Unravelling the sleepy brain: A neuroimaging study in central hypersomnolence disorders

Published: 23-07-2019
Last updated: 12-04-2024

The objective is to identify non-invasive neuroimaging biomarkers and mechanisms characterizing different phenotypes of central disorders of hypersomnolence (narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia) as compared to groups of...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Sleep disturbances (incl subtypes)
Study type	Observational non invasive

Summary

ID

NL-OMON49234

Source
ToetsingOnline

Brief title
Neuroimaging in central hypersomnolence disorders

Condition

- Sleep disturbances (incl subtypes)

Synonym
central hypersomnolence disorders, narcolepsy

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: The principal researcher in Canada (Dr. Dang-Vu) received funding from the Canadian government-related funding agency to carry

out this research project.

Intervention

Keyword: EEG, Hypersomnolence, MRI, Narcolepsy

Outcome measures

Primary outcome

We will aim at assessing non-invasive MRI-related neural biomarkers in narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia by comparing them with acutely sleep-deprived controls and healthy controls. To create a reliable and elaborate combination of possible markers, the following neuroimaging will be used:

- Brain responses across the sleep-wake cycle using simultaneous EEG-fMRI
- Brain responses during wakefulness using fMRI, especially in correlation with behavioral results in attentional and rewarded-associative memory tasks
- Regional brain volumes and cortical thickness using MRI morphometry
- White matter connectivity using DTI
- Brain connectivity using structural covariance and resting-state fMRI functional connectivity
- Regional GABA levels in the medial prefrontal cortex and posterior cingulate using MRS

Secondary outcome

The secondary analyses will include:

- Correlation between neuroimaging activation maps and behavioral performance on the cognitive tasks.

- Relationship between neuroimaging activation maps and clinical patient profiles (e.g. disease duration, subjective sleepiness and depression and anxiety scores)

- Effect of sleep inertia on performance on the rewarded-associative memory task

- The difference in molecular composition of exhaled breath between NT1, NT2 and IH and secondary in comparison to acutely sleep-deprived controls and HC

- Effect of acute sleep deprivation on molecular exhaled breath composition in healthy controls

As an exploratory objective, patients with idiopathic hypersomnia will be subcategorized in short (< 11 hours) and long (> 11 hours) sleepers and their neuroimaging profiles as defined in the primary objectives will be compared.

Study description

Background summary

Central disorders of hypersomnolence are mainly characterized by excessive daytime sleepiness despite normal timing of nocturnal sleep. All disorders greatly impair daily functioning. Three subtypes of central disorders of hypersomnolence are being distinguished: narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia. While narcolepsy type 1 originates from a selective loss of hypothalamic hypocretin-producing neurons, the pathophysiology underlying narcolepsy type 2 and idiopathic hypersomnia remains to be fully elucidated. It is probable that different causes may lead to these phenotypes.

The underlying brain circuit abnormalities of only narcolepsy type 1 