STUDIES INVESTIGATING EXPERIMENTALLY INDUCED PAIN IN ADULT HEALTHY VOLUNTEERS

Please note that this approved procedure should only be submitted to the Medical Sciences IDREC for use in connection with research undertaken within the UK which is not funded by the US National Institutes of Health or another US federal funding agency; such research that is to be undertaken outside the EU and/or with US funding should be submitted for review to OxTREC using OxTREC’s full application form.

1. SCOPE

The goal of pain research is to acquire new knowledge on the mechanisms, pathogenesis, diagnosis, and treatment of acute and chronic pain. Pain may also be used, however, as a proxy for the study of something else (e.g. endorphins). This requires research on humans and involves experimentally induced painful stimuli. There are many methods to experimentally activate painful sensations in a safe, controlled and temporary manner. All listed procedures and experimental methods were previously ethically approved and are widely used in pain research and clinical diagnosis. The minimal intensity of noxious stimulus necessary to achieve the goals of the studies is established. Participants are always able to terminate a painful stimulus at will and stimulation intensities will not exceed the individual tolerance level. All researchers involved in data acquisition must undergo safety training for the stimulation device they intend to use. Studies under this approved procedure will include adults aged 18+ years. In case-study samples that include older participants (> 60 years), researchers must be trained to accommodate all procedures to age-related changes (e.g. more delicate skin with age). During study procedures the stimulation device must be supervised by a second researcher who is not involved in other tasks related to the study.

Pain studies can be conducted with or without non-invasive neuroimaging techniques such as Magnetic Resonance Imaging (MRI), Electroencephalography (EEG), and/or Magnetoencephalography (MEG). In studies where neuroimaging techniques are used, such techniques have been approved in CUREC approved procedures 17 for MRI, 03 for EEG, and 08 for MEG. When used in an MRI environment, all stimulation devices will first be checked for safety on the specific MR scanner by a radiographer.

This procedure allows for two different pain methods to be used in tandem (e.g. chemical stimulation followed by pinprick), provided each method is calibrated separately for individual participants prior to use in tandem.

1.1 Sensory stimulation techniques
(i) Touch Pain:
Sensations related to touch that range from light touch to sharp pinprick can be elicited using punctuate probes and von Frey hairs specifically designed to deliver a constant force to the skin surface. Furthermore, a purpose-built pressure device can be used to induce deep tissue pain (e.g., joint pain). None of these devices penetrate the skin. The maximum force delivered will be 512 mN for punctate probes and von Frey hair and 250 N for the pressure device. There are no known side effects to any of these stimulations. In studies where neuroimaging techniques are used, these devices are MRI-compatible. These have been approved in earlier NHS ethics applications for use in the fMRIB pain laboratory:

C02.086 “Mapping brain function with fMRI”; PI: Prof. Paul Matthews; OREC
C03.092 “The effect of gabapentin on the brain response, as measured by functional magnetic resonance imaging (fMRI), to a heat/capsaicin challenge in healthy volunteers”; PI: Dr. Giandomenico Iannetti; OxREC
C02.327 “fMRI investigations of clinical pain processing mechanisms and their modulation by ‘Gold Standard’ analgesic compounds”; PI: Prof. Paul Matthews; OREC

(ii) Heat/Cold Thermal Pain:
To induce heat or cold pain, radiant heat, using an infrared laser stimulator, or conductive heat/cold using a contact heat thermode can be applied. These devices are safe, several are CE-approved and all are widely and routinely used for clinical diagnostic purposes. The FMRIB pain laboratory has many years’ experience using these devices.

The limitations for contact heat/cold are:
- minimum temperature: 0°C (Medoc©), 5°C (Somedic©) for a stimulus duration of 3s, max. ramp time: 0.5°C/s
- maximum temperature: 55°C for a stimulus duration of 3s (max. ramp time: 0.5°C/s)
- maximum size of stimulation site: 12 cm² mm (Somedic©) or 9 cm² (Medoc©).

Only laser stimuli that are non-injurious and acceptable to the subject will be used. The laser used to produce painful sensations may cause temporary redness lasting about 20-30 minutes over the skin where it is applied. The main risk is accidental eye damage due to direct or reflected laser beams. To minimise the risk, trained researchers will ensure that all precautions according to University safety guidelines are taken, which includes both the researcher and subject wearing the appropriate safety goggles to protect the eyes whenever the laser is used. All researchers involved in the use of the laser must be trained according to University laser safety guidelines to minimise risk. All procedures currently used in the lab have been amended to adhere to the University laser policy as reviewed by the Health Protection Agency (see: http://www.admin.ox.ac.uk/safety/policy-statements/s2-09). The Nd:YAP laser (DEKA©; wavelength of 1340 nm) in the FMRIB pain laboratory has been certified for energy levels between 0.5 and 15 J, a pulse length of 1-20 ms and a spot diameter of up to 15mm.

