Research plan

1. Study background and scientific issue

The effects of railway noise on sleep have been studied extensively. However, it is less known how vibration from rail traffic affect sleep, especially for vibration levels that are around current Swedish guideline values.[1,2] It also remain unclear how combined exposure to noise and vibration together affect response, compared to only noise or vibration. As sleep disturbances are judged to be a critical factor for long-term health effects, sleep disturbances through noise and vibrations are prioritised in this project. Recent results from the EpiVib project show that there is a higher prevalence of diabetes among residents exposed to higher levels of railway vibration.[3] The effect may be caused by vibrations and effects on sleep, but the biological link is not well understood. Therefore, in addition to investigating the effects of vibrations on sleep, we will investigate effects on biological mechanisms that can lead to diabetes in the long term.

There is an established link between adequate sleep duration and sleep quality and the maintenance of neurobehavioral performance, although differential effects between individuals can be pronounced.[4,5] Chronic partial sleep restriction can induce cognitive performance decrements equivalent to total sleep deprivation,[6] and we recently found that sleep debt due to chronic sleep restriction leads to decreases in accuracy across cognitive domains, specifically on tests of spatial orientation and vigilant attention.[7] The concentrations of several metabolites, including lipids, amino acids and steroids are associated with cognitive decline and incident dementia,[8-10] and a study in chronically sleep interrupted mice found a close association between cognitive decline and lipid metabolism, as well as purine, amino acid and retinoid metabolism.[11] These data point to metabolic mechanisms between sleep disruption and adverse cognitive consequences. However, studies on the impact of nighttime noise on cognitive performance are scarce, and there are no existing studies for vibration exposure. There is some evidence from cross sectional field studies that nighttime noise may induce deficits in attention, memory, executive function and reading comprehension in children,[12] and two studies found small but significant impairments in reaction time on a test of vigilant attention.[13,14] The cognitive consequences of sleep disturbance by noise and, in particular, vibration and the mechanisms underlying inter-individual differences in vulnerability to nocturnal exposure are therefore unclear. A deeper understanding in this area may offer insights into observations that disturbed sleep is a potential risk factor for cognitive decline.[15]

2. Study aim

The experimental sleep study has the overarching goal of deepening our understanding of sleep disruption by railway vibration and noise and changes in cardiometabolic and cognitive function. To this end, the study will address the following study aim:

Aim 1: Determine the biological and neurobehavioural consequences of sleep disruption by railway vibration. We will measure the sleep of healthy volunteers, and each morning we will obtain blood samples for metabolomics metabolic function analysis and administer a neurocognitive test battery. We will compare effects on sleep, metabolomics, metabolic function and cognitive function between quiet nights and nights with railway traffic vibration and noise in different combinations of levels. Dose-response relationships will be determined by comparing nights with different combined levels of noise and vibration.

3. Study setting

This study will take place in the sound environment laboratory (SEL) at the University of Gothenburg Department of Occupational and Environmental Medicine (Arbets- och miljömedicin [AMM]). The SEL is a high fidelity research laboratory equipped to simulate a typical apartment, including three individually light-, sound- and vibration-isolated private bedrooms. Ceiling mounted speakers in each room and electrodynamic transducers mounted to the underside of each bed allow us to create a realistic acoustic environment by transmitting sound and vibration exposures from the control room to each bedroom individually. We have shown previously that results from this lab with high ecological validity are comparable with results from the field.[16]

4. Study protocol

This study has a prospective within-subjects cross-over design. Participants (total N=24) will each spend five consecutive nights in the SEL, with a sleep opportunity between 23:00-07:00. Daytime sleep will be prohibited, confirmed with measures of daytime activity via wrist actigraphy monitors worn continuously throughout the study. Three subjects will take part concurrently, in separate bedrooms. The first night is a habituation period to the study protocol and for familiarisation with the test procedures. One night will be a quiet condition without noise or vibration, to determine normal baseline sleep, cardiometabolic profile, and cognitive performance. Three nights are the noise and vibration exposure nights and will be randomly assigned across participants using a Latin square design to avoid first-order carryover effects. In these exposure nights, vibration and noise from railway freight will be played into the

bedrooms to determine the effects of vibration and noise on sleep, cardiometabolic function and cognitive performance. Thirty six trains will occur each night, randomly distributed across the 8-hour sleep period.

