrenal glands is part of the acute stress response in man comprising a range of physiological and psychological changes. Cortisol crosses freely into the brain where it acts on a number of receptors. Exogenous administration of a single dose of hydrocortisone (a cortisol analogue) in man mimics the acute stress response.

Predictions of the immediate sites of cortisol's brain can be made from animal experiments where, pharmacological MRI (phMRI) data collected after administration of exogenous corticosteroids in rat suggest that a number of brain areas are affected including the caudate putamen, anterior cingulate and dorsolateral prefrontal cortex (Schubert et al., 2003, 2005). Some of these brain areas are intimately involved in affective responses. Since rat and human brains are quite different, these predictions will have to be validated in man.

Thus we plan to investigate such changes in man by using MRI (phMRI and Arterial Spin Labelling) to map changes in brain perfusion after the administration of hydrocortisone intravenously. In order to control for the effects of the experiment itself on stress and anticipation the study will be double blind and placebo controlled. In addition, in order to reduce the amount of uncontrolled stress during the experiment, all subject will undergo some habituation in a mock scanner beforehand and will not be asked to perform any tasks while the scanning is ongoing.

The dose of hydrocortisone has been selected to give a maximal response as in response to surgery, life threatening conditions or in exogenous administration of corticosteroids in such a situation. The reason for selecting a high dose is that cortisol is actively extruded from the brain and has a short half-life (about 60-90 minutes). With a high dose we are confident that an absence of signal in this experiment is a definite negative signifying that there is no specific neuronal response to the pharmacological signal of acute stress.

12 male healthy volunteers aged 18-55 will be recruited by advert in local press, billboards and by contacting volunteers on our registers. Respondents will have an explanation of the experiment and will be given written information to take away. Having read the explanation sheet volunteers who agree to take part in principle will be asked to attend a screening session where a history will be taken checking for inclusion and exclusion criteria. Volunteers will also have a physical examination including blood pressure measurement, a urine drug screen and routine blood tests including urea and electrolytes, liver function tests, random blood sugar and whole blood count.

Exclusion criteria include significant abnormalities on routine medical screening and investigations, taking any medication on a regular basis, history of significant medical disorder, alcohol dependence, recreational drug use, past or family history of psychosis, not being right handed (as determined by the Annett questionnaire), obesity impairing scanner access and inability to lay still in an MRI. People with metal or electronic implants and people with metal /schrapnel injuries to the eye will also be excluded. Women will also be excluded because the numbers funded for this research exclude the possibility of studying both men and women since there may be gender related biological differences in the response to stress hormones. Further, the increased difficulty in controlling and matching exactly for hormonal status make it logistically much harder to study women alone in a feasibility study such as this where a signal has not yet been demonstrated in human experiments.

Volunteers will undergo an habituation session with a mock MRI prior to the scanning sessions. They will subsequently attend two sessions on separate afternoons. Volunteers will have two intravenous cannulae inserted in the arms. One cannula will be used for the administration of hydrocortisone or placebo and the other for blood tests. The reason for performing the experiments in the afternoon is that they should coincide with a nadir in endogenous plasma cortisol levels when the anticipated levels of exogenous corticosteroids will cause a significant change in peripheral levels. Subjects will have had a light meal more than 2 hours prior to scanning.

Volunteers will then enter the MR scanner and 25 minutes after scan start they will receive either 7 mg/kg hydrocortisone or normal saline infusion over 2 minutes. The administration will be randomised and double blind. Scanning will carry on for up to 90 minutes after infusion end. Other measures will include cortisol levels, glucocorticoid receptor assay in white blood cells, pulse and blood pressure, visual analogue scale measure of mood (depressed, anxious, tense, elated). These will be carried out at ?50,(outside the scanner) ?25, -10, 2, 5, 20, 40, 60 and 90 minutes from start of infusion. At each time point 10-15 ml blood will be withdrawn. At the end of the experiment the cannula will be removed. The study supervisor will ensure that the volunteer is well enough to leave. Volunteers will have a copy of the written information with contact details in case of emergency.

