Study Title: The cerebral signature for pain perception and its modulation

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The investigators declared there is no conflict of interest in this research.

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SYNOPSIS

Study Title	The cerebral signature for pain perception and its modulation
Study Design	Prospective study
Intervention Group	All chronic neuropathic pain patients treated with deep brain Stimulation**,** Spinal Cord Stimulation including targeted stimulation of the Dorsal Root Ganglion, and noninvasive neurostimulation.
Number in Intervention Group	Approximately 50 patients minimum
Control Group	Healthy volunteers with no history of chronic pain, no acute pain, no previous neurosurgery and , no neurological/psychiatric comorbidities.
Number in Control Group	Approximately 50 minimum
Planned Study Period	September 2013 to December 2019
Primary Objective	To determine whether there is cerebral pain signature
Secondary Objectives	To understand how the cerebral pain matrix, including brainstem, anterior cingulate cortex, thalamus and cerebral cortex interact with one another and with the spinal cord and dorsal root ganglia for pain perception and its modulation. Also, to determine whether stimulation has an effect on the autonomic nervous system.
Primary Endpoint	Differences of LFPs of various cerebral nuclei induced by endogenous pain modulation and DBS in chronic pain compared to healthy controls

Secondary Endpoints	Differences of LFPs of various cerebral nuclei induced by Analgesics, Difference in Muscle Sympathetic Nerve Activity (MSNA), Magnetoencephalographic (MEG) or Electroencephalographic (EEG) signals on and off stimulation and other autonomic parameters
Intervention (s)	Quantitative Sensory Testing, and patients' everyday analgesics, Micro-neurography, EMG, and LFP, EEG or MEG recording of brain or DRG, Non-invasive brain stimulation (TMS/tDCS) in chronic pain compared to healthy controls

ABBREVIATIONS

ACC	Anterior Cingulate Cortex
DBS	Deep Brain Stimulation
DRG	Dorsal Root Ganglion
EEG	Electroencephalogram
EMG	Electromyography
GCP	Good Clinical Practice
IPG	Internal Pulse Generator
ICF	Informed Consent Form
LFPs	Local Field Potentials
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
MSNA	Muscle Sympathetic Nerve Activity
PAG	Periaqueductal Grey
PIL	Participant/ Patient Information Leaflet
QST	Quantitative Sensory Testing
R&D	NHS Trust R&D Department

REC	Research Ethics Committee
SCS	Spinal Cord Stimulation
SOP	Standard Operating Procedure
tDCS	Transcranial Direct Current Stimulation
TMS	Transcranial Magnetic Stimulation
VPL	Ventral Posterolateral thalamic nucleus
VPM	Ventral Posteromedial thalamic nucleus

BACKGROUND AND RATIONALE

We want to know whether there is a brain signature of pain. Pain perception is very subjective, but if we can find a pain signature, we can detect the objective pain feeling of patients, and we can modulate it to relieve patients' chronic pain.

Besides this, we also want to study the endogenous pain modulation pathway. The more we understand it, the more effective pain treatment we can provide. Pain perception can be altered, and abundant evidence has demonstrated that stimulation of the brainstem (ventrolateral column of the PAG) can activate the endogenous pain modulation pathway to inhibit the pain signal input at the level of the spinal cord[1-5]. Richardson and Akil [6,7], and Hosobuchi and colleagues [8] translated this body of knowledge to clinical use and reported pain relief in patients given chronic stimulation of the PAG. Since then, deep brain stimulation (DBS) of the PAG has been successfully carried out all over the world and has been proved as an effective treatment for pain relief in chronic medicine-refractory pain patients [9,10].

Even though the aforementioned mechanism is well-studied, it is still unclear whether the PAG may exert its pain-modulation effect by alternative pathways in addition. Animal studies have shown that the PAG has direct projections to the thalamus in many species [11,12]. Likewise imaging studies in humans have demonstrated direct connections between the PAG and the thalamus [13]. Therefore, it is reasonable to suggest that the PAG may affect the thalamus to modulate pain perception, and the thalamus, traditionally regarded as a sensory relay centre, may also be able to project to the PAG to modulate pain. However, much less attention has been paid to this suggestion.

