Protocol IRB19-1442

Protocol Title: Implications of Anesthetics on Sleep Consolidation

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I. Background and Objectives

Sleep leads to consolidation of learning in humans, restoring memories that were forgotten over a waking day and protecting memories against future forgetting. Although theories of consolidation have linked sleep spindles seen on electroencephalography to consolidation due to their putative role in hippocampal transfer to the neocortex (Antony et al, 2019; Antony & Paller, 2017), spindles have not yet been linked to consolidation of perceptual learning or generalized learning. Prior research by a collaborator on this project has shown that sleep specifically aids in the consolidation of generalized perceptual learning of speech (Fenn, Nusbaum, & Margoliash, 2003). Subjects show a 10-point reduction in performance after a waking retention period, while no loss is found after a retention period containing sleep (Fenn et al., 2003).

Sleep spindles and K-complexes (microarchitectural components of sleep) are correlated with learning and retention (Antony & Paller, 2016), but their role in consolidation of skill learning is unknown. Whether the presence and morphology of these oscillations cause consolidation or simply co-occur with consolidation during sleep is also unknown. Some aspects of sleep can be simulated using pharmacologic agents. The $\alpha 2$ adrenergic receptor agonist, dexmedetomidine, is "biomimetic" of non-REM 2 sleep, preserving natural sleep spindle morphology (e.g., frequency and amplitude; Huupponen et al., 2008). Dexmedetomidine acts on subcortical areas of the brain, primarily the locus coeruleus, but does not bind to GABA receptors. (Funai et al., 2014)

II. Specific Aim

Specific Aim 1: The objective is to administer intravenous dexmedetomidine in healthy human subjects and compare the consolidation of perceptual learning that occurs to that previously seen in natural sleep.

Hypothesis 1.1 The gain in perceptual learning after a 90 minute natural sleep nap will also occur after 90 minutes of a sufficient dose of IV dexmedetomidine to replicate sleep. This result would suggest that consolidation can occur under this anesthetic state of consciousness.

Specific Aim 2: To quantitatively and qualitatively relate sleep spindles seen on electroencephalography (EEG) evoked under natural sleep (previously collected data, supported under a separate IRB protocol) to those seen under dexmedetomidine induced sleep to understand how these brain oscillations relate to perceptual learning.

Hypothesis 1.2 The number and quality of sleep spindles seen on EEG in subjects administered dexmedetomidine will correlate with this gain in perceptual learning. This result would suggest that biomimetic sleep spindles are sufficient for producing memory consolidation.

III. Volunteer Selection and Enrollment

Only those subjects capable of giving their own consent will be considered for this study. We will select 20 healthy subjects for this study between the ages of 18 and 35.

The volunteers will be recruited using an announcement of the study distributed either via (1) email methods: participants who took previous studies from our lab may be contacted again via email for their participation in future studies (this will ONLY occur if they explicitly agree to be contacted about other related studies in the future on the consent form), (2) flyers/posters or brochures: single-page

flyers/posters will be posted around the UChicago campus and in the general Chicago community (with permission), (3) website/social media such as Amazon Mechanical Turk, UChicago Marketplace, Craigslist, and Facebook, (4) the University's SONA system in which we will post a description of our experiment and provide times in which participants can sign up to take part in the study, (5) in person, (6) word of mouth.

All volunteers will be healthy, meeting the American Society of Anesthesiologists (ASA) physical status classification ASA 1 (normal healthy subjects) and ASA 2 (stable chronic condition) and unlikely to obstruct during anesthesia administration. Prior to the study enrollment, each volunteer will sign an informed consent form. A standard anesthetic medical history will be taken in addition to performing a focused standard pre-anesthetic physical examination in order to rule out active and chronic medical problems.

Medical History

Subjects who do not have any serious chronic medical conditions that are judged by the MDs (or other research personnel) to put the subject at an increased risk of receiving dexmedetomidine or to impact learning or sleep architecture will be recruited.

***Meeting quarantine criteria will be grounds for exclusion.**

Physical Examination

The volunteer will be given a standard pre-anesthetic physical examination. Abnormal findings on physical examination will provide reason for exclusion from the study. Abnormal finding(s) will be reported to the affected volunteer and recommendation(s) for medical follow-up will be given as needed.

