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Can slow wave activity saturation (SWAS) be used to detect exactly when a person has lost consciousness under general anaesthetic, so that the dose of anaesthetic used is not too much or too little?

Submission date 27/01/2020	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 06/07/2022	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 04/04/2023	**Condition category** Surgery	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims

General anaesthesia is delivered during an operation to stop patients being aware of what is going on, prevent any pain and immobilise the body so that surgery can be carried out safely. Unfortunately, the specialist doctors who deliver anaesthesia do not currently have a reliable way of measuring when an individual's brain becomes unconscious during the surgery. They judge the amount of anaesthetic to give depending on when the average person would lose consciousness, and adapt the dose for that person depending on how the heart or lungs react during the operation.

We have discovered an interesting change in the brain's electrical activity that potentially indicates the point when an individual person under anaesthesia loses perception of the outside world. This could mean that anaesthetists are able to give just the right amount of drug for each person. This is important because, whilst anaesthesia is very safe, some patients who are older or particularly sick may suffer from long-term side effects if they are given too much anaesthesia. It will also prevent the rare event that someone is aware during the operation.

We have called this observation slow wave activity saturation (or SWAS) and it can be measured by applying electrical sensors to the scalp - a technique called electroencephalography (or EEG for short). We plan to record EEG in up to 30 patients before surgery to show that we can give anaesthesia to achieve this SWAS endpoint. After this, we plan to use brain imaging in 30 healthy volunteers to understand what happens in the brain as it reaches SWAS and how it affects sensory experiences like pain and hearing. We also want to know how the person’s sleep patterns influence the anaesthetic dose needed to achieve SWAS, thereby improving our understanding of anaesthesia.

Who can participate?

Patients who are having a procedure that involves general anaesthesia and healthy volunteers

What does the study involve?
The patients will receive the general anaesthesia and surgery as normal, except that the research will measure their brain activity and test whether they can respond to an instruction to squeeze the researcher's hand during the general anaesthesia set-up.
The healthy volunteers will undergo general anaesthesia while in an MRI scanner. The researchers will investigate their brain activity and their response to spoken instructions and pain at different stages of consciousness.

What are the possible benefits and risks of participating?
There are no immediate benefits to the individuals taking part in the planned research studies, apart from the knowledge that they are contributing to scientific research that we envisage will advance future medical care.
By performing this scientific research, we will improve understanding of anaesthetic mechanisms and consciousness. Specifically, a better understanding of the brain mechanisms underlying SWAS will help us develop individualised measures of depth of anaesthesia. In the longer term, we hope that using SWAS to guide the optimum anaesthetic dose to achieve perception loss within an individual will help prevent both under- and over-anaesthesia during surgery.
This optimization of anaesthetic dosing has cost implications for all sectors of the health care system. Even a small reduction in the quantity of anaesthetic drugs required for the 2.9 million anaesthetics delivered annually in the UK would have significant cost savings. Anaesthetists and other healthcare professionals would also welcome any reduction in the unpredictability of patient responses.
Excessively deep anaesthesia has been linked to an increased risk of side effects such as death, stroke, heart attack, delirium and cognitive dysfunction. Patients at higher risk of these side effects will benefit most from this optimization of anaesthetic dosing. These include the elderly, people with poor cardiovascular function and those who are obese. With an aging population, effects on brain function following surgery have become increasingly important in the risk-benefit decision of whether to operate or not. Improved recovery due to optimal dosing will reduce the time to discharge, enabling patients to return home more quickly.

Where is the study run from?
University of Oxford (UK)

When is the study starting and how long is it expected to run for?

Who is funding the study?
The European Union via its Horizon 2020 programme and the National Institute of Health Research (UK)

Who is the main contact?
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Type(s)
Scientific

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215699

Central Portfolio Management System (CPMS)
37176

Study information

Scientific Title
Is slow wave activity saturation a good electroencephalographic brain-based marker to deliver general anaesthesia in patients and healthy volunteers?