In this human study, we take advantage of the DBS of various cerebral nuclei related to pain perception, and use a mental task to induce patients' endogenous pain modulation, to determine whether there is cerebral signature of pain, and to test our two hypotheses: 1. that the PAG modulates pain perception not only via its pathway to the spinal cord, but also via more direct ascending connections to the thalamus; 2. that the thalamus can also affect the PAG to modulate pain, rather than being merely a relay centre.

In addition to these questions, we would also like to investigate the effects of stimulation on the autonomic nervous system to see whether modulation of this system is responsible (at least in part) for the effects of stimulation on pain relief. We have previously shown that stimulation can alter sympathetic nerve activity[1] but would like to investigate this further, especially looking at the peripheral part of the system (dorsal root ganglion (DRG)).

Previous unpublished data suggests that the left side of the brain may modulate pain differently than the right side. In order to ascertain these differences we would utilize the high temporal and spatial resolution of MEG to compare brain signals in various patient states.

In order to validate the clinical significance of MEG-identified signatures, we intend to recruit healthy controls for comparison of neural signatures in pain-free individuals. Furthermore, we wish to evaluate this objectively identified pain signature by localizing the brain structures involved from MRI scans and conducting non-invasive targeted inhibition of these signal with TMS/tDCS to evaluate its impact on pain relief and cognitive function.

OBJECTIVES

Primary Objective

To determine whether there is a cerebral pain signature

Secondary Objectives

To understand how the cerebral pain matrix, including brainstem, anterior cingulate cortex, thalamus and cerebral cortex interact with one another, and with the spinal cord and peripheral nervous system, for pain perception and its modulation.

To determine whether stimulation of the DRG, Spinal Cord, Brain, or periphery alter sympathetic nervous system activity and whether these changes (if present) are related to pain relief.

STUDY DESIGN

This is a prospective study. Participants are chronic pain patients admitted to the John Radcliffe Hospital to receive deep brain stimulation, spinal cord stimulation, DRG stimulation, or noninvasive stimulation treatment for pain relief. Their standard clinical treatment involves two operations: stage 1 operation for deep brain or spinal electrode implantation, and stage 2 for pulse generator implantation, which is usually performed one week after stage one operation (for DBS/SCS/DRG patients). The baseline Quantitative Sensory Testing (QST), EEG, MEG, EMG, and Microneurography will take place pre-operatively, within 6 weeks post-operatively and at 6 months. LFP recording will take place between stage 1 and 2 (where appropriate). None of the tests will interfere with the patient's usual treatment.

In addition, a control cohort of healthy subjects that have not experienced chronic pain will be recruited as a comparator group to observe the cerebral signature during non-painful states.

Summary of Study Design

Pre-operatively, before 6 weeks post-operatively and at 6 months post-operatively, patients will undergo standard Quantitative Sensory Testing (QST), EEG, MEG, EMG, microneurography and measurement of autonomic parameters (heart rate, 24 hour ambulatory blood pressure, ECG and galvanic skin response). These sessions will not last longer than 2 hours each.

Patients with externalized electrodes are expected to spend one hour a day for 2 days during their stay in the hospital or will be tested intraoperatively. We use computer-based mental tasks to distract patients from their pain, decreasing their pain perception. We record their brain, spinal or DRG electrophysiological signals - local field potentials - to analyse what happens to their nervous system when pain decreases. We will also use electrical, thermal and pressure/ pin prick stimulation on patients' limbs, producing graded painful feeling, and record and analyse their signals during the time to see what kind of signals are related to pain.

A control cohort of healthy age-matched subjects that have not experienced chronic pain will be recruited as a comparator group to observe the normal cerebral signature during unaffected by chronic pain**.**

Primary and Secondary Endpoints/Outcome Measures

In the intervention group, we will observe the changes of LFPs of various cerebral, spinal and DRG nuclei induced by endogenous pain modulation, therapeutic DBS and TMS/tDCS. We will also investigate the differences of LFPs of various nuclei induced by medications.

Cortical signatures of pain will be recorded to identify global changes in neural excitation under chronic pain and therapeutic states. This will be identified using MRI, MEG/EEG recordings and Quantitative sensory testing (QST). In the intervention group, this will be undertaken during endogenous pain modulation, therapeutic DBS, SCS, DRGS and TMS/tDCS. We will also observe changes in autonomic parameters induced by stimulation.

