Ambulatory thermoregulatory system identification in relation to vigilance disturbances.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Sleep disorders and disturbances
Study type	Interventional

Summary

ID

NL-OMON40230

Source
ToetsingOnline

Brief title
Sleep, fatigue and body temperature in health and disease.

Condition

- Sleep disorders and disturbances

Synonym
fatigue, sleep problems

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Technologiestichting STW

Intervention

Keyword: ambulatory, sleep, thermoregulation, vigilance

Outcome measures

Primary outcome

The study aims to identify disease-specific deviations in the multivariate thermoregulatory and vigilance response-parameter profile with possible value for diagnosis and for a better understanding of the involvement of thermoregulatory state in vigilance complaints. As such, rather than a single variable, the multivariate thermoregulatory and vigilance response-parameter profile is the main outcome measure. The multivariate profile will be reduced to significant variables with discriminative value to differentiate the vigilance (more-fatigued vs less-fatigued) and diagnostic profiles (i.e. different disorders) in laboratory and ambulatory recordings.
The multivariate profile will consist of three descriptive outcomes (delay to response onset, sensitivity slope of the response and saturation level) for each of the physiological variables described above. The vigilance response profile will consist of objective vigilance (EEG and PVT) and subjective vigilance, fatigue, sleepiness and effort. In addition, the participants will have a diagnostic profile based on their clinical diagnosis.

The multi-parameter profile approach has a risk of including parameters that differ between groups by mere chance. Therefore, using the leave-one-out cross-validation approach, the optimally discriminating multivariate profile for any specific diagnostic group will be determined for 29 patients each time

and evaluated for the remaining one to obtain overall classification

reliability.

Secondary outcome

* Circadian rhythms of skin temperature, activity and posture.

* Sleep quality estimates derived from actigraphy.

* Daily exposure to environmental temperature, humidity and light.

* Daily average and variability of subjective feelings of thermal comfort,

sensation, arousal, vigilance, stress and caffeine intake.

* Descriptive statistics of the participants obtained through questionnaires on

the website of the Netherlands Sleep Registry (www.slaapregister.nl), which

includes medical history, history of or current sleep disorders, chronotype,

sleep quality, level of sleepiness and fatigue.

Study description

Background summary

Vigilance disturbances, among which fatigue, sleepiness and sleeplessness, are a common denominator of functional impairments that affect quality of life in disorders of the central nervous system. The brain areas involved in sleep and wakefulness regulation are sensitive to temperature, which in an evolutionary sense is among the oldest cyclically varying physical aspects of the environment. They include the hypothalamic suprachiasmatic nucleus (SCN) and preoptic area (POAH); key players in the regulation of both temperature and vigilance * with demonstrated response overlap even for single neurons. Indeed, we have recently observed that the spontaneous time-variance of skin temperature * determined by thermoregulatory cardiovascular blood flow control - is a significant predictor for fluctuations in vigilance both in healthy controls and narcoleptic patients.1 Also, we demonstrated a prominent response of sleep and vigilance parameters to very mild manipulations of skin temperature.2-4
It is often forgotten that the major thermoregulatory effector in humans, the skin, is in fact the largest organ of the body. Not surprisingly therefore, a

large proportion of the paravertebrate sympathetic chain ganglion motorneurons is dedicated to the regulation of skin blood flow. And, other than suggested by the older handbooks, studies during the last decades,5 have clearly shown that autonomic outflow is somatotopically differentiated rather than generalized. Indeed, the paravertebrate sympathetic chain motorneurons innervating the skin vasculature are small and consequently show little integration, allowing for topographic specificity of skin vasoconstriction. Thus, there is good reason to suppose that the spatiotemporal characterization of spontaneous fluctuations and evoked responses in skin vasoconstriction, and consequently skin temperatures, could provide a magnifying glass view on subtle abnormalities in autonomic function.
These spatiotemporal fluctuations and responses are part of a closed loop that includes the POAH, as mentioned an area that is strongly involved in vigilance regulation. In brief, the POAH controls skin vasoconstriction by acting, through the medulla, on paravertebrate sympathetic chain ganglion motorneurons. In turn, skin temperature changes associated with changes in skin blood flow are sensed by a dense network of nerve endings, ascending to project back to, among others, the POAH. Consequently, we obtained considerable evidence for a hypothesized1, 6 causal effect of spontaneous and evoked skin temperature fluctuations on the normal and abnormal variation in vigilance level and sleep in health and disease.1-4, 7-10

