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Cortisol effects on brain activity and cognition (CEBAC) study
Participant Information Sheet (PIS)

You are being invited to take part in a research project. Here we detail some information to help you decide whether to take part. Please take the time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Please do ask the research team if there is anything you do not understand or if you would like more information on any aspect of the project. Take time to decide whether you wish to take part.

This project has been reviewed by the Faculty of Health Science Research Ethics Committee (FREC) at the University of Bristol.

What is the purpose of the study?

Cortisol is a steroid hormone that the body produces naturally. It is normally produced in a 'diurnal rhythm'. This means that its levels change throughout the day and your body produces in short bursts approximately every hour (these are known as pulses). When people are healthy, they produce high levels of cortisol in the morning reaching a maximum just prior to waking up, these levels then start to tail off during the day and reach a minimum at midnight (therefore you feel awake in the morning and sleepy in the evening). Cortisol is an important stress hormone that is critical to maintain a healthy balance in the body i.e. homeostasis.

There are groups of people who do not produce cortisol e.g. patients with Addison's Disease, and therefore require cortisol replacement in the form of hydrocortisone (synthetic cortisol) tablets. These patients never feel quite as well as a people who produce cortisol naturally and suffer from symptoms such as a lack of motivation, erratic sleep and general lethargy. They also have a decreased life expectancy (a risk similar to that of smoking). The hydrocortisone tablets we give to patients attempt to mirror normal cortisol levels; however, as cortisol levels start to rise before you even wake up, tablets cannot currently mimic this, and so patients wake up in the morning with no cortisol and then take their tablets. It is believed that the lack of pulses of cortisol may be the reason these patients do not feel healthy after taking these tablets, even though they are receiving the same total amount of daily cortisol as healthy people.

As we know cortisol is produced as individual pulses (with larger more frequent pulses in the morning and smaller less frequent ones in the evening). Previously this was overlooked as "noise" in the system. However, research has shown that these pulses of steroids are in fact very important for regulating biological signals, brain circuitry, hormonal and behavioural responses.

Previous studies by our group have investigated the effects of a pulsatile cortisol treatment in both healthy volunteers and in patients with cortisol insufficiency (including those with Addison's Disease). The fMRI (brain scan) data from these studies have shown interesting changes in brain activity in response to cortisol pulses. In this study, we hope to understand how brain activity changes over the course of a typical normal stress level cortisol pulse. This pulse is at a healthy level (equivalent to what we would expect in the event that a friend was to surprise you from behind!) The study will examine your brain responses to a faces task and at rest using fMRI brain scanning. We also so investigate how you respond in a reward-based task using pupillometry (a method of tracking your eye's pupil response to a visual stimulus) and a working-memory task.

Why have I been chosen?

You have been chosen because you are a healthy male individual aged 18-64, with a BMI of 18-28, and you meet all the conditions required for participating in this study.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether to take part or not. If you do decide to take part, we will ask you to sign a consent form and give you a copy of this information sheet and the consent form to keep. You will also receive a short description of the study to carry with you in the event you need to seek any external medical care and your GP will receive a letter explaining the study. If you decide to take part, you are still free to withdraw at any time. If you decide not to take part you do not have to give a reason, nobody will be upset by your choice.

The study will be carried out at the Clinical Research and Imaging Centre (CRIC), University of Bristol, 60 St Michael's Hill, Bristol, BS2 8DX and in the Experimental Psychology Department, 12a Priory Road, Bristol, BS8 1TU. These centres are 10 minutes' walk apart from one another.

What will happen to me?

Your suitability for the study will initially be assessed in a telephone call or by email by one of our team. We have given you this information sheet since we have found that you are potentially suitable to take part and this sheet gives you additional information on the study and will help you to decide if this is something you are interested in doing. If you decide to take part, you will be invited to discuss the study further and provide written consent as well as attending a screening visit which includes providing a urine sample to confirm that you have not been exposed to or have taken any substances that would affect the study. You will need to provide another urine sample on the start date of the study to ensure the results are consistent.

During the screening visit the researcher will take your medical history to make sure that you are fit and healthy enough to take part in the study. Other information including your date of birth, smoking status, height and weight will also be recorded. At this stage you will be asked to complete some questionnaires to measure your mood, anxiousness, impulsiveness and sleep quality for the first time. These questionnaires will also be repeated during the study period.