In the control group, we will identify the brain wave patterns via MEG/EEG during quantitative sensory testing (QST), TMS/tDCS and during cognitive tasks in order to compare the chronic pain cerebral patterns with that of the healthy brain.

STUDY PARTICIPANTS

Overall Description of Study Participants
Patients with chronic medicine-refractory neuropathic pain that are referred to the Department of Neurological Surgery for DBS, SCS or DRG treatment, or for treatment with noninvasive electrical/radio wave stimulation. Controls will also be recruited.

Chronic pain patients:

Inclusion Criteria
Patients who are willing and able to give consent to the study.
Male or Female, aged 18 years or above.
Treatment includes DBS of ACC, PAG or sensory thalamus (VPL or VPM), SCS or DRG stimulation, or peripheral analgesic stimulation.

Exclusion Criteria
Patients may not enter the study if any of the following applies:
Patients who do not wish to be in the study.
Patients with extreme language barrier that cannot understand the purpose of the study despite the use of an interpreter.
(see below for non-invasive stimulation-specific exclusion criteria)

Controls:

Inclusion Criteria
Patients who are willing and able to give consent to the study.
Male or Female, aged 18 years or above.

Exclusion Criteria
Participants may not enter the study if any of the following applies:
Participants who do not wish to be in the study.
Patients with extreme language barrier that cannot understand the purpose of the study despite the use of an interpreter.
Participants with a history of neurological disorders.
Participants with a history of psychiatric disorders.
Participants who have chronic pain.
Participants who have acute pain.
Participants who had ever undergone neurosurgery.

Participant recruitment:
The intervention group will be recruited from neurosurgery clinics lists of patients with known DBS, spinal or DRG electrodes implanted. They will be invited to participate in the study either in

person at clinic appointments or by telephone. Participant information leaflets will be given to patients ahead of participation in the study to allow for informed consent for participation.

To recruit an appropriately age and sex-matched control group, spouses and partners of participants within the intervention group will simultaneously be invited to participate and will receive the relevant participant information sheet. Participants will also be recruited by word-of-mouth[18] as a passive recruitment strategy. This will allow willing members of the participants' community to self-identify interest in partaking in the study. Exclusion criteria can be found above.

STUDY PROCEDURES

Experimental protocol

Participants

Participants will be patients who have suffered from chronic pain, and undergone insertion of DBS electrodes into various cerebral areas, including the ACC, sensory thalamus and PAG or Spinal Cord Stimulation including targeted stimulation of the Dorsal Root Ganglion (DRG stimulation), or who have been offered noninvasive analgesic stimulation, such as transcutaneous electrical nerve stimulation (TENS) or pulsed shortwave therapy (PSWT).

Procedure:

Intervention Group:

Pre-operatively and post-operatively (<6 weeks and 6 months), participants will undergo a full Quantitative Sensory Testing (QST) protocol and Autonomic protocol including microneurography. Participants will also undergo EEG/MEG recording and pre-operative MRI at the Oxford Centre for Human Brain Activity (OHBA) if this has not been done prior to recruitment.

During their inpatient stay, participants will perform a distraction mental task four times. Each time they will be in an 'assigned' state, such as 'resting', with therapeutic stimulation (DBS, SCS, DRG, or noninvasive stimulation), with 'medication' or with 'painful stimulation'. Local field potentials are recorded from the electrodes whilst doing the mental task. Cortical activity will also be recorded using EEG. The order of the patients' states will be randomised. Any experiments in the off medication state will be after 24 hours off analgesics such as paracetamol and codeine-based drugs, making sure that the drug effect has vanished.

Participants will also perform a short computer-based task to measure cognitive performance, including attention, working memory and task-switching. Each subtask is less than 5 minutes, and participants will perform no more than 6 such tasks in succession.

Control Group:

In the control group, participants will undergo a full Quantitative Sensory Testing (QST) protocol and Autonomic protocol including microneurography. Participants will also undergo MRI, EEG/MEG analysis at the Oxford Centre for Human Brain Activity (OHBA) and TMS/tDCS at the John Radcliffe Hospital.

During EEG/MEG recordings, participants will perform a short computer-based task to measure cognitive performance, including attention, working memory and task-switching. Each subtask is less than 5 minutes, and participants will perform no more than 6 such tasks in succession.

