Noradrenergic and cholinergic modulation of sleep and dreams

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The overarching objectives of this proposal are: 1) To evaluate the effect of noradrenergic modulation on type I potentials in wakefulness (vertex potentials), and NREM sleep (vertex sharp waves, K-complexes) and on dreaming in NREM sleep; 2) To…

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON57413

Source
ToetsingOnline

Brief title
Pharmacological modulation of sleep

Condition

- Other condition

Synonym
NA

Health condition

normal brain physiology, no disease

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Herseninstituut
Source(s) of monetary or material Support: ERC Starting Grant Dreamscape 101039782

Intervention

Keyword: Acetylcholine, Consciousness, Noradrenaline, Sleep

Outcome measures

Primary outcome

The two main study parameters are 1) The topography and amplitude of the evoked and spontaneous type I slow waves measured by EEG in wakefulness, NREM and REM sleep. 2) Number of mental experiences reported and features of the mental experiences (e.g. vividness) assessed with a questionnaire in RedCap.

Secondary outcome

Secondary study parameters are 1) Physiological arousal measures, including electrocardiographic (ECG), breathing and skin conductance, pulse wave amplitude. 2) physical arousal measured with EMG. 3) Subjective arousal measures including sleepiness, alertness and subjective perception of sleep quantity and quality during the serial awakenings and falling a sleep period.

Study description

Background summary

The study of consciousness and conscious experiences during sleep, such as dreaming, have long fascinated humankind, yet the precise neural mechanisms behind these experiences remain unclear. Understanding these mechanisms by researching brain activity and the neuromodulatory systems during sleep could provide new insights and treatments for sleep disorders and broaden our understanding of consciousness. These results could provide potential applications for conditions involving abnormal mental activity during sleep,

such as recurring nightmares, parasomnias (i.e. abnormal dream-related behaviors), epic dreaming disorder (i.e. excessive and exhausting dreams), and paradoxical insomnia (i.e. feeling awake during sleep and experiencing persistent ruminations), which affect about 5% of the population and significantly impair sleep quality. Additionally, studying conscious experiences during sleep can shed light on related phenomena like hallucinations and delusions in psychiatric disorders such as schizophrenia, as both involve the brain generating experiences without external stimuli.

Conscious experiences during sleep (i.e. dreaming) can occur in both rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep, each characterized by distinct EEG patterns. A neural signature of dreaming shared by both REM and NREM sleep, is local activation of posterior brain regions, named the *posterior hot zone*. Furthermore, dreaming seems closely related to two types of brain waves, which will be referred to here as type I and type II potentials. Specifically, a dream was particularly likely to be reported when in NREM sleep, a high amplitude and widespread frontocentral slow wave (i.e., type I potential) appeared in the EEG recording shortly before the awakening, and when, at the same time slow waves in the posterior hot zone of the brain (i.e., type II potentials) were particularly small. However, it remains unknown which neurophysiological processes underlie this neural signature of dreaming, and how the contents of dreams are generated.

Type I potentials may be associated with noradrenergic activity stemming from the locus coeruleus (LC). Animal studies indicate that LC neurons discharge intermittently, synchronized with sleep spindles and slow-wave up-states, suggesting that the LC could drive cortical activity during NREM sleep slow waves. In humans, functional magnetic resonance imaging (MRI) has shown activation in the pons, including the LC, during high-amplitude slow waves in NREM sleep, potentially corresponding to spontaneous type I slow waves, as well as during sound-evoked K-complexes. Furthermore, the cortical regions where type I slow waves originate from, such as the posterior medial parietal cortex and the sensorimotor cortex, also have the highest concentrations of noradrenaline, while the occipital cortex, typically spared by type I slow waves, has the lowest levels of cortical noradrenaline. During wakefulness brain waves similar to type I potentials (i.e. vertex potentials) are observed in response to unexpected sensory stimuli. These results suggest that noradrenergic activity (i.e. LC activation) in the absence of sensory stimulation may underlie spontaneous type I potentials in NREM sleep.