The study also involves you having fMRI (functional Magnetic Resonance Imaging) brain scans; you will be specially questioned to find out if you are eligible to have these done. This type of brain scan involves lying down into a large tunnel (an MRI scanner, see Figure 1) and can make people feel claustrophobic. Due to this, if you want to take part in the study and are eligible, as part of the screening process you will be asked to sign a consent form and the opportunity to see the scanner and have a short trial if you so wish. This would be to confirm that you are comfortable being in the scanner. We would also need to measure the amount of cortisol in your system at various times throughout the study, ideally this would be from saliva samples.

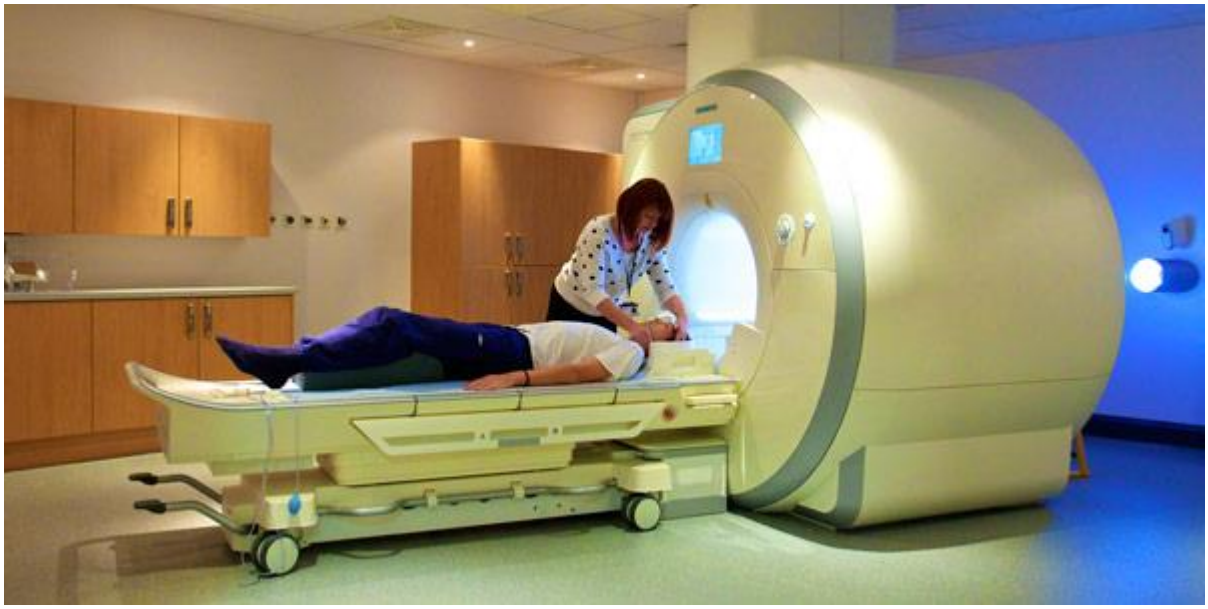

Figure 1: The MRI Scanner at CRIC Bristol where brain scans for the CEBAC study will take place

This study itself takes 8 days to complete. You will receive a medication called Metyrapone three times a day to switch off your natural cortisol production; the dose of this will gradually increase and it is important to take it on a full stomach, this keeps any side effects to a minimum. At the same time, you will be given cortisol replacement therapy in the form of hydrocortisone. The hydrocortisone will be given via an infusion pump (Figure 2), in a pulsatile rhythm (short pulses at regular intervals, similar to your natural rhythm of cortisol in healthy people) via a small subcutaneous cannula (a small needle that penetrates the skin of the abdomen) and infusion line and once this is inserted, you will not be able to feel it. The pump itself is worn on a belt such as those used by runners to carry a mobile phone. This 'block and replace' treatment for cortisol is done to ensure that yourself and all the other participants are receiving the same amount of hydrocortisone at the same times of the day, as your natural rhythms are unlikely to be synchronised with those of other people. On days 6 and 7 of the study you will receive an elevated dose of cortisol at 09.00 am (this dose will be 15 milligrams, around 3 times the normal 09.00 am dose you will have received on previous days).

