Study Title: Investigating brain activations in the premonitory and postdrome phases of triggered migraine and during chronic migraine using functional imaging

Using functional brain imaging to see which brain areas are involved early in a migraine attack before the pain starts, during the headache, and after the headache has ceased and to observe where painkillers work.

We would like to invite you to participate in this research project. You should only participate if you want to; choosing not to take part will not disadvantage you in any way. Before you decide whether you want to take part, it is important for you to understand why the research is being done and what your participation will involve.

Please take time to read the following information carefully and discuss it with others if you wish. You can contact any of the study team whose details can be found at the end of this information sheet if there is anything that’s not clear or if you would like more information.

What is the purpose of the study?

Migraine attacks start some time before the headache is experienced and persist after the headache has finished. We are trying to understand which areas of the brain are activated during the different stages of a migraine. We want to investigate the symptoms that you may experience before the start of a migraine headache, such as needing to pass water more frequently, yawning and feeling thirsty (called the premonitory symptoms), as well as during the headache pain itself, and the symptoms after the pain has settled (called postdrome symptoms) like fatigue, inability to pay attention, reduced memory and increased sleepiness. We will use a brain scanning technique called functional Magnetic Resonance Imaging (fMRI). We are also interested in seeing whether we can observe changes in brain activity in response to migraine relief following administration of aspirin which is an approved treatment for migraine, and if we can understand the differences between people that occasionally experience migraine attacks and people that have frequent migraine.

We hope that this study will help us understand the mechanisms behind the various stages of a migraine attack and help guide future work looking at drugs that may work early in the attack, before the onset of pain, to prevent pain occurring. We also hope to be able to develop new techniques for understanding the body’s response to pain and other symptoms.
**Why have I been invited to take part?**

You have been selected to take part in the study as you have demonstrated to the doctor that you have been diagnosed with migraine and also usually experience the premonitory symptoms before the migraine attack or postdrome symptoms once the migraine resolves.

**Do I have to take part?**

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

**How do I know that I am eligible?**

You are eligible to take part in this study if you are aged between 18 – 50 years and have a diagnosis of migraine. You must be willing to comply with the study scheduled visits, procedures and lifestyle guidelines. A member of the research team will thoroughly check your eligibility to ensure that there are no particular reasons why you should not take part.

**Where is the study being held?**

The study and all of your visits will take place at the Clinical Research Facility at King’s College Hospital, Denmark Hill. The visits are most commonly day visits between 9am and 7pm, however in some circumstances if clinically or logistically relevant, subjects may be offered the chance to stay overnight in the Research Facility under medical supervision at the end of each study visit.

**Who is organising and funding this study?**

This study is being organised by Dr Nazia Karsan and Dr Pyari Bose under the supervision of Professor Peter Goadsby. Other researchers in the team may also be involved, all of whom work under the Headache Group at King’s College London. The study is funded by The Migraine Trust charity.

**What will happen to me if I take part?**

If you take part in the study, you will first of all be invited for an initial visit which will help to decide if you are suitable to continue for the full duration of the study.

In study arms 1 and 2 (the premonitory and postdromal studies), during the first visit (visit 1), you will be given the drug nitroglycerin (NTG) to trigger a migraine and then treated with either aspirin or sumatriptan injection and if you develop the premonitory symptoms before the headache, or the postdromal symptoms after the headache has been treated with sumatriptan, you will be asked to come back for 2-3 further visits at a minimum of 2 weekly intervals. A study doctor will assess your symptoms and migraine characteristics and assign you to Study Arm 1, focusing on the premonitory symptoms, or Study Arm 2, focusing on the postdrome symptoms for the remaining duration of the study depending on which arm of the study the investigators think you are more suitable for. At each of these visits you will undergo a triggering and treatment sequence, MRI brain scanning, clinical and questionnaire assessments.