Study objectives
General anaesthesia is delivered during an operation to stop patients being aware of what is going on, prevent any pain and immobilise the body so that surgery can be carried out safely. Unfortunately, the specialist doctors who deliver anaesthesia do not currently have a reliable way of measuring when an individual's brain becomes unconscious during the surgery. They judge the amount of anaesthetic to give depending on when the average person would lose consciousness, and adapt the dose for that person depending on how the heart or lungs react during the operation.

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We have called this observation slow wave activity saturation (or SWAS) and it can be measured by applying electrical sensors to the scalp - a technique called electroencephalography (or EEG for short). We plan to record EEG in up to 30 patients before surgery to show that we can give anaesthesia to achieve this SWAS endpoint. After this, we plan to use brain imaging in 30 healthy volunteers to understand what happens in the brain as it reaches SWAS and how it affects

sensory experiences like pain and hearing. We also want to know how the person's sleep patterns influence the anaesthetic dose needed to achieve SWAS, thereby improving our understanding of anaesthesia.

Hypothesis
We hypothesise that during the transition to SWAS there is a hierarchical breakdown in how the thalamus communicates to other brain regions. Additionally, we hypothesise that at SWAS there is an absence of pain-related brain activity, and that the individual has no awareness as assessed by the absence of a hand open/close in response to verbal request.

Overview of study design
The research aims will be achieved through experiments in two study populations: patients undergoing surgery and healthy volunteers. Study 1 will demonstrate that it is feasible to titrate anaesthesia to achieve (and maintain) SWAS in an individual patient using real-time EEG feedback. Study 2 is a healthy volunteer neuroimaging study that will identify changes in thalamocortical connectivity at SWAS and confirm that SWAS indicates perception loss.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/02/2018, West Midlands - Coventry & Warwickshire Research Ethics Committee (no mailing address; +44 (0)207 104 8101; NRESCommittee.WestMidlands-CoventryandWarwick@nhs.net), ref: 18/WM/0030

Primary study design
Interventional

Study design
Non-randomised; Interventional; Design type: Treatment, Prevention, Drug, Imaging, Active Monitoring, Other

Study type(s)
Treatment

Health condition(s) or problem(s) studied
General anaesthesia

Interventions
Patient study - Study 1
This study will be performed in up to 30 patients who are having general anaesthesia for elective plastic surgery in the Oxford University Hospitals (OUH) NHS Foundation Trust. The study will be conducted as follows:

Recruitment and screening
The researchers will advertise and recruit for the study in collaboration with clinical staff on participating elective surgical lists. The surgical, anaesthetic and pre-operative assessment teams will identify patients who meet the study inclusion criteria in collaboration with the research team. Additionally, the researchers will seek to recruit patients who will not be operated on first on a surgical list so as to reduce the potential for introducing timing delays.

Suitable patients will be invited to participate at either their i) outpatient or ii) pre-operative assessment appointment. They will be given a brief explanation of the study and a patient information sheet (PIS) to take home. It will be clearly explained to the patient that there is no obligation to participate and that non-participation will not influence their future medical care. After the initial explanation of the study, patients will be asked if they are happy to be contacted by the research team. The research team will also be available at the pre-operative assessment appointment to answer any questions about the study, and check eligibility should the patient wish.

Study eligibility assessment
The research team will contact interested patients by telephone or email to discuss the study further. At this time, they will confirm that the patient understands what is involved in the study and a full eligibility assessment will be carried out. It will be explained to the screened participants that they will be contacted again to confirm their date of surgery. This will also serve to check the patient is still happy to take part closer to the time of their operation. The potential participants will also be given contact details for the research team should they have any further questions.

Informed consent
Full informed consent will take place either on the morning of surgery, or at the earlier pre-operative assessment clinic if the patient is happy to proceed at this time. The participant will be allowed as much time as they wish to consider the information, and have the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The participant must provide written Informed Consent form before any study specific procedures are performed.