The syringes and cannula/infusion line in the pump require changing approximately every 3-4 days, for this you will be required to attend a short 20-minute appointment with one of the researchers on Day 3 of the treatment scheme. At this time, we will once again check that you are happy to continue with the study and if you have any queries that have arisen since your last visit.

Throughout the study, you will be able to remove the pump in order to take a shower, however this will have to be between the times of the pulse. We will clearly outline the times between which it would be safe to remove the pump to wash. Other than to wash, we recommend you wear the pump at all times in order to ensure you do not miss any of the cortisol pulses as this would be unsafe as you will not be producing your own cortisol during this study due to the suppression of this by the metyrapone pills. Missing a daytime cortisol pulse could result in you feeling very unwell and possibly cause you to experience adrenal crisis (caused by a lack of cortisol; the research team will explain the signs and symptoms of adrenal crisis prior to the start of the study, so you know how to recognise it) for which you must seek emergency medical attention.

Figure 2: The infusion pump used in this study to deliver the cortisol pulses and the wearable belt in which it is carried. A 500ml drinks bottle has been included for size reference.

Whilst you are on the hydrocortisone replacement therapy, we will ask you to perform the following series of tests to assess your general well-being and brain circuitry:

Leeds Sleep Evaluation Questionnaire (LSEQ): This is a simple sleep questionnaire that is widely used to compare the sleep you have during the study to your usual sleep and gives more information about your sleep.

Mood, Anxiety and Impulsiveness Questionnaires: These are simple questionnaires widely used to assess wellbeing. You will complete these at screening, and once more during the study visit.

Functional Magnetic Resonance Imaging (fMRI)
You will take part in 3 scan sessions over 2 visits (including a structural MRI scan taken alongside the third fMRI scan). This will take 3 hours in total; however, you will only be in the scanner for 1 hour at a time. For the fMRI visits you will have an MRI brain scan performed whilst you rest in the scanner looking only at a blank screen with a cross on which to focus. The scan will allow us to see if your brain "lights up" in different ways depending on what time point during a cortisol pulse you are in. You will also complete two tasks, for which you will be trained in advance of the study: these are a simple computer test that involve pressing buttons when you are in the scanner and one that involves staring at a fixed image for a short period of time. Before and after each period in the scanner you will have oral samples taken in order for us to find out the exact level of cortisol in your body at the time of each scan.

After the first two scans that evening you will receive a new syringe to be inserted that evening. This will contain saline and therefore you will not receive a cortisol pulse on the following morning. Cortisol levels are usually low at night and therefore the risk associated with being cortisol supressed are very small. The risks associated with the study are detailed later in this information sheet.

On the final day (Day 8) you will return to CRICBristol. You will have a final, fMRI scan. Immediately after this you will be given oral hydrocortisone tablets to take with you for the remainder of the day. This will replenish your cortisol back to a normal level. It is important that you take these as it will take a few hours for the metyrapone to wear off and your natural cortisol production to restart. We will call you the following day to see how you are feeling.

Pupillometry and N-back study

The study also involves a pupillometry experiment, which will measure your pupil diameter using a specialized camera whilst you complete a reward task. This will take place on day 6. This part of the study aims to investigate how pupil diameter changes when people are presented with certain auditory tones and reward, as this has been found to correlate with brain activity in the region of interest. You will be seated in front of a computer screen and listen to a series of auditory tones. You will be asked to respond to one of these tones as quickly as possible by pressing a key on the computer keypad. At the end of the task one of the trials will be chosen at random and you will receive the reward associated with this trial if you have responded within the time limit. This task will take up to 45 minutes to complete. You will then have a break for about an hour after which you will be asked to complete the same task again. During this visit, you will also complete a short computer-based working memory task called an N-back task, immediately after each run of the eye-tracking experiment. At the end of each run of the pupillometry task, a random reward program will be run, where you can win either 20p or £20.

We have conducted studies using this cortisol 'block and replace' treatment using metyrapone and hydrocortisone in previous research studies; it is a safe and validated procedure. Furthermore, our hydrocortisone delivery pump has been used in a licensed clinical trial conducted by our group. Please do not hesitate to ask us any questions or highlight any concerns you might have regarding your participation.