Recent unpublished interesting findings support the validity of focusing on the thermoregulatory system. Firstly, we found a redistribution of topographical coupling of thermoregulated skin areas after sleep deprivation. Traditionally, the skin is subdivided into distal areas characterized by arteriovenous anastomoses (AVAs) and a proximal area without. AVAs are constricted under sympathetic control, and if released, a manifold increase in skin blood flow results, facilitating the transfer of heat from the core of the body, by radiation and convection from the skin to the environment. Therefore, a dichotomy is usually presumed, with the distal AVA-rich areas as primary targets for thermoregulation regulated and fluctuating independently from the proximal area. Our new results suggest that the distinction between the two is flexible and co-varies with sleepiness. In brief, temperature was continuously measured at 15 sites along the proximal to distal axis of the body in twelve healthy volunteers for two whole days controlled to be identical with regards to environment, behavior and food intake; once after a normal night of sleep and once after a night of total sleep deprivation. The multivariate time series of the two days were subjected to principal component analysis in order to quantify co-varying skin areas. Interestingly, there appeared to be a shift in the border between proximal and distal; the temperature of the lower legs and feet started to co-vary with proximal skin areas. This suggest that the sleepiness of a person may be reflected in the topographical profile of skin temperature fluctuation coupling under controlled yet relatively normal ambulatory conditions.

A second example concerns an abnormality in the thermoregulatory changes

response to a postural *perturbation* in a neurological disease, narcolepsy. We previously published that the distal skin temperature of narcoleptic patients measured under ambulatory conditions is increased during the day, and that the amount of increase correlates with the difficulty to stay awake.1 In a recently completed, unpublished lab study where both narcoleptic patients and controls were kept in a supine position, narcoleptic patients and controls however reached the same high level of distal skin temperature that is normal in a supine position. Together, these two studies suggest a possible deficiency in narcolepsy of the cardiovascular vasoconstrictive response (and consequent temperature decrease) of the skin that normally occurs with orthostasis. Whereas in healthy controls an upright position reduces the central venous pressure, unloads cardiopulmonary baroreceptors and consequently leads to strong distal vasoconstriction and the consequent decrease in skin blood flow and temperature, this response appears to be attenuated in narcolepsy. A third example indicates that deficiencies in regulation of skin temperature and its relation to daytime sleepiness are not limited to distal sites, neither to narcolepsy. We recently completed ambulatory skin temperature recordings in 45 patients with early stage Alzheimer*s disease, as well as in matched healthy controls and disease controls, i.e. subjects with only subjective memory complaints. On top of the normal changes with aging11 only Alzheimer patients, but not disease controls, showed a significant increase in daytime, but not nocturnal proximal skin temperature. Of note, the increase correlated with daytime sleepiness.

Concertedly, our published results as well as our new unpublished findings illustrate how spatiotemporal characteristics of skin temperature may be disease-specific and possibly have diagnostic value and provide clues towards autonomic nervous system abnormalities that may lead to a better understanding of the vigilance disturbances that are so common to nervous system disorders. The present protocol aims for an extensive spatiotemporal characterization of skin temperature regulation and fluctuation both in controlled laboratory conditions and under unconstrained ambulatory conditions. A validation of the ambulatory profile against the laboratory profile will provide insight in the applicability of the ambulatory approach as a cost-efficient tool to aid neurological examination.