Day of surgery
Patients will attend the Oxford University Hospitals Trust on the day of surgery as normal. The NHS standard procedures will be carried out to prepare the patient for surgery. In addition, both the clinical anaesthetist and the study anaesthetist will meet with the patient to discuss the anaesthetic procedure. Once the clinical anaesthetist is happy with the standard preoperative check in, informed consent will be obtained by study personnel (if required). The additional study procedures will then be performed as follows:

Set-up of EEG monitoring
Consented patients will have an EEG cap or an arrangement of single electrodes applied to the scalp while waiting for surgery. A CE-marked EEG system (PortiEEG, TMSI, Netherlands) will be used that has previously been used in the operating room environment in a small pilot study carried out at Milton Keynes General Hospital (LREC ref: 14/SC/0145, IRAS ref: 138286). Depending on room availability and expected surgical list timings on the day, the researcher will either apply the EEG cap or electrodes in a separate room or in the anaesthetic room where the patient will be prepared for surgery.

Sensor placement and preparation of the scalp EEG requires about 20-30 min. The procedure typically involves the use of a snugly fitting cap made of an elasticated cloth material and containing tin or silver/silver chloride electrodes, and establishing electrical contact between the scalp and the electrodes by means of an electrolyte gel or water solution. In order to achieve a low-impedance connection, it is often necessary to prepare the area of the scalp under the sensor by cleaning it with rubbing alcohol and rubbing an abrasive substance using a cotton swab or by scratching the surface of the scalp with a blunt wooden stick. The procedure does not ordinarily cause pain or harm to the participant.

Questionnaire booklet completed by patient
The patient will be asked to fill out a short questionnaire booklet either while they wait for surgery or when they are having the EEG cap/electrodes applied. The questionnaire booklet will include the following validated questionnaires:
1. State and trait anxiety index (STAI) -Trait component
2. Amsterdam Preoperative Anxiety and Information Scale
3. Pittsburgh sleep quality index (PSQI)
4. Tellegen absorption scale (TAS)

The researchers have included these questionnaires as pre-operative anxiety is known to affect how much anaesthesia is required and they would like to investigate the same relationship with the SWAS biomarker. Poor sleep and anxiety are also highly correlated and exploring the commonalities of sleep and anaesthesia is one of the secondary study objectives. The PSQI tells us about the participant's general sleep in the last month. The research team will also ask additional questions about the quality of their previous night's sleep.

The researchers have also included a questionnaire to evaluate a personality trait called absorption, which is a sub-scale of the multi-dimensional personality questionnaire. It has been suggested that absorption measures the readiness of an individual to restructure their representation of self and its boundaries, and has been found to correlate well with hypnotic susceptibility. The researchers' previous work suggests that individuals experience a loss of selfhood when they become unresponsiveness under anaesthesia. In the MRI study, the researchers would like to investigate whether the degree of thalamocortical connectivity changes that occur at loss of responsiveness reflect this ability for individuals to disengage from their representation of self and their external environment.

Randomisation
Randomisation will not be used. Patients will receive either intravenous propofol or inhalational sevoflurane anaesthetic induction to SWAS. The researchers will start with sevoflurane anaesthetic inductions as this agent will be used in the healthy volunteer study. Propofol anaesthesia inductions will be used for the remaining participants once the study endpoint has been achieved with sevoflurane anaesthesia. Should an eligible patient not tolerate the inhalational sevoflurane agent well during induction, they may be give intravenous propofol induction to SWAS rather than lose that patient from the study. Similarly, if a needle-phobic patient was interested in participating, they may be given inhalational sevoflurane instead of intravenous propofol anaesthesia induction.

Anaesthetic delivery to SWAS by study anaesthetist
Patients will be administered either a propofol and/or sevoflurane anaesthetic induction to the SWAS endpoint by an appropriately qualified anaesthetist. These procedures will take place in the anaesthetic room, and the recommended standards of patient monitoring and trained anaesthetic assistance will be met for each patient as per standard clinical practice (Royal College of Anaesthetists' Guidelines for the Provision of Anaesthetic Services (GPAS) 2016, http://www.rcoa.ac.uk/node/21849).There will also be an Anaesthetic nurse or Operating Department Practitioner present during this time.

The researchers will use their recently developed SWAS prediction model to deliver anaesthesia to achieve SWAS before their surgery begins. By applying the computer software program to the real-time EEG brain signals recorded from the scalp, the patient's level of anaesthesia will be titrated to the SWAS end-point and maintained at this level for 10 min. The patient's airway will be managed as, and when, is clinically appropriate through the insertion of a laryngeal mask or intubation as is standard clinical practice. If the clinical anaesthetist's standard practice requires

conversion to a volatile anaesthetic agent after a propofol induction of anaesthesia, the researchers will use EEG feedback and the SWAS prediction model again to titrate sevoflurane to the SWAS endpoint.

Each time the individual is held at the SWAS endpoint they will be asked "[PATIENT'S NAME], squeeze my hand" to assess for any conscious content. When appropriate, the care of the patient will be transferred to the NHS consultant anaesthetist on the surgical list. EEG monitoring will continue throughout surgery and emergence from anaesthesia but will not interfere with clinical care. Collection of physiological data and recording of drug concentrations will also be performed throughout. All other clinical procedures including the delivery of anaesthesia will then continue as normal. Any major emergencies during surgery will be dealt by the clinical team as per OUH NHS Foundation Trust guidelines.

Study 1 end-point
The researchers will use an adaptive study design where refinements to the SWAS prediction model will be made after each patient to optimise the real-time application of the model in the operating room and decrease the anaesthetic time required to achieve SWAS. In the initial stages, the researchers expect the session to take up to 1 h extra in the anaesthetic room, with an increased anaesthetic drug delivery time of approximately 30 min per person. The Study 1 end-point is defined as the ability to reliably achieve SWAS on induction within 15 min using either propofol or sevoflurane anaesthesia (i.e. comparable with a normal clinical anaesthetic induction).

Post-operative follow-up
The EEG cap or electrode removal will take place when the patient is fully awake and responsive, and the clinical anaesthetist believes the patient has recovered sufficiently from the anaesthetic. They will be asked to complete the brief validated Brice Awareness questionnaire to assess for any intraoperative experiences under anaesthesia. If the patient reports any intraoperative experiences at this time, they will be contacted again at a later date (3-4 weeks) to review their account, as per the questionnaire guidelines. With informed consent, the researchers will record the patient's answers to the Brice questionnaire.

Participants will also be sent a feedback sheet approximately 3-4 weeks after study completion. It will be made clear that its completion is entirely voluntary but if returned will be used to guide patient involvement in future studies. The researchers will also ask patients if they wish to be invited to future Patient-Public Involvement (PPI) initiatives or Public Engagement events. For participants who have expressed a wish to be contacted about the success of the study, the team will write to them detailing the study outcomes at its conclusion.

Healthy volunteer study - Study 2
Recruitment and eligibility assessment
Participants will be recruited by word of mouth, email, previous participant databases, posters and social media. Subsequent inclusion in the study will be subject to appropriate and timely scheduling of the medical screening and MRI sessions. The research team will initially assess the suitability of potential volunteers against the study inclusion/exclusion criteria over the telephone. Volunteers will be screened carefully with regard to the risks associated with undergoing anaesthesia, EEG and MRI. They will be asked to complete an MRI screening form at this stage (and return by post or email) to identify any concerns relating to their safety in the MR environment. These will be reviewed in collaboration with the radiographers at the WIN to assess any safety concerns.

Visit 1 - Medical Screening
Suitable volunteers will be invited to attend a screening appointment at a mutually convenient time. This visit will involve a full medical and safety screening by a study researcher and an anaesthetist (post-FRCA or equivalent). Prior to obtaining informed consent, the study researcher will review the study inclusion/exclusion criteria and completed MR screening form in person with the volunteer. As mentioned previously, the researchers will follow the WIN Safe Surgery/Implant Policy to ensure eligibility and their safe participation. An additional consultation with the MR radiographers will be sought should any concerns arise as part of this discussion. On some occasions, for example to assess the safety of an implanted device, this may require access to the subject's medical notes. In these cases, informed consent will be obtained prior to accessing medical notes.

Participants will also receive an in-depth explanation of the study before informed consent is obtained. This will involve a demonstration of the equipment and procedures that will be used during the study sessions. For example, the researchers will ask them to briefly try on the EEG cap and the facemask that will be used to deliver the sevoflurane anaesthesia. The researchers may also ask the volunteer to briefly lie on the MRI scanner table (outside of the bore) so that the researchers can assess how the facemask fits with the MRI head coil. The responsibilities of the participant as part of the study will be highlighted at this visit. For example, the importance of fasting prior receiving anaesthesia will be explained, and in particular how they will need to be accompanied at home on the evening following the anaesthetic session.

As with the patient study, the participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. Again, the participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. The person who obtains the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained in the study site file.

Finally, the researchers will perform a separate medical assessment to ensure that the volunteer can safely be administered sevoflurane anesthesia in the scanner. This will include:
1. Medical history: participants will be asked about any current or past medical problems including adverse reactions to anaesthesia. They will also be asked about current medications, including both prescription and over-the-counter drugs, and pregnancy status. Women who are unsure if they are pregnant will be offered a pregnancy test.
2. Demographics: the participants' age, weight and height will be recorded.
3. Social history: participants will be asked about their smoking history, alcohol use, illicit drug use and caffeine consumption. They will also be assessed against the vulnerable group criteria.
4. Family history: participants will be asked whether any of their first-degree relatives have/had any allergies, adverse reactions to anaesthesia, and psychiatric or neurological illnesses.
5. Formal airway assessment: participants will be screened by an anesthetist to exclude individuals with potential for obstruction in the scanner. They will be asked if they have any history of airway obstruction or known difficult airway. They will have a physical examination to assess for clinical signs of potential susceptibility.
6. Assessment of venous thromboembolic event risk: a formal assessment will be performed by an anesthetist against the current NICE guidelines.

Visit 2- Baseline assessment
MRI data acquisition
On arrival, participants will be asked if they have any relevant changes in their personal

circumstances since their medical screening appointment. Participants will fill in another MRI screening form that will be checked by designated and trained scanner operators. They will then get changed into loose fitting comfortable clothing (scrubs) provided by WIN in a private room. They will be positioned in the 3T Siemens Prisma scanner. Foam padding will be placed around the participant's head to minimise movement. Participants will wear earplugs to attenuate the noise of the scanner. At all times, participants will be able to indicate immediately if they wish the scanning to be terminated by squeezing a buzzer placed in the hand. During scans, the participant is monitored from the control room visually.

The scanning session will last approximately 60 minutes, and will consist of several different brain imaging sequences. Specifically, these MRI scans will include:
1. Structural scan (T1) - high resolution anatomical image of the brain
2. Diffusion tensor imaging (DTI) - structural white matter pathway measurement
3. Magnetic resonance spectroscopy (MRS) - neurotransmitter measurement
4. Arterial spin labeling (ASL) – cerebral blood flow measurement

The researchers will also use physiological monitoring during MR scanning to monitor the participant's heart and respiration rate. These will be used at the analysis stage to clean up the breathing and pulse artifacts in the obtained MR images.

Questionnaires
During this visit, the participant will also fill in a questionnaire booklet containing the same validated questionnaires as in the patient study:
1. State and trait anxiety index (STAI) -Trait component
2. Pittsburgh sleep quality index (PSQI)
3. Tellegen absorption scale (TAS)

Additionally they will be asked to complete the Embodied sense of self scale (ESSS) and Locus of control (LOC) questionnaire. The researchers hypothesise that loss of behavioural responsiveness is associated with a loss of selfhood, the researchers have therefore included the ESSS to evaluate how strong each individual's sense of self is and how this relates to anaesthetic requirement and SWAS. As an exploratory analysis the researchers have also included the locus of control questionnaire to see how the individual's need for control influences the disruption of their brain activity under anaesthesia.

Sleep EEG and overnight requirements
When the MR scanning has completed, the participants be removed from the scanner and will be able to get changed into their own clothes. They may choose to change into comfortable night clothing or pyjamas at this time. After a short break, they will have an ambulatory sleep EEG kit applied to their scalp. They will then be sent home in a (fare-paid) taxi to sleep in their own home. They will be asked to stay at home for the evening, eat a good substantial meal and go to bed at their normal bedtime or whenever they feel tired. They will also be asked to refrain from eating or drinking for 6 h before receiving anaesthesia the next day. They will be allowed still water for up to 2 h before receiving the anaesthesia. It will be made clear that if they have any food or drink the next morning that the experiment may be cancelled. They will also be reminded that they may not drive, use machinery, drink alcohol or engage in sporting activities on the evening after receiving anaesthesia.

Visit 3 – MRI scanning with sevoflurane anaesthesia delivery
Preparation
The volunteers will return by taxi early the following morning and have the sleep EEG kit removed. They will be asked to confirm that they have not eaten during the preceding 6 h.

Participants will get changed in a private room into loose-fitting clothing before having the MRI-compatible 32 channel EEG cap applied. They will also apply compression stockings to help prevent blood clots due to prolonged immobilisation.

Questionnaires and MR safety
Participants will fill in another MRI screening form that will be checked by the trained scanner operators. Volunteers will also complete questionnaires relating to their level of state anxiety, and sleep quality the previous night. The researchers will use the following questionnaires:
1. State and trait anxiety index (STAI) - State component and the
2. Pittsburgh sleep quality index (PSQI) – adapted for the previous nights sleep.

Delivery of anaesthesia
Volunteers will be positioned in the scanner as described in Visit 2. They will have a facemask fitted that will be used to deliver inhalational sevoflurane anaesthesia. The facemask will be connected to an anaesthetic delivery machine. The anaesthesia will be delivered by/under the supervision of a consultant-grade anaesthetist, who will stop the study at any time if concerned for the safety of the participant. The researchers will follow the Anaesthetic Association of Great Britain and Ireland's (AAGBI) guidelines for day case surgery. In addition to monitoring of their heart and respiration rate during scanning (see Visit 2), the researchers will also record their ECG, blood pressure, oxygen saturation levels, end-tidal CO2, and end-tidal sevoflurane concentration levels.

MRI-EEG data acquisition
The researchers will collect EEG data using the MR compatible EEG amplifier system (MRplus, BrainVision GmbH). A short recording of resting EEG brain activity will be acquired outside of the scanner to check data quality before proceeding. Simultaneous EEG-MRI data will be acquired at baseline and during sevoflurane anaesthesia delivery. Firstly, there will be a baseline EEG-MRI data acquisition prior to anaesthesia delivery (approximately 40 minutes). These MRI scans will include MRS, ASL, resting and task FMRI sequences. The task FMRI sequences will use painful stimulation and a modified form of the isolated forearm test used in the patient study.

Sevoflurane anaesthesia will then be delivered slowly during EEG-FMRI data acquisition until the volunteers stop responding to auditory stimulation that are delivered via headphones. Due to differences in individual susceptibility to anaesthesia, this time period is expected to be variable and take between 5-15 min. The subjects will be then held at this level of anaesthesia (i.e. loss of behavioural responsiveness, LOBR) and the MRI protocol will be repeated.

The researchers will then use the SWAS prediction model to titrate anaesthesia to achieve and maintain the SWAS end-point using real-time feedback of the individual’s EEG (as in Study 1). Again, due to individual differences in susceptibility to anaesthesia, this time required to achieve SWAS will be variable across volunteers but having optimised this aspect in the previous study in patients the researchers envisage this to take around 10-15 min. They also hope to collect resting FMRI data whilst the anaesthesia is being titrated to SWAS, if this does not prove to be too technically challenging. Finally, the same MRI protocol will be repeated while the individuals are maintained at SWAS.