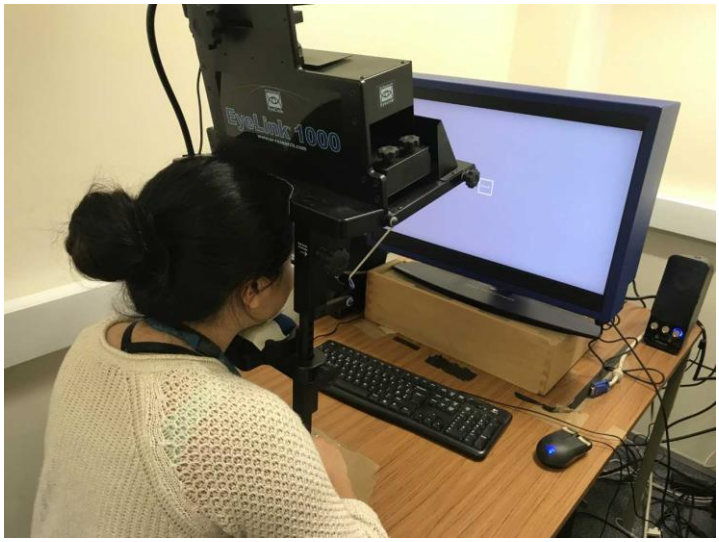

Figure 3: Pupillometry task set up. The Eyetracker measures changes to your pupil size using a camera, while you perform the reward task.

A summary of the visits and study events can be seen in Table 1.

So, what exactly is the time commitment?

In brief, this commitment amounts to a screening visit, 4 study visits including 3 MRI scans and 2 short line change visits. Prior to the pump fitting you will undergo a training session, to ensure you are familiar with the tasks that you will carry out during the fMRI visits. After this you will wear the pump and take the tablets for a total of 8 days, and the complete study time is also 8 days. During this time, you will not be able to drink alcohol, take any drugs (aside from prescription medications discussed with our medical doctor), nor remove the pump unless it is to shower or bathe. You will have oral cortisol samples taken at various points throughout the study. Your height and weight will also be monitored. After the study is complete you will not have to visit CRICBristol for a follow-up, these will be conducted 1 and 3 days after completion.

Table 1: Example study timetable for participants.

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Morning		Breakfast metyrapone	Breakfast metyrapone	Breakfast metyrapone	Breakfast metyrapone	Breakfast metyrapone	Breakfast metyrapone	Breakfast metyrapone
08:00						Pulse 15mg, Line change Pupillometry, (Psych Dept - 4 hr)	Pulse 15mg, Scan Day 1 (CRIC - 4 hr)	Saline Pulse, Scan Day 2 (CRIC - 4 hr)
09:00		Pulse	Pulse	Pulse	Pulse			
10:00								End of study replenishment
11:00								
12:00	Training visit, pump connect (CRIC - 2 hr)	Pulse	Pulse Line change – flexible time (CRIC -20 min)	Pulse	Pulse	Pulse	Pulse	
Lunch	Lunch metyrapone	Lunch metyrapone	Lunch metyrapone	Lunch metyrapone	Lunch metyrapone	Lunch metyrapone	Lunch metyrapone	Lunch
15:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	2 x 5mg cortisol doses to take at home
18:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse Saline pump swap (CRIC- 20min)	
Dinner	Evening meal	Evening meal	Evening meal	Evening meal	Evening meal	Evening meal	Evening meal	Evening meal
21:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Saline Pulse	
Bedtime	Bedtime metyrapone	Bedtime metyrapone	Bedtime metyrapone	Bedtime metyrapone	Bedtime metyrapone	Bedtime metyrapone	Bedtime metyrapone	
24:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Saline Pulse	
03:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Saline Pulse	
06:00	Pulse	Pulse	Pulse	Pulse	Pulse	Pulse	Saline Pulse	
Showering possible around pulse times.								

What are the possible disadvantages and risks of taking part?

There is a small risk of a localized allergic reaction to the needle/lines used in the pump and infection. To minimize this, we use clean medical technique when inserting the line.

You will be receiving a cortisol blocking agent (metyrapone) and cortisol replacement therapy therefore you will have adequate cortisol levels throughout the study, except for the final night of the study, before the final scan, after which you will receive a tablet to ensure your cortisol level is replenished (see above). As your cortisol levels will be within a normal range you should feel no obvious adverse effects. The individual medications can sometimes cause nausea, vomiting, sleep disturbances (difficulty in going off to sleep or sleepiness) and rarely abdominal pains. If during the study, you have any of these symptoms, please always let us know. Throughout the study, you will be able to contact Jamie Thakrar during working hours and via text message on her mobile telephone outside these, however, you must go to hospital immediately if you feel very unwell.