Slow waves can also occur during REM sleep, although with a smaller amplitude compared to NREM sleep. Similar to NREM sleep, REM sleep features two types of slow waves: sawtooth waves and medio-occipital slow waves. Sawtooth waves, which are considered a type I potential, share several characteristics with ponto-geniculo-occipital (PGO) waves, originally identified in cats. Both sawtooth and PGO waves last between 60-360ms, appear at the NREM-REM sleep transition several seconds before the first rapid eye movement, occur in

bursts, are activating, and are often, but not always, associated with trains of rapid eye movements. One of the few studies documenting potential PGO-wave equivalents in humans with intracranial recordings described indeed the presence of a concomitant sawtooth waves in the scalp EEG, supporting the analogy between sawtooth and PGO waves. Animal studies have demonstrated that the aminergic system inhibits PGO waves, while cholinergic stimulation triggers PGO wave bursts. This suggests that cholinergic transmission may also be responsible for generating sawtooth waves (type I potentials) during REM sleep in humans.

The associations between the noradrenergic and cholinergic systems and type I potentials and their association with conscious experiences (i.e. dreaming) have not been explored in humans. In this study, we therefore aim to examine the relationship between type I potentials to arousal systems and dreaming through pharmacological modulation n of the noradrenergic and cholinergic neuromodulatory systems. This study will contribute to our understanding of the neurophysiological processes of dreams and how dreams are generated in the brain.

Study objective

The overarching objectives of this proposal are: 1) To evaluate the effect of noradrenergic modulation on type I potentials in wakefulness (vertex potentials), and NREM sleep (vertex sharp waves, K-complexes) and on dreaming in NREM sleep; 2) To evaluate the effect of cholinergic modulation on type I potentials (sawtooth waves) and dream features in REM sleep.

Specifically, we hypothesize that:
1. compared to placebo, the amplification of noradrenergic modulation induced by atomoxetine will increase the amplitude of evoked and spontaneous type I potentials (vertex wave in wakefulness, vertex sharp waves and K-complexes in NREM sleep) but will not substantially affect type II slow waves. It will result in an increase in the incidence of dream reports in NREM sleep.

2. compared to placebo, the attenuation of noradrenergic modulation induced by clonidine will decrease the amplitude of evoked and spontaneous type I potentials (vertex wave in wakefulness, vertex sharp waves and K-complexes in NREM sleep) but will not substantially affect type II slow waves. It will result in a decrease in the incidence of dream reports in NREM sleep.

3. compared to placebo, the amplification of cholinergic modulation induced by donepezil/ galantamine will increase the amplitude of sawtooth waves but will leave other slow waves of REM sleep unaffected. It will induce an accentuation of dream-like features (vividness, perceptual aspects of dreams). This study will not examine a reduction in cholinergic transmission because REM sleep is expected to be too strongly inhibited by anticholinergics, even at low doses.

Secondary, the association between type I potentials and dreaming under different drug conditions and physiological arousal (i.e. heart rate, respiration, skin conductance and pulse wave amplitude), physical arousal (i.e. electromyographic (EMG)) and subjective arousal (i.e. sleepiness/alertness (Karolinska Sleepiness Scale - KSS; Pre-Sleep Arousal Scale) and subjective estimation of sleep quality and quantity) will be examined. This will allow us to further explore the association between type I potentials, dreaming and the arousal system.

Study design

Dit is een dubbelblinde, placebogecontroleerde, gerandomiseerde cross-over studie met vier middelen. Deelnemers krijgen eenmalig een enkele dosis van 40 mg atomoxetine (een selectieve noradrenaline heropname remmer die de extracellulaire noradrenaline verhoogt), 0.05 mg clonidine (een α2-noradrenerge auto-receptoragonist die de LC-activiteit remt en daarmee de afgifte van noradrenaline remt in de cortex), 5 mg donepezil (een selectieve cholinesteraseremmer die centrale cholinerge transmissie bevordert), of placebo in pseudo-gerandomiseerde volgorde, op verschillende onderzoekavonden 2 uur voor het slapen gaan. Er zitten ongeveer 2 weken tussen de afspraken om er zeker van te zijn dat de betreffende middelen het lichaam hebben verlaten voordat een nieuwe middel wordt ingenomen. Elke deelnemer (cluster) wordt willekeurig toegewezen aan een van de vier reeksen, volgens een Latin Square Design, zodat elk middel één keer aan elk ander middel voorafgaat. Tijdens de overnachting worden door geluiden geïnduceerde type I-hersenpotentialen geregistreerd en tussen de middelen vergeleken. Tijdens de overnachting worden de deelnemers ook op verschillende tijdstippen van de nacht wakker gemaakt en gevraagd naar hun dromen en de kenmerken van de dromen.