Painful stimulation
The researchers will either use mechanical, heat or electrical pain stimulation for the task-based FMRI assessments at loss of behavioural response and SWAS. They will apply pain stimulation at a maximum subjective pain intensity rating of 8 out of 10, where 10 is maximum pain. This level

will be assessed by a short thresholding procedure when the participants are fully awake and responsive in the scanner. This intensity level will be maintained for subsequent pain testing under anaesthesia at LOBR and SWAS.

The researchers will use the Medoc Pathway contact heat thermode to induce heat pain, which is CE-approved is widely and routinely used for clinical diagnostic purposes. 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.

Mechanical pain is elicited through sensations related to touch. These can range from light touch to sharp pinprick are 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. There are no known side effects to any of these MRI–compatible stimulations. The FMRIB/WIN pain laboratory has many years of experience using these painful stimulation devices (e.g. ethics references: C02.086, 05/Q1604/160, 06/Q1605/126, 09/H0604/90, 10/H0301/17 and CUREC Approved Procedure: IDREC_19_Version 4.0).

Auditory stimulation and modified isolated forearm test
Auditory stimulation will be delivered by Presentation (Neurobehavioral Systems) via the headphones that are used to communicate with the subject. The researchers will use single-syllable words compiled from the MRC Psycholinguistics Database to determine the loss of behavioural response as in a previous study. Subjects will respond using a two-option button box as to whether the two words presented are the same or different.

In order to assess for conscious content at loss of responsiveness and SWAS, the researchers will use a modified form of the isolated forearm test, where they ask subjects to respond with a hand opening and closing to indicate whether they have perceived the stimulus and whether it was painful. In the same way as for the patient study, the researchers will ask "[VOLUNTEER'S NAME], open and close your hand if you felt the stimulation" and "[VOLUNTEER'S NAME], open and close your hand if you felt pain".

Recovery from anaesthesia
Emergence from anaesthesia will take place outside of the scanner bore. Volunteers will be removed from the bore and allowed to emerge naturally from the anaesthesia. They will remain on the scanner table in the presence of the anaesthetist while EEG data acquisition continues. The volunteer's level of recovery will be assessed using the Modified Aldrete scoring system. When participants are awake and oriented (as defined by a Modified Aldrete score of at least 9), they will be administered the Nursing Delirium Screening Scale and a semi-structured interview will be performed. This will be recorded via the scanner intercom system (or alternative method) for scoring and evaluation. Volunteers will then be transferred to an adjoining room where they will be supervised and have as much time to recover as they need. Individuals will be given a light meal afterwards and will discharged when they meet the appropriate criteria as for day-case surgery. Volunteers will be contacted later in the evening by the study anaesthetist to check that they are feeling well after the experiment.

In the event of an unexpected emergency incident, the emergency response team in the adjacent John Radcliffe Hospital covers the FMRIB building that is part of the WIN. Emergency supplies (e.g. defibrillator) are available on site.

Due to individual variability in the susceptibility to anaesthesia, the time to complete this session will vary across volunteers. The researchers expect the whole session to last between 4-5 h in total, with delivery of sevoflurane anaesthesia for approximately 2 h.

Sample size
For the healthy volunteer study, the researchers estimate that they will need a sample size of at least 20 participants for analysis of their primary outcome based on their previous experience with neuroimaging of anaesthesia. This sample size is equivalent to or in excess of other contemporaneous FMRI experiments performed under anaesthesia. However, it is anticipated that between 25-30 healthy volunteers will need to be recruited for the neuroimaging study to achieve completion by 20 volunteers. This will allow for subject attrition due to experimenter /anaesthetic safety concerns associated with anaesthesia delivery in the scanner (e.g. unacceptable cardiovascular instability or obstruction) or withdrawal by the subject for other reasons, such as claustrophobia in the scanner.

