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UPMC | University of Pittsburgh Medical Center

Department of Anesthesiology

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: **Modulation of long-term memory by the experience of pain during sedation with anesthetics**

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PRINCIPAL INVESTIGATOR: Keith M. Vogt, M.D., Ph.D.
Dept. of Anesthesiology
Montefiore Hospital, Suite 467
3459 Fifth Avenue, Pittsburgh, PA 15213
Telephone: 412-999-8570

CO-INVESTIGATORS:

Julie Fiez, PhD
Psychology & Neuroscience
605 LRDC
3939 0'Hara Street
Pittsburgh, PA 15260

James W. Ibinson, MD, PhD
Anesthesiology
Montefiore Hospital, Suite 467
3459 Fifth Avenue, Pittsburgh, PA 15213

SOURCE OF SUPPORT: Foundation for Anesthesia Education and Research
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Why is this research being done?
The purpose of this study is to better understand what factors allow or prevent memory formation while sedated with intravenous anesthetic agents and experiencing periodic pain. Understanding the interaction between these two elements may allow future anesthetics to more precisely prevent memory formation during surgery.

Who is being asked to take part in this research study?
Any adult who is 18-39 years of age, free from any serious medical condition, has never had a history of psychological or neurological disease, has never had a reaction to or abused any of the study medications, is not pregnant, and can undergo an MRI can participate in this study.

What procedures will be performed for research purposes?
If you decide to take part in this research study, you will undergo the following procedures:

Screening Procedures:
Procedures to determine if you are eligible to take part in a research study are called "screening procedures". For this research study, the screening procedures include:

1. Women will be asked questions about the possibility of pregnancy. Pregnant women will not be allowed to take part in this study. In female subjects with the ability to be pregnant, a commercially available urine pregnancy test will be administered at the beginning of each visit that involves drug administration or MRI

scanning. Any subject with a positive pregnancy test will be removed from the study.

2. All people having an MRI are asked standard questions about the possibility of materials that are incompatible (like some metal implants or implanted medical devices) with the strong magnetic field. Every potential subject for this study will be asked these same questions.
3. Questions will be asked to make sure you are free from any psychiatric or neurologic diseases that may interfere with the analysis of the data from this study. You must not be taking any type of prescription or non-prescription drugs that could interfere with memory formation, level of sedation (sleepiness), or with pain. You will be asked about all medications and supplements that you are taking. Certain items, like birth control pills, antacids, and multivitamins are permitted. Medications like sleep-aids, pain-killers, stimulants, anti-anxiety medications, anti-depressants, or anti-psychotics are **not** allowed. Over-the-counter cold/allergy medicine is allowed, if not taken in the week prior to the study. You will also be asked to describe your tobacco, alcohol, and illicit substance use. Recent or daily use of these substances may disqualify you from the study.
4. You will be asked questions about your health and medical history to ensure it is safe for you to receive the anesthetic agents used in this study.

Experimental Procedures:

If you qualify to take part in this research study, you will undergo the experimental procedures listed below. The study will occur in two phases; you may be asked to participate in phase 1 or phase 2. Each involves multiple visits, described below. The experimental procedures for phase 2 are the same as in phase 1, except that portions of the experiment are performed in an MRI scanner.

1. Visit 1 begins with completing the written informed consent form. 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 simple way to predict someone's response to anesthetic medications. These will require about 15 minutes for you to complete.

2. A nerve stimulator will be connected to your right index finger with two small electrodes. A small electrical current will then be delivered to that finger, starting at zero current. The intensity will slowly be increased until you report a pain of 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 randomly for a few seconds at a time during the rest of the experiment. The level of current delivered (pain intensity) will not be changed after adjustment to the level you rate as 7 out of 10 pain.

3. This study uses low doses of intravenous sedation drugs, dexmedetomidine (Precedex), ketamine (Ketalar), and midazolam (Versed). These drugs are used routinely in the practice of anesthesia. Subjects receive only one drug in a visit. Some subjects will receive only one medication, while others will be scheduled to receive 2 or 3 drugs on different days. Subjects will know in advance how many drug sessions they will be scheduled for. The drug that was used will be disclosed to subjects after their final memory testing session is complete. For this study, drugs are administered by a physician anesthesiologist (a doctor with specialized training in the administration of these medications). You will be interviewed and examined to determine the safety to undergo sedation. These will include questions about your medical conditions, past surgeries, medications, allergies, substance use, and any symptoms that you have during physical activity. The examination will consist of (at least) looking in your mouth and listening to your heart and lungs with a stethoscope.

4. Intravenous access (an IV) will be placed in your hand or arm. This will be used to give 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, skin conductance, and breathing.

5. You will listen to words played and asked to make a decision about the word, for example if it represents something big or small. You will press different buttons with one of your fingers to indicate your answer. This list of words will be repeated 3 times, and you will be instructed to make different decisions in each round. About one-third of the time, the word will be accompanied by a brief electric shock when it is played. This part of the experiment will take about 20 minutes.