Each night we will record physiologic sleep with polysomnography (PSG) and cardiac activity with electrocardiography (ECG). Each study morning, subjects will provide a 7 ml blood sample, complete cognitive testing and answer questionnaires and will depart the SEL to follow their normal daytime routine. They will return to the SEL at 20:00 each evening to complete cognitive testing and prepare for sleep measurements.

Caffeine will be prohibited after 15:00 and alcohol will be prohibited at all times. Because extreme and/or variable dietary behaviour can affect the metabolome/lipoprotein profile,[17] participants will be given guidance that they should eat a similar evening meal on each day of the laboratory study, confirmed with a food diary. The actual meal itself can be different for different study participants, because the study has a within-subjects design. The study will be performed in accordance with the principles of the Declaration of Helsinki. Subjects will provide informed written consent prior to the study start, will be free to discontinue at any point and without providing a reason. Subjects will be compensated 1000 SEK per night for their participation (total 5000 SEK for full completion of the study).

5. Participant recruitment

This study will target a focused age range of 18-30 to minimise age-related differences in sleep structure.[18] Participants will be recruited from on and around the University of Gothenburg campus via posters and flyers, and online via accindi.se, which is an approach we have successfully used in multiple previous studies.[19-23] Interested participants will be screened for eligibility with the following exclusion criteria: 1) aged <18 or >30 years; 2) habitual sleep and wake timings more than ±1 hour different from the study sleep times (i.e. habitual sleep time should be 22:00-00:00 and habitual wake time should be 06:00-08:00, confirmed with actigraphy measured for one week before participation in the sleep study); 3) BMI>25 kg/m^2; 4) regular sleep medication use (prescribed or "over-the-counter"); 5) poor hearing acuity (measured during screening via pure tone audiometry); 6) diagnosed with sleep disorders 7) indication for high risk of sleep apnoea on the STOP-BANG questionnaire[24]; 8) shift work; 9) smoking, vaping, snus, or other nicotine use; 10) pregnant or breastfeeding. We will record blood oxygen saturation via pulse oximetry during the habituation night to further screen for moderate sleep apnoea, defined as more than 15 apnoea and hypopnoea events per hour of sleep. We will also measure general health,[25] noise sensitivity,[26] chronotype,[27] habitual sleep quality,[28] and annoyance and sleep disturbance at home by various noise sources,[29] but these do not form part of the eligibility criteria.

6. Railway vibration and noise exposure

For railway vibration we will use synthesised signals based on measured data. We have used these vibration signals in previous laboratory studies.[19-21] It is necessary to use synthesised vibration, rather than recorded signals, so that we can accurately adjust the acoustical character of the exposure as needed. Railway vibration will be accompanied by high fidelity recordings of railway freight noise. This is to maximise ecological validity of the exposures since vibration rarely occurs without noise, and to mask any mechanical sounds from the vibration transducers.

Vibration and noise exposures will reflect realistic railway freight traffic noise levels that occur in dwellings alongside railway lines in Sweden. The maximum W_m-weighted vibration amplitudes in the three exposure nights will 0.9 mm/s. Maximum sound pressure levels of individual train passages will be 55 dB $L_{AF,max}$. Trains will be 24s or 46s in duration.

All vibration amplitudes will be calibrated on the mattress of the bed, under a 75 kg reference weight to simulate the bed being occupied. All sound pressure levels will be calibrated to 10 cm above the pillow in each bedroom prior to the study, so that these levels accurately reflect the noise exposure of the subjects during sleep.

7. Study outcomes

Sleep: Physiologic sleep will be measured with ambulatory PSG. We will analyse sleep using novel markers of sleep depth and sleep disturbance (Odds Ratio Product [ORP],[30] sleep spindle density and amplitude,[31,32] EEG inter-hemispheric correlation[33,34]) that can reveal short duration and/or subtle alterations in sleep activity which nevertheless may be functionally relevant. These indicators will provide measures of overall sleep architecture and the dynamics of changes in sleep across the night and in response to noise. Analyses will be supplemented with classical sleep and EEG arousal scoring by an experienced sleep technologist according to current criteria.[35] Sleep-wake activity will also be measured using wrist actigraphy for one week before the laboratory study and during the laboratory study itself. These actigraphy data are to confirm habitual sleep and rise times, and to confirm that participants do not nap during the daytime. Each morning subjects will self-assess different dimensions of sleep quality and disturbance in the preceding night with questionnaires, which we have previously developed and validated for studies on the effects of noise on sleep.[36] We will also include validated items on sleepiness[37] and sleep disturbance by noise.[29]

