Official Title: Modulation of Memory and Conditioning by Pain During Sedation With Anesthetics

ClinicalTrials.gov ID: NCT04062123

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STUDY consent form

KEY INFORMATION

Study Title: **Modulation of memory and conditioning by pain during sedation with anesthetics**

1. You are being offered the opportunity to participate in a research study. One of the investigators will explain the study to you and will answer any questions you might have. You should take your time to make your decision, which is completely voluntary.

2A. Summary of the research

Purpose of the research: The purpose of this study is to better understand what factors allow or prevent memories to be formed in people receiving IV anesthesia and experiencing pain.

Duration, number of study visits: There are four visits associated with participation in this study. The first visit will last approximately 3-4 hours. The second visit must occur the next day and will last approximately 1 hour. At least 5 days later, the third visit will occur, lasting 3-4 hours. The fourth visit, which will occur the day after visit 3, will last approximately 1 hour.

Overview of study procedures:

- urine pregnancy & drug screen
- questionnaires about your sleep, stress, anxiety, depression, and pain
- nerve stimulator calibration to a pain intensity of 5-7/10
- brief physical exam including evaluation of the health of your lungs, heart, neck and mouth
- questions about medical conditions, past surgeries, medications, allergies, substance (drug) use, and any symptoms that you have during physical activity
- intravenous (IV) catheter placement (using a needle)
- connection to monitor that measures your heart rate, blood pressure, and breathing
- potential MRI scanning and MRI safety screening questions
- enter the high magnetic field environment of the MRI scanner
- connection to monitor that measures your heart rate, blood pressure, and breathing
- placement inside the MRI scanner
- listen to recordings, look at images while experiencing painful stimulation and being scanned by the MRI
- next-day memory testing using a computer
- additional questionnaires about sleep, stress, anxiety, depression, and pain

3. Reasonable, foreseeable risks or discomforts

Risks and side effects related to the MRI scanning include those which are:
Likely: Discomfort from loud noise, positional discomfort
Rare but serious: claustrophobia, risk of interaction with undetected/undisclosed metal in/on subject's body that could cause physical injury; hearing damage/loss

Risks and side effects related to the collection & storage of personal health information include those which are:
Rare but serious: Breach of confidentiality

Risks and side effects related to the electric nerve stimulation include those which are:
Likely: Pain due to electric shock
Rare but serious: Theoretical risk of burns due to an interaction with MRI scanner

Risks and side effects related to the deep anesthesia include those which are:
Likely: Residual sedation that will resolve over time
Rare but serious: Corneal abrasion, need for airway intervention leading to nasal, pharyngeal, or laryngeal soft tissue injury, need for resuscitative medication administration

Risks and side effects related to the fentanyl administration include those which are:
Likely: Itching, nausea, sedation
Less Likely: constipation
Rare but serious: Allergic reaction (rash, itching), low blood pressure, slow heart rate, shallow or absent breathing, addiction/dependence, abdominal pain,

Risks and side effects related to the dexmedetomidine administration include those which are:
Likely: Sedation, low or high blood pressure, slow or fast heart rate, dry mouth
Rare but serious: Nausea and/or vomiting, difficulty breathing, dizziness/light-headedness, blurred vision/visual disturbance, allergic reaction (rash, itching), abdominal pain/diarrhea

Risks and side effects related to the propofol administration include those which are:
Likely: Sedation, burning on injection, dizziness/light-headedness
Rare but serious: shallow or absent breathing, low blood pressure, allergic reaction

Risks and side effects related to IV access include those which are:
Likely: Discomfort or pain, bleeding or bruising, skin sensitivity
Rare but serious: infection, thrombosis (blood clot), possibility of multiple needle punctures

Risks and side effects related to the psychometric questionnaires include those which are:
Less Likely: Discomfort with disclosure of personal information

Risks and side effects related to the pre-visit restrictions include those which are:
Less Likely: Discomfort from hunger or strong urge to urinate

4. Reasonable, expected benefits
There will be no direct benefit to you from participating in the study. However, this study will help the researchers learn more about how the brain forms memories when under sedation and experiencing pain.