6. You will receive sedation medication through your IV, which will take 10-15 minutes to reach effect. You will then repeat the procedures in #5 above, using a different list of words. A qualified anesthesia provider will monitor your response to the medication at all times. This part of the study will take about 20 minutes, after this you will have completed the experiment for this visit.

7. You will then be monitored while you recover from the effects of sedation. Once it is safe to do so, you will be discharged, typically 1-2 hours later. You will be paid $50 for completing this first study visit, which will overall take 2 – 3 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 involve drug administration.

8. You will return for the second study visit the next day, which will be one hour long and consist of memory testing. You will be played a list of words that include the ones you heard in the prior visit. You will indicate whether you remember the word or if it seems new to you by pressing different buttons. You will be paid $10 for completing the procedures involved in this visit. If you are scheduled to receive only one medication (which you will know in advance), then this is your last visit and you will also receive a $30 study completion bonus. Thus, the total compensation is $100 for completing all study procedures (including the $10 you already received for the memory screening visit).

9. **If you are scheduled to receive 2 study medications over 4 visits** (which you will know in advance), Study Visit 3 will occur at least 1 day after Study Visit 2, and will involve the procedures described in #1-7. This will overall take 2 – 3 hours, and you will be paid $50 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 #8 above). You will be listening to words and deciding if you heard them in the prior visit. You will be paid $10 for completing this visit. At the end of this visit, you will also receive a bonus of $70 for completing all Study Visits. Thus, subjects enrolled to receive both medications will receive a total of $200 for completing all required study procedures, including the payments you already received for previous study visits.

10. **If you are scheduled to receive all 3 study medications over 6 visits** (which you will know in advance), Study Visits 3 and 4 will occur as described in #9 above. You will be paid $50 for completing this third visit and $10 for completing the fourth visit. According to a similar schedule, you would return for Study Visit 5 (and undergo procedures described in #1-7) and be paid $50; then you would complete Study Visit 6 (memory testing) the next day and be paid $10 for completion. At this last visit, you would additionally receive a bonus of $70 for completing all Study Visits. Thus, subjects enrolled to receive 3 medications will receive a total of $260 for completing all required study procedures, including the payments you already received for previous study visits.

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11. Phase 2 (MRI scanning) follows the same Study-Visit schedule with the experimental procedures and reimbursement described in #'s 1-10 above. However, in Phase 2, the word-list experiments of Study Visits

involving drug administration are performed while in an MRI scanner. You will know in advance if you are being scheduled for Phase 2 or Phase 1.

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

Risks related to intravenous (IV) access
Some discomfort will occur in all subjects with needle insertion. There is a risk of a small bruise or soreness at the IV site for several days after the study. During IV placement, there is a less than 1% risk of fainting, or nausea/vomiting. The risk of serious bleeding or infection is very rare. There is a risk of 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 of the fluid. There is also an extremely small risk of serious bleeding or infection related to IV placement. Study personnel who are also healthcare professionals 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 constant 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.

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

Common side effects include:

Low or high blood pressure	Slow or fast heart rate	Dry mouth
Shallow breathing	Nausea and/or vomiting	

Uncommon possible side effects include:

Difficulty breathing or wheezing	Dizziness / light-headedness	Blurred vision / visual disturbance
Abnormal heart rhythm	Confusion / hallucination	Allergic reactions: rash, itching

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

Common side effects include:

High blood pressure	Fast heart rate	Sleep disturbances
Visual disturbances	Nausea and/or vomiting	

Uncommon possible side effects include:

Difficulty breathing or wheezing	Confusion / hallucination	Allergic reactions: rash, itching
Abnormal heart rhythm	Slow heart rate	Low blood pressure
Airway obstruction	Redness or irritation at injection site	Nightmares

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

Common side effects include:

Hiccups or coughing	Discomfort at injection site	Headache
Nausea and/or vomiting	Redness or irritation at injection site	Drowsiness / sedation

Uncommon possible side effects include:

Difficulty or shallow breathing	Anxiety / restlessness	Lethargy / sleep disturbance
Airway obstruction	Dizziness / light-headedness	Blurred vision / visual disturbance
Abnormal heart rate or rhythm	Confusion / hallucination	Allergic reactions: rash, itching

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 stopped and the study will 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 can include insertion of tubes in your nose, mouth, or throat. Such interventions would only be undertaken if necessary, but can result in injury or damage 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 illness or death. 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 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 of MRI scanning

It is possible that you can feel nervous and 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 constant contact with the operator of the MRI machine, and you can request that the investigators stop the scanning and remove you from the scanner at any time. 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 side effects from MRI scanning on adults. The effects of MRI on children and fetuses are less well-known, and for this reason children and pregnant women cannot participate in this study. 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 questions or your answers.

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.

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 either $100 (if enrolled for one drug visit), $200 (if enrolled for 2 drug visits), or $260 (if enrolled for 3 drug visits) for completing all experimental procedures in the study.

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.

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.

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 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 Research Conduct and Compliance Office may review your research information.

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 safety concerns arise that do not allow you to participate.

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VOLUNTARY CONSENT

The above information has been explained to me and all of 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. 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