Study on the use of broadband sounds (pink noise) to mitigate sleep disruption due to aircraft noise

Principal Investigator: Mathias Basner, MD, PhD, MSc
Department of Psychiatry/Unit for Experimental Psychiatry
1019 Blockley Hall, 423 Guardian Drive
Philadelphia, PA 19104-6021
215-573-5866
basner@pennmedicine.upenn.edu

Funding Sponsor: Federal Aviation Administration

800 Independence Ave SW
Washington, DC 20591
202-267-7211

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Background and Study Rationale

1 Introduction

This document is a research protocol. This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including the following regulations as they apply 45 CFR 46, 21 CRF Parts 50, 54, 56. All episodes of noncompliance will be documented.

The Federal Aviation Administration (FAA) is interested in how aircraft noise at night affects the sleep and health of residents living in the vicinity of airports, and how any negative effects can be mitigated. The goal of this project is to investigate the effects of different kinds of aviation noise (AN) on sleep under controlled laboratory conditions, and to investigate whether some of the sleep disturbing effects can be mitigated by introducing a type of broadband noise (BN) known as pink noise into the bedroom or by wearing earplugs (EP). The sleep of 24 subjects will be monitored with polysomnography, actigraphy and ECG over 7 nights. Subjects will fill out surveys, and perform cognitive, driving simulation and hearing tests in the evening before bed and in the morning after waking up. Blood will be drawn each morning to identify changes in gene expression induced by the experimental conditions. Subjects will be investigated in groups of 4 in the Chronobiology Isolation Laboratory (CIL) in the Hospital of the University of Pennsylvania. This newly constructed facility includes 4 acoustically isolated bedrooms and a high-fidelity sound system.

1.1 Background and Relevant Literature

Undisturbed sleep of sufficient duration and quality is of paramount importance for recuperation and health.[1] Aircraft noise has been shown to disturb sleep and be associated with long-term health consequences like cardiovascular disease.[2,3] While sound insulation can lower noise levels in the bedroom, it is expensive and only residents living close to the airport are eligible for compensation for sound insulation. Furthermore, residents often fail to close windows during the night to increase ventilation and decrease bedroom temperatures, which renders the sound insulation measures ineffective. Therefore, the identification of inexpensive and effective interventions to reduce the adverse effects of aviation noise on sleep is warranted.

Broadband noise (BN) is a promising and inexpensive intervention that could help mitigate the negative effects of aviation noise on sleep for large parts of the population that are either ineligible for sound insulation or still suffering from aviation noise-induced sleep disturbance despite sound insulation. This study will be the first to investigate – using the gold standard measure of sleep, polysomnography – the effectiveness of BN in mitigating the sleep-disturbing effects of aviation noise. Machines and apps that produce BN (e.g., white noise) are very popular (>200 different sound masking apps exist that have been downloaded >10 million times), but according to our own systematic review of the literature[4] rigorous studies corroborating the sleep promoting effects of BN are missing. Also, as continuous BN exposure during the night could affect hearing, it will be important to assess temporary hearing threshold shifts after BN exposure nights.

This study will investigate whether BN promotes or disturbs sleep in an otherwise noise-free environment and whether BN played back at two different sound levels mitigates the negative effects of aviation noise on sleep. Furthermore, this study will evaluate the effectiveness of earplugs, an inexpensive method to reduce perceived noise levels, as a countermeasure to aviation noise. To date, earplugs have been mostly studied as noise countermeasures in intensive care units; one study[5] in 40 participants investigated the effects of earplugs and eye masks in a simulated ICU environments (noise and light) and found sleep protective effects of this combined intervention. To our knowledge, no study has investigated the effectiveness of earplugs on mitigating aviation noise effects on sleep.

In addition to jet engine noise, we plan to investigate noise from new aviation noise sources that are either under-studied (i.e., helicopter noise) or emerging as important new noise sources (i.e., noise from drones and low sonic booms). This project will thus help assessing the relative impact of these under-studied and new aviation noise sources relative to jet engine noise. We will also play back an alarm sound and the sound of a baby crying, as one of the negative consequences of broadband noise and earplugs may be that these important events are missed.

2 Study Objectives

The overall objective of this study is to investigate how different kinds of aviation noise affect polysomnographically assessed sleep, whether these effects can be mitigated by BN exposure at two different intensities or by earplugs, whether these countermeasures affect the perception of relevant sounds (i.e., alarm, baby crying), and whether the different kinds of aviation noise differ in their sleep disturbing properties. The study will also investigate how any aviation noise-induced sleep disturbance affects next day performance, hearing thresholds, gene expression and self-reported well-being (see 3.4).

2.1 Primary Objective

The primary objective of this study is to investigate whether BN exposure at two intensities or wearing earplugs mitigates the negative consequences of aviation noise on sleep.

2.2 Secondary Objectives (if applicable)

- To investigate the effects of the different noise conditions (see 3.1) on next day cognitive and driving simulator performance, gene expression in the blood, hearing thresholds, and subjective well-being.
- To investigate in an event-related analysis whether the different sources of aviation noise (e.g., jet engine, helicopter, drone, low sonic boom), at the same maximum sound pressure levels, differ in their potential to arouse subjects from sleep, and whether BN and EP differ in their potential to mitigate the arousing effects of the different kinds of aviation noise on sleep.
- To investigate to what degree BN and EP prevent arousal to meaningful sounds like alarms or a crying baby.

3 Investigational Plan

3.1 General Design

Subjects will be screened in two screening sessions to determine study eligibility prior to participating in the in lab protocol. The sleep of 24 subjects will be monitored with polysomnography over 7 consecutive nights in groups of 4 where the entire group has been randomly assigned to 1 of 6 noise exposure condition patterns.

After an adaptation night, subjects will be exposed to:

1. Control night without any noise exposure and without earplugs (CTRL);
2. Aviation noise only (AN);
3. Broadband (pink) noise 50 dBA only (BN50);
4. Aviation noise plus earplugs (AN+EP);
5. Aviation noise plus broadband (pink) noise 40 dBA (AN+BN40);
6. Aviation noise plus broadband (pink) noise 50 dBA (AN+BN50).

We will investigate participants in 6 groups of 4 subjects each (we also plan for a reserve 7th study run to account for study drop-outs). Each group will be exposed to the same condition in each study night. Each subject will receive each exposure– in a randomized and balanced fashion – according to the randomization table in 3.2.

Noise Exposure
The AN nights will consist of up to 120 noise events with maximum sound pressure levels $L_{AS,max}$ of 45, 50, 55, 60 and 65 dB, including noise from jet engine aircraft, helicopters, drones, and low sonic booms. The jet engine noise events will be identical to events used in a prior study at the German Aerospace Center (DLR) and another study on broadband sounds on sleep performed by collaborator Dr. Michal Smith in Sweden, which allows for a direct comparison to these studies. We will choose a few events within each dB category and repeatedly play those back. Due to the limited sample size, playing every event back only once would not provide us with enough data for averaging. We will also include an alarm sound and/or sound of a baby crying, as a potential caveat of using EP/BN is that meaningful sounds may be missed. The sequence and spacing of noise events will be identical within a study group but different across study groups. Noise scenarios will be pre-programed. They will be started at the next full minute after lights out. Planned lights out is 11 pm and planned lights on is 7 am (i.e., 8 hour sleep opportunity).