Study objective

The present study aims to systematically investigate whether the thermoregulatory profile of spontaneous fluctuations and responses to perturbations differs in association with diagnosis and with individual differences in the severity of vigilance complaints.

Secondary objective is to determine whether the profile of thermoregulatory parameters of spontaneous fluctuations and responses to perturbations as obtained in the laboratory can be approximated using a more cost-efficient ambulatory assessment approach.

To determine the relative contribution of the baroreceptor and skin temperature to the drop in vigilance that results from changing from an upright to a supine posture.

Study design

A within-subject 7 day ambulatory observation period and 2 lab days, one of which will be a randomized laboratory protocol of 1 day. The lab protocol includes manipulation of light (dim, bright), temperature (mildly cool, mildly warm), posture (seated, supine) applied across time of day. The other lab day will be used to explain the protocol and do some short tests.

Intervention

Eight of the non-active duty pilots will be requested to shorten their habitual sleep duration by 1 hour in the 4 nights preceding the lab measurements. Another eight non-active duty pilots will be requested to lengthen their habitual sleep period with 1 hour in the 4 nights precending the lab measurements. The remaining pilots will be instructed not to change their habitual sleep pattern.

During the intervention study in the lab, participants will be admitted to the institute from 9:00 in the morning and stay until approximately 18:00 in the afternoon. Each participant will sequentially be subjected to 12 manipulation blocks. Each block will consist of one of the following manipulations: change of posture (supine, seated), mild warm versus cool skin temperature manipulations within the thermoneutral zone or no skin temperature manipulation, bright and dim light exposure.

To allow for an assessment of skin temperature responses and fluctuations the thermosuit should not contain any heated or cooled water. Therefore, all free running temperature conditions are presented sequentially in a 2 (light) x 2 (posture) full factorial design. A separate 2 (light) x 2 (posture) x 2 (temperature) full factorial design will be applied that includes the temperature manipulations. The order of the blocks and the designs is randomized across subjects within the same clinical population.

Each manipulation block will last 30 minutes. The first 19 minutes of a block allow for the consumption of an isocaloric snack (60 kcal and 100ml ice tea) and adaptation to the new conditions. From time t = 00:19 to t = 00:26 of each manipulation the participant performs the psychomotor vigilance task. At time t = 00:26 participants rate their subjective fatigue, sleepiness, stress, thermal comfort and sensation and arousal. Each block concludes with a 2 1-minute eyes-open and eyes-closed resting state EEG recordings.

Study burden and risks

The burden of participating filling out questionnaires multiple times a day for 7 days as well as wearing the small ambulatory sensors. The burden of the lab protocol will mainly be attaching the sensors (including a rectal temperature sensor) and wearing the body suit for skin temperature manipulations.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Participants will only be included if they can be classified to one of the four most prevalent insomnia phenotypes, narcolepsy, vasovagal syncope or hypothalamic pituitary insufficiency. Participants have to be at least 18 years old and less than 70 years old.
Active duty pilots will be included if they are currently employed by an airline, in possession of a valid Air Transport Pilots License (ATPL), valid medical clearance and a type rating. Non-active duty pilots possess a frozen ATPL (i.e. they completed their training, but don*t have

the required 1500 hours of flying experience yet). All pilots will be between 20 and 58 years of age.

Exclusion criteria

Participants will be excluded if they report an eye disease incompatible with light manipulation (ocular pathology or color deficiency).
Comorbidity of other clinically diagnosed primary somatic or psychiatric disorders. Women that are pregnant or currently breast feeding. Current shift work, or shift work in the month before the study. Crossing several time zones in the month before the study.
Shift work and travel will NOT be exclusion criteria for active duty pilots.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-08-2014
Enrollment:	150
Type:	Actual

Ethics review

Approved WMO

Date:	28-10-2013
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL43319.029.13