Screening Tests

Each volunteer will provide a urine specimen for a toxic substance screen at the beginning of Visit 2. Each female volunteer will be administered a urine pregnancy test at the beginning of Visit 2. Positive toxicity screening and/or positive results on the pregnancy test will prompt exclusion from the study. An ECG screening and vital sign measurement will take place at Visit 1. A 12-lead ECG and repeat vital sign measurement will be performed on all study volunteers at the second, experimental visit, if they pass the informal screening ECG during Visit 1 (or the 12-lead ECG will take place during Visit 1). In the case that they do not pass the ECG screening during Visit 1, they will be excluded from participating further in the study.

Primary Inclusion Criteria for “Healthy” volunteers

- Age between 18-35
- Native English speaking
- No hearing or speech difficulties
- No sleep disorders
- No chronic, severe medical conditions
- Non-smokers (within 3 months)
- Non-abusers of recreational or illicit drugs (including marijuana), caffeine, or alcohol
- Must be willing and able to pass the drug tests (no psychoactive substances), no ingestion of alcohol or sleep-altering drugs for the 48 hours prior to the study session.

- A weight which is deemed by the anesthesiologist to not increase the chance of obstruction
- *Not meeting quarantine criteria for COVID-19

Primary Exclusion Criteria for "Healthy" volunteers

- Speech difficulties/disorders
- Hearing difficulties (including occluded or infected ear canals)
- Current hairstyles that do not allow the high-density EEG cap to make contact with the scalp (e.g., individuals with hair extensions, braids, dreadlocks or hairstyles that restrict the ability of electrodes to touch the scalp)
- Metal on/in the body which is suspected to impact the quality of study recordings
- Serious abusers of alcohol, drugs or caffeine.
- Taking psychoactive medications or medications suspected to affect sleep
- Pregnancy or suspected pregnancy (urine pregnancy test at visit 2)
- Active sleep disorder
- Abnormal sleep habits, such as:
    - Sleeping less than 5 hours each night
- Currently taking medications that regulate blood pressure; a history of high blood pressure, diabetes or stroke
- Chronic smokers
- Current use of aspirin, or other medications which increase bleeding, prior to the study session.
- Known drug allergies to anesthetics or a history of an adverse reaction to anesthesia.
- Known allergy to adhesives or electrode gel

<u>Remuneration</u>

For successful completion of this protocol volunteer remuneration will be $320 ($270 for study procedures, $25 for parking/transportation for Visit 1, $25 for parking/transportation for Visit 2). If the study volunteer is unable to complete the entire protocol, the proration will be as follows:

- If subjects withdraw from the study prior to completing all of the study tasks, they will be compensated $10 for each hour they have spent in the lab
- If the study must be stopped after the anesthesia sedation portion has begun due to concerns for the study volunteer's medical safety, volunteers will receive the full $320 (includes the $25 for parking/transportation for Visit 1, and $25 for parking/transportation for Visit 2).

Subjects are paid an additional $135 for completing all study procedures (maximum payment of $270 for study procedures). We reserve the right to withhold payment in the case that the subject does not return the Actigraph watch.

All parts of the study, including clinical encounters, tests, and procedures are for research purposes and paid for by the study.

IV. Study Procedures

The pre-screening visit and visit 1 will take place in the Beecher-Kelly-Green psychology building or in an academic office on the medical campus. Visit 2 will take place in the Duchossois Center for Advanced Medicine (DCAM) pain clinic. The DCAM pain clinic is a facility which is used for IV

sedative medication administration. There is piped oxygen and air, wall suction, and a backup oxygen tank. There is an automated record keeper and standard anesthesia monitors. A fully equipped code cart is also available, and the hospital code team responds to emergencies in this location. Personnel from the pharmacy check the code cart and medications at intervals, and the anesthesia equipment is checked and maintained by the bioengineering department. In summary, the level of physiological monitoring and clinical care that can be delivered in this facility is the standard of care for IV anesthesia. *Study personnel will wear a surgical mask for the entirety of the experiment. Subjects will also be required to wear a surgical mask during all of Visit 1 and parts of Visit 2 which are deemed feasible by the researchers.

The initial starting doses and maximum dose for dexmedetomidine are consistent with those doses recommended in the dexmedetomidine product manual. We will administer a 0.5 mcg/kg bolus followed by an infusion of 0.5-0.7 mcg/kg/hr, titrated up by 0.1 mcg every 1 minute until the subject spontaneously closes his or her eyes. When the subject spontaneously closes his or her eyes, we will then continue the infusion for 90 minutes.

Overview of Study procedures:

1) Pre-screening over the phone:
    a) Pre-screening questionnaire
        i) Note: the results of the pre-screening questionnaire are for the purposes of determining whether someone can participate in the study. This form will be destroyed immediately upon completion.
        ii) *This pre-screening questionnaire also encompasses the COVID-19 questionnaire
2) Visit 1 (1 hour-1.5 hours):
    a) Consent form, contact information collected
    b) Otoscope exam and/or Etymotic Home Hearing Test
    c) ECG Screening (via Kardia Mobile or 12-lead), vital signs
    d) Instructed to start sleep log
    e) Instructed on actigraph, given actigraph, signs actigraph responsibility form
    f) Given the “Fasting Instructions” sheet to take home with them
    g) Working memory task (defined below)
    h) Subjects will be instructed that they cannot ingest caffeine, alcohol, or other sleep altering drugs for 48 hours before visit 2
3) Prior to Visit 2:
    a) COVID-19 questionnaire
    b) Subject may be asked to provide information included on their Sleep Log prior to coming in for visit 2

Visit 2 - no food after 7 AM, only water or sugared water to drink until 1 PM:

    c) Anesthetic in-person focused history (use of the Anesthesia Preoperative Evaluation Form) and physical exam including ECG (if 12-lead ECG not taken during Visit 1) and vital signs
    d) Collect and review actigraph and sleep log data
    e) Urine drug screen and pregnancy test
    f) Application of electroencephalography (EEG)

g) Perceptual learning paradigm pretest, training, first perceptual learning post-test
h) Study questionnaires: Language Experience Questionnaire, Demographics, Sleep Questionnaire
i) Second perceptual learning post-test
j) Application of polysomnography (PSG) sensors
k) 3 PM anesthesia administration with recording of EEG and PSG. Recovery from anesthesia monitored by anesthesiologist. No longer NPO when subject has recovered (~5-5:30 PM)
l) 5-5:30PM: third perceptual learning post-test
m) 9 PM (delay is to reduce sleep inertia), subjects come back to the study: Final (fourth) perceptual learning post-test

4) 24 hr follow-up phone call: A member of the study team will call the subject 24 hours after visit 2, to make sure they are fully recovered. This call should take about 10 minutes to complete. Once the phone call has been completed, the subject's participation in this study will end.

Otoscope Exam

To determine eligibility (ability to hear the perceptual learning test), study personnel (not necessarily the anesthesiologist) will use an otoscope to inspect each participants' ear canals. The otoscope examination will allow the researcher to see if the ear canal is obstructed by wax or if the tympanic membrane is damaged, which can affect hearing or make the wearing of insertable earphones uncomfortable. In the consent form as well as before doing the inspection, study personnel will tell the participant that his or her ears will be inspected to see if they meet the requirements to participate in the current study. The participant will be informed that during the examination of each ear, the ear will be pulled back to straighten out the ear canal, then the researcher will look inside their ear canal using an otoscope that has been cleaned with an alcohol swab. If the participant does not pass visual inspection, the participant will be simply informed that he/she does not meet our criteria for the current experiment, and be compensated for the amount of time they spent up until that point in the experiment.

Working Memory Task

Subjects will participate in an auditory working memory assessment, titled 'The auditory n-back'. The auditory n-back task requires participants to actively monitor a string of spoken letters, pressing a button labeled ''Target'' if the currently spoken letter matches the letter presented n trials previously, and pressing a button labeled ''Not Target'' if the currently spoken letter does not match the letter presented n trials previously. This task takes approximately 15 minutes.

Anesthesia sedation

Subjects will be asked to not have anything to eat or drink for 8 hours prior to sedation except for water up to 2 hours prior to sedation. All anesthesia sedation procedures will be conducted by an anesthesiologist who is credentialed by the University of Chicago, with a second anesthesiologist who is also credentialed by the University of Chicago available. An intravenous line (IV) will be inserted into a vein in the subject's arm and an arterial line will be inserted into an artery in the patient's wrist. A small needle will be used to inject lidocaine at the insertion sites prior to line insertion. After IV insertion, standard anesthesia sedation monitoring will be used (telemetry, SaO2, arterial line blood pressure, end-

tidal CO2) with the subject continuously monitored as they would be for any anesthetic. Fluids will also be given as needed via the IV. Before starting the anesthesia sedation, the subject will be provided with oxygen via a nasal cannula and/or face mask. The subject will be given an IV anesthetic, dexmedetomidine, which induces unconsciousness. The dose of dexmedetomidine will be a 0.5 mcg/kg bolus and an infusion of 0.5-0.7 mcg/kg/hr, titrated up by 0.1 mcg every 1 minute until the subject spontaneously closes his or her eyes (if not needed to achieve subject eye closing and/or sleep spindles, will omit bolus). Within a few minutes, the subject will become sedated. We expect that during dexmedetomidine administration that a proportion of subjects will have bradycardia and/or hypotension. In a study done by the manufacturer for patients undergoing procedural sedation, which is similar to the level of sedation we are using in this study, 54% of subjects experienced hypotension and 14% experienced bradycardia. These are expected issues commonly treated addressed by anesthesiologists and we will address them if they occur following the as the standard of care by giving a vagolitic or vasopressor agent, as appropriate. Administration of these vagolytics and vasopressors as deemed appropriate by the anesthesiologists will not disqualify the subject from participating in the remainder of the study.

The subject will be breathing spontaneously, and if needed, breathing will be assisted per our usual anesthesia protocols. If an unexpected breathing problem occurs, there is a procedure that we follow to solve any problems (called the American Society for Anesthesiologists difficult airway algorithm). This is a plan used in all operating rooms in case of problems.

Also per our usual anesthesia protocols, during the period of anesthesia sedation and recovery, we will make sure that the subject's blood pressure remains stable. If the blood pressure falls, we will first give IV fluids to replace the fluid deficit. If that is not sufficient to raise the subject's blood pressure, we will reduce the concentration of anesthetic. Medicines to raise blood pressure will be available. If the subject's blood pressure does not respond as expected to the medicines to raise the blood pressure, we will stop the study drug and allow the subject to recover fully, and dismiss the subject from participating in the last perceptual learning test.

An anesthesiologist will be present during the entire period of anesthesia sedation and a second anesthesiologist will be available.

We will measure the time between stopping the anesthesia sedation and the subject's awakening. We will record the time until the subject's eyes open and until they can respond to a command to grip the hand of the anesthesiologist. The subject will be under the care of an anesthesiologist until they meet the standard discharge criteria in our post anesthesia care unit in our hospital following ambulatory surgery. The subject will be awake and alert with stable vital signs. The subject will be able to drink clear liquid, go to the bathroom by themselves and walk easily before they are discharged from the anesthesia portion of the study. The volunteer must have stable vital signs, i.e., within 20% of pre-study values, be able to respond appropriately to normal commands, be pain free, be free from any nausea and vomiting. Volunteers will be advised not to drive, operate heavy equipment, or make important decisions for 24 hours. We will verify that subjects are transported home by another individual in the following way: If the subject arranges for someone to pick them up after the experimental session, we will require that they provide us with their name and contact information and we will call to confirm. Alternatively, they may take an Uber/Lyft or other ride share service. A member of the study team will escort subjects out of the DCAM building at the end of Visit 2. A hospital staff member or campus security may additionally accompany the study team member and the subject to the car, for the safety of the researcher.

Devices

Actigraph watch: Participants may be asked to wear actigraph watches for up to 7 (may be several days longer depending on scheduling of Visit 1 and 2) days leading up to the experiment and fill out a sleep log. Actigraph watches are similar to the popular industry-standard activity monitors such as the FITbit. It measures continuous physical activity and sleep/wake information. This information is used to know if people display typical levels of activity and sleep levels which could influence the impact of sleep on learning, and will be used to make sure that subjects can proceed in the study.

EEG: We will use a BrainVision EEG system for research purposes only, not medical purposes. Per the manufacturer (BrainVision) "our products are scientific equipment for research use only ("Investigational Devices for Research Use Only", FDA 801.1)". A 64 electrode EEG cap will be applied to the subject's head which uses water-soluble electrode gel/paste. The collection of electrophysiology data using electroencephalography (EEG) is noninvasive (nothing will be inserted or injected into the body) and is accomplished with a sensor cap placed around the head. EEG allows us to measure the change in voltage on the scalp. Participants will be asked to remove any clothing, jewelry, hairpins, eyeglasses, or other metal objects that may interfere with the test. EEG may be recorded as the participant sits quietly for 5 to 10 minutes (resting EEG activity), and/or while they engage in the behavioral tasks.