To define precisely the parameters of thermal stimulation, both skin temperature and skin thickness may be measured using an infrared thermometer, thermal camera and a confocal microscope. These measurement methods are safe and non-invasive. Thermal stimuli have been safely used as part of the FMRIB pain research programme in other ethically approved pain research projects:

C02.086 “Mapping brain function with fMRI”; PI: Prof. Paul Matthews; OREC
Central University Research Ethics Committee (CUREC)

Approved Procedure: IDREC_19_Version 3.0

**Title:** Studies Investigating Experimentally Induced Pain in Adult Healthy Volunteers

- **06/Q1605/126** “Functional magnetic resonance imaging of visceral and somatic pain in chronic pelvic pain patients and healthy controls: variation across the menstrual cycle”; PI: Prof. Irene Tracey; NRES
- **09/H0604/90** “Perceptual decision-making in the context of pain”; PI: Prof. Irene Tracey; NRES

(iii) **Electrical Pain:**

For electrical pain, an electrode is applied to the skin surface, after it has been prepared with a commonly used cream that enhances conductance. Controlled current is applied only to this prepared surface area, without passing internally into the body. Equipment, such as Digitimer DS7A, Hertfordshire, UK, will be used to elicit a low-level of electrical output that is sufficient to induce a moderate-to-strong pain sensation. Equipment is certified for an output current of 0-100 mA, a source voltage of 100-400 V and stimulus durations between 50 $\mu$s to 2ms. Electrical stimulation has been used previously in ethically approved studies conducted in the University:

- **C02.086** “Mapping brain function with fMRI”; PI: Prof. Paul Matthews; OREC
- **05/Q1604/160** “Effects of religious belief and perceived control on the perception and processing of pain”; PI: Prof. Irene Tracey; NRES
- **10/H0301/17** “Role of the DLPFC in pain modulation: a combined fMRI and TMS study”; PI: Prof. Irene Tracey; NRES

(iv) **Chemical Stimulation:**

Chemical stimulation will be administered by applying low-doses of capsaicin (the active ingredient that gives chilli peppers their hot taste) or menthol (a cooling agent) to the surface of the skin. Capsaicin can produce a moderate burning sensation, which may last for a few hours even after removal of the capsaicin cream. Capsaicin cream has been used safely when applied in accordance with the following parameters:

- Dose: 1 % Capsaicin
- Volume: 5 ml
- Surface Area: 2x3 inch
- Exposure: 2 hours [maximum] in any 48-72 hour period

If necessary, capsaicin-evoked burning sensations can be instantly relieved by removing the capsaicin cream and applying a cold stimulus to the site where the cream was applied. Any skin tenderness that is experienced should return to normal after a couple of days and there are no known long-term side effects. Participants will be given contact details to get in touch with a researcher in the event that skin does not return to normal within 48 hours of chemical stimulation.

Menthol may produce a moderate cooling sensation that can last for a few hours, which may remain for a period of time after removal of the menthol cream. Menthol is a well-known cooling agent that on contact would act to cool the skin and/or reduce or eliminate capsaicin-induced burning sensations. When using menthol, a low dose concentration (max: 2%) will be used to cover the site of the skin being treated. For most subjects, the volume of cream needed will approximately be 10 ml spread over a small surface area of the skin. Menthol cream can be removed immediately at any time to stop the sensation.

Chemical stimulation has been safely used as part of the FMRIB pain research programme in other ethically approved pain research projects:
Title: Studies Investigating Experimentally Induced Pain in Adult Healthy Volunteers

11/SC/0249 “Human Pain Processing”; PI: Prof. Irene Tracey; NRES
08/H0606/50 “Validation of functional imaging in conjunction with a central sensitisation model for evaluating analgesic efficacy”; PI: Prof. Irene Tracey; NRES

References

(v) Others:
In order to investigate different aspects of the pain experience other sensory stimuli (e.g., visual, auditory, olfactory) may be administered using standard experimental equipment. Examples of this may include: word cues, facial cues, auditory tone cues, or flashing checkerboards. These are standard experimental techniques that are not harmful and are widely used at FMRIB/OCMR, and elsewhere in the University.

