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Official Title: Memory and Conditioning Under Anesthesia

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Overview: The purpose of this study is to determine the effects of pain on long-term memory and conditioned physiologic responses in the presence and absence of distinct intravenous anesthetics. Functional magnetic resonance imaging will be used to identify the neural correlates of these phenomena The study will occur over 5 visits and involves no long-term follow up.

Background: Sedative-hypnotic and analgesic agents (termed "anesthetics") are routinely used during medical procedures to prevent or ease suffering, suppressing the conscious experience of pain and its encoding into memory. While overt awareness under general anesthesia is a rare clinical event, implicit memory may still form. Further, at sub-hypnotic anesthetic doses, animals show enhanced fear conditioning and humans may have enhanced amygdala activity. This motivates the investigator's study, as poorly-contextualized aversive memories are theorized to initiate anxiety-spectrum disorders, which may explain the high incidence of post-traumatic stress disorder after anesthetic awareness.

Objective: How anesthetics facilitate or inhibit poorly-contextualized aversive memories is incompletely understood, with little mechanistic work done in human subjects. Thus, there is a critical need to understand how anesthetics modulate the memory and threat response systems during painful stimulation. The overall scientific objective is to determine the memory-modulating effects of propofol, dexmedetomidine, and fentanyl in the context of periodic painful stimulation.

Aim 1: Determine how behavioral and physiologic measures of memory are modulated by pain and the individual effects of three pharmacologically distinct drugs: propofol, dexmedetomidine, and fentanyl. Hypotheses: Based on previous results, 1a) explicit memory will be significantly reduced by propofol and dexmedetomidine, but only modestly by fentanyl. Consistent with my preliminary data, 1b) priming effects will be seen for pain-paired words under all drugs. Electrodermal activity changes still occur with opioids and propofol, thus 1c) pain-related physiologic responses will persist with these two drugs but be blunted by the anti-adrenergic effect of dexmedetomidine.

Aim 2: Determine the brain structures differentially engaged in memory encoding under pain and drug conditions. Task-related functional magnetic resonance imaging (MRI) activity for behavioral measures of explicit or implicit memory will be determined, comparing pain-paired vs non-pain items across drug and no-drug datasets. Functional connectivity (FC) MRI (fcMRI) will be compared between task and drug conditions. The entire brain will be explored, but predictions for key structures follow. Hypotheses: 2a) Hippocampal activity, will be blunted by propofol and dexmedetomidine, while fentanyl will have minimal effect. 2b) Amygdala activity, responsible for physiologic responses, will parallel the predictions in 1c across drug and pain conditions. 2c) Insula activity will be greater for pain-paired items, and this will be attenuated by fentanyl > dexmedetomidine > propofol, corresponding to their anticipated analgesic effect. 2d) Pain has been shown to affect fcMRI during a cognitive task, and thus FC between the key regions in 2a-c will be reduced by all three drugs, in characteristic patterns.

Subjects that are interested and think that they are eligible will be scheduled for a memory pre-screening visit. During this <30 min visit they will undergo a memory task and be paid $10 for completing this test. This will be subsequently scored by the investigators. Subjects whose performance is > 1 standard deviations above random chance (guessing) will be eligible for further participation. If able to be scheduled for further study visits, the subjects will be contacted to undergo phone screening. This call involves reviewing detailed medical information by one of the study physicians, to ensure they are an appropriately low-risk subject for the sedation portion of the study. Substance use history will be assessed with the NIDA “Quick Screen." Absence of illicit substance use will be confirmed with a urine drug screen at each session. If the subject is eligible and still interested, they will be enrolled as a subject in the study. Text messaging and email will be used for appointment reminders and to address and scheduling issues.

Full study procedures begin after completing all screening procedures. Prior to study visits, Subjects will be instructed to abstain from solid food and any glucose or caffeine for 8 hours, and from clear liquids for 2 hours prior to visits that will involve drug administration. Subjects will be reminded that they are free to withdraw at any time. Subjects will not be permitted to drive after receiving the sedative agents, and will be advised to plan for alternative transportation after visits of the study that involve medications.

The study will occur over multiple visits. During the first of these visits, subjects will receive saline, and during the other they will receive one of the three anesthetic medications (propofol, dexmedetomidine, or fentanyl). They will not be informed whether they are receiving drug or saline, and will not be told which drug they received until the study is completed.

On arrival for the first study visit, the research protocol will be reviewed, and consent obtained after all questions answered. The screening consent will include consent for the medical history and NIDA screening if subject is eligible from memory screening test. Surveys will be completed via REDCap. Subjects will complete psychological tests for sleepiness, stress, depression and anxiety, using a combination of the Epworth sleepiness scale, Brief Inventory of Perceived Stress), State-Trait Inventory for Cognitive and Somatic Anxiety, STICSA, and portions of the NIH toolbox. Subjects will also complete the Pain-Anxiety Symptom scale, the Pain Vigilance and Awareness Questionnaire, and the Pain Catastrophizing Scale. As in previous studies, an electric nerve simulator will be applied to the subject’s finger(s) and current level slowly titrated to their subjective rating of 5-7/10 pain. Subjects will specifically assess whether the level of pain will impair their ability to participate in the experiment. This self-adjusted current level will be employed for brief painful stimulation during memory encoding. These screening and psychometric tests are expected to take 15 minutes total. Physiologic monitoring of the electrodermal activity (also called galvanic skin response) and the electrocardiogram will be obtained throughout the experiment, to measure subject’s sympathetic response to the painful shock, or experimental items previously paired with pain.

The memory encoding experiment will involve exposure to a number of experimental cues (typically recorded tones and spoken words). Some of these cues will be paired with a painful shock, and the order of these randomized among other non-pain-paired cues. Subjects may respond to the

experimental cue by pressing a button, allowing response time to be electronically recorded. Several repetitions of the experimental cues will be employed to produce a conditioned response to some stimuli and later asses for memory encoding. The entire conditioning/encoding portion of the experiment is anticipated to take 20-30 minutes.

The anesthetic to be administered during the visit will be titrated using a target-controlled infusion strategy for effect-site concentration doses previously shown produce amnesia for 40-60% of experimental cues. This approach should achieve and maintain, based on subject parameters and drug pharmacokinetics, a steady-state plasma concentration of the drug that is equal across subjects. Because the subject's sedative response to the medications is known to vary (in fact, this is one of the dependent variables to be measured in the study) drugs are not dosed or titrated to a specific observer-rated level of sedation. However, the level of sedation is expected to range between no perceptible sedation to light sedation, in which subjects follow verbal commands.

The infusion parameters will be custom calculated, using well-established pharmacokinetic models for each drug that account for each subject's age, gender, weight, and height. Total doses (over 20-30 min) will vary between subjects and also by the length of the experiment (some of which is subject-paced). These are low doses compared to those used clinically, especially since the total dose will not be administered as a single bolus, but rather, predominantly as an infusion that slowly decreases in rate over time to maintain a steady-state concentration. These doses do not exceed the manufacturer's recommended doses for procedural sedation or analgesia for these agents. The standards for monitoring during anesthetic administration established by the American Society of Anesthesiologists will be used.

At the conclusion of the experiment, subjects will be allowed to fully recover from the anesthetic prior to discharge and asked not to operate a car or machinery the rest of the day. The recovery period will vary based on each individual subject's recovery profile, and is expected to take less than 1 hour. The total time spent for the visit will thus be between 2 and 3 hours.

The follow-up memory testing visit will occur 1 day later in Study Visit 2. Subjects will begin with long-term memory testing for the items from the previous visit. Psychometric questionnaires to assess factors that may have affected memory consolidation since the encoding session will be administered (caffeine intake, over-the-counter medication use, and sleep logs, and Pittsburgh Sleep Quality Index). This testing visit is expected to take about 1 hour.

During the third and fourth study visits, subjects will then repeat all the experimental procedures described above for visits 1 & 2, using different experimental cues, and receiving either saline or drug (whichever they did not receive previously). The total time for the memory encoding experiment will again take 1.5-2 hours, with 1 hour for anesthetic recovery. Thus, subsequent conditioning and encoding visits will also be a total duration between 2 and 3 hours. The follow-up memory testing study visit (study visit #4) will be scheduled 1 day after visit #3, and consist of long-term memory testing and psychometric data collection, as described for the first set of visits. This brief visit will take about 1 hour. The total time spent for the screening visit and all 4 experimental visits will vary between 6 to 8 hours.