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: **Modulation of memory and conditioning by pain during sedation with anesthetics**

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SOURCES OF SUPPORT:
- Department of Anesthesiology & Perioperative Medicine, University of Pittsburgh, School of Medicine
- National Institute of General Medical Sciences

Why is this research being done?
You are being offered the opportunity to take part in a research study. Research Studies include only people who choose to take part. The study team members will explain the study to you and will answer any questions you might have. You should take your time to make your decision. The purpose of this study is to better understand what factors allow or prevent memories to be formed in people receiving intravenous (IV) anesthesia and experiencing pain. We also want to understand how pain affects some of your body's automatic responses, such as sweating or rapid heart beating. Knowing this may improve the ability to control pain and prevent unpleasant memories during medical procedures, using these types of drugs.

Who is being asked to take part in this research study?
Any adult who is 18-39 years of age, not pregnant, free from any serious chronic medical condition, has never had a history of psychological or neurological disease, and who has never had a reaction to or abused a drug similar to any of the study medications may be able to participate in this study. To qualify to be a part of the study, you must also have completed the medical pre-screening and screening memory testing.

To re-iterate, specific exclusion criteria include:
- being pregnant or attempting to conceive
- having a body mass index (BMI) > 35
- having significant memory impairment or hearing loss
- having sleep apnea
- having chronic pain or other chronic medical problems
- having neurologic or psychiatric disease, including benign tremor, anxiety, and depression
- having significant cardiac disease or hypertension
- having diabetes
- having significant pulmonary disease
- being claustrophobic
- have metal implants or non-removable metal piercings
- having a history of adverse reaction to anesthetics
- have no history of illicit substance abuse

- taking: antiepileptics, antidepressants, anti-psychotics, antihistamines, anti-anxiety medication, stimulants, sleep-aids, or pain medication

We will recruit 150 people to participate. The total time for you to participate is 8-10 hours over 5 visits, spaced over a few weeks.

What procedures will be performed for research purposes?

There are four visits associated with participation in this study. The first visit will last approximately 3-4 hours, the second visits will last approximately 1 hour, the third visit will last approximately 3-4 hours, and the fourth visit will late approximately 1 hour. Each visit will occur on a separate day. The experimental procedures will take place either in a research testing room or MRI scanner. Research testing facilities are within the UPMC Presbyterian/Montefiore hospital complex. The MRI scanners that will be used for this project are located either within UPMC Presbyterian Hospital or the Biomedical Science Tower (a research facility connected by bridge to UPMC Presbyterian/Montefiore). Subjects will be informed in advance which specific locations will be used for their experimental sessions, and the intended location will not change between enrollment and study completion. Depending on experimental needs, different groups of subjects may undergo the different visits in the experiment under different conditions (in vs. out of an MRI scanner).

If you decide to take part in this research study, you will undergo the following procedures:

Experimental Procedures:
If you qualify to take part in this research study, you will undergo the experimental procedures listed below,

1. We will ask you to abstain from solid food and caffeine for 8 hours prior to your scheduled visit, consume only clear liquids until 1 hour prior to your scheduled arrival time, and not urinate in the hour before the visit.

2. We will collect a urine sample to test for pregnancy in females and drugs of abuse screening in all subjects. Afterwards, you will complete several questionnaires about your sleep, stress, anxiety, possibility of depression, and your attitudes about pain. Your responses will be kept secure and only reported in a way that cannot link your answers to your identity. When averaged with other subjects, the results from this survey will be analyzed to determine if these factors provide a way to predict someone's response to anesthetic medications. These will require about 15 minutes for you to complete.

3. A nerve stimulator will be connected to one or two of your fingers with two small electrodes. A small electrical current will then be delivered. Starting at zero, the intensity will slowly be increased until you report a pain of 5 - 7 out of 10, where 0 is no pain and 10 is intolerable pain. The nerve stimulator will then be turned off and then used periodically for a few seconds at a time during the rest of the experiment. Unless you request an adjustment, the level of current delivered (pain intensity) will not be changed after adjustment to the level you rate as 5-7 out of 10 pain.

   This study uses low doses of intravenous sedation drugs: dexmedetomidine, propofol, and fentanyl. These drugs are used routinely to medicate/sedate patients, for example before and during surgery. A physician anesthesiologist will interview you and do a brief physical exam to be sure you are safe to receive any of the study drugs. These will include (at least) questions about your medical conditions, past surgeries, medications, allergies, substance (drug) use, and any symptoms that you have during physical activity. The examination will consist of (at

least) looking in your mouth, feeling you neck, and listening to your heart and lungs with a stethoscope.