Evening and Morning Procedures
Subjects will arrive in the lab around 8 pm in the evening and they will be able to leave the lab around 9 am in the morning (by 10 am at the latest). As our noise exposures can affect sleep and impair recuperation to some degree, participants will be informed in the consent form that they should not operate heavy machinery during the study. We will also offer a cab for those who would otherwise use a car to come to the lab. We will provide snacks in the evening and a light breakfast in the morning. Subjects can shower in the morning (after all tests) if they wish.
In the evening (before bed) and in the morning (after waking up), subjects will do the following:

(1) Blood draw (for gene expression analyses to be performed by the FAA Civil Aerospace Medical Institute (CAMI); morning only).
(2) Fill out surveys that ask about sleepiness, mood states, the previous day or the previous night;
(3) Cognition test battery (10 cognitive tests);
(4) Driving simulator task;
(5) Hearing test;
(6) Blood pressure measurement; and
(7) Resting ECG measurement.

3.2 Allocation to Interventional Group

We will investigate participants in 6 groups of 4 subjects each. Each subject of a group will be exposed to the same condition in each study night, and each subject will receive each exposure– in a randomized and balanced fashion – according to the randomization table below.

Group	Night 1	Night 2	Night 3	Night 4	Night 5	Night 6	Night 7
1	Adaptation	A	B	C	D	E	F
2	Adaptation	B	D	A	F	C	E
3	Adaptation	C	A	E	B	F	D
4	Adaptation	D	F	B	E	A	C
5	Adaptation	E	C	F	A	D	B
6	Adaptation	F	E	D	C	B	A

Please note that in this randomization paradigm, each exposure appears in each position exactly once, and is preceded by each other exposure exactly once. The letters A-F will be randomly assigned to the exposure conditions 1-6 listed in 3.1 above by the principal investigator using a random number generator. Study participants and staff will be blinded to the condition of each night. Staff will only be unblinded after the start of the measurements each night (i.e., after subjects went to bed) so that the correct playback of the conditions can be monitored.

3.3 Study Measures

During the **telephone screening** session, the following surveys will be completed on sleep disorders for eligibility assessment:

1. Cambridge-Hopkins Restless Leg Syndrome Questionnaire;
2. Insomnia_Severity Index;
3. STOP BANG Questionnaire as a measure of sleep apnea.

During the two **in-office screening** sessions, the following measures will be completed:

Surveys

1. Epworth Sleepiness Scale as a measure of fatigue;
2. SF36-Health Survey as a measure of general health;
3. Positive and Negative Affect Schedule (PANAS) as a measure of affect.
4. Profile of Mood States Short Form (POMS-SF) as a measure of mood states.
5. Beck Depression Inventory (BDI-II) as a measure of depression.
6. Beck Anxiety Inventory (BAI) as a measure of anxiety.
7. Horne-Ostberg Morningness-Eveningness Questionnaire;
8. Karolinska Sleepiness Scale; and
9. Pittsburgh Sleep Quality Index as a measure of quality and patterns of sleep.

Survey Information

The Cambridge-Hopkins Questionnaire (CH-RLSq) (Allen & Burchell, 2008) is a diagnostic self-report tool of 13 questions used to ascertain restless leg syndrome (RLS) and to exclude similar conditions that mimic RLS such as leg cramps. Subjects will complete this once, during the telephone screening, in order to determine initial eligibility by ruling out exclusionary criteria of sleep disorders.

The Insomnia Severity Index (ISI) (Morin, 1993) is a set of 7 questions using a range of 0-4. Scores between 15-21 suggest moderate clinical insomnia, while scores >21 suggest severe cases. Subjects will complete this once, during the telephone screening, in order to determine initial eligibility by ruling out exclusionary criteria of sleep disorders.

The STOP BANG Questionnaire (Chung, 2008) is used to measure risk of sleep apnea. The 8 Yes/No questions ask about snoring, daytime sleepiness, obstructive breathing, blood pressure, BMI, age, neck circumference and gender. Scores of 3-4 suggest intermediate risk of Obstructive Sleep Apnea, while scores in the 5-8 range suggest high risk of OSA. Subjects will complete this once, during the telephone screening, in order to determine initial eligibility by ruling out exclusionary criteria of sleep disorders.

The Epworth Sleepiness Scale (ESS) (Johns, 1991) is a measure of fatigue by asking likelihood of dozing in 8 different situations. Responses range from 0 [no chance of dozing] to 3 [high chance of dozing] for each prompt. Scores between 10-15 suggest excessive sleepiness, and over >15 that may require medical attention. Subjects will complete this once, at the first in-person screening, to rule out excessive tiredness that may interfere with their ability to maintain the requirement of limited daytime naps during the study.

The Short Form Health Survey (SF-36) (Ware et al., 1993) is a 36-item self-report measure used as an indicator of general wellness. An algorithm is used to assign values to each response, generating a mental health score and a physical health score. Subjects will complete this once, at the first in-person screening, to determine their fitness to proceed with the study.
The Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) lists a set of 20 emotions and moods, and asks how often the subject experienced each in the past week. An algorithm is used to generate Positive and Negative Affect Scores, where higher scores represent higher levels of the respective affects. Subjects will complete this during their in-person screening to establish baseline scores and again twice daily as part of their morning and evening surveys during the in-lab study to see the effects of the interventions.

The Profile of Mood States (POMS-SF) (Shacham, 1983) asks to what extent subjects are experiencing each of 37 emotions, moods or affects at that moment. Responses are scored using an algorithm, resulting in 6 sub-scores, with 4 representing negative affect: Tension, Anger, Fatigue, Depression and Confusion, and 2 representing positive affect: Esteem-Related Affect and Vigor. A Total Mood Disturbance score is then generated by summing the negative sub-scores and subtracting the positive sub-scores. Subjects will complete this during their in-person screening to establish baseline scores and again twice daily as part of their morning and evening surveys during the in-lab study to see the effects of the interventions.

The Beck Depression Inventory (BDI-II) (Beck, 1996) is a common self-report tool used to evaluate the severity of depression. Subjects respond to 21 questions related to clinical symptoms of depression using a scale of 0-3, where higher scores represent higher depression. Scores between 14-19 suggest mild depression, 20-28 moderate, and 29-63 severe. Subjects will complete this during their in-person screening.

The Beck Anxiety Inventory (BAI) (Steer & Beck, 1996) asks how often a subject has experienced 21 symptoms associated with anxiety in the past month on a scale of 0 to 3, with higher scores representing more often occurrences. Responses are summed, with scores of 22-35 suggesting moderate anxiety and scores 36-63 suggesting severe anxiety. Subjects will complete this during their in-person screening.

The Morningness-Eveningness Questionnaire (MEQ) (Horne & Östberg, 1976) asks 19 questions about daily sleep-wake activities and time preferences in order to assess a subject's circadian rhythm. Responses are assigned values, which are summed and used to indicate on a sliding scale whether a subject falls towards being an 'evening' type (scores of 16-30) or a 'morning' type (70-86). Subject will complete this once, at their first in-person screening, in order to establish their chronotype.

The Karolinska Sleepiness Scale (Åkerstedt & Gillberg, 1990) is one-question scale asking a subject to rate their current sleepiness. The scale is 1 to 9, with 1 labeled 'extremely alert', 5 as 'neither alert nor sleepy', and 9 as 'very sleepy, great effort keeping awake, fighting sleep'. Subjects will complete this at their first in-person screening and twice daily as part of their morning and evening surveys during the 7-night in-lab study for an acute tracking of subjective sleepiness.