MR scanning will be carried out on a conventional 3 Tesla scanner by means of a modified FLASH technique to obtain BOLD T2* signal and analysed using a boxcar design. Anatomical images will be collected at the start of the first scan on day 1. In addition two sets of Arterial Spin Labelling data will be obtained to provide absolute quantification of blood flow at beginning and end of each scanning session. We will acquire whole brain data sets in order to apply robust motion correction. We hypothesise that maximal signal changes will be in basal ganglia, frontal and medial temporal areas about 40 minutes after end of infusion.

There has been no involvement of healthy volunteers in the design of this protocol. The protocol has however been discussed at research review meetings at the Centre for Neuroimaging Science (Institute of Psychiatry), at the Laboratory for Integrative Neuroendocrinology and at the Psychopharmacology Unit (University of Bristol) and at Organon.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
Change in BOLD MR brain signal in the 60-90 minutes after administration of hydrocortisone or placebo.

Secondary outcome measures
1. Change in Arterial Spin Labelling brain signal after administration of hydrocortisone or placebo
2. Correlation of measures of brain function with pharmacokinetic (plasma levels and receptor translocation measures), pharmacodynamic (pulse, blood pressure, visual analogue scales) and baseline measurements (anxiety scales)

Overall study start date
20/05/2006

Completion date
20/05/2007

Eligibility

Key inclusion criteria
1. Males, right handed, age 18-50 inclusive
2. Healthy as determined by medical history and physical examination
3. Body weight > 50 kg and <120 kg
4. Standard clinical laboratory tests within normal reference range for the population, investigator site or, results with acceptable deviations that are judged to be not clinically significant by the investigator
5. Normal blood pressure and heart rate as determined by the investigator
6. Have given written informed consent approved by the Ethical Committee

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
50 Years

Sex
Male

Target number of participants
12 volunteers

Key exclusion criteria
1. Females; males outside 18-50 age range
2. As a result of the medical interview, physical examination or screening investigations (haematology, clinical chemistry including random blood sugar), the physician responsible considers the subject unsuitable for the study. In particular a blood sugar of >8 mmol/l is an explicit exclusion criterion.
3. The subject has a history or presence of drug or other significant allergy that, in the opinion of the responsible physician, contra-indicated their participation.
4. The subject has participated in a clinical study with an investigational or a non-investigational drug or medical device during the previous three months or has participated in more than three studies in the previous year.
5. The subject has a history or presence of any illness (cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, haematological, or neurological disorders) capable of significantly altering brain responses to hydrocortisone.
6. History of psychiatric or neurological disorder which, in the investigators opinion, is likely to influence the experiment, or compromise safety.
7. The subject has history of presence of seizures or risk factors for seizure.

8. History of aspirin-sensitive asthma or nasal polyposis.
9. Use of drugs with known vasodilator or vasoconstrictor activity and intra-nasal steroids/anti-histamines within seven days of or five half lives (whichever was the longer) prior to any study day.
10. The subjects has used or is using other regular prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within seven days or five half lives (whichever was the longer) prior to the first dose of study medication, unless in the opinion of the Investigator and Sponsor the medication would not have interfered with the study procedures or compromised subject safety.
11. The subject had a history of drug or alcohol abuse, or had a positive pre-study urine drug / alcohol screen. Abuse of alcohol is defined as an average weekly intake of greater than 21 units. One unit is equivalent to a half-pint (220 mL) of beer or one (25 mL) measure of spirits or one glass (125 mL) of wine.

Date of first enrolment
20/05/2006

Date of final enrolment
20/05/2007

Locations

Countries of recruitment
England

United Kingdom

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Record Provided by the NHSTCT Register - 2007 Update - Department of Health

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Funder(s)

Funder type
Government

Funder Name
United Bristol Healthcare NHS Trust

Funder Name
NHS R&D Support Funding

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration