Nitrous Oxide Neuroimaging

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University of Pittsburgh UPMC LIFE CHANGING MEDICINE

Department of Anesthesiology & Perioperative Medicine

Nitrous Oxide Neuro-Imaging Study Consent Form

KEY INFORMATION

1. You are being offered the opportunity to participate in a research study. The principal investigator, Dr. Vogt, 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.

2. *Purpose of the research*: The purpose of this study is to better understand what factors allow or prevent memory formation and the experience of pain in people receiving nitrous oxide anesthesia.

3. Duration, number of study visits: There are two visits associated with participation in this study. The first visit will last approximately 3-4 hours. The second visit must take place the next day and will last approximately 1 hour.

4. Overview of study procedures:

- Urine drug screen and pregnancy test
- questionnaires about your sleep, stress, anxiety, depression, and pain
- nerve stimulator calibration to a pain intensity of 7/10
- brief physical exam including evaluation of the health of your lungs, heart, neck and mouth
- answering detailed questions about medical history, past surgeries, medications, allergies, substance (drug) use, and any symptoms that you have at rest and during physical activity
- intravenous (IV) catheter placement (using a needle)
- receive ondansetron; a medication that helps prevent nausea which can occur with anesthesia drugs
- answering MRI safety screening questions
- connection to monitors that measure your heart rate, blood pressure, and breathing
- application of a tight-fitting face mask
- enter the high magnetic field environment of the MRI scanner
- connection to monitor that measures your heart rate, blood pressure, and breathing
- MRI scanning, including exposure to loud noise
- receive nitrous oxide; a medication you will inhale that will make you sleepy and relaxed but likely not unconscious (unlike general anesthesia for surgery, you may not completely loose awareness of your surroundings in this study).
- memory task while experiencing painful stimulation and being scanned with MRI

- return and perform next-day memory testing using a computer
- additional questionnaires about sleep, stress, anxiety, depression, and pain

5. Risks and side effects of study procedures:
- The anesthetic gas administered for this experiment may cause nausea or loss of consciousness
- The stimulation generated by the nerve stimulator and the placement of the IV placement may cause discomfort.
- The sounds produced and the equipment worn in the MRI scanner may be uncomfortable.

There is additional information on risks on page 6.

4. Reasonable, expected benefits
There will be no direct benefit to you from participating in the study. There is a small possibility that an undiagnosed medical condition could be discovered as part of your participation, and this could be of benefit in these rare cases.

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CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: **NONI: Nitrous Oxide Neuro-Imaging Study**

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

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 inhalational anesthesia and experiencing pain. Knowing this may improve the ability to control pain and prevent unpleasant memories during

medical procedures, using nitrous oxide anesthesia.

Who is being asked to take part in this research study?
Any adult who is 18-59 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 ondansetron or nitrous oxide 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 memory screening test.

To re-iterate, specific exclusion criteria include:
You cannot be in this study if have any of the following:

- are pregnant or attempting to conceive
- body mass index (BMI) > 35
- significant memory impairment or hearing loss
- sleep apnea
- chronic pain or frequently taking pain medication (including tramadol)
- any severe or poorly-controlled medical problem (hypertension, diabetes)
- neurologic or psychiatric disease, including anxiety, and depression
- severe cardiac disease
- history of methylenetetrahydrofolate reductase (MTHFR) deficiency or variant mutation
- recent ear or eye surgery
- being claustrophobic
- have metal implants or non-removable metal piercings
- having a history of adverse reaction to nitrous oxide
- daily alcohol or heavy alcohol use; history of alcohol abuse
- current daily smoker
- regular or recent marijuana use (including prescribed/medical marijuana)
- illicit drug use, i.e., street drugs
- regularly taking: antiepileptics, antidepressants, anti-psychotics, antihistamines, anti-anxiety medication, stimulants, or sleep-aids

We will recruit up to 60 people to participate. The total time for you to participate is 4-5 hours over 2 visits, that happen on two consecutive days.

What procedures will be performed for research purposes?
There are two visits associated with participation in this study. The first visit will last approximately 3-4 hours, the second visit will last approximately 1 hour. Each visit will occur on a separate day. Experimental procedures will take place in an MRI scanner (day 1) and then a subject testing room (day 2). The MRI scanners that will be used for this project are located within UPMC Presbyterian Hospital. This study uses low doses of an inhalation anesthetic, nitrous oxide. This drug, at higher doses, is used routinely to cause general anesthesia (loss of consciousness), for example before and during surgery. All subjects will receive nitrous oxide during the day 1 visit.

An MRI is a medical imaging test can produce images of the internal structures of the body. MRI scanners create these images using a large magnet and radio waves. There is no radiation involved. During an MRI exam, you will lie on a table that will move your head and

chest into a large tube-shaped machine. We will use the images of your brain from this study to learn more about how the brain processes pain and forms memories, and how the anesthetic gas nitrous oxide affects these brain functions.

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

Experimental Procedures:

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. You should not urinate in the hour before the visit in order to provide a urine sample.

2. On arrival, you will provide a urine sample and a drug screen will be performed. For females, a pregnancy test will be performed, and you will be informed of the result.