MRI

Once contraindications to magnetic resonance imaging are excluded by use of the facility's screening forms, the risks of undergoing a scan are minimal. A trained scanner operator or radiographer will go through a list of possible risks with the participant before scanning. The MRI scanner consists of a large powerful magnet. Magnetic resonance imaging uses no ionising radiation. There are, however, potential hazards associated with MRI and the scanning of participants including the presence of surgical implants, participants' clothing, jewellery (such as body piercings) bodily habitus, or medical conditions. A comprehensive list of potential risks has been compiled, and the participant should be checked against this by the operator, prior to entering the controlled areas of the MRI scanners. During the actual scanning procedure, the scanner produces loud banging noises and the participant will be given suitable hearing protection (earplugs). There is a small mirror that will allow them to see out of the scanner. During the experiment, the participant will be able to communicate with the operator in the control room. In addition, they will be given a call button, which allows them to alert the operator at any time. People with a history of claustrophobia may be excluded from participation in the study. All participants will still be introduced carefully to the scanner and allowed to leave at any stage, should they wish to do so. Once in the scanner, participants will be able to indicate immediately if they wish the scanning to cease by pressing a call button in their hands

Rationales behind this protocol

In order to be able to determine whether LFP 'signatures' are related to pain states per se, we need to be able to look at the LFPs during modulation of those pain states. If a particular signature correlates with the degree of pain (measured using a visual analogue score), we can only show cause and effect by either endogenous modulation (distraction mental task) or exogenous modulation (increasing or decreasing the pain using painful stimulation or analgesia respectively). The rationale behind the QST is to precisely define the pain characteristics for each patient. The autonomic parameters need to be tested before the intervention and after acute and chronic stimulation to look at possible plasticity effects

Microneurography

This technique entails insertion of two very fine needles (microelectrodes, 30-40 microns in diameter, less than the diameter of a human hair) below the knee. The first will record directly from the common peroneal nerve whilst the second will lie subcutaneously as a reference. We will perform this bilaterally. This is an established technique and the only one enabling direct measure of peripheral sympathetic nerve activity. Neurograms will be recorded with stimulation On and then Off during the same sitting. The maximum time the needle will remain within the tissue will be 45 minutes. We will measure galvanic skin response (sweating), continuous non-invasive blood pressure, ECG and tilt table testing during the same sitting. In some patients, we will measure ambulatory blood pressure for 24 hours (whilst at home).

Quantitative Sensory Testing

A standard battery of tests (e.g. the German Research Network on Neuropathic Pain (DFNS) protocol will be used. This consists of measurements of pain threshold and sensation using heat, pressure, pin prick, vibration, and electrical stimuli. Proprioception will be tested by measurement of tendon reflexes and surface electromyography. We will use a Somedic Sensebox and ThermoTest equipment. QST has been used in a number of studies involving neuromodulation and spinal cord stimulation in particular[15]. The rationale for its use is that we are looking for an 'objective' measure of pain which can be provided by looking at pain thresholds etc. whereas simply monitoring 'visual analogue score' will not validate our cerebral signature as an objective measure as it is subject to reporting bias.

Magnetoencephalography

This procedure is a non-invasive method of detecting changes in the magnetic fields around the scalp which correspond to underlying neural activity. The protocol would involve recording these signals from both hemispheres of the brain, during "on" and "off" stimulation periods to determine if there is a difference in laterality of brain processing during dorsal root ganglion stimulation. We will simultaneously evaluate the aforementioned vital sign evaluations (ECG, blood pressure) and QST to determine the differences between stimulation-induced brain signals and sensory signals and how they correlate with autonomic nervous system function. For those patients who have not undergone MRI Brain pre-operatively, this will be facilitated at the time of MEG recruitment for purposes of pain signal localization.

Non-invasive Brain Stimulation

Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) have arisen as novel non-invasive brain stimulation (NIBS) techniques used in experimental and therapeutic applications for a variety of neurologic disorders. Depending on the placement of anode and cathode, they have been found to produce intracortical facilitation and inhibition, which provides a unique opportunity to identify causal relationships between brain region activity and clinical/behavioural effects.