Intervention

N/A

Study burden and risks

None of the procedures included in this study are considered to be therapeutic or diagnostic. In this respect, the study offers no direct benefits to the subjects.

No serious side effects from the single doses of atomoxetine, clonidine and donepezil/ are expected. Considering the extensive exclusion criteria, the recruitment of healthy young participants, screening procedure, and constant monitoring of the participants the chances of side-effects are minimal. However, if participants experience side effects of the medication during the study such as headache, diarrhea, nausea, dizziness, sedation, low blood pressure upon standing, dry mouth, decreased appetite, insomnia, increase in

blood pressure/increased heart rate, the experiment will not be continued until the participant feels better. If participants need medical assistance for any reason, there is always at least one person present at the institute who can provide first aid, including resuscitation. If necessary, the researcher approaches this person and calls an ambulance. In addition, the research takes place next to the Amsterdam UMC, so help is in close proximity.

Rarely, skin irritation and allergic reactions to the electrode gel or the material of the net can occur. In case a subject presents an allergic reaction to the electrode gel or the material of the net, the experiment will be discontinued. According to the severity of the reaction, the participant will either be monitored, encouraged to contact the general practitioner or referred to the first aid.

Fatigue and sleepiness the next day will likely occur due to sleep fragmentation (by multiple awakenings/interviews on mental activity). Sleep restriction could impair someone*s ability to drive or safely perform other potentially dangerous tasks. For this reason, participants will be advised not to drive or participate in other potentially dangerous tasks the day after the study nights.

Sleep restriction or deprivation might trigger a manic/hypomanic episode or seizures in vulnerable persons. For this reason, people with a known history of bipolar or manic/hypomanic episodes or of seizures will not be able to participate. However, some people may still have this risk and not know about it. If investigators observe any unusual behavior or manifestations, medical care will be sought.

Sleep reduction or deprivation may trigger or aggravate a migraine headache in susceptible people. Subjects with a history of migraine may choose not to participate in the experiments. If they do participate, they are instructed to inform the investigators if they begin to experience a headache. They will be able to stop the experiment and take their usual headache medications, if this medication does not interact with the study medication. They may stay in the lab to sleep and or return home.

There are no risks associated with auditory stimulation. Auditory stimuli will be delivered at a volume that are compatible with sleep and thus safe for human hearing.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Age 18-35 years
• Good sleep quality (Pittsburgh Sleep Quality Index <5 and Epworth Sleepiness Scale < 11)
• Regular sleep-wake patterns
• Habitual sleep duration of at least 7 hours per night
• Good English language proficiency

Exclusion criteria

• Inability to follow procedures (for example because of insufficient knowledge of project language, cognitive or hearing disturbances etc.)
• Individuals with known structural brain lesions
• Individuals with a history of seizures or suspected epilepsy
• History of a medical condition that may influence sleep and/or brain activity
• History or presence of psychological/psychiatric disorders that may affect sleep and/or the ability of the individual to follow experimental procedures
• History or presence of a cardiovascular, metabolic or neurological disorder
• Individuals with substance abuse (alcohol or other substances) in the last 6