The active (up to) 64 gel/paste EEG system: EEG electrodes will be attached to the skin. Most of the electrodes will be mounted in a cap, which is fitted over the head and held in place with elastic straps near the chin. Some additional electrodes will also be placed next to the eyes, on the forehead, or behind the ears, and are held in place with adhesive collars or gel with adhesive tape. The electrodes are high quality active Ag/AgCl sensors with integrated noise subtraction circuits. The electrodes are enclosed in a plastic shell, and they won't directly contact the skin; electrical contact between the skin and the electrodes is achieved via a water-soluble electrode gel. For electrode locations on hairless skin (e.g., lateral to the eyes or on the forehead), the first step is to rub the skin with an alcohol pad to remove oils and some of the dead skin cells that lie on the surface of the skin to ensure a good signal. For electrode sites in the hair, the electrodes will be mounted in an elastic cap, and this cap will be placed on the head. Each electrode has a small hole (approximately 1.5 mm) that can be used to reach the underlying skin. Participants will wear a net containing 64 sensors, which will be positioned on their scalp, while they sleep. The electrodes are held in place with an adjustable cloth cap that is fastened below their chin. After the cap is placed around their head, we will use q-tips to degrease the areas of the scalp where electrodes will be placed by inserting the q-tip into each cap hole and rubbing gently. After this, the electrodes will be snapped into place in each of the labeled electrode holders of the cap. The electrodes will be filled with an electrode gel or paste in order to increase the conductivity of the sensors. The water-soluble electrode gel is inserted through these small electrode holes. In the event that a good signal is not achieved, we will use the standard EEG abrading method of passing a blunt sterile needle into the electrode slot and gently rub across the surface of the skin (never poking the skin). The purpose is to remove some of the dead skin cells that lie at the surface of the skin. A very slight amount of force is needed when abrading, with previous participants typically reporting that they can just barely feel the contact made with their skin. This gel or paste will get into their hair, but it will not affect its color (even if the participant has bleached or colored hair). The gel will wash off on all areas of their skin and hair with the use of warm, soapy water. The cap is designed to offer minimal discomfort while being worn and will conform to the contours of your scalp.

Before the cap is taken off after the nap portion of the study, the participant may be asked to have pictures taken of them while wearing the electrode cap; these pictures will only be used to find the three-dimensional coordinates of the electrodes as they conform to the participant's scalp. The pictures will be kept on a password protected laboratory computer. Once the picture is taken, the cap will be removed by pulling the cap away from their face. After the cap is removed, we will work to remove a large portion of the gel/paste with some combination of isopropyl alcohol, lukewarm water, and baby shampoo.

Physiologic Sensors and polysomnography (PSG): This may consist of peripheral non-invasive sensors which will collect information about muscle movements, breathing, and pulse. To better process sleep data, we may also record physiological measures from participants using electrodes/sensors that collect electromyogram (EMG) data from muscles, electrocardiogram data, respiratory rate/effort, blood-oxygen levels, body position, and body temperature. These sensors are attached to the face, chest and legs. Additionally, belts around the chest and waist are used to monitor breathing. The air going in and out of the subject's nose will be monitored with sensors that will go slightly into the subject's nostrils (nasal cannula).

Perceptual Learning Protocol

The perceptual learning tasks will be completed with insert earphones, which are foam inserts placed inside the participant's ear canal, similar to ear plugs or over-the-ear headphones.

This study will use a pretest/multiple posttest design—subjects are tested in the morning (Fenn et al., 2003 shows no circadian effects) for word recognition on hard-to-understand speech, then trained on this speech (never hearing the same words twice) which produces about 20 percentage points of improvement. During the morning, afternoon and evening post-tests, subjects will be tested on new spoken words. This design is comparable to previously published studies in the lab (e.g., Fenn et al., 2003). We will compare the results to what we have already seen in normal naps without anesthesia (previous study conducted by members of the lab; Uddin, Fenn, & Nusbaum, under review). This will help us see if sleep spindles on EEG or a state of unconsciousness are sufficient for perceptual memory consolidation.