Metabolomics and insulin resistance: Participants will provide a 7 ml blood sample via venepuncture performed by a qualified clinician each study morning. Samples will be immediately centrifuged, aliquoted, and stored in -80C freezers in the same building as the SEL. Blood plasma will be analysed by nuclear magnetic resonance (NMR) spectroscopy, and metabolomics analysis will be performed in collaboration with the Swedish NMR Centre at the University of Gothenburg. Insulin and glucose levels will be analysed by the unit for Clinical Chemistry at Sahlgrenska University Hospital.

Cognitive function: Each morning and evening subjects will complete the *Cognition* test battery, lasting 15-20 minutes. *Cognition* is a computerised battery of 10 neuropsychological tests that are sensitive to sleep loss and cover a range of cognitive domains.[38,39] The 10 tests are summarised in Table 1 with a screenshot of each test in Figure 1. Neurobehavioral outcomes from *Cognition* are one key accuracy and one key speed outcome for each of the 10 tests.

Cardiovascular arousal: We will measure cardiac activity during sleep each night using Lead II ECG[35] and finger photoplethysmography. The primary outcomes are event-related change in heart rate following onset of traffic noise events, pulse transit time as a surrogate measure of changes in blood pressure,[40-42] and heart rate variability measures of sympathovagal balance.[43]

Mood and emotion: Young adults are especially susceptible to impaired mood and emotion regulation following sleep restriction compared to older adults.[44] We will therefore measure positive and negative affect each study morning and evening using the PANAS scale.[45]

Screen use: Evening use of smarthphones before bedtime can negatively affect sleep quantity and quality.[46] We will therefore measure screen use time throughout the pre-lab and in-lab study weeks on the subjject's own phones via an already-developed application.

Table 1 Overview of Cognition test battery

Test	Procedure	Cognitive domains assessed	Brain regions primarily recruited
Motor Praxis (MP)	Click on squares that appear randomly on the screen, each successive square smaller and thus more difficult to track.	Sensory-motor speed	Sensorimotor cortex
Visual Object Learning (VOLT)	Memorize 10 sequentially displayed three-dimensional figures. Later, subjects are instructed to select those objects memorized from a set of 20 such objects also sequentially presented, some of them from the learning set and some of them new.	Spatial learning and memory	Medial temporal cortex, hippocampus
Fractal 2-Back (F2B)	Presentation of a set of fractals, each potentially repeated multiple times. Respond when the current stimulus matches the stimulus displayed two fractals ago	Working memory	Dorsolateral prefrontal cortex, cingulate, hippocampus
Abstract Matching (AM)	Subjects presented with two pairs of objects at the bottom left and right of the screen, varied on perceptual dimensions (e.g., color and shape). Subjects presented with a target object in the upper middle of the screen that they must classify as more belonging with one of the two pairs, based on a set of implicit, abstract rules.	Abstraction, concept formation	Prefrontal cortex
Line Orientation (LOT)	Presented with two lines at a time, one stationary and the other can be rotated. Subjects rotate the movable line until it is parallel to the stationary line.	Spatial orientation	Right temporo-parietal cortex, visual cortex
Emotion Recognition (ERT)	Presented with photographs of faces portraying emotional facial expressions of varying intensities. Subjects given a set of emotion labels (“happy”; “sad”; “angry”; “fearful”; and “no emotion”) and must select the label correctly describing the expressed emotion.	Emotion identification	Cingulate, amygdala, hippocampus, fusiform face area
Matrix Reasoning (MRT)	A series of patterns are overlaid on a grid. One element from the grid is missing, the subject must select the element that fits the pattern from a set of alternative options.	Abstract reasoning	Prefrontal cortex, parietal cortex, temporal cortex
Digit Symbol Substitution (DSST)	Subjects required to refer to a displayed legend relating each of the digits one through nine to specific symbols. One of the nine symbols appears on the screen and the subject selects the corresponding number as quickly as possible.	Complex scanning and visual tracking	Temporal cortex, prefrontal cortex, motor cortex
Balloon Analog Risk (BART)	Inflate an animated balloon or collect a reward. Participants are rewarded in proportion to the final size of each balloon, but a balloon will pop after a hidden number of pumps, which changes from trial to trial	Risk decision making	Orbital frontal and ventromedial prefrontal cortex, amygdala, hippocampus, anterior cingulate cortex, ventral striatum
Psychomotor Vigilance (PVT)	Monitor a box on the screen, and hit the space bar once a millisecond counter appears in the box and starts incrementing.	Vigilant attention	Prefrontal cortex, motor cortex, inferior parietal and some visual cortex