An intravenous needle (IV) will be placed, likely in your hand or arm. The needle is removed, and a small plastic catheter (tube) will remain in your arm throughout the study. The IV will be used to give you fluid and the sedative medications used in the study. You will also be connected to vital sign monitors, to measure your heart rate, blood pressure, and breathing. These procedures will take between 15 and 60 minutes.

You will receive either saline (a saltwater solution) or one of the drugs at each visit. Saline acts as a placebo, meaning it will have no effect on your brain or behavior. All subjects will receive one drug (or none) during this study visit. The drug that was used will not be disclosed to you until after your final session is complete. For this study, drugs are administered by a physician anesthesiologist (a doctor with specialized training in the administration of these medications).

4. Portions of the experiment may take place in an MRI scanner, and you will be informed in advance if you are in one of the subgroups that will undergo MRI scanning, and during which visits this will occur. If your recruitment occurs during the phase of the study in which MRI scanning is being performed, you would be asked additional screening questions to ensure that it is safe for you to undergo MRI scanning (no metal or electronic implants, etc). Prior to entering the MRI environment, you will be asked to remove any jewelry or glasses and be asked to change into a hospital gown if your clothes contain any metal.

5. You will receive sedation medication or saline (placebo) through your IV, which will take 10-15 minutes to reach effect. You will both listen to auditory cues (typically recorded words or tones) and view visual cues (images) that may require you to respond by pressing a button. A proportion of the cues will be paired with brief painful stimulation, as described above. A qualified anesthesia provider will monitor your response to the medication at all times. This part of the study will take about 30 minutes, after this you will have completed the experiment for this visit.

6. You will then be monitored while you recover from the effects of sedation. Towards the end of this time, you will do a few more paper-based questionnaires. Once it is safe to do so, you will be discharged, typically 1 - 2 hours later. You will be paid $175 for completing this first study visit, which will overall take 3 - 4 hours. You are advised not to drive a vehicle or operate machinery for 24 hours after receiving either medication. You will need to arrange for a way to get home (without driving) from the study visits that potentially involved drug administration.

7. You will return for the second study visit the next day, which will be approximately one hour long and consist of memory testing. You will again experience both auditory and visual cues. You may also experience some painful stimulations at the previously-determined level. Your response may be required by pressing a button. You will also complete a few brief paper-based questionnaires. You will be paid $50 for completing the procedures involved in this visit.

8. Study Visit 3 will occur at least 1 day after Study Visit 2 and will involve the procedures described in #1 - 6. This will overall take 3 - 4 hours, and you will be paid $175 for completing this third visit. Visit 4 will occur the next day, will be one hour long and consist of memory testing, similar to visit 2 (described in #6 above). You will be paid $50 for completing this visit. At the end of this visit, you will also receive a bonus of $40 for completing all Study Visits. Thus, subjects will receive a total of $500 for completing all required study procedures, including the payments you already received for previous study visits.

What are the possible risks, side effects, and discomforts of this research study?
Performing the experimental tasks pose no risks to subjects. Other aspects of the study involve some risk, which are described below.

Known risks of the specific medications to be used
Receiving **dexmedetomidine** can cause the following effects:

Common side effects include

Sedation	Low or high blood pressure	Slow or fast heart rate
Dry mouth	Shallow breathing	

Uncommon possible side effects include:

Nausea and/or vomiting	Difficulty breathing	Dizziness/light-headedness
Visual disturbance	Abnormal heart rhythm	Confusion/hallucination
Allergic reaction	Abdominal pain/diarrhea	

Receiving **fentanyl** can cause the following effects:

Common side effects include:

Itching	Nausea	Sedation
Low blood pressure	Slow heart rate	Respiratory depression
Addiction/dependence		

Uncommon possible side effects include:

Allergic reaction (rash, itching)	Abdominal pain	Constipation
Apnea		

Receiving **propofol** can cause the following effects:

Common side effects include:

Sedation	Burning on injection	Dizziness/light-headedness

Uncommon possible side effects include:

Respiratory depression	Low blood pressure

Risks related to painful electric nerve stimulation
Because the effects of pain on memory are being studied, pain will be repeatedly experienced in this study. Each occurrence of the pain will be brief, and you can have the painful stimulus (and the entire experiment) stopped at any time by notifying any research team member. Once electrical stimulation is stopped, there will be immediate pain relief.