1.2 Behavioural measures

The behavioural measures listed below are commonly used clinical methods of gauging general physiological measures of a subject’s overall health, and allow the researcher to ensure that the subjects are healthy and awake throughout the study procedure. The different pain rating scales are essential for collecting perceptual data about how each subject perceives the different stimuli. These data can be useful in terms of explaining the different neurophysiological recordings (e.g. whether the magnitude of BOLD activation correlates with the intensity of perception). All measures listed below were ethically approved previously through the HRA for use at FMRIB and OCMR.

(i) Physiological monitoring:
   a) heart rate and other cardiac measures (MRI-compatible ECG electrodes are available)
   b) oxygen saturation (using pulse oximeter)
   c) breathing rate (using respiratory bellows)
   d) CO₂ via nasal cannulae
   e) Galvanic Skin Response using surface electrodes
   f) eye-blink conditioning (using surface EMG or non-invasive eyetracker)

(ii) Rating Scales:
   a) Visual Analogue Scale (VAS). The VAS is a measurement instrument that tries to quantify a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. For example, the amount of pain a person feels ranges across a continuum from none to extreme amount of pain. This can be translated by the use of a scale with two anchors of extremes on either side.
   b) Numerical Rating Scale (NRS). Employs the same continuum as the VAS but includes a numerical spectrum. For example, in the case of a painful sensation, no pain/sensation =0; while an intense pain =10. The numerical value could vary depending on the resolution required.
   c) Graphic Rating Scale (GRS). The GRS is a commonly used self-report instrument (Jensen and Karoly, 1992). It consists of a scale that is anchored with descriptive adjectives related to the magnitude of a particular subjective experience. For example, a common application of the GRS is to quantify the
extent to a particular stimulus experienced by the subject was lower or higher than expected. Here, the scale is anchored by -5 on the left side of scale (lower than expected) and +5 on the right side of the scale (higher than expected). The GRS can also be used to gauge how distracted the participant was by a particular stimulus. Here, the scale is anchored with 0 (not at all distracted) and 10 (very strongly distracted).

d) **Categorical Rating Scale.** Used in circumstances where either the NRS or VAS are inappropriate. Here, subjects are asked to assign an adjective to best explain their pain (e.g. none, mild, moderate, or severe).

e) **Quality of perception.** After each stimulus presentation, subjects will be asked to qualify the perceived sensation, using a predefined list of descriptors (e.g. ‘tingling’, ‘pricking’, ‘warm’, ‘burning’, ‘touch’...).

(iii) Questionnaires:
Questionnaires are a clinically common, widely used method of accounting for essential psychological factors that are known to affect pain perception. Specific details of each questionnaire will be listed in study-specific applications. Subjects will be instructed to complete questionnaires at a designated time either before or after the study procedure(s). Subjects will complete the questionnaires and all data must be anonymised and entered into an electronic database that must be stored on a secure server (see Data Protection Issues below). Anonymised paper and pencil versions of questionnaires must be kept confidential, stored in a secured filing cabinet. The data will be available only to the primary researcher conducting the study. Detailed explanation of each questionnaire must be given, as will the participants’ rights to confidentiality.

(iv) Other behavioural measures:

a) **Reaction times.** A timer is initiated upon the onset of the sensory stimulus. The subject is asked to press a button upon perception of the stimulus. Pressing the button halts the timer. The reaction time is measured as the delay (in milliseconds) between the onset of the stimulus and the motor response. The average reaction-time measurement, as well as their distribution, will be compared across experimental conditions.

b) **Decision.** The participant is prompted to select an option (e.g. yes or no) with the use of a button box or a rating scale.

c) **Nociceptive reflexes.** To assess the nociceptive flexion reflex, EMG activity is recorded from the biceps femoris muscle (using surface electrodes) following electrical stimulation.

### 1.3 Cognitive-affective modulations of pain

The psychological paradigms listed below are commonly used techniques to gauge different aspects of a person’s engagement and experience of pain. Each test is designed to study a separate component of this complex experience. The main psychological components of interest are those factors known to be associated with and affect the experience of pain. The aim of such research is to see how these factors correlate with and affect pain perception in different subjects who have variable personality influences that additionally modify the experience. Each of these measures are commonly used in clinical practice and primarily rely on subjects filling out questionnaires or scales during experimentation (see Section: Behavioural Measures), where we might have manipulated one component of for example their attention or mood state, by classical conditioning task often using visual or auditory inputs, to change their pain experience. Results from each paradigm can be used to explain how each component of pain perception changes the results acquired with the
neurophysiological recordings (e.g. whether a person’s emotional state changes the relationship between BOLD activation and the intensity of pain perception).