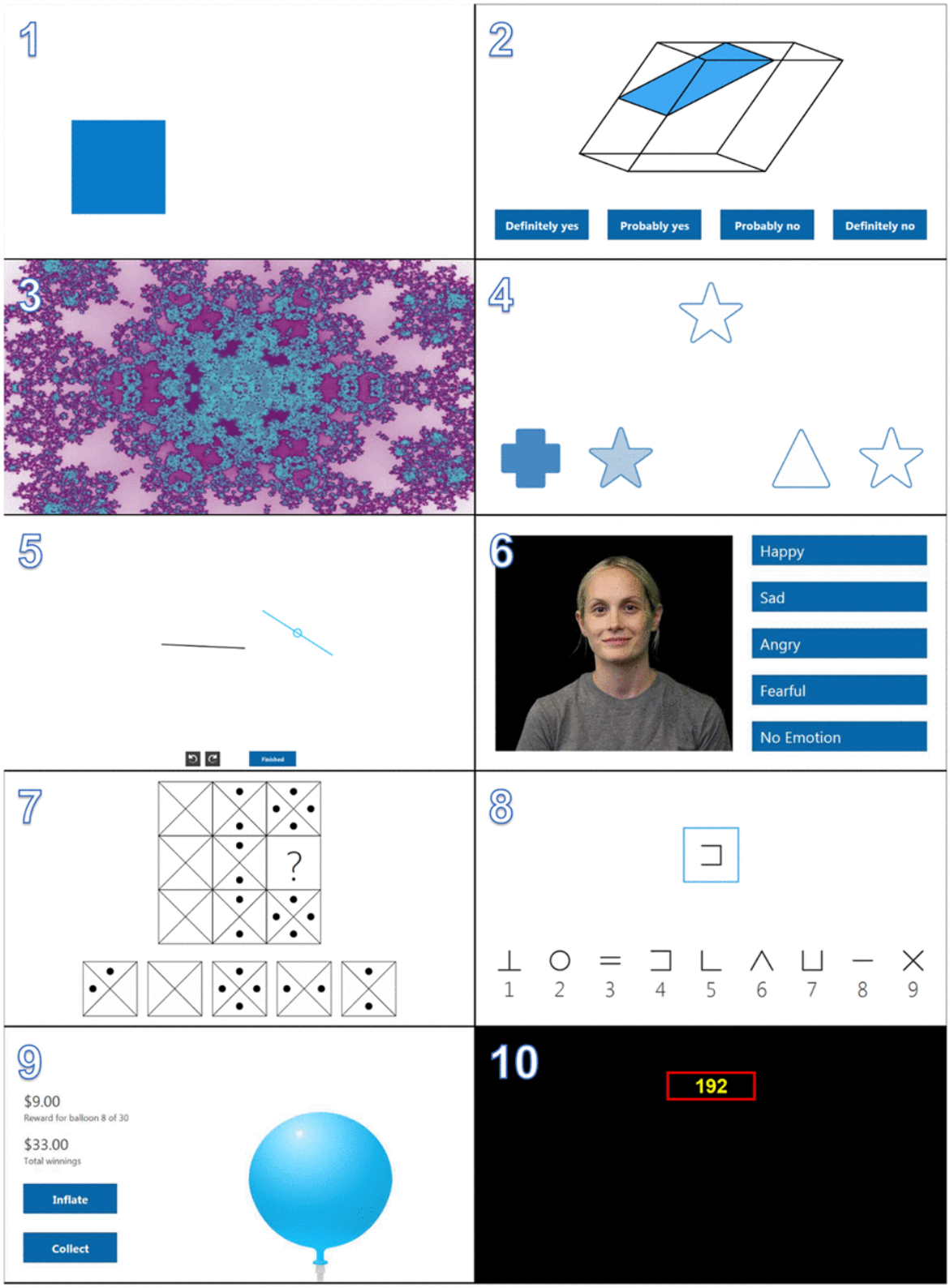

Figure 1 Screenshots of the 10 individual tests comprising the *Cognition* test battery. The tests are listed in the standard order of administration: 1) Motor Praxis (MP); 2) Visual Object Learning (VOLT); 3) Fractal 2-Back (F2B); 4) Abstract Matching (AM); 5) Line Orientation (LOT); 6) Emotion Recognition (ERT); 7) Matrix Reasoning (MRT); 8) Digit Symbol Substitution (DSST); 9) Balloon Analog Risk (BART); and 10) Psychomotor Vigilance (PVT).

8. Data analysis and interpretation

We will analyse each outcome separately in mixed-effects regression models, accounting for repeated measures on the same individuals. Models will minimally adjust for sex and time in study, comparing differences across study nights. Within-night data (traffic noise-induced cortical and autonomic arousal) will also be minimally adjusted for vibration

amplitude, noise level, sleep stage and time of night. *Cognition* data will be adjusted for practice and stimulus set difficulty effects.[38,47]

9. Project group

Principal Investigator Michael Smith is Associate Professor of Occupational and Environmental Medicine at AMM at the University of Gothenburg Sahlgrenska Academy. He has expertise in both environmental medicine and acoustics, has conducted multiple laboratory studies on the effects of noise, vibration and other environmental stressors on physiological and subjective sleep and cognition.[7,19-23,48-52] He is currently secretary of the International Commission on the Biological Effects of Noise (ICBEN).

Natalia Vincens is a full-time researcher at AMM and medical doctor specialised in internal medicine and nephrology with clinical experience in cardiometabolic health care. She has expertise in the effects of noise and ground-borne vibration on health, including cardiometabolic health outcomes.

Leo Stockfelt is a consultant medical doctor ("överläkare") at Västra Götalands Regionen and researcher specialised in occupational and environmental medicine.

Mikael Ögren is a full-time researcher and acoustician at AMM and VGR with extensive expertise in noise and vibration modelling and measurement.

Alexandra Weinenmann is Professor in Interaction Design and head of the Division of Human Computer Interaction at the Department of Applied Information Technology, University of Gothenburg. She has expertise in developing different methodological approaches to capture mobile situated practices and the users' engagement with their technologies and services.