3. A nerve stimulator will be connected to one 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 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 (stimulator intensity) will not be changed after adjustment to the level you initially rate as 7 out of 10 pain. Shocks will be delivered to your left index finger, at the level you set in advance. 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.

4. A physician or qualified anesthesia provider will interview you and do a brief physical exam to be sure it is safe to receive nitrous oxide. 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 your 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. You will receive ondansetron for prevention of nausea. These procedures will take between 15 minutes.

5. The day 1 experiment will take place in an MRI scanner, and you will be asked additional screening questions by an MRI technologist 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.

6. Once in the MRI scanner (if applicable, otherwise once positioned in a clinical testing area) you will be connected to monitoring equipment to measure heart rate, blood pressure, and breathing. You will then begin to perform the memory encoding and pain perception experiment that takes about 6 minutes. 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. This task period will be followed by a 6-minute resting scan. This will first be done under a no-drug baseline condition. This part of the study will take about 15 minutes.

7. You will then begin to receive the anesthetic gas nitrous oxide through a breathing circuit. A qualified anesthesia provider will deliver the anesthetic and monitor your response at all times. You will likely feel sedated and relaxed, may become unconscious, and could experience one of the side effects listed below. It will take about 10 minutes to achieve steady-state for the low-dose condition. Though some subjects may remain responsive, it is expected that you may become unconscious (unresponsive). If you are tolerating the anesthetic gas with no undesirable side effects, we will continue the experiment, in which you will undergo the same task and resting scan over about 15 minutes. Once completed, the anesthetic will be discontinued, and you will be removed from the scanner.

8. You will then be monitored while you recover from the effects of the anesthetic. Towards the end of this time, you will do a few more questionnaires. Once it is safe to do so, you will be discharged, typically 1 - 2 hours later. You will be paid $300 for completing this first study visit, which will take 3 - 4 hours overall. You are not permitted to drive a vehicle or operate machinery for 12 hours after receiving nitrous oxide. You will need to arrange for a way to get home (without driving) from the study visits that potentially involved drug administration.

9. You will return for the second study visit the next day, which will be approximately one hour long and consist of memory testing sitting at a computer. You will again experience both auditory and some visual cues and be asked which you recognize from the previous day's session. Your response will be required by pressing a button. You will also complete a few brief questionnaires about your current feelings of sleepiness, stress, depression, anxiety, and pain. You will be paid $50 for completing the procedures involved in this visit.

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.

<u>Nitrous oxide anesthesia administration and recovery include:</u>
Likely: Euphoria, lightheadedness, dizziness, headache, nausea
Less likely: numbness and tingling, excessive sweating, shivering, fatigue, vomiting
Rare but serious: hallucinations, anemia

Other uncommon risks possible with anesthetic delivery:
You may become unconscious and it is possible you will not remember portions of your participation in the experiment. 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, anesthetic administration would be reduced or stopped and the study may be terminated. The anesthesiologist on the research team may support your airway and breathing using oxygen, the ventilator attached to the anesthesia gas machine, and/or a mask manually placed over your face. Providers could also need to lift forcefully on your jaw. Although not anticipated to be necessary, further airway support that is a routine part of anesthesia care can include insertion of plastic devices and/or 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. In this very unlikely scenario, you would be admitted to the hospital for monitoring and treatment. 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.

Ondansetron administration includes:
Less Likely: Headache, dizziness, anxiety/agitation, itching, feeling unable to urinate
Rare but serious: Abnormal heart rhythm, allergic reaction

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

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. The device is shielded from the magnetic field, but there is a small risk of interaction of the device with the MRI scanner, which would result in progressive heating under the electrodes. If warmth is felt in your finger between periods of electrical stimulation, you should inform the investigators immediately.

Shocks will be delivered to your left index finger, at the level you set in advance. 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.

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

What to expect for MRI scanning

- You may feel nervous and/or claustrophobic during the MRI scans.
- While the MRI is running, the scanner will make a loud knocking or beeping sound.
- You will lie on your back for one hour and need to hold still. You may feel some discomfort related to this positioning.
- 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.
- 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.

Collection & storage of personal health information include those which are:
Less Likely: Discomfort with disclosure of personal information
Rare but serious: Breach of confidentiality

Psychometric questionnaires include those which are:
Less Likely: Discomfort with disclosure of personal information
Rare but serious: Breach of confidentiality

Pre-visit restrictions include those which are:
Less Likely: Discomfort from hunger, thirst, or strong urge to urinate

Electronic communication includes those which are:

- **Text Messages:** Text messages may not be encrypted or secure during their transmission or storage and it is possible they could be intercepted and used by others not associated with this study.
- **Email**: Emails may not be encrypted during transmission or storage and may be intercepted and used by others not associated with this study.

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 $ 300 for completing all visits and all associated experimental procedures in the study. Pilot phase subjects will receive the same compensation. The study team will discuss the payment options with you. 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) may 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.

Representatives from the University of Pittsburgh Office of Research Protections and the National Institutes of Health may access your identifiable information for the purpose of monitoring the conduct of this study. 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.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, if 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. If a possible abnormality on your brain MRI imaging is detected, the images would be sent to a neuroradiologist for review. The results of their interpretation would be shared with you, realizing that the images obtained for the research project may not be suitable for clinical diagnosis.

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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