All measures listed below were ethically approved previously for use at FMRIB and OCMR.

Pain perception is influenced by certain individually specific psychological features such as personality, emotion, attention, anxiety, depression and beliefs. In this way, it is important to measure and control for these aspects of the pain experience. These would be monitored through the use of behavioural measures such as scales and/or questionnaires during testing. All of the above features have been approved previously by NHS ethical review, as follows:

a) Personality
   07/Q1605/4 "Personality and pain perception; PI: Prof. Irene Tracey; NRES

b) Emotion
   C02.086 "Mapping brain function with fMRI”; PI: Prof. Paul Matthews; OREC
   09/H0604/90 "Perceptual decision-making in the context of pain”; PI: Prof. Irene Tracey; NRES

c) Attention
   C02.086 "Mapping brain function with fMRI”; PI: Prof. Paul Matthews; OREC

2. TRAINING OF RESEARCH STAFF

All researchers will undergo Good Clinical Practice (GCP) training in order to be involved in research involving volunteers. All researchers involved with MRI are required to undergo annual MRI safety training – failure to undergo this training will automatically involve revocation of access to the centres. All researchers involved in data acquisition will undergo safety training for the stimulation device they intend to use.

Where MRI is also used, all scanning will be conducted by a fully trained MRI operator or licensed radiographer.

3. METHODS FOR RECRUITING PARTICIPANTS

Potential participants may be identified by poster adverts (sample enclosed) word-of-mouth and e-mail postings to departmental and college mailing lists, which must contain the contact details of the researcher who will send further study information sheets (sample enclosed) to interested participants. This approved procedure also covers recruitment of volunteers from the community (general public) as well as students and staff of Oxford University and Oxford Brookes University. It does not cover participants recruited as having particular symptoms (e.g. low mood, chronic pain). Contact details of study researchers will be detailed in individual study Adverts and Information Sheets.

4. INFORMATION PROVIDED TO PARTICIPANTS

The specific details provided will vary depending on the study, but should always be on University Headed paper, showing the Departmental name and address.
The Information Sheet must be written in simple but non-patronising language. Most word-processing packages provide readability statistics for a document, and one should aim for a 12-year-old (Year 7) reading level for adults. Information sheets must be submitted with the CUREC 1 form for specific projects. The Information Sheet must contain information on risks and side-effects of the specific stimulation used - as specified in this protocol – and should be appropriately modified for studies using different modes of stimulation or taking place in a different laboratory. For example, the information sheet for a study using laser stimulation should include a statement that 'Very occasionally laser stimuli produce slight marks to the skin, these are harmless and disappear completely within a few days' - or whatever is accurate and scientifically correct - but in lay language.

Please refer to the Information Sheet associated with this Approved Procedure.

5. CONSENT OF PARTICIPANTS

Written consent must be obtained from all participants using the Consent Form associated with this approved procedure. Consent will be obtained for each study by a researcher trained annually in GCP. Vulnerable populations and volunteers who are unable to provide informed consent or who are younger than 18 years old are not covered by this approved procedure. Please see http://www.admin.ox.ac.uk/curec/resources/informed-consent/.

Please refer to the Consent Form associated with this Approved Procedure

Guidance on the informed consent process can be found at: http://www.admin.ox.ac.uk/curec/resources/informed-consent/

6. FINANCIAL AND OTHER REWARDS TO PARTICIPANTS

Compensation (either financial or in kind) may be offered to subjects for their time and inconvenience incurred, as well as reasonable travel expenses. Some studies (for example, those investigating reward processing) may offer a performance-related reward. Individual study proposals will detail the value (if any) of compensation to be offered. The amount may be stated on the Participant Information Sheet, but cannot be disclosed on the advert as this could be coercive.

7. POTENTIAL RISKS TO PARTICIPANTS/RESEARCHERS/OTHERS AND WHAT WILL BE DONE TO MINIMISE

Risks associated with imaging techniques (MRI, EEG, MEG) and methods to meet them are described in Approved Procedures 17 for MRI, 03 for EEG, and 08 for MEG).

All stimuli that are used to experimentally induce pain have been safely used as part of our pain research programme in ethically approved projects. The minimal intensity of noxious stimuli necessary to achieve goals of the study is established. The stimulation intensity does not exceed the individual tolerance level. Participants are always able to terminate a painful stimulus at will.