This study is known as a randomised study, which means that, the order in which you receive the ‘trigger’ or ‘treatment’ (in the case of Study Arm 1) or the order of each visit (in the case of Study Arm 2) is random. A computer generated code is used to decide the order.
If you are assigned to Study Arm 1, you will receive either NTG or a dummy drug (placebo) at the start of the study to trigger a migraine, followed by aspirin or placebo once the migraine becomes intense. Neither you nor the member of the study team analysing the data will know what you are getting on each visit. As you pass through the study you will go through each possible treatment sequence in a variable order to other participants. This takes away any patient or investigator-based bias when looking at the study results. If you received NTG during a visit at the start but placebo once the migraine becomes intense, you will be given aspirin after scanning at the end of the study to ensure sufficient pain relief. If you are still in pain after this is given, you are permitted to take some of your usual migraine pain relief.

If you are assigned to Study Arm 2, you will be randomised to the order at which you attend the subsequent visits (visit 2 and visit 3). One of these visits will involve having a migraine triggered with NTG and MRI brain scanning, the other will involve placebo instead of NTG but still undergoing scanning. In visit 2 or visit 3 (depending on randomised order) once you develop a migraine following NTG, this will be treated with an injection of sumatriptan. At the visit where you receive placebo instead of NTG, you will receive an injection of placebo at the correct time instead of sumatriptan. Once the migraine headache resolves, your symptoms after the migraine headache (postdrome symptoms) will be assessed. During each visit, we will monitor how much pain you are feeling through standard questionnaires about your symptoms. If your pain becomes unbearable for you, or you have been in pain for a prolonged period over 2 hours, then we will immediately provide pain-killers as needed.

MRI Scanning

The MRI scanner is a noisy and confined environment, which may cause you to feel slight discomfort and claustrophobia. The clinical staff is trained to manage the occurrence of such events. In the event that you experience distress in the MRI scanner, the scanning process will be ceased immediately. During scanning you will be continually monitored from the MRI control room. If you feel discomfort scanning can be stopped by pressing a distress button that you will be given before entering the scanner. There will always be a fully trained first aider and qualified and experienced radiographer present within the vicinity of the scanner room. Scanning is always performed in the presence of both clinical radiographers and nursing staff and your heart rate is continuously monitored.

How is the study conducted?

The study will involve three or four visits, depending on the arm of the study you are assigned to. Visit 1 is common to both arms of the PREMON/POSTD studies, following which you will be assigned to either Study Arm 1 or Study Arm 2 depending on your clinical characteristics and information gathered from Visit 1.

For study arms 1 and 2, the visits will each be at a minimum of 2 weekly intervals. You will receive a phone call from a member of the study team prior to each study visit to confirm that you are headache and symptom free. In some circumstances, if you fail to trigger in Visit 1, and you are amenable, you may be asked to re-attend for another Visit 1 to see if you trigger on a repeat visit. This has never been assessed before. If you fail to trigger on this visit, you will then be excluded from the study.

Visit 1 (Study arms 1 and 2) - Screening, Questioning, Examination, Test infusion of NTG, Familiarisation of MRI scanner and Consent.
Questions regarding migraine history, symptoms usually experienced prior to onset of migraine headache, and general health screening questions will be completed followed by screening to ensure eligibility for the study. A physical examination including height and weight, blood pressure check and routine hospital observations will be taken, followed by a pregnancy test (if applicable). An ECG will also be taken, which may involve removal of shirts or tops to allow the ECG stickers and leads to be applied, as well as lowering of trousers or skirts, to allow the lower limb leads to be applied on the thighs. In male subjects, small areas of chest hair may need to be shaved to allow application of the ECG stickers if necessary. Written consent will be taken by an investigator. You will be able to enter the MRI scanner so as to become familiar with the scanning environment.

A fine plastic tube (cannula) will be put into one of the veins in your arm and you will be given an infusion of NTG over 20 minutes to try and induce a migraine and its associated symptoms. If your migraine can be triggered with NTG your symptoms will be characterised and if you are happy to continue in the study you will be assigned to either Study Arm 1 or Study Arm 2 by a study doctor. Questionnaires to assess how disabling your migraines typically are will be administered at the start of the day. If you do not have a migraine triggered with NTG you will leave the study at this point and you will not be required for any further visits or study investigations. Information collected from you up to this point may still be included in the study.