Words will be taken from previously used word lists found in the literature (e.g. IEEE Subcommittee on Subjective Measurements, 1969), using IEEE recommended practices for speech quality measurements (IEEE Trans. Audio Electroacoust. 17 227–246). Words used can be found in the document titled "Perceptual Learning Stimuli (Words) File Names" in Section 8.1 Supporting Documents. These stimuli (words) will either be synthesized (similar to Siri on a phone). All stimuli will be played at a comfortable listening volume (between 60 and 75dB).

The training, pre-test and post-tests are similarly formatted, however, the training and each test will use a different series of synthetically generated words. For training, subjects will hear a word, be asked to type the word, and then receive auditory and visual feedback of the correct response. There are 100 trials within the training portion of the experiment. During each test, subjects will hear a word and be asked to type what they perceive the word to be (50 words in each test).

V. Biostatistical analysis

Our primary endpoint for this pilot study is whether there is evidence of perceptual learning under dexmedetomidine similar to that which occurs after a normal nap.

Sleep data will also be scored abiding by American Academy of Sleep Medicine (AASM) criteria (Berry et al., 2018) and spindle density, frequency, amplitude, and duration on EEG will be quantified.

These measurements will be analyzed to test the role of sleep spindle morphology in consolidation of perceptual learning.

Description of Analyses for IRB19-1442

Past research has demonstrated that sleep has both a restorative and protective effect on the retention of recently learned information and skills. Fenn, Nusbaum & Margoliash (2003), in particular, demonstrates that after the acquisition of a novel perceptual skill, task performance deteriorates over time until sleep occurs, after which performance jumps back to post-training levels and stays there. We use a very similar testing paradigm to Fenn et al. and additional currently unpublished work that has been performed in Dr. Nusbaum's lab, i.e. test, training, re-test, break, re-test, sleep, re-test, break, re-test. Using a five-level ANOVA or a comparable non-parametric or Bayesian statistical method, we will compare performance across tests; if, similar to sleeping subjects from prior research, dexmedetomidine has a protective effect on recently learned information and cognitive skills, performance should be restored after sedation for immediate post-test (after sleep) and be protected against loss after a break from study activities (final post-test at 9PM).

To better understand the neurophysiological basis of learning consolidation while sleeping and under anesthetic drugs, we record EEG during the perceptual learning tests, training period, and during anesthetic sedation. An established result from the literature on sleep consolidation is that the number of sleep-specific brain oscillations (spindles, K-complexes, slow waves) that occur during sleep, as well as time spent in specific sleep stages as defined by the AASM standards, predict the consolidation of learning (e.g., Ruch et al., 2012; Rasch & Born, 2013). If the basis of consolidation under anesthetic drugs is similar to that of natural sleep, we expect that these same qualities (spindles, K-complexes, slow waves, "sleep" stage durations) will predict the difference in performance between the test preceding administration of the anesthetic and those following the administration of the anesthetic, which we will assess using a multivariate regression analysis using those quantitative and qualitative aspects of sleep as predictors.

The subjects' ability to learn a new skill, such as our perceptual learning protocol, is affected by the recent sleep history of the subject (Dijk, Hayes, & Czeisler, 1993), therefore it is necessary to control for recent sleep history as a potential confound in our results. Thus, the regression analysis mentioned above also must include sleep biometrics collected via an ActiWatch. For example, total sleep time per night, as measured by the ActiWatch, will likely be included as a predictor in our analysis. Additionally, working memory capacity is known to predict the efficacy of natural sleep in producing a consolidation effect (Fenn & Hambrick, 2012), and also directly affects performance in learning tasks (Van Hedger, Heald, Koch, & Nusbaum, 2015). Thus, working memory capacity, as measured by an "n-back," a common cognitive task (Jacola et al., 2014), will also be included as a predictor in our regression analysis.

EEG measured during testing and training will be compared between tests using an event-related potential (ERP) analysis (Luck & Kappenman, 2011). Recent findings by Heald et al. (in review) have demonstrated that changes in early sensory responses (specifically the amplitudes of the electrical responses at 100 ms and 200 ms following the onset of an acoustic stimulus) occur following training in the same perceptual skill we are measuring in this study, suggesting that this sort of learning is supported by short-term plasticity in sensory systems. Sleep consolidation is thought to preserve plastic changes in

neural connectivity that are relevant to consolidated information (Tononi & Cirelli, 2014); it is therefore of interest whether ERP changes between pre-training and post-training tests are preserved after the anesthetic intervention; thus, we will mimic the ERP analysis of Heald et al. (in review) to gain a holistic understanding of consolidation effects (or the lack thereof) under dexmedetomidine.