The Pittsburgh Sleep Quality Index (PSQI) (Buysse, 1989) is a set of 19 questions to assess sleep quality and patterns over a given time period. It asks questions about bed time, wake time, sleep latency, use of sleep medication and how often certain occurrences have caused sleep disturbances and affected daytime activities in the past month. Subjects will complete this at their first in-person screening and once daily as part of their morning survey during the 7-night in-lab study to log their sleep quality during the noise interventions.

Subjects will receive a pulse oximeter during the first screening session. They will wear this device for one night. Subjects with multiple relevant dips in blood oxygen saturation will be ineligible to participate in the study due to suspected sleep apnea.

Subjects will also receive a wrist actiwatch that measures movement activity and provides information on sleep-wake activity. They will be instructed to wear it 24/7 and only take it off during showers/swimming or while doing contact sports. Additionally, subjects will fill out a sleep log every morning (online if possible). Subjects will start wearing the actiwatch and filling out the sleep log after first screening and continue until the end of the in-lab study or until ineligibility is determined.

We will also perform a hearing test (see below) during first screening. Subjects will be familiarized with the driving simulator in the first screening and the cognitive tests during the second screening session.

During the **7-night in-lab portion** of the study, the following measures will be performed:

Sleep Measurements
Subjects' sleep will be measured polysomnographically (PSG) with the Prodigy system, which includes frontal electroencephalogram (EEG) electrodes, an electrooculogram (EOG) and a submental electromyogram (EMG). Data will be transmitted wirelessly to a bedside tablet. The tablet will also record sound pressure levels that will help synchronize PSG and acoustic data. Subjects will also wear a Bittium Faros device that measures the ECG (1 kHz) and body movements (25 Hz).

Cognitive Tests
Subjects will perform the Cognition test battery[6] each evening and morning of the study on a laptop computer. Cognition consists of 10 cognitive tests that cover a range of cognitive domains (including sensory-motor speed, memory, abstraction, emotion recognition, risk decision making and vigilant attention). The battery is preceded by a brief alertness and mood survey as a measure of, among others, mental fatigue, tiredness, physical exhaustion, level of stress, sleep quality, and sleepiness. It takes approximately 20 minutes to complete the survey and the cognitive tests.
Subjects will also perform a 15-minute driving simulator task (STISIM Drive M300WS) each evening and morning of the study. Subjects are not required to have a valid driver's license for this study, and those without a license will still be asked to complete the driving simulation task, with the understanding that they may be less familiar with driving procedures.

Hearing Test
We will perform a pure-tone audiometry using the Békésy technique preceded by a tympanometry during the first screening session as well as each evening and morning of the study. We will administer the test with a headphone system.

Blood Tests
During the first in-person screening, we will draw blood and urine in the Center for Human Phenomic Science (CHPS) to determine the presence of HIV antibodies and other active infections, such as the cold or flu virus (from blood), and current use of stimulant or hypnotic (sleep promoting) drugs (from urine). We require an objective measure that subjects are free of these conditions or drugs before proceeding with the study. The HIV antibody test results are confidential, and if positive, the subject will be offered counseling about HIV infection from a physician on our research team.

We will also draw approximately 4.5 mL of blood in the morning after each of the 7 study nights (~2 mL into a vacutainer to clear the draw site, followed by 2.5 mL collected into a PAXgene® RNA tube). In accordance with the University of Pennsylvania's Human Research Protections Program's Maximum Allowable Blood Draw Volumes, no more than 3% of total blood volume may be collected in a 24-hour period or 5% over a 30-day period. We anticipate drawing 40 mL of blood during the in-person screening and 4.5 mL of blood each morning of the 7-day study for a total of 71.5 mL, which is significantly under the 163 mL maximum allowable draw per day or 544 mL limit per month for a healthy, 150-lb adult.

The 2.5mL PAXgene blood samples will be sent to the FAA's Civil Aerospace Medical Institute (CAMI) for RNA analysis. The initial 2mL draw, which is necessary to collect per the PAXgene manufacturer's instructions in order to guarantee a clean sample and which would otherwise be discarded, will be stored in our -80°C freezers in HUP for later biomarker analysis by Penn. Samples will be deidentified (labeled only by subject ID and time of collection).

Blood Pressure Measurements
Before and after each sleep period, subjects will have three consecutive blood pressure measurements taken by trained study staff following a 5-minute rest period. As the BP measurements taken in-lab will be used for research purposes only, the values will be recorded under subjects' deidentified study IDs. BP values will not be entered into their electronic medical record (EMR) or otherwise associated with subjects' names or other identifiable information. Except in the emergency exceptions listed below, the data will be limited to research staff.

If the average blood pressure over the week is elevated (with a systolic BP above 120 or a diastolic BP above 80), the subject will be informed at the end of the study and provided with a record of the values so that they may follow up with their primary care physician. If a subject falls into the hypertensive category at any point throughout the course of the study (SBP above 140 or DBP above 90), study staff will consult the PI and/or physician of record. In the event that a subject enters hypo- or hypertensive crisis while in the study (SBP below 80 or above 180, or DBP above 120), study staff will take immediate action and transfer the subject to the emergency department.

AM and PM Surveys
Subjects will complete a survey once in the evening before bed and another in the morning before departure. These surveys include questions about sleep duration and quality, daytime activities outside of the lab (e.g. napping, exercise and caffeine intake), mood states, positive and negative affect, and other general questions about fatigue. It takes approximately 10 minutes to complete each survey, for a total of 20 minutes daily. The morning questionnaire involves the POMS, PANAS, Karolinska Sleepiness Scale (KSS), and parts of the Pittsburgh Sleep Quality Index (PSQI) that specifically address the quality of sleep during the preceding night. The evening questionnaire includes the POMS, PANAS and KSS.

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary endpoint of the study is time spent in slow wave sleep (SWS) plus time spent in rapid eye movement (REM) sleep during an 8-hour sleep opportunity (11 pm – 7 am).

3.4.2 Secondary Study Endpoints

We plan to investigate the following secondary endpoints in relation to the different noise exposure conditions.

Sleep-related secondary endpoints:

1. Time spent awake and in different sleep stages (N1, N2, N3, REM)
2. Sleep fragmentation, i.e. number of awakenings and EEG arousals per hour sleep
3. Latency to sleep stages N2, N3 and REM
4. Frequency, density and amplitude of sleep spindles, K-complexes and vertex sharp waves
5. Power-spectral density in alpha, beta, theta and delta frequency bands
6. Event-related analysis with the following endpoints
    a. Awakening
    b. EEG arousal
    c. Odds Ratio Product (ORP)[7,8]

Non-sleep-related secondary endpoints:

1. Cognition test battery performance
    a. One standard speed and one standard accuracy outcome for each of the 10 tests[9]
    b. Accuracy, speed and efficiency across cognitive domains
2. Driving simulator performance
    a. Standard deviation of lateral position (i.e., continuous location of a vehicle with respect to a lane reference)
    b. Standard deviation of speed
3. Hearing test
    a. Threshold shift in dB at the following frequencies: 500 Hz, 1,000 Hz, 2,000 Hz, 4,000 Hz, 6,000 Hz, and 8,000 Hz
4. Blood test
    a. Change in RNA expression levels

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

The study will last approximately four weeks, including 2 days of screening ~1-3 weeks prior to the in-lab phase (each session lasting approximately 4 hours), up to a 21-day at-home phase, and a 7-night period of staying in the laboratory overnight (during which time the participants will be able to leave during the day to resume normal activities).

4.2 Total Number of Subjects and Sites

The enrollment goal of the study is N=24 subjects with completed evaluable data. However, if a subject withdraws or is withdrawn from an in-laboratory study run, we will need an additional back-up run(s), each of up to n=4 individuals to account for the loss of data. Therefore, it is expected a total of N=28 subjects may begin the in-lab phase, thus allowing for completed evaluable data on up to ~n=27 subjects. Recruitment is expected to end when approximately 84 subjects have been screened. It is expected that approximately 84 subjects will need to be screened in order to enroll 24 evaluable subjects. The University of Pennsylvania is the only site enrolling participants for this research protocol.

4.3 Inclusion Criteria

Study inclusion criteria:

- Age between 21–50 years.
- Free of psychological/psychiatric conditions that preclude participation.
- BMI >18.5 and < 35.
- Self-reported regular sleep schedule; able to maintain their sleep schedule during the course of the study.
- Self-reported sleep duration of 6-8.5 h per night (verified by ambulatory sleep monitoring with wrist actigraphy and daily logs).
- Ability to read/write English.
- Fully vaccinated for or recovered from Covid-19

4.4 Exclusion Criteria

Study exclusion criteria:

- Subjects habitually use broadband noise to promote sleep at home.
- Hearing loss > 25 dB in any frequency band up to 8 kHz
- History of neurological, psychiatric, or other medical condition that excludes participation.
- Current mania or psychosis.
- Current depression as determined by the Beck Depression Inventory (Beck, 1996).
- Alcohol or drug abuse in the past year based upon history and urine toxicology screen.
- Excessive alcohol intake (≥ 21 drinks per week) or binge alcohol consumption (> 5 drinks per day).
- Excessive caffeine consumption (> 650mg/day combining all caffeinated drinks regularly absorbed during the day).
- Current smoker/tobacco user, or using nicotine replacement therapy. Those that have been nicotine-free for ≥ 30 days will be included.
- Body Mass Index ≤18.5 or ≥ 35.
- Acute, chronic, or debilitating medical conditions, major Axis I psychiatric illness based on history, physical exam, blood and urine chemistries, and CBC.
- Individuals who self-report a history of recurrent seizures or epilepsy or have a history of medical conditions that could increase the chance of seizures (e.g. stroke, aneurysm, brain surgery, structural brain lesion).

- Cardiovascular, neurological, gastrointestinal, or musculoskeletal problems that exclude participation.
- Major controlled or uncontrolled medical condition such as congestive heart failure, neuromuscular disease, renal failure, cancer, COPD, respiratory failure or insufficiency, cardiac arrhythmia, or patients requiring oxygen therapy (as determined by self-report).
- Currently working night, swing, split or rotating shift.
- Current use or use of within the past month of a prescription or over-the-counter sleep medication or stimulant; use of psychoactive medication (based on self-report and review with a study clinician).
- Pregnant or currently breast feeding. People that menstruate will have a pregnancy test performed via a urine sample during screening, as those that are currently pregnant are unable to participate in the study.
- Prior history or diagnosis of any sleep disorder including Obstructive Sleep Apnea (AHI ≥15 events/hour) – from ambulatory or in lab polysomnography; Restless legs syndrome or periodic limb movement disorder; Insomnia; Parasomnia; High Risk of OSA based on STOP-BANG Questionnaire ("yes" on at least 4 of 8 questions); High Risk of Restless Legs Syndrome (RLS) based on Cambridge-Hopkins Screening questionnaire; High Risk of Insomnia based on Insomnia Severity Index (score of 22 or higher)
- Individuals who self-report severe contact dermatitis or allergy to bandages, silicone, nickel or silver.
- Planned travel across more than one time zone after screening #1 and/or during the anticipated period of the study.

Habitual daytime napping.

4.5 Subject Recruitment

Subjects will be recruited via flyers and advertisements that may include, but are not limited to: print media, University and department websites, electronic message posting systems, internet posting websites, free internet advertising websites (e.g. Craigslist), and email message posting systems (e.g. the UPHS broadcast messaging system). Upon expressed interest in participation, all respondents will be initially screened via telephone. Following the telephone screening, participants will complete 2 in-person screening sessions.

4.6 Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

5 Study Procedures

Procedures/Measures/Questionnaires that will take place at each of the study visits.

Questionnaire	# of Items	Telephone Screening	Screening Sessions	In-Lab (1x pm; 1x am)
Epworth Sleepiness Scale (ESS)	8	x		
Insomnia Severity Index (ISI)	7	x		
Cambridge-Hopkins Questionnaire (CH-RLSq)	13	x		
STOP-BANG Questionnaire	7	x		
Informed Consent			x	
Blood and Urine Specimens (CHPS)			x	

Height & Weight (CHPS)			x	
History and Physical (H&P) (CHPS)			x	
ECG (CHPS)			x	
Vital signs (CHPS)			x	
Blood Pressure			x	x
Standardized Hearing Test			x	x
Health Survey Short Form (SF-36)	36		x	
Beck Anxiety Inventory (BAI)	21		x	
Beck Depression Inventory (BDI-II)	21		x	
Morningness/Eveningness Questionnaire (MEQ)	19		x	
Karolinska Sleepiness Scale (KSS)	9		x	x
Pittsburgh Sleep Quality Index (PSQI)	10		x	X
Positive and Negative Affect Schedule (PANAS)	20		x	x
Profile of Mood States (POMS) Short Form	37		x	x
Visual Analog Scales (VAS)	15			X
Cognition test battery	10		X	X
Driving simulator			X	X
Blood draw for RNA analyses (am only)				X
Polysomnography				X
Actigraphy			X	X
Sleep log			X	
ECG and body movement measurement				X
Pulse oximetry			x	
Morning Survey				X
Evening Survey				X

5.1 Screening

Potential participants who are interested in participating in the study will have the study explained to them and will be asked a series of questions by telephone to determine their initial eligibility. The **telephone screening** will include the following questionnaires to rule out potential sleep disorders:

a. The telephone screening questionnaires include the Cambridge-Hopkins Restless Legs Syndrome (Allen & Burchell, 2008), Insomnia Severity Index (Morin, 1993), and the STOP-BANG Questionnaire (Chung, 2008).

If they meet the inclusion/exclusion criteria, they will be scheduled for an individual screening session (screening session #1). If the participant meets inclusion/exclusion criteria from screening session #1, they will be scheduled for screening session #2. If the participant meets inclusion/exclusion criteria for both screening session #1 and #2, they will be enrolled in the study.

Screening session #1: The subjects will first attend an initial 4-hour laboratory session which includes the following:

a. Informed consent
b. Standard Hearing Test (pure-tone audiometry) and tympanometry
c. Questionnaires to ascertain health and medical history in order to determine study eligibility. The screening questionnaires include the Epworth Sleepiness Scale (Johns, 1991), Beck Depression Inventory (BDI-II) (Beck, 1996), the Health Survey Short Form (SF-36) (Ware et al., 1993), Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), Profile of Mood States Short Form (POMS-SF) (Shacham, 1983), Beck Anxiety Inventory (BAI) (Steer & Beck, 1996), Morningness-Eveningness Questionnaire (Horne & Östberg, 1976), Karolinska Sleepiness Scale (KSS) (Åkerstedt & Gillberg, 1990), and the Pittsburgh Sleep Quality Index (PSQI) (Buysse, 1989).
d. Confidential medical screen which includes a 10-hr fasting blood draw (approximately 40mL) and a urinalysis (approximately 9 mL). Blood and urine samples will be drawn in the Center for Human Phenomic Science (CHPS), which is located in the Hospital of the University of Pennsylvania and the Perelman Center for Advancement Medicine. These samples will be used for determining the presence of HIV antibodies and other active infections, such as a cold or flu virus (from blood), and current use of stimulant or hypnotic drugs (from urine).
e. In addition, a History and Physical (H&P), vital signs, height and weight, and a cardiac screening (EKG) will be performed at CHPS during either screen #1 or screen #2, subject to CHPS nurse practitioner availability (however, the drug screen will always be performed on screen #1).
f. Subjects will complete a test drive on the driving simulator to check for signs of motion sickness, as those who are unable to complete the task for physical reasons will not be eligible for the in-lab study.
g. Subjects will receive a REDCap link to the daily morning questionnaire (and physical copies of the survey to use as a backup if unable to connect to the internet) to complete at home, which take about 5 minutes each morning, and their activity will be monitored by a small device worn on the wrist called an actiwatch (which is about the size of a wrist watch) during the subsequent 7-14 days, until the second laboratory appointment. In addition, a Pulse Oximeter (a small device that is worn on the fingertip to measure pulse and oxygen levels) will be distributed for use on one night at home.

Subjects meeting all screening eligibility criteria for the study will be scheduled for a second 4-hour screening approximately 7-14 days after screening session #1.

Screening session #2 includes the following:

a. An additional blood and/or urine sample collection if necessary.
b. The History & Physical (H&P) with EKG at CHPS, if unable to schedule for screen #1.
c. Review of actiwatch, Pulse Oximeter, and sleep log.
d. Initial training related to the Cognition test battery.
e. Scheduling of the 7-night in-laboratory phase of the study.
f. Subjects will continue to wear the wrist activity monitor and complete the morning survey on REDCap.

Participants meeting all inclusion/exclusion criteria will be enrolled in the 7-night in-laboratory phase of the study. Subjects will be scheduled for the 7-night in-laboratory phase of the study in groups of up to 4 until total study enrollment (N=24) is achieved.

In the event that we have five fully qualified participants for one study run, we may see if one of the subjects is willing to serve as a backup subject. The subject would still arrive to the lab on Night 1 and be available to participate for the full 7-night study if any of the four primary subjects is unable to participate.

If the backup subject **IS** needed, they will continue the study as a primary subject.

If the backup subject is **NOT** needed for the 7-night study (i.e. the four primary subjects show up on Night 1 and are able to participate), the backup subject will receive compensation have transportation costs reimbursed to return home that evening. Also, if the backup subject is still available and eligible in the future, we may offer them a spot as a primary subject in a subsequent study run.

5.2 Study Intervention Phase

5.2.1 In-Laboratory Phase

The **in-laboratory phase** consists of 7 consecutive overnights. Subjects will wear a wrist actiwatch that measures movement activity 24/7 during the in-laboratory phase. The sleep of approximately 24 subjects will be monitored with polysomnography over 7 consecutive nights in groups of 4 in the Chronobiology Isolation Laboratory (CIL) in the Hospital of the University of Pennsylvania where the entire group has been randomly assigned to 1 of 6 noise exposure condition patterns (see 3.2 above).

After an adaptation night, subjects will be exposed to one of the following in each night:

1. Control night without noise and without earplugs (CTRL);
2. Aviation noise only (AN);
3. Broadband (pink) noise 50 dBA only (BN50);
4. Aviation noise plus earplugs (AN+EP);
5. Aviation noise plus broadband (pink) noise 40 dBA (AN+BN40);
6. Aviation noise plus broadband (pink) noise 50 dBA (AN+BN50).

The aviation noise night is described in greater detail in 3.1. We will investigate participants in 6 groups of 4 subjects each. Each group will be exposed to the same condition in each study night. Each subject will receive each exposure in a randomized and balanced fashion.

Measurements During Sleep
Subjects sleep will be measured polysomnographically (PSG). Subjects will also wear a Faros device that measures the ECG (1 kHz) and body movements (25 Hz).

Evening and Morning Procedures
Subjects will arrive in the lab around 8 pm in the evening and they will be able to leave the lab around 9 am in the morning (by 10 am at the latest). As our noise exposures can affect sleep and impair recuperation to some degree, participants will be informed in the consent form that they should not operate heavy machinery during the study. We will also offer a cab for those who would otherwise use a car to come to the CIL. We will provide snacks in the evening and a light breakfast in the morning. Subjects can shower in the morning (after all tests) if they wish.

In the evening (before bed) and in the morning (after waking up), subjects will do the following:

(1) Blood draw (for RNA analyses performed by the FAA Civil Aerospace Medical Institute (CAMI); morning only).
(2) Fill out morning/evening surveys that ask about sleepiness, fatigue, and mood states::

a. The morning questionnaire involves the Karolinska Sleepiness Scale (KSS), PANAS, POMS, and parts of the Pittsburgh Sleep Quality Index (PSQI) that specifically address the quality of sleep during the preceding night.
    i. Karolinska Sleepiness Scale (KSS) (Åkerstedt & Gillberg, 1990)
    ii. Positive and Negative Affect Schedule (Watson et al., 1988), and
    iii. Profile of Mood States Short Form (Shacham, 1983).
    Pittsburgh Sleep Quality Index (Buysse, 1989)
b. The evening questionnaire includes the KSS, PANAS and POMS.

(3) Cognition test battery (10 cognitive tests) preceded by a brief alertness and mood survey;
(4) Driving simulator task;
(5) Hearing test (pure tone audiometry);
(6) Blood pressure and resting ECG measurements.

5.2.2 End of Study Visit

Prior to departure on the last day of the in-laboratory phase, an individual debrief will occur with a research team member to provide an opportunity for a subject to discuss their experience during the study and elicit feedback. This session will be held in a private room and will not be shared with other study participants. The results of the study will not be shared with the subject.
In addition, study equipment (actigraph) will be collected and subjects will receive compensation via a physical Greenphire ClinCard.

5.3 Unscheduled Visits

Not applicable.

5.4 Subject Withdrawal

A subject may be withdrawn from the study prior to the expected completion of the project if the PI or Physician of Record determines that the subject is at risk, the subject fails to return for visits, the subject fails to adhere to protocol requirements, the subject is unable to be located, and/or if the subject withdraws his/her consent. If a subject elects to withdraw his/her consent, he/she needs to notify the PI, Co-Investigators and/or the Study Coordinator of his/her desire to withdraw from the protocol. This notification of withdraw may be verbal or in writing. If necessary, the Physician of Record will speak with the subject to provide services or information for conditions noted during the study.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

Not applicable.

5.5 Early Termination Visits

A subject may be withdrawn from the study prior to the expected completion of the project if the PI determines that the subject is at risk, the subject fails to return for visits, the subject fails to adhere to protocol requirements, the subject is unable to be located, and/or if the subject withdraws his/her consent. If a subject elects to withdraw his/her consent, he/she needs to notify the PI, Co-Investigators and/or the Study Coordinator of his/her desire to withdraw from the protocol. This notification of withdraw may be verbal or in writing. If necessary, the Physician of Record will speak with the subject to provide services or information for conditions noted during the study. The subject will return the equipment (actigraph) and they will be compensated for time and effort up to the point of withdraw via a physical Greenphire ClinCard. The subject will be escorted out of the laboratory for return home.

5.6 Efficacy Evaluations (only if applicable)

Not applicable.

5.7 Pharmacokinetic Evaluation (only if applicable)

Not applicable.

5.8 Genetic Testing (only if applicable)

The FAA CAMI plans to investigate changes in gene expression through RNA blood analyses. This analysis is exploratory in nature.

5.9 Safety Evaluation (only if applicable)

Not applicable.

6 Statistical Plan

We will perform similar analyses for the secondary outcomes. We will adjust for multiple testing using the false discovery rate method making sure that we keep the family-wise type I error rate at 5%. Multiple exploratory genetics analyses may be performed by FAA CAMI.

6.1 Sample Size and Power Determination

Power calculations were conducted using PASS (Version 21 NCSS), assuming a 5% type I error rate and using two-sided hypothesis tests. We used data collected in the AIRORA study performed at DLR to inform power calculations.[10] With a proposed sample size of 24 subjects, we expect to have at least 80% power to detect a medium effect size of 0.60 for the mitigation effect of BN on our primary outcome due to aviation noise.

6.2 Statistical Methods

The primary outcome of the study is: time spent in slow wave sleep (SWS) plus rapid eye movement (REM) sleep during an 8-hour sleep opportunity (11 pm – 7 am). We will use linear mixed effect regression models with random subject intercept to investigate whether SWS+REM duration differs significantly between the 6 study conditions (we will use non-linear mixed effect models for binary secondary outcomes). If $p<0.05$ of the omnibus test, we will perform post-hoc tests contrasting all conditions with each other. Our primary contrast of interest for which the study was powered is the difference in SWS+REM duration in aviation noise nights with and without broadband noise of 50 dB.

6.3 Control of Bias and Confounding (if applicable, typically observational study or if randomization is not taking place)

All statistical models by the Pennsylvania study team will be adjusted for age and sex. We will consider other relevant confounders depending on the investigated outcome variable. Genetics analyses by FAA CAMI may employ a variety of exploratory models.

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender).

6.3.2 Analysis of Primary Outcome of Interest

Our primary contrast of interest is the difference in SWS+REM duration in aviation noise nights with and without broadband noise of 50 dB. In the mixed model framework, this is equivalent to a paired t-test.

6.3.3 Pharmacokinetic Analysis (only if applicable)

Not applicable.

6.3.4 Interim Analysis (only if applicable)

Not applicable.

7 Safety and Adverse Events

7.1 Definitions

7.1.1 Adverse Event

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.1.2 Serious Adverse Event

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- required intervention to prevent permanent impairment or damage
- a congenital anomaly or birth defect
- an important medical event

  Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

7.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study intervention or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study intervention or study participation will be recorded and reported.

7.3 Relationship of AE to Study

The PI will be determining the relationship of each adverse event to the study procedures, and the relationship of each event will be classified under one of the following categories: definitely related; probably related; possibly related; unlikely or unrelated.

7.4 Reporting of Adverse Events and Unanticipated Problems

The Investigator will promptly notify the Penn IRB and FAA IRB of all on-site unanticipated, Adverse Events that are related to the research activity. Other unanticipated problems related to the research involving risk to subjects or others will also be reported promptly. Written reports will be filed using the HS-ERA and in accordance with the Penn IRB timeline of 10 working days.

7.4.1 Follow-up Report

If an AE has not resolved at the time of the initial report and new information arises that changes the PI's assessment of the event, a follow-up report including all relevant new or reassessed information will be submitted to the IRB.

7.4.2 Investigator reporting: notifying the study sponsor (if applicable)

The FAA IRB has designated that the University of Pennsylvania IRB serve as the reviewing IRB for the human subjects work, and in so doing requires that copies of all Pennsylvania IRB approved protocols and amendments be submitted to the FAA IRB. In addition, the FAA IRB plans to oversee a separate protocol governing the genetics research by FAA CAMI (to include analysis of RNA in blood and de-identified data provided by the Pennsylvania PI).

7.4.3 Data and Safety Monitoring Plan

The Chronobiology Isolation Lab (CIL) is staffed by clinical research coordinators and professional staff with extensive experience (some >20 years) in subject recruitment, screening and IRB-compliant protocol implementation for research studies. They are supported by post-baccalaureate research technicians and part-time undergraduate student workers, who are trained in the administration of neurobehavioral tests and supervised by our full-time staff.

During the 7-night in-laboratory phase, subjects will be monitored by trained staff during all phases of the study with a combination of the core study team and research assistants who have been trained in study procedures. There will be at least two staff members present during the study. In the case where one staff member becomes unavailable, the study coordinator will be notified, and a replacement will be arranged.

Subjects will be told explicitly that they are free to discontinue participation at any time and without jeopardy. The PI also reserves the right to discontinue participation if it is necessary for a subject's welfare or for research purposes. The PI of the project will manage confidentiality of the records. All paper-based records will be stored in a secure location in 1020 Blockley Hall with limited personnel access. Computer-based files will be stored on a secure server with limited access privileges and passwords. For all manually entered data, a second individual will proofread the entries to check for accuracy. If there are any discrepancies, the data will be reviewed and corrected prior to analysis. All consent forms and any other document with identifiable information will be kept in a locked cabinet. Data will be de-identified. Data will be kept confidential throughout the study by using subject ID numbers and restricting access to the data. Code number identifiers will be kept separate from the research data. Any web-accessed surveys will be implemented using Redcap software.

Emergency Plan: Subjects will be in the lab for 7 consecutive nights and will not have contact with the outside world during the overnight in-laboratory phase. Subjects will be provided the phone number of the study coordinator to give to friends or family who will be able to contact the coordinator 24/7 during the

study. In the event of an emergency in which the research team is contacted by the subject's family, the subject will be allowed to contact their family and decide if they wish to continue with the study.

In the event a subject requires medical attention, the study team will contact the physician of record for evaluation and the recommendation of further care. Necessitating medical attention may include complaints of headache, nausea, lightheadedness etc. If the subject experiences a medical emergency, hospital policy will be followed. A medical emergency may include syncope, altered mental status or a fall with injury. Phones in the study control room include contact numbers for security, fire/smoke, command center, rapid response/code and STAT code. Study personnel will have training for when to activate emergency response and in the response procedures (as described in HUP Clinical Emergency policy). In the event of a fire or natural disaster, hospital policy will be followed. The research protocol will be broken and study staff will open the isolation area and lead the subjects to safety.

Subject Safety: Each subject will have their own private sleeping quarters with bathroom. There will be no time when subjects will not be under staff supervision. In addition, subjects will be monitored continuously via video and audio observation (except in the restrooms). Staff will communicate directly with the subjects during all aspects of the study.

7.4.3.1 Data Safety Monitoring Board (if applicable)

Not applicable.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Subjects will be assigned a de-identified study code. Their survey responses, performance task data, and biospecimen will be saved under this code without unique identifiers. Although data will be deidentified to the extent feasible and reasonable for research, the fingerprint inherent in genetic information cannot be entirely removed. Blood samples may undergo analyses to generate genetic information, such as whole transcriptome sequencing (a subset of data from whole genome sequencing).

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The following personal health information will be collected, used for research, and may be disclosed during a subject's involvement with this research study:

- Name, address, telephone number, date of birth;
- Personal and family medical history;
- Psychiatric history;
- Current and past medications and therapies;
- Social Security Number;
- Medical Record number;

- Information from a health history and physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature; and
- Results of screening tests and CHPS nursing notes.
- Dates and times that study events occurred, such as the day and time of sample and data collection

If a subject prefers to have a reminder of study appointments sent via email (identifiable information), the study staff will accommodate this request after obtaining permission from the subject.

8.2 Data Collection and Management

Subject information will be housed in both the electronic medical record (EMR) and as de-identified data on our secured servers. Data housed in the EMR will only include that information which relates to medical care (health history and physical assessment, EKG, CHPS notes) and laboratory results from the screening sessions. All surveys, questionnaires, mental health exams, biomarker results and performance task results will be obtained directly from the research team and will not be entered in the medical record (see below). In the event a subject requests no information be entered in the EMR as described in the informed consent, the subject will not be enrolled in the study.