Risks related to intravenous (IV) access

- Discomfort will occur in all subjects with needle insertion.
- There is a risk of a small bruise or soreness at the IV site, that may last for several days after the study.
- Less than 1% risk of fainting (syncope), or nausea/vomiting with IV placement
- IV infiltration (leaking out of the vein), in which case fluid would temporarily accumulate in your arm. This would resolve spontaneously, though this situation poses a very small risk of blood clot or tissue damage as a result.
- Extremely small risk of serious bleeding or infection related to IV placement. Study personnel who are trained in IV access will implement precautionary measures including ensuring your

physical comfort, proper disinfection of the needle insertion site, application of pressure after removal of the needle, and monitoring for any problems.
- Individuals with sensitive skin may experience some temporary irritation or skin rash from the adhesive dressing or tape used to cover the puncture site.
- Some individuals have veins that are unexpectedly difficult to access, and these subjects could experience multiple needle sticks in an attempt to obtain a functioning IV. As IV access is required for the study procedures, inability to obtain IV access could result in involuntarily withdrawal from further participation in the study.

Other risks common to anesthetic delivery:
A corneal abrasion (scratch of the surface of the eye) can occur when under sedation, and you will be reminded not to rub your eyes to reduce this risk. If your breathing were to become significantly impaired at any time, drug administration would be reduced or stopped and the study may be terminated. The anesthesiologist on the research team would support your airway and breathing using an oxygen mask placed over your face, while lifting on your jaw. Although not anticipated to be necessary, further airway support that is a routine part of anesthesia care can include insertion of tubes in your nose, mouth, or throat. Such interventions would only be undertaken if necessary, but can result in injury to the lips, teeth, dental work, tongue, throat, neck, or vocal cords. Although extremely unlikely, more severe problems could occur when you receive anesthetic agents, including heart, lung, or blood pressure problems that could cause serious injury or death. In the unlikely event that these were to occur, immediate emergency treatment would be administered by the physician (anesthesiologist) investigator, which could include the administration of IV medications like epinephrine or atropine. The effects of anesthetic agents on children and fetuses are less well-known, but probably include miscarriage. For this reason, children and pregnant women cannot participate in this study.

Risks of MRI scanning
- You may feel nervous and/or claustrophobic during the MRI scans.
- While the MRI is running, you will be asked to lie still on a narrow bed inside of the scanner and the scanner will make a loud knocking or beeping sound. The noise level is within safety limits, but you will be asked to wear earplugs, since this noise is uncomfortable for some people. You will be in verbal contact with the investigators and operator of the MRI machine, and you can request that the experiment (and scanning) be stopped at any time, and you would be immediately removed from the scanner.
- During the scanning process, you are lying on your back, and it is possible that you may feel some discomfort related to positioning.
- There are no known long-lasting side effects from MRI scanning.

If your clothing is uncomfortable, or contains metal, you will be asked to change (in a private dressing room) into a hospital gown prior to entering the MRI scanner.

Risks of Questionnaires
We will ask you to fill out a set of questionnaires about your current feelings of sleepiness, stress, depression, anxiety, and pain. If you feel uncomfortable about answering a question, you can choose not to answer it. Research staff will be available to answer any questions you may have about the questionnaires or your responses.

Risks of Breach of Confidentiality
There is a potential risk of breach of confidentiality that is inherent in all research protocols. There is a possibility that if research data were to become known, this knowledge could potentially impact a subject's future or have a negative impact on family or social relationships.

With your permission, we will use text messaging and email to remind you of appointments and scheduling issues. No personal information will be transmitted; however, know that both email and text messages are NOT secure.

Risks of Pre-Visit Restrictions
There is a small risk of discomfort from the pre-visit restrictions, such as hunger and strong urge to urinate.