Studies have shown that anodal tDCS to primary motor cortex (M1) and dorsolateral prefrontal cortex (dlPFC) can result in short-term and long-term relief of neuropathic pain [Ngyernam et al, 2013]. Possible mechanisms of this pain relief are posited to occur via restoration of defective intracortical inhibition at M1 in patients suffering from neuropathic pain [Portilla et al, 2013]. The goal of the proposed experiment would be to investigate the effect of intracortical inhibition of the identified MEG pain signals, or, intracortical facilitation of pain relief centres, to validate whether they are representative of pain signalling or a cortical epiphenomenon of neurostimulation. The following treatment groups:

M1 NIBS-SCS/DRG Stim(positive control) vs. MEG signal-targeted NIBS-SCS/DRG Stim vs. sham NIBS-SCS/DRG Stim (negative control)

Would be evaluated before and after 30 minutes of stimulation with Visual Analogue Scale (VAS), Neuropathic Pain Symptom Inventory (NPSI) and EuroQol 5D (EQ-5D) as primary, secondary and tertiary endpoints for evaluation of the effect of cortical facilitation/inhibition on spinal/dorsal root ganglion stimulation. Each participant will undergo a maximum of 5 sessions, each session taking place at least one day apart.

Whereas non-invasive brain stimulation has been used safely in patients with spinal cord stimulators (Schlaier et al., 2007) this technology has not been explored for safety in patients with metallic head/brain implants, and as such, tDCS will not be implemented in patients treated with Deep Brain Stimulation.

The seizure risk from rTMS is usually during low frequency (<0.1%), whereas therapeutic pain relief has been shown with high frequency TMS[19,20]. Nevertheless, prior to TMS participants will be excluded from participation if they are sleep deprived prior to study, have a family history of seizures, have a significant history of alcohol use or previous neurological condition, factors which may increase the risk of TMS-induced seizure.

Distraction mental task

The task includes 15 sections, including 5 rest, 5 easy and 5 difficult ones. Each section lasts around one minute. The sequence of these sections will be randomised.

In the rest section patients will just need to concentrate on their pain, and after the section patients will choose a score on the visual analogue scale on the screen, indicating how their pain is during the section.

In the easy task section patients will need to remember the colour of the T-shape figure shown on the screen before starting the easy section. When the section begins, the screen will show many T-shape figures, one by one, with various colours. Whenever seeing the correct colour, as shown before the section, patients need to push a button of the computer's keyboard. After the section patients will choose a score on the visual analogue scale, indicating how their pain is during the task section.

In the difficult task section patients will need to remember the colour and the orientation of the T-shape figure shown on the screen before starting of the section. When the section begins, the screen will show many T-shape figures, one by one, with various colours and orientations. Whenever seeing the figure with the correct colour and orientation patients need to push a button of the computer's keyboard. After the section patients will choose a score on the visual analogue scale, indicating how their pain is during the task section.

Various patients' states

State 1 – resting state, without stimulation or drugs

Participants will do the mental task when their stimulator is off. In addition, they will not take their everyday pain medications for at least 24 hours before the task

State 2 – Therapeutic stimulation state, with stimulation on

Participants will do the mental task when their stimulators are on and at the stimulation parameters producing the most pain relief.

State 3 – medication state, with patients' everyday medications for pain relief
Participants will do the mental task with their usual pain medications. Their stimulators will be turned off too.

State 4 – pain stimulation state, with peripheral stimulation to induce patients' pain symptom
Participants will do the mental task when their stimulator is turned off. We will use peripheral stimulation to induce pain when they are doing the task. This peripheral stimulation will take the form of a Somedic Thermotest or equivalent heat stimulus, an electrical stimulus, or a mechanical stimulus, just above the pre-measured pain threshold.

Summary of the possible combinations of participants' experimental states and the mental task they are having, and the questions that each combination can address (explained below)

State / Task	Resting	Therapeutic Stimulation on	Medication	Pain stimulation
Rest	Rest LFPs	Neuro modulation effect	Drug effects on the target	Effect of painful stimulus on targets
Easy	Endogenous pain modulation	Stim + endogenous pain modulation effect	Drug + endogenous pain modulation effect	Effect of endogenous modulation on pain signatures induced by painful stimulus
Difficult	Endogenous pain modulation	Stim + endogenous pain modulation effect	Drug + endogenous pain modulation effect	Effect of endogenous modulation on pain signatures induced by painful stimulus