**Study Arm 1 (Premonitory Arm)**

**Visits 2-4 - Imaging and intervention**

Once you have demonstrated that we are able to trigger migraine premonitory symptoms in you using NTG, you will be invited to three more visits. During each of these visits, you will have one of the treatment sequences in random order with four 30 - 45 minute MRI scans.

During these visits, you will also have a cannula put into one of the veins in your arm to administer NTG/dummy drug (placebo), a sugar solution for “feeding” via a drip and aspirin.

The first scan of the day will take place at the start of the day, when you have no symptoms of a migraine and before a migraine is triggered with NTG, or a placebo is given - this is called a baseline MRI scan. After a baseline MRI scan, you will undergo an infusion of NTG or placebo and have a second scan during the ‘premonitory’ stage of your migraine (before the headache starts). The study doctor will ask you questions to document the premonitory symptoms. You will have a third scan during your headache - the onset of the ‘headache stage’ will be monitored by the study doctor and questions will be asked to determine the severity of the pain. At this point you will be given 1 gram of aspirin or a placebo drug and have a final ‘treatment’ scan. This is to identify the effect that aspirin has on the changes to activity in the brain caused by NTG and to make sure it does not have the same effect without any migraine symptoms (in the normal state). Your symptoms will be assessed with questionnaires and clinical assessment pre-triggering, post triggering and following treatment of the headache. At the end of scanning if you did not receive any pain relief during the scanning, you will receive intravenous aspirin. If you still have pain after this, you may take your own usual migraine medication, including sumatriptan. Rescue anti-sickness medication will also be available at the end of the scanning if it is needed, and you are also welcome to bring your own migraine pain and sickness medication if needed. If at any point during any of the study visits, you encounter unbearable pain or have been in prolonged pain or significant nausea for over 2 hours then you will be offered appropriate rescue medication (paracetamol, ibuprofen or sumatriptan and/or domperidone or ondansetron), as determined by the study doctor and the study assessments will terminate for that session if needed.
**Study Arm 2 (Postdrome Arm)**

**Visits 2-3 – Imaging and intervention**

Once you have demonstrated that we are able to trigger migraine postdrome symptoms in you, using NTG, you will be invited to two more visits - the order of which will be randomised. During each of these visits, you will have four 30 – 45 minute MRI scans.

During these visits, you will also have a cannula put into one of the veins in your arm to administer NTG or a dummy drug (placebo) and a sugar solution for “feeding” via a drip. During one of these visits you will be given a 20 minute infusion of NTG through the cannula to trigger a migraine, during the other you will receive a 20 minute infusion of placebo instead and your migraine may not be triggered. You will not be told at which visit your migraine will be triggered with NTG and this information will not be known by the study doctor either so as to allow unbiased analysis of the results of the study.

The first scan of the day will take place at the start of the day, when you have no symptoms of a migraine and before a migraine is triggered with NTG/placebo, this is called a baseline scan. The second scan during the ‘premonitory’ stage of your migraine (before the headache starts). The third scan will occur during your headache. The onset of the ‘headache stage’ will be monitored by the study doctor and questionnaires will be used to document the severity of the pain. You will receive treatment with sumatriptan injection into the skin to treat the migraine. Once the headache pain has been relieved you will undergo the fourth scan during the postdrome stage of the migraine. Your symptoms will be assessed with questionnaires and clinical assessment pre-triggering, post triggering and following treatment in the postdrome. During the visit when a migraine is not triggered through NTG infusion, you will still be administered sumatriptan injection at the approximate time of your migraine onset from information gathered at visit 1. You will undergo four brain MRI scan at times corresponding to the timeframe of your migraine, as documented in visit 1.