There is a very small chance that the line may fall out or the pump stop working during the study. We will therefore teach you how to change your pump and supply you with an emergency kit in case you cannot get hold of, or it is inconvenient for you to see, a study researcher immediately. However, wherever possible, we will be available to do this for you.

The MRI scan involves being in a tunnel shaped machine and so you may feel slightly claustrophobic. Additionally, you must be aware that the scans are not a clinical investigation and therefore have no diagnostic capabilities; they will be reviewed by students and research staff and therefore not by medically qualified radiologists. i.e. we would not be able to diagnose any medical conditions that an MRI scan would normally be used for in a hospital setting.

If, at any time during the study, new information becomes available, the researchers will talk to you about this and discuss whether you want to continue in the study and you will have the opportunity to speak to one of our doctors at any time, if you have any concerns, or should an emergency arise.

Will I receive any reimbursement for my time?

You should be aware that you would receive no direct benefit from taking part in this study. However, you will receive £200 to cover all expenses related to the study and you will receive a sandwich lunch after each extended visit session that runs into lunch time.

You may also receive an additional amount of up to £20 depending on the outcome of each part of the pupillometry reward task (up to a possible total of £40 can be won).

Confidentiality – Who will know I will be taking part?

All information collected about you during this study will be kept strictly confidential. Any information about you will be made anonymous so that you cannot be recognized from it. Your personal details will never be published with any study results. Only the research team and anybody you wish to tell yourself will know about your participation.

What will happen to any data/results that I supply?

All data/results will be anonymous and will be kept for the duration of the study and follow up period (5 years). If you decide to withdraw from the study, you can ask for your data to be destroyed. Following the study anonymised data maybe used by other bona fide researchers upon request, none of your personal information, however, will be available to them.

Who is organizing and funding the research?

A team from the Henry Wellcome Laboratories for Integrative Neuroscience, which is part of the University of Bristol, is carrying out the research. The research is currently funded by a Wellcome trust PhD studentship and an SWBIO DTP studentship. Funding pays for the direct costs of doing the research in addition to the salary of the PhD student researchers, Miss Jamie Thakrar and Miss Laura Cole. None of the researchers are receiving any payments other than their usual salaries.

What will happen to the results of the study?

Results will be written up into Miss Jamie Thakrar's PhD thesis, submitted to scientific journals for publication, and presented at scientific conferences. Results from the pupillometry study will be written into Miss Laura Cole's PhD thesis, submitted to scientific journals for publication, and presented at scientific conferences.

What do I do now?

If, after reading this information, you decide that you would like to take part, please contact one of the study researchers and we will arrange some convenient times for you to attend. Thank you for considering taking part in this study. Our researchers will be happy to answer any questions you have. If you are prepared to take part, you will be asked to sign a consent form to confirm this. You will be given this information sheet to keep. We suggest you keep it carefully so that you can contact us if you have any further questions, at any time.

You do not have to take part, and if, at any stage during the study you wish to withdraw, for whatever reason, you are able to do so.

Contact for further information

For any further information on this study you can contact one of the study researchers:

Miss Jamie Thakrar	jamie.thakrar@bristol.ac.uk, Study mobile: 07746260911
Miss Laura Cole	lc12365@bristol.ac.uk
Dr. Georgie Russell	georgina.russell@bristol.ac.uk
Prof. Stafford Lightman	stafford.lightman@bristol.ac.uk
Secretary to Prof. Lightman	Tel: 0117 331 3167

If you would like to discuss the science behind the study with an independent person, please phone Prof. Lightman's secretary on 0117 331 3167 and she will be able to suggest someone suitable.

If you would like to inform/consult your GP, we are able to provide a letter for you to take along to an appointment with them.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions.

If you wish to make a formal complaint, please write to:
Research Governance Team (research-governance@bristol.ac.uk)
Research Enterprise and Development (RED)
University of Bristol
Senate House, Tyndalls Ave
Bristol
BS8 1TH

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends and your GP if you so wish.