Questions that each state of the experiment could address

Resting state

1. Brain signals (MEG/EEG/LFPs) recorded during rest sections of the task: the baseline of targets' local field potentials and patients' pain scale.
2. Signals recorded during easy task sections: the response of the targets to the endogenous pain modulation (compared with baseline signals).
3. Signals recorded during difficult task sections: the response of the targets to the endogenous pain modulation (compared with baseline signals)
4. The change of targets' brain signals with different degrees of pain modulation (easy versus difficult task

Therapeutic Stimulation state

1. Brain signals recorded during rest sections of the task: Stimulation effect on the targets
2. Brain signals recorded during easy and difficult sections of the mental task: compared with the data gathered in resting state, we can see if stimulation can enhance the endogenous pain modulation or have no effect on it.

Medication state

1. Brain signals recorded during rest sections of the mental task: Drug effects on the targets
2. Brain signals recorded during easy and difficult sections of the mental task: compared with the data gathered from resting state, we can see if medications can enhance endogenous pain modulation or have no effect on it.

Pain stimulation state

1. Brain signals recorded during rest sections of the mental task: pain signatures of the targets induced by painful stimulus
2. Brain signals recorded during easy and difficult sections of the mental task: we can investigate how endogenous pain modulation affects the pain signatures induced by painful stimulus

Informed Consent

Informed consent to this study will be obtained prior to the participants' inclusion in the study. In addition, verbal consent will also be acquired at the point of each research intervention. The patients will be supplied with Patient Information Sheets in advance of the surgery while participants will be provided with the Healthy Volunteer Information Sheet at least 2 weeks prior to involvement in any imaging or testing. Consent will be taken by the pain nurse or someone else independent of the direct care team.

Definition of End of Study

The end of study is the date of the last research experiment of the last participant.

INTERVENTIONS

Pre-operatively and Post-operatively we will perform microneurography, QST, tilt table tests, ECG, ambulatory blood pressure, and GSR.

During the distraction and MEG/LFP experiments we will measure patients' ECG, blood pressure and respiratory rate. We will also record their LFPs, MEG, EEG and visual analog scale of pain.
In order to know the neural signature for pain, we will use painful stimulation to induce patients' pain perception. This stimulation will take the form of Contact Heat-Evoked Potential Stimulation, electrical stimulation, or mechanical stimulation, with selective stimulation of A-Delta & C-fibers.

SAFETY

There is no risk that participants are exposed to other than they may experience more pain or a different type of pain to their usual pain. Patients will be given the ability to stop the experiment at any time should they feel uncomfortable.

Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

Results in death,
Is life-threatening,
Requires inpatient hospitalisation or prolongation of existing hospitalisation,
Results in persistent or significant disability / incapacity, or
Is a congenital anomaly / birth defect.
Other important medical events.*

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

*Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed in the protocol as an expected occurrence). Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES report of serious adverse event form (see IRAS/NRES website).

STATISTICS AND ANALYSIS

Number of Participants
The expected number of participants involved in this study is approximately 50. This is based on the annual number of neuromodulation operations for pain relief at the John Radcliffe Hospital.

Analysis of Outcome Measures
Outcome measures of both intervention group and control group (QST, EEG/MEG) will be analysed using statistical analysis software and MATLAB. All participant data will be utilized in analysis unless they have withdrawn consent.

Analysis of Endpoints
The endpoint analysis will be performed using statistical analysis software and mathematical computational modeling licensed by the University of Oxford. The analysis involves complex signals analysis techniques where significant difference in power at certain frequencies can be determined using custom-made software (based on MATLAB®).

ETHICAL AND REGULATORY CONSIDERATIONS

Declaration of Helsinki
The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki

Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

Approvals
The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

Reporting
The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties

Participant Confidentiality
The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised when it is practical to do so.

Expenses and Benefits
Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

Other Ethical Considerations
This study does not require any involvement of vulnerable participants, participants who are unable to consent for themselves or indemnity provision.

In the unlikely event of seeing any structural abnormalities on an MRI scan, the scan will be checked by a clinical specialist. If the specialist feels that the abnormality was medically important, they will discuss the implications with the participant and arrange for further investigations as necessary. Participants will not be informed unless the doctor considers the finding has clear implications for their current or future health. It is important to note that scans are not carried out for diagnostic purposes, and therefore the scans are not a substitute for a clinical appointment. Rather, the scans are intended for research purposes only.