The collection of EEG (including sleep; during Visit 2) data is done using BrainVision software (Pycorder and Recorder). These files are then imported into Python to be preprocessed (filtered, corrected for artifacts, baseline corrected, interpolating bad electrodes) and analyzed. Sleep will be scored abiding by American Academy of Sleep Medicine guidelines (Berry et al.). The collection of the behavioral perceptual learning data (during Visit 2) is collected using MATLAB, and will also be imported into Python and/or R and analyzed using Python and/or R. N-back data is collected using E-prime (during Visit 1), and will be imported into Python and/or R and analyzed using Python and/or R. Actiwatch data is collected by the Actiwatch itself (during the week prior to the subject coming in for Visit 2), is downloaded using the lab's ActiLife desktop application (at Visit 2), and is later imported into Python as well for analysis.

VI. Risk and Discomfort

Dexmedetomidine: The risks involved in the administration of dexmedetomidine include nausea, xerostomia, atrial fibrillation, and transient hypertension during drug loading. The significant risks involved are directly related to a drug induced reduction in sympathetic activity, resulting in hypotension and bradycardia. Rare case reports of sinus arrest in instances of rapid drug administration and in subjects with a high resting vagal tone have also been described. Drug discontinuation, dose reduction, or the use of vasoactive substances causes a return of these hemodynamic parameters to baseline. As such, hemodynamic parameters will be continuously monitored in study volunteers during drug administration and standard recovery to ensure that appropriate medical intervention will be instituted for any clinically significant hypotensive or bradycardic episodes.

Polysomnography and electroencephalography risks: Electrodes and adhesives may cause temporary redness on the sites where they are located.

Psychological testing risks: As this can be a fairly long study, you may experience some boredom.

Intravenous line risks: Pain at the needle insertion site, infection, tissue injury, and bleeding.

Arterial Line risks: The most concerning risk is a <0.01% of permanent ischemic injury with placement of an arterial catheter in the radial artery. The risk factors that have been identified in the medical literature include high severity of illness (American Society of Anesthesiologists IV and greater), low cardiac output, use of vasopressor therapy, prolonged duration of catheter placement (greater than 4 days), large catheter size, multiple punctures for catheter insertion, predisposing comorbidities (i.e. peripheral vascular disease), diabetes. The study volunteers we will enroll are healthy ASA I/II and by definition are without any of these comorbid conditions. Other risks include pain at the needle insertion site, infection, bleeding, tissue injury, AND arterial thrombosis (blood clots).

VII. Potential Benefits

There are no direct benefits to the individual volunteers involved in this study. The potential benefits of this study to society are a clearer understanding of the extent to which dexmedetomidine affects perceptual learning and sleep architecture in healthy volunteers. If successful, this study may

eventually lead to an expanded use of dexmedetomidine in medical disorders in which impaired perceptual learning occurs.

VIII. Monitoring and Quality Assurance

During anesthesia sedation, all blood pressure, heart rate, oxygen saturation, electrocardiography, and capnography data will be visualized in real time for safe monitoring by the anesthesiologist who is credentialled by the hospital. These data will also be stored for later off-line analysis. Unanticipated problems involving risks to volunteers or others, including adverse events will be reported to the IRB in accordance with IRB unanticipated problems reporting guidelines.

Serious Adverse Events (SAEs)

Expedited review will occur for all events meeting the FDA definition of SAEs – i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization. This also includes any event that a study investigator judges to impose a significant hazard, contraindication, side effect, or precaution. For purposes of this study, all SAEs are required to be reported to the IRB, regardless of any judgment of their relatedness to the study drug. All relevant information will be reported to the IRB for each SAE including information about the event and its outcome, dosing history of all study drugs, concomitant medications, the volunteer's medical history and current conditions, and all relevant laboratory data. Notification by e-mail of all related study forms shall be made to the IRB within 2 days of the occurrence of any SAE. Information will be reviewed and a determination made of whether there was any possible relevance to the study drug. Additional reporting to the IRB will be done within 24 hours of the SAE.

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