If at any point during any of the study visits, you encounter unbearable pain then you will be offered rescue medication (paracetamol, ibuprofen or sumatriptan), as well as rescue anti-sickness medication (domperidone or ondansetron) after the scanning has finished, as determined by the study doctor and the study assessments will terminate for that session if needed.

**Can I eat and drink as normal during the visits?**

In study arms 1 and 2

It is known that food and drink intake can interfere with what we see on the MRI scans. Additionally, many people feel sick and vomit when they get a migraine. During visits when scanning is taking place you may eat a small breakfast before you leave home to attend the visit, but you will be required to abstain from eating and drinking for the duration of the day until scanning has finished. A sugar drip will be given through the cannula to keep you hydrated, and is good treatment for a migraine and you should not feel hungry.

**What are my responsibilities during the study?**

- You will be required to bring your usual migraine medications during each visit.
- You will be given a migraine diary to fill in at home about every headache or migraine you experience for the duration of the study.
- You will be asked to complete a premonitory and postdrome symptom checklist for your next spontaneous migraine attack at home.
During each visit when scanning will take place you will need to **abstain from eating and drinking.** You may have a light breakfast and an uncaffeinated drink the morning of each study visit.

Please attend all study visits in a timely fashion and bring along any requested information to each visit. If there is any reason why you cannot attend a visit or you have some additional information that you think the investigator would need to know we ask you to contact them as detailed at the contact details section at the bottom of this leaflet.

If you have private health insurance you should contact the company to inform them that you are taking part in this study to ensure that it does not affect your cover.

**Female specific responsibilities**

- If you are of child bearing age, you will need to have a **pregnancy test** at each visit. If you are discovered to be pregnant you will be excluded from the study at that point.
- You should not attend a visit if you are actively **menstruating**. Your study doctor will try to schedule the visits to accommodate this.
- You will be asked to keep a **menstrual diary** for the duration of the study and record menstruation and your temperature daily (you will be provided with a special thermometer for oral use and trained on how to do this).

There are some lifestyle guidelines which we ask patients to comply with throughout the duration of the study, which are detailed below:

**Lifestyle guidelines**

- You will need to abstain from alcohol for 24 hours prior to each visit
- You will need to abstain from caffeine-containing products for 12 hours prior to each visit
- You will need to abstain from taking Ibuprofen/Nurofen-like drugs or paracetamol for 12 hours prior to each visit
- You will need to abstain from the use of tobacco- or nicotine-containing products for 4 hours prior to admission until discharge for each visit
- You should not smoke more than 5 cigarettes per day or consume more than 6 cups of caffeinated drinks per day from enrolment to the study.
- You should maintain your regular sleep routine for the duration of the study. Any disruption can potentially disrupt the study; therefore you should let the doctor know if you have any concerns.

**What are the risks and inconveniences to me?**

Before recruitment into the study, the study doctors will need to do a full assessment and screening.

For study arms 1 and 2, if you are on a single migraine preventive, such as topiramate, propranolol, pizotifen and amitriptyline, and the dose is not adequate and/or you feel the drug is not working for you then the Study Investigator may, with your consent, ask you to hold these for 2 weeks prior to the study and for the duration of the study. This should be no longer than 12 weeks in total. If you take 8 or more days a month of Paracetamol and/or opioid-containing pain killers, such as Co-codamol and Tramadol, the study investigators may ask to you to reduce this use down to 8 or less days. The same applies if you take 10 or more days a month of triptans and/or NSAID-containing pain
killers such as Ibuprofen, Naproxen and Diclofenac. No study visits will occur until at least 4 weeks after medication overuse has been addressed appropriately.

The NTG infusion has a likelihood of inducing migraine headache, which is its purpose in the study. In previous studies, in the selected group of patients receiving this infusion, no other complications have been found, if inappropriate individuals with other medical problems are excluded (as per the relevant exclusion criteria based on other medical problems). The drug can cause a transient and rarely troublesome drop in blood pressure, which may manifest as feeling faint or light-headed. In this circumstance, the infusion will be stopped and you would be laid flat with your legs elevated.