DATA HANDLING AND RECORD KEEPING
The participants will be identified by a study specific participant number. The name and any other identifying detail will NOT be included in any study data electronic file.

Publication Policy
The investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

FINANCE AND INSURANCE

Funding
The late Prof Francis John Gillingham Legacy Grant as attached.

Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

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APPENDIX A: Funding Statement

We write sum receipt.

RECEIPT

From Estate of Prof Gillingham
8-10271034

We, THE UNIVERSITY OF OXFORD (an exempt Charity under the terms of the Charities Act 1993) of University Offices, Wellington Square, Oxford, OX1 2JD hereby acknowledge to have received from Turcan Connell, as agents acting for the executors in the administration of the estate of the late Professor Francis John Gillingham CBE, late of Prebendal Court, Station Road, Shipton Under Wychwood, Oxfordshire, OX7 6BB, the sum of £20,000 in full and final settlement of the legacy from the late Professor Gillingham, to be applied for the study led by Professor Tipu Aziz into Dystonia, in terms of the Project Summary attached. This receipt shall be sufficient as a discharge to the executors.

TURCAN CONNELL
SOLICITORS AND ASSET MANAGERS

BANK OF SCOTLAND
Turcan Connell
New Uberior House
11 Earl Grey Street Edinburgh EH3 9BN