Mattias Rost is Associate Professor in Interaction design, and head of division of CLIC - Cognitive science, Learning and IT, Interaction design, and Communication at the University of Gothenburg. He has expertise in mobile interaction, digital wellbeing and health, and processes for research design and development.

Mathias Basner is Professor in Psychiatry and Director of the Behavioral Regulation and Health Section in the Department of Psychiatry, Division of Sleep and Chronobiology, at the University of Pennsylvania, USA. He is an international expert in the noise-induced effects on sleep and developed the *Cognition* test battery that will be used in this study.

Magdy Younes is Distinguished Professor Emeritus and medical doctor at Sleep Disorders Center at the University of Manitoba, Canada. He is an expert in respirology, critical care medicine and sleep medicine, and developed the ORP marker of sleep depth and stability that will be used in this study.

10. Feasibility

The multidisciplinary team has extensive experience conducting studies on the effects of noise on sleep and health. The SEL is managed solely by the project group, and we have full and 24/7 access to the facility. We have expertise investigating the effects of noise and vibration on sleep using and with the methods in the proposed study, have conducted multiple noise-related in-laboratory sleep experiments, and have protected time for research.

11. Significance

Investigating biological mechanisms linking sleep disruption by vibration and noise and the development of disease may provide an exciting new research direction to mitigate the significant public health problem of transportation exposure. Identifying metabolites that are impacted by sleep fragmentation may not only improve our understanding of the pathogenesis of diseases associated with sleep disruption by medical, lifestyle and environmental factors, but can also offer insights for future therapeutic and preventative interventions to improve sleep. A deeper understanding of the cognitive consequences of noise-disturbed sleep and the mechanisms underlying inter-individual differences in vulnerability to nocturnal noise exposure may offer insights into observations that disturbed sleep is a potential risk factor for cognitive decline.[15]

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