Some study drugs will both be given through a small needle in a vein, called a cannula. Insertion of this can sometimes be uncomfortable and may cause some bruising.

Intravenous aspirin has been proven in previous studies as being effective for the treatment of migraine headache. The main side effect of intravenous aspirin is nausea or feeling sick. It is very important that you let the study investigators know if you suffer any of the side effects. Subcutaneous Sumatriptan has been proven in previous studies as being effective for the treatment of migraine headache. Subcutaneous injections can cause some discomfort at the site of injection which is transient. Side-effects of Sumatriptan include sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body. In the unlikely event of a side effect from Sumatriptan, this will be recorded as an adverse event and treated appropriately. Please note that you are not allowed to drive after sumatriptan unless you feel completely back to normal. You should be accompanied by someone on discharge after being treated with sumatriptan unless you feel completely back to normal.

**What are the benefits to me?**

There are no direct benefits to you for partaking in this study. However this study allows you the chance to be involved in new research which will hopefully help current understanding into migraine and guide future research.

**Will my taking part be kept confidential?**

The study will need to allow investigators to have access to your medical notes. All results of the study which are published will not contain any means of identifying you. Records identifying you will be kept and stored in a confidential manner during the study and will only be available to the study investigators and the study radiographers who perform the scans. People conducting the study will abide by the Data Protection Act 1998, and the rights that you have under this Act. Your own GP will be informed of your participation. As with any investigation, it is possible that we discover an abnormality that you were not aware of. If this should happen, your GP will be notified and will contact you for relevant discussions regarding your medical care.

**What will happen to the results of the study?**

The investigators hope to be able to publish the results in a scientific medical journal, so as to increase the understanding of migraine in a wider audience. All published information will be entirely anonymised so there will be no means of anyone identifying you from any of the data, descriptions or results. If you would like, a copy of any published articles can be sent to you after completion of the study.
How and when will I be contacted in case of a problem?

During the study, if any information becomes available which may affect your willingness to stay in the study you will be contacted as soon as possible. Before every study visit you will be contacted by telephone to ensure everything is OK for you to attend.

Is there any reason why I may need to stop being a part of the study?

If you develop any study-related complications, lose the ability to comply with the lifestyle guidelines or the ability to attend for every study visit you may need to be excluded or withdrawn from the study. This will be discussed with you as needed on a one-to-one basis by the investigator.

How long do I need to be part of the study for?

The study should last for a minimum of 6 weeks but can last up to 12 weeks. Each visit will be scheduled a minimum two weeks apart and we will try to ensure the study finishes in the minimum possible time. Your records will need to be kept on file for longer than this.

Expenses and payments:

You will be given £80 per visit in appreciation for partaking in this research. If you complete all three of four visits you will receive £240 or £320 respectively, if you do not complete all the visits you will receive less than this. The amount you receive will depend on how many visits you have completed. In addition you will be reimbursed for all reasonable travel expenses, up to a maximum of £50 per visit. Please contact the research team for advice on reasonable travel expenses. You will receive all expenses and payments at the end of the study. Please keep ALL receipts for travel expenses.

How many other people are taking part?

We aim to recruit 32 people to take part in the full study after visit 1.

How do I get in touch with someone for further information?

You can contact the main investigators, Dr Nazia Karsan on 0203 299 5528 (working hours only) or Dr Pyari Bose on 02032995525 (working hours only) or email headache-research@kcl.ac.uk.

What if there is a problem?

If you are concerned or wish to complain, please contact Professor Peter Goadsby 0203 229 3106 or email peter.goadsby@kcl.ac.uk

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 remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure (or Private Institution). If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone’s negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Details of how to complain can be obtained from Patient Advice and Liaison Service (PALS):
It is entirely your decision whether to take part or not. If you decide to take part you are still free to withdraw at any time and without giving a reason. If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you agree to take part, you will be asked whether you are happy to be contacted about participation in future studies. Your participation in this study will not be affected should you choose not to be contacted again.