months
• Lactating women, or female subjects of child-bearing potential who are pregnant or planning to become pregnant.
• Current or recent use of medications with psychotropic effects (e.g. antipsychotics, antidepressants, anxiolytics, psychostimulants, antihistamines or beta blockers - based on individual*s report and/or clinician judgement).
• Traveling to time zones with a time difference of more than 1 hour in the 2 weeks preceding the study days
• Individuals with extreme chronotypes (30 points or lower, or 70 points or higher on the morningness-eveningness questionnaire)
• Presence of snoring
• Blood pressure < 90/60 mmHg or > 140/90 mmHg or heart rate < 55 beats per minute
• Any medications or conditions contra-indicative of the use or interacting with atomoxetine, clonidine, or donepezil. Including: Medical Conditions
• Liver and Kidney Disorders: Liver insufficiency, kidney insufficiency
• Cardiovascular Diseases: Severe hypertension, heart failure, arterial occlusive disease, angina pectoris, congenital heart disease (hemodynamically significant), cardiomyopathy, history of myocardial infarction, life-threatening arrhythmias, channelopathies, sick sinus syndrome (brady-tachycardia syndrome), supraventricular conduction disorders (e.g., sino-atrial or atrioventricular block), electrolyte imbalances (hypokalemia, hypomagnesemia), prolonged QT interval (acquired or familial history), cerebrovascular disorders (aneurysm, stroke)
• Respiratory Disorders: History of asthma, obstructive pulmonary disease
• Neurological and Psychiatric Conditions: Epilepsy, neuroleptic malignant syndrome, psychiatric disorders (e.g., psychosis, depression), polyneuropathy, cerebrovascular or peripheral vascular disorders, autonomic neuropathy (e.g., due to diabetes mellitus)
• Gastrointestinal Disorders: Ulcers (or concurrent use of NSAIDs), constipation
• Metabolic and Genetic Disorders: Galactose intolerance, lactase deficiency, glucose-galactose malabsorption
• Other Conditions: Pheochromocytoma
• Hypersensitivity to specific compounds of the medications
• Gelatin
• Sodium lauryl sulfate (E487)
• Titanium dioxide (E171)
• Indigotine (E132)
• Hydroxypropylmethylcellulose (E464)
• Propylene glycol (E1520)
• Talc (E553b)
• Polyethylene glycol (PEG 6000)
• Yellow iron oxide (E172) (for 10 mg formulations)
• Donepezil hydrochloride monohydrate
• Lactose monohydrate
• Microcrystalline cellulose
• Dried maize starch

• Hydroxypropylcellulose
• Sodium stearyl fumarate
• Medication Interactions
• Cardiovascular Medications:
• Class IA antiarrhythmics (e.g., quinidine)
• Class III antiarrhythmics (e.g., amiodarone, sotalol)
• Beta-blockers, calcium channel blockers, ACE inhibitors, vasodilators, alpha-2 blockers (e.g., fentolamine, tolazoline)
• Medications that affect blood pressure (e.g., decongestants such as pseudoephedrine, phenylephrine, salbutamol)
• Psychiatric Medications:
• Monoamine oxidase inhibitors (MAOIs)
• Antidepressants:
• Tricyclic antidepressants (e.g., amitriptyline, imipramine)
• SSRIs (e.g., fluoxetine, paroxetine, citalopram, escitalopram)
• Serotonin-norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine, mirtazapine)
• Antipsychotics: Neuroleptics, phenothiazines, butyrophenones, sertindole, pimozide, ziprasidone
• CYP2D6 inhibitors that are psychiatric medications: Fluoxetine, paroxetine
• Antibiotics and Antifungals:
• Certain antibiotics (e.g., erythromycin, clarithromycin, levofloxacin, moxifloxacin)
• CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin)
• Antifungals (e.g., terbinafine)
• Other Drug Classes:
• CYP2D6 inhibitors (non-psychiatric): Quinidine, terbinafine
• Enzyme inducers (e.g., rifampicin, phenytoin, carbamazepine, alcohol)
• Medications affecting electrolyte balance (e.g., thiazide diuretics)
• Cholinergic system modulators (e.g., cholinesterase inhibitors, cholinergic agonists, neuromuscular blockers such as succinylcholine)
• Sleep medications

Study design

Design

Study type: Interventional

Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2025
Enrollment:	32
Type:	Anticipated

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	15-04-2025
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL88917.100.25