However there are a few possible risks:

Laser. In some cases, application of laser stimuli may produce a slight punctate erythema. On rare occasions, these spots may subsequently become hyper pigmented. They always vanish completely
within a few days. The main risk is accidental eye damage due to direct or reflected beams. To minimise this risk, trained researchers must ensure that all precautions according to local safety guidelines are taken, which includes both the researcher and subject wearing the appropriate safety goggles to protect the eyes whenever the laser is used. All researchers involved in the use of the laser must be trained according to University laser safety guidelines to minimise risk. All procedures currently used in the lab must be amended to adhere to the University laser policy as reviewed by the Health Protection Agency (see: http://www.admin.ox.ac.uk/safety/policy-statements/s2-09/).

Contact thermode. Regarding the thermal device, the stimuli used to produce painful sensations may produce temporary redness lasting about 20-30 minutes over the skin where it is applied, when used repeatedly. However, an upper limit will must set to prevent permanent skin damage and calibrated to each subject’s tolerable limits. See also Documentation on Pathway Safety and Regulatory Summary for the Medoc® Pathway Device attached.

Chemical stimulation. Although the risks associated with the use of chemical stimulation – specifically capsaicin and menthol - are low, risk potential increases without appropriate training. Therefore, it is the responsibility of the individual researcher to undergo training and approval for capsaicin use by a member of the fMRIB pain group and to adhere fully to standard operating procedures set out for capsaicin use. The main risk when using chemical stimulation is the accidental irritation of non-target areas of skin of either the researcher or participant when applying the creams. To minimise this risk, trained researchers must adhere to all precautions according to local standard operating procedures, including wearing disposable gloves and protective eye-wear when applying or removing creams.

All participants with private health insurance should be advised to contact their insurers to ensure that participation in this study does not contravene the terms and conditions of their policies.

8. MONITORING AND REPORTING OF ADVERSE OR UNFORSEEN EVENTS
Adverse or unforeseen events associated with MRI scanning are covered in CUREC_AP_IDREC_17 and for MEG in CUREC_AP_IDREC_08.

In the unlikely event that noxious stimulation produces an adverse event, the participant should immediately be referred to an appropriate clinician.

9. COMMUNICATION OF RESULTS
Study results may be written up for publication in peer-reviewed scientific journals, presented at scientific conferences (in abstract or presentation formats), entered into fully-anonymised repositories of imaging data, submitted as part of course degrees and may form part of grant applications. In all cases, results will be fully anonymised and not contain any data that could be linked to the volunteers.

10. DUTY OF CARE ISSUES / CONFIDENTIALITY
Personal data (such as date of birth, and personal questions relating to MRI safety) as well as questionnaire responses may be necessary for individual studies. Study Information Sheets will detail this and explain that any personal information will be anonymised wherever possible, and information about volunteers maintained in strict confidentiality.
Central University Research Ethics Committee (CUREC)

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Some studies may use validated questionnaires asking volunteers about state and trait anxiety and/or depression to interpret how these factors influence processing and perception of study stimuli. These questionnaires are not used for recruitment or screening purposes. However, if a researcher, as a result of these questionnaires, has concerns that a volunteer may have an undiagnosed psychiatric condition that is causing distress, CUREC guidelines (MSD/GUIDE/1.1) will be followed. The researcher must seek advice from the Principal Investigator who may discuss the symptoms in greater detail with the volunteer and/or offer the opportunity to speak with a senior clinical researcher if they are not clinically trained themselves.

11. **DATA PROTECTION ISSUES**

Imaging data is automatically coded at source with an anonymisation code that cannot be directly linked to the volunteer. Any electronic data (e.g. MRI/EEG/MEG files, behavioural reaction time files, questionnaires) must be labelled with a code number rather than a name or initials and must be stored on a secure server. With the written informed consent of the volunteer, fully anonymised data may be shared with other research institutions, including researchers outside of the EU, for other and future research studies.

If it is necessary to retain any personal information (such as contact details), the keys linking codes to personal details must be kept in lockable filing cabinets with access only by the researcher within the FMRIB Centre/OCMR. Personal data may be retained after the end of the study where the participant agrees to be contacted for future studies. For volunteers who do not wish to be contacted in the future, personally identifiable data must be shredded as soon as possible after completion of the study and within one year of completing study analyses. Personal data may be viewed by regulatory bodies and designated individuals within the University of Oxford for the purposes of monitoring and auditing the research with the written consent of the volunteer.

12. **FURTHER INFORMATION**

Sample consent form, participant information sheet and poster advert.

13. **CHANGE HISTORY**

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Central University Research Ethics Committee (CUREC)

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