80-26-02

Date 25 February 2011

Pay The University of Oxford

Twenty thousand pounds only

A/C PAYEE

£ 20,000.00

For and on behalf of
Turcan Connell

TURCAN CONNELL
CLIENT ACCOUNT

MPM
G.3051.001

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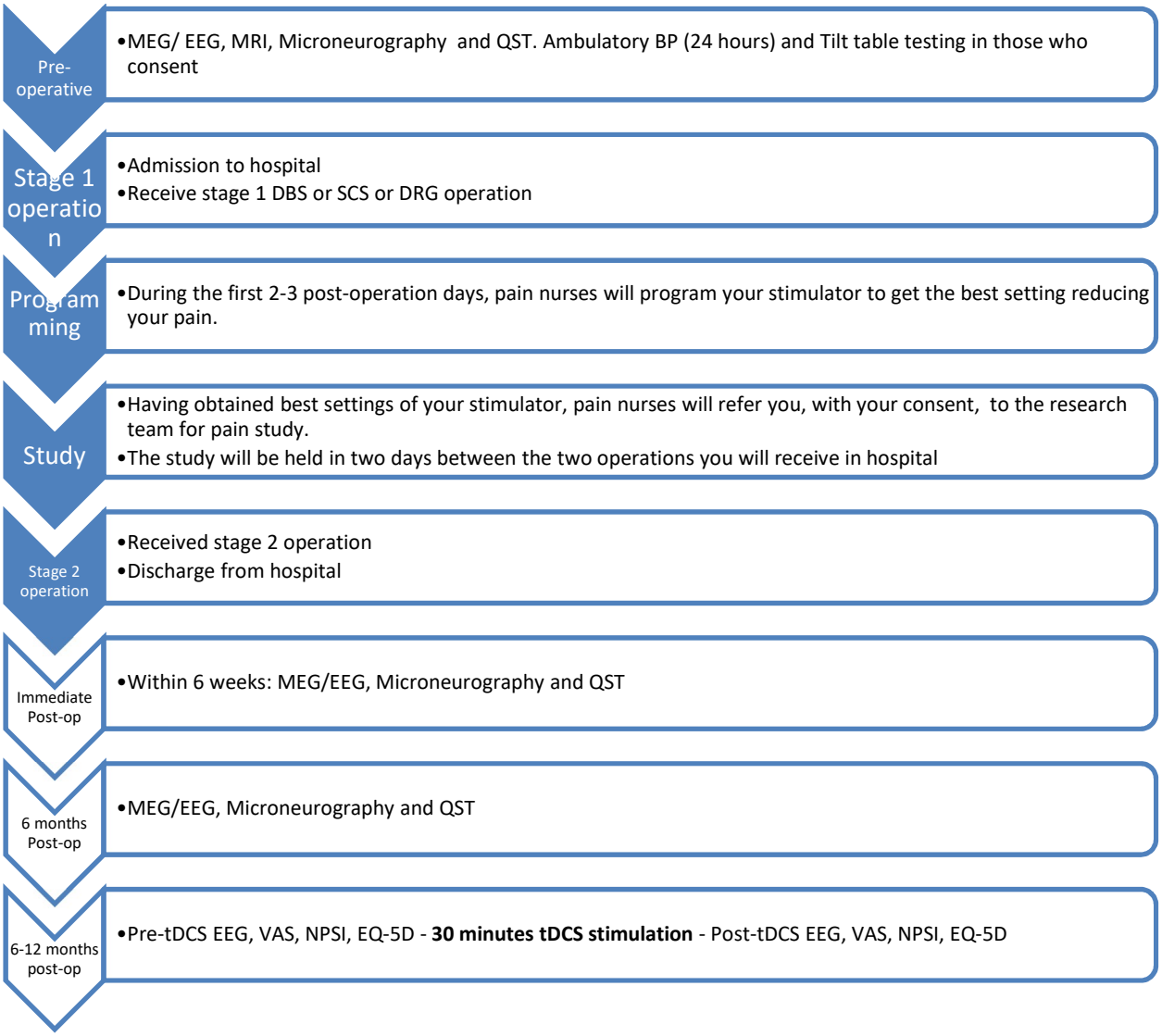
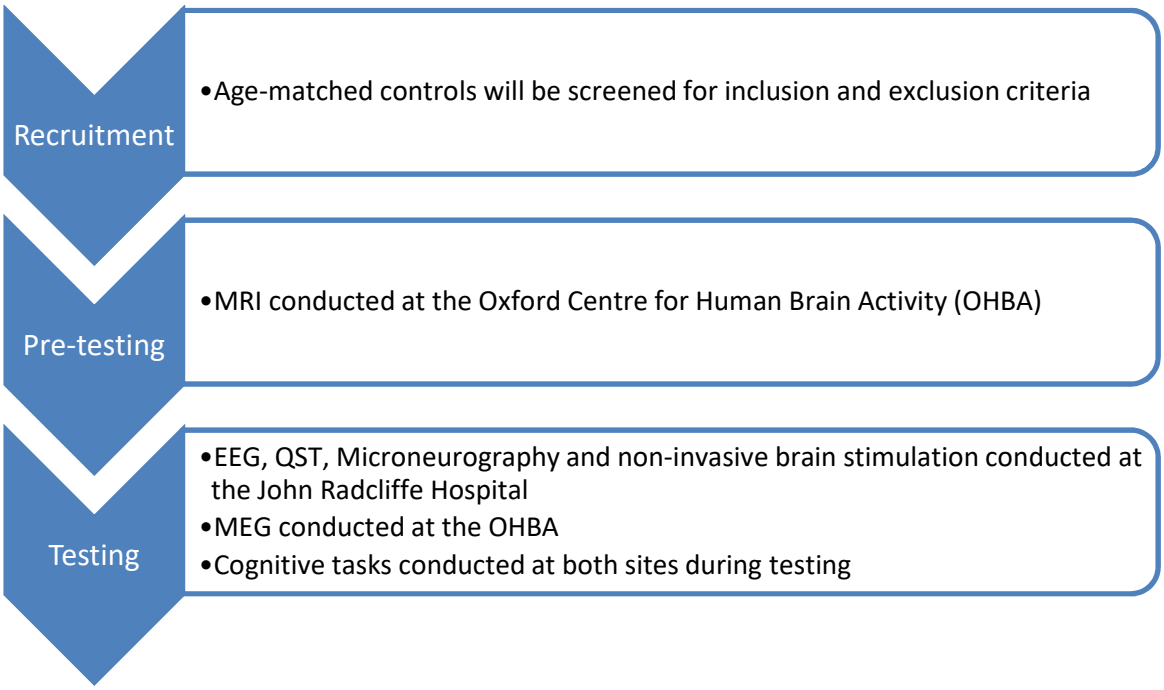
APPENDIX B: Flowchart of patient events



Flowchart of Healthy volunteer events



APPENDIX C: AMENDMENT HISTORY

Amend-ment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
7	7	28/01/2018	Tariq Parker, John Eraifej	This amendment makes provision for the recruitment of a healthy control group, acquisition of a pre-operative MRI in chronic pain partici-pants, as well as the use of non-invasive brain stimulation (TMS/tDCS).