All electronic data collected by the research team will be collected in a de-identified fashion when possible. All subjects will be given a unique study ID. The data files will be encrypted and stored locally and/or transmitted to our secure servers. The servers are managed by Penn Medicine Academic Computing Services (PMACS) and are located in the secure PMACS data center.

De-identified and encrypted polysomnography data are securely transferred to a server of the polysomnography system. They are then securely transferred to and stored on our secure PMACS servers.

The questionnaires and daily logs will be administered on study laptops via the online REDCap Survey System. The data from REDCap will be downloaded and stored on secure servers in the PMACS data center. Encrypted data may be transmitted to our secure servers via sFTP.

For the Cognitive Task (Cognition) and Driving Simulation Task, encrypted data will be stored locally on the PMACS managed system PCs and will be either transmitted to our secure servers or transferred to our secure servers via encrypted USB flash drives.

Actigraphy and ECG data will be downloaded from the devices at the end of the study and uploaded to our secure PMACS servers.

Bodily fluid samples (blood) will be de-identified and coded before freezing. Approximately 2mL of the 4.5mL drawn daily will be stored at Penn in secured freezers, and the remaining 2.5mL will be sent to the Civil Aerospace Medicine Institute (CAMI) of the Federal Aviation Administration for analysis. Data collected (e.g., results of polysomnography, actigraphy, surveys, cognitive and driving simulator tests, basic demographics such as age and body mass index) will also be de-identified and coded before being sent to CAMI. However CAMI may receive some elements of date/time information relative to the time when study events occurred, such as the time/date of sample and data collection.

As audio/video data cannot be de-identified, it will be stored on encrypted hard drives, which are located in locked cabinets.

The Federal Aviation Administration (FAA) Center of Excellence for Alternative Jet Fuels and Environment (COE ASCENT) has established a Data Management Plan. In all cases the terms of the awarded grant and sponsor-approved Data Management Plan takes precedence.

- The COE ASCENT project Principal Investigator (PI) will be the interface with the FAA Technical Monitor to ensure consistency and data quality control. COE ASCENT principal investigator will

provide all research results to the FAA technical monitor who will be responsible for determining if the project data should or should not be publicly available. At the time of submitting quarterly reports for this project, the team will review any data generated during the quarter and will ensure that this data has been provided to the FAA Technical Monitor. The sound files are in Waveform Audio File Format (wav).

- The polysomnography system and the Faros device will store data in European Data Format (EDF) which can be viewed with publicly available software (e.g., https://www.teuniz.net/edfbrowser/).
- Results from blood analyses, surveys, cognitive tests, driving simulator performance and hearing tests are stored as comma separated value (csv) files that can be processed with any text editor or, for example, Microsoft Excel.
- The project will generate data dictionaries that allow making sense of the different types of data in each file.
- The data provider information along with the data specifications will be compiled using the ASCENT standard Metadata Contact Sheet and accompany all data files associated with the project.
- The project will distribute acoustic data (i.e., sound files of noise events played back in the laboratory) and the schedules detailing when they were played back. With concurrence of the COE ASCENT project FAA Technical Monitor, such data will be submitted to the FAA Technical Library.
- The other data collected in this project (physiological, cognitive performance, driving performance, survey and genetic transcription data from study participants) may contain identifiers (e.g., privacy health information/personally identifiable information (PHI/PII)) considered too sensitive to be shared with the general population. Data will be de-identified when possible and then distributed. Sensitive data that cannot be de-identified will be posted to secure government databases, such as posting of genetic sequence data in NIH's database of Genotypes and Phenotypes (dbGAP) (https://www.ncbi.nlm.nih.gov/gap/), where appropriate and in accordance with IRB guidance and federal regulations. The COE ASCENT PIs, and their academic institutions, own and maintain the intellectual property rights for the data created by their respective institutions. As the funder of this project, the FAA, and its parent agency, the Department of Transportation, will have a comprehensive non-exclusive, world-wide, perpetual, paid-up, royalty-free license to all data created hereunder and to any publications submitted to the FAA Technical Library Digital Repository, including rights to use, analyze, and distribute data in compliance with laws, regulations, policies, and other requirements involving and impacting public access to federally funded research. For further information please refer to the project's the full ASCENT Data Use Agreement document.
- Rights in and to genetics and other data and analyses created solely by DOT/FAA employees, including that data derived/arising from the relating of genetics data to other data generated under this project, will be owned by the FAA. The COE ASCENT and University of Pennsylvania will have a comprehensive non-exclusive, world-wide, perpetual, paid-up, royalty-free license to all such data.
- Public project data files from ASCENT COE PIs will be available via the National Transportation Library (NTL) and the ASCENT community on the WSU Research Exchange. Reports, papers, conference presentations, etc. resulting from the project will also appear on the COE ASCENT website. Author ORCiD numbers and document DOI numbers, when they exist for documents that are archived elsewhere – e.g., a professional society website, a journal website, etc. - will appear along with or instead of these documents. In order to post documents to the ASCENT website, the Project PI (or PIs) must use a password protect against accidental modification or deletion.
- The PIs of COE ASCENT research tasks will maintain copies of all data files they generate for a period of three (3) years past the end of the project in a manner consistent with data storage at their institution. This provides an additional redundant storage strategy.
- Personally Identifiable Information (PII) and data that is generated to support decision making within ICAO CAEP will not be publicly posted and is not included within the Data Management Plan.

8.3 Records Retention

The PI will maintain copies of all data files generated by the University of Pennsylvania for a period of three (3) years past the end of the project in a manner consistent with data storage at the University of Pennsylvania.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The study PI will be responsible for ensuring the ongoing quality and integrity of the research study.

9.2 Auditing and Inspecting

The PI will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor (if applicable), government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. the CIL, etc.). Access to some data may be limited due to the Certificate of Confidentiality that will be obtained from NIH.

10 Ethical Considerations

All protocols, amendments, and continuing reviews will be submitted to, reviewed, and approved by the Institutional Review Board at the University of Pennsylvania via the HSERA system. Work by FAA CAMI on coded blood samples and de-identified data provided to CAMI will be governed by a separate FAA IRB.

10.1 Risks

1. There is a chance that a subject's sleep will be disrupted by the noise interventions. As a consequence, the subject may feel less rested the next morning which can cause symptoms such as fatigue, sleepiness, difficulties concentrating, or irritability. Based on similar previous studies, we do not expect major daytime symptoms due to sleep disruption. We will monitor the subject's alertness with a cognitive test in the morning and alert the subject if we notice a relevant performance impairment. A subject should not operate heavy machinery during the study if they experience any symptoms of non-restful sleep. We will pay for transportation to take a subject to and from their home or to and from their work if needed.
2. While in the study, subjects will be required to perform mental performance tests and simulators. These tests can become difficult to perform under certain conditions or when one is sleepy and may, therefore, cause some distress. Should a subject feel that they are unable to perform these tasks during the course of the study, they are free to withdraw their consent to participate in this experiment and then sleep in the laboratory, if needed.
3. There may be some discomfort associated with the collection of the blood samples, including possible bruising of the arm, dizziness, fainting, and a small risk of infection.
4. Measuring heart activity involves minor risks. The Faros device used to record electrocardiogram (ECG) is electrically isolated and conforms to hospital standards for electrical safety.
5. Wearing of the Cerebra Prodigy device on the head may cause slight discomfort.
6. The ECG-electrodes attached to the chest and the EEG electrodes attached to the head may cause some minor discomfort and/or skin irritation. If skin irritation occurs, there is a potential risk of changes in skin pigmentation where the ECG electrodes were worn, which results in a darker or lighter skin color. These rare changes in skin pigmentation typically resolve over time. To decrease the likelihood of skin irritation, we will slightly change the position of the electrodes from night to night. We also have alternate ECG electrodes from a different manufacturer available should there be a