What are possible benefits from taking part in this study?
You will receive no direct benefit from taking part in this research study. Participation in this study will help further the understanding of how the brain forms memories when under sedation and experiencing pain.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Although unlikely, you would be promptly notified if any new information develops during the course of this research study which suggests that you were put at any increased risk as a result of your participation.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
Neither you, nor your insurance provider, will be charged for the costs of any of the procedures performed for the purpose of this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

Will I be paid if I take part in this research study?
You will be paid a total of up to $500 for completing all visits and all associated experimental procedures in the study. This payment will be processed on a reloadable debit card. Since you are being compensated for your participation in this study, your name, address, date of birth, and social security number will be released to the Accounting Office. All compensation is taxable income to the participant regardless of the amount. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

Commercialization statement

Your data from this research study may contribute to a new discovery or treatment. In some instances, these discoveries or treatments may be of commercial value and may be sold, patented, or licensed by the investigators and the University of Pittsburgh for use in other research or the development of new products. You will not retain any property rights nor will you share in any money that the investigators, the University of Pittsburgh, or their agents may realize.

Who will pay if I am injured as a result of taking part in this study?
If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency

treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. At this time, there is no plan for any additional financial compensation. You waive no legal rights by signing this consent form.

What information will be collected about me and who will know about my participation in this research study?

We will not be reviewing your medical record information for the purposes of this study. However, we will collect information directly from you including: demographic information such as age, weight, and height; your responses to the questionnaires about pain, sleep, stress, depression, and anxiety; and portions of your medical history (including substance use history) necessary to determine your ability to safely undergo sedation and /or MRI scanning. Your permission to store this information last indefinitely. You may withdraw your authorization to store your private medical information by submitting it in writing with a date to the PI on page 1. You will be withdrawn from the study if you withdraw this authorization.

To protect your privacy, we will store this collected information separately from personal identifiers such as your name and contact information. Thus, your research data will only be identified by a code and not linked to you personally. Although we will do everything in our power to protect your privacy and the confidentiality of your records, just as with your medical information for health care purposes, we cannot guarantee the confidentiality of your research records. The identifiable link between your personal formation and your data will be stored for a minimum of 7 years after final reporting of study results, and then this link (your personal information) will be destroyed. All de-identified data from this study will be kept securely for an indefinite period of time. No third party, including relatives, personal physicians, or insurance companies will be granted access to the identifiable information we collect. It is possible that we may share the scientific information from this study, so that it may be combined with other data in larger future studies. However, your information would only be shared with other researchers without any personal identifiers, so no one would be able to learn your identity.

For the purpose of monitoring the conduct of this study, authorized representatives from the University of Pittsburgh Office of Research Protections may review your research information. Additionally, an Independent Medical Monitor, Dr. Tetsuro Sakai, MD, PhD (who is a UPMC anesthesiologist not involved in conducting the study) will review the medical information (such as heart rate, blood pressure and reported adverse events) that are collected during the study. This data will be shared with the Independent Medical Monitor in de-identified format, such that your name and personal information is not linked to the medical information.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings; if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

When you are admitted to the CTRC for your study visit, a UPMC medical record will be created (or added to your existing records.) The study team will access your CTRC chart for study related data about the medication administered, your vital signs and information specific to being in the study needed to complete the research. It will be available to the research team indefinitely; this

authorization is valid until all study data needed is collected. You have the right to not give permission or to cancel your permission for the study team to collect this information. You must do so in writing to Dr. Vogt. If you cancel your permission, you will be withdrawn from the study.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time. Representatives from the National Institutes of Health will have access to identifiable private information for purposes of monitoring the study.

Is my participation in this research study voluntary?
Yes! Your participation in this research study is completely voluntary. Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the investigators, the University of Pittsburgh, or UPMC. Your participation will not affect your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with any healthcare insurance provider.

May I withdraw my consent for participation in this research study?
You may withdraw your consent for participation in this research study at any time. Any identifiable research information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To withdraw your consent for participation in this research study, contact the principal investigator of this research study at the address/phone number listed on the first page of this form.

If I agree to take part in this research study, can I be removed from the study without my consent?
You may be removed from the study by the researchers if any practical considerations or safety concerns arise that do not allow you to participate.

Will clinically relevant results be available to me?

Any clinically-relevant abnormalities would be disclosed to you, at the discretion of one of the study physician investigators.

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VOLUNTARY CONSENT

The above information has been explained to me and my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that have occurred during my participation. By signing this form, I agree to participate in this research study and allow the use of my private health information. A copy of this consent form will be given to me.

_____	_____	_____
Participant's Signature	Printed Name of Participant	Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

I further certify that no research component of this protocol was begun until after this consent form was signed.

_____	_____
Printed Name of Person Obtaining Consent	Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date