For Study 1, the researchers also estimate that the study will require around 30 patients. The researchers have calculated this as 10 participants per anaesthetic type - i.e. either sevoflurane or propofol anaesthesia with an extra 10 patients to allow for attrition. As mentioned previously, the researchers expect the time taken to achieve SWAS to decrease with each patient with the subsequent optimisation and refinement of the model after each session.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Resting and functional thalamocortical connectivity at loss of behavioural responsiveness (LOBR) and slow wave activity saturation (SWAS) assessed by fMRI

Key secondary outcome(s)
1. Achievement of stable SWAS within 15 min assessed using EEG
2. Response to pain of individuals held at SWAS assessed by the isolated forearm test
3. Behavioural response (as assessed by hand open/close) to verbal request when held at SWAS
4. EEG power at SWAS under anaesthesia assessed using EEG
5. Maximum EEG power observed during slow-wave sleep assessed using EEG

Completion date
10/03/2020

Eligibility

Key inclusion criteria
All study participants will be required to meet the inclusion criteria outlined below:
1. Willing and able to give informed consent
2. Aged 18-60 years
3. American Society of Anesthesiology (ASA) score of 1 or 2
4. English-speaking

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
60 Years

Sex
All

Key exclusion criteria
For all participants:
1. Smoker (tobacco or electronic cigarettes)
2. Illicit drug use
3. High alcohol intake (>14 units/week)
4. Pregnancy
5. Prescription medication that could influence the EEG or interact with anaesthesia
6. Personal or familial history of allergies and/or adverse reactions to anaesthesia
7. History or clinical signs of potential susceptibility to airway obstruction, and known difficult airway
8. Personal or familial history of epilepsy, other neurological disorder or psychiatric disorder
9. History of psychological pathology, chronic pain, migraines or dementia
10. Increased risk of venous thrombo-embolic event (VTE), defined by:
10.1. Obesity (body mass index >30 kg/m2)
10.2. Personal history or first-degree relative with a history of VTE
10.3. Use of hormone replacement therapy
11. Vulnerable group status:
11.1. Drug, alcohol or substance abuse issues
11.2. Learning difficulties
11.3. Difficulty reading or speaking English
11.4. Homeless, asylum seekers/refugees or those with no recourse to public funds
11.5. In contact with prison or probation services

For patients undergoing surgery (Study 1):
12. Surgery involving the head or neck, or the prone position
13. Patients involved in litigation cases
14. Other surgical reason at the research or clinical team's discretion

For healthy volunteers (Study 2):
15. Left-handed
16. Claustrophobia
17. Certain metallic implants
18. Metallic injury to eye
19. Tattoos (depending on location)

Date of first enrolment

10/07/2018

Date of final enrolment
10/03/2020

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Sponsor information

Organisation
University of Oxford

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Government

Funder Name
Horizon 2020

Alternative Name(s)
EU Framework Programme for Research and Innovation, Horizon 2020 - Research and Innovation Framework Programme, European Union Framework Programme for Research and Innovation

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Funder Name
National Institute for Health Research (NIHR) (UK)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Data will be shared with other organisations both within and outside of the European Economic Area (EEA), most notably with our collaborators in New Zealand and the United States. Personal identifiable data will not be shared with these parties, only anonymised data. Consent for data sharing at this level will be obtained as part of the informed consent process.
Anonymised raw data and its associated metadata will be deposited on Zenodo (https://zenodo.org/). This is a tool from the Open Access Infrastructure for Research in Europe (OpenAIRE, https://www.openaire.eu), which is a public research data repository that links publications to their underlying research data. Using these methods, third parties will be able to access, mine, exploit, reproduce and disseminate our data and other data collected in the wider LUMINOUS consortium. OpenAIRE has requirements for data allocated on their services, and uploading it through Zenodo guarantees these standards. Data deposited in Zenodo for third-party use will be secured according to Zenodo's security, backup and access control policies, which comply with EU directives. Data stored in Zenodo will also comply with their policies of preservation and archiving required from OpenAIRE. According to Zenodo information, the servers are located at CERN Data Center, this CPD has multiple independent replicas which ensure the data integrity and accessibility.

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No

Participant information sheet	Healthy volunteer version 1.1	12/02/2018	15/06/2022	No	Yes
Participant information sheet	Patient version 1.0	13/12/2017	15/06/2022	No	Yes
Protocol file	version 1.0	13/12/2017	06/07/2022	No	No