skin reaction to our standard ECG electrodes. Additionally, we will offer to apply a cream to the site where the electrodes were worn to reduce skin irritation.
7. The earplugs may cause minor discomfort due to the pressure, but they should not cause pain.
8. There is minimal risk associated with video and audio recording during the study. There is a possible risk of a loss of confidentiality in very rare circumstances. As the data collection and analysis for this study will continue, the recordings (with no personal identification) will be kept in a secure location. Access to these recordings will be restricted to the Principal Investigator, his staff, the University of Pennsylvania IRB, and as required by law.
9. As a volunteer subject in this research study, a subject is not considered a patient at the Hospital of the University of Pennsylvania. During the 7 nights in the laboratory for this study, the subjects will be staying overnight in a clinical research facility. In the unlikely event that a subject should require emergency hospital treatment during their stay in our research facility, located within the Hospital of the University of Pennsylvania, there will be a resident emergency physician on call who may be summoned for part of their medical care.
10. The investigators reserve the right to terminate a subject's participation in the study at any time if they feel it is necessary for their welfare or for research purposes.
11. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will be informed. The PI will notify the subject if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about the subject's condition and to further work-up by their physician.

Risks of Genetic Sequencing

This research includes genetic sequencing. Even without a subject's name or other identifiers, their genetic information is unique to them. The researchers believe the chance that someone will identify a subject is very small, but the risk may change in the future as people come up with new ways of tracing information.

There can be a risk in knowing genetic information. New health information about inherited traits that might affect a subject or their blood relatives could be found during a research study. Even though genes are unique, some of the same genes may be shared with a blood relatives. Although we are not able to know all of the risks from taking part in research on inherited traits, we believe that the risks to the subject and their family are very low, because the samples will be coded and only a portion of a subject's genes will be sequenced.

Very rarely health or genetic information could be misused by employers, insurance companies, and others. For example, it could make it harder for a subject to get or keep a job or insurance, or life insurance companies may charge a higher rate based on this information. We believe the chance these things will happen is very small, but we cannot make guarantees.

A federal law (Genetic Information Non-Discrimination Act, GINA) helps reduce the risk from health insurance or employment discrimination. The law does not include other types of misuse by life insurance or long term care insurance. Further information about GINA may be found on the internet or by asking the study staff.

10.2 Benefits

There is no direct benefit to a subject; however, a subject's participation could help us understand how aviation noise can disrupt sleep and to better understand how we may mitigate this disruption using broadband noise and/or earplugs. In the future, it is possible that findings from this study lead to developing viable alternatives to maintain sleep health in people who are adversely affected by aviation noise, as expensive soundproofing measures are typically only granted to those living within a certain radius of the airport, and not typically offered to all those outside the immediate area who may still be suffering sleep disturbances.

10.3 Risk Benefit Assessment

There are minimal risks involved in this research that are outweighed by the potential benefits of understanding how aviation noise can disrupt sleep leading to a better understanding of how we may mitigate this disruption using broadband noise and/or earplugs. In addition, the results could be of great utility to developing viable alternatives to maintain sleep health in people who are adversely affected by aviation noise.

10.4 Informed Consent Process / HIPAA Authorization

Informed consent will be obtained from adult subjects who are competent to give it. All verbal and written communication will be in the English language. Informed consent forms will be given and signatures will be obtained before the start of the study. After consent is given, it can be withdrawn at any time and the subject can be removed if they choose. In the event that a subject withdraws their consent, data collected up to the point of withdrawal may be retained as it would not be possible to completely eliminate all data collection. In order to avoid potential coercion, Penn employees, Penn students, educationally or economically disadvantaged persons will not be specifically targeted or unjustly excluded. Subjects will be able to sign their consent form after an individual meeting where they will be able to ask any questions they may have to a member of the research team. There is no time limit to this session which will be held in a private room.

10.4.1 Alterations to Typical Consent Process (only include if applicable)

Not applicable.

10.4.1.1 Waiver of Consent (In some cases for screening/portions of that study that qualify as minimal risk, a waiver of documentation of consent may be permissible IRB SOP)

Not applicable.

10.4.1.2 Waiver of Written Documentation of Consent

Not applicable.

10.4.1.3 Waiver of HIPAA Authorization

Not applicable.

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the Federal Aviation Administration (FAA) Center of Excellence for Alternative Jet Fuels and Environment (COE ASCENT).

11.2 Conflict of Interest

Not applicable.

11.3 Subject Stipends or Payments

For completion of the entire study, each subject will be paid approximately $1210 via a physical Greenphire ClinCard plus reimbursement for transportation costs. The total amount may vary depending on how much of each study component is completed. If a subject decides to withdraw from the study before the study is over or are otherwise unable to finish the study, the subject will be compensated for participation up to the point when they chose to withdraw or were unable to continue.

The compensated amounts for completing each section of the study are as follows:

- $60 for two screening visits (at 30 each);
- $105 for up to 21 days of actigraphy and completed sleep logs ($5/day);
- $875 for the 7-night in-lab phase ($125 for each night spent in the lab);
- $70 for blood draws ($10/draw, performed each morning of the in-lab stay);
- An additional $100 at the end of the study for your time and effort.

In the event that we have five fully qualified participants for one study run, we may see if one of the subjects is willing to serve as a backup subject. The subject would still arrive to the lab on Night 1 and be available to participate for the full 7-night study if any of the four primary subjects is unable to participate. The backup subject would be compensated $100 for their time and effort, regardless of whether they were needed as a primary subject.

If the backup subject is **NOT** needed for the 7-night study (i.e. the four primary subjects show up on Night 1 and are able to participate), the backup subject will receive the $100 back-up compensation and have transportation costs reimbursed to return home that evening.

If the backup subject **IS** needed, the backup subject will still receive $100 for their willingness to be flexible, and will then continue the study as a primary subject earning the standard subject compensation of $875 ($125/night for 7 nights) in addition to the back-up compensation of $100.

The $100 back-up compensation is in addition to what the backup subject would have already earned for screenings, at-home actigraphy and sleep logs. Also, if the backup subject is still available and eligible in the future, we would guarantee them a spot as a primary subject in a subsequent study run, where they would receive full standard subject compensation of $875 for the 7-night study ($125/night for 7 nights), as well as any necessary repeated screening compensation.

In addition, the backup subject will be compensated for transportation to and from home and work if needed for screening sessions and the overnight stays.

If a subject receives more than $600 compensation in one year for participation in research studies at the University of Pennsylvania, they must provide an Individual Tax Identification Number or Social Security Number for tax purposes.

12 Publication Plan

Results of the study will be published in scientific journals and/or technical reports following the standards of good scientific practice.

13 References

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14 Attachments

The following pertinent documents associated with the management of the study will be submitted to the IRB for review.

- Consent Form
- Study Protocol
- Study Procedures
- Recruitment Materials (print ads, flyer)
- Screening Script
- Questionnaires/Surveys
- Letter of Support
- FAA Data Management Plan
- FAA IRB approval
- FAA IRB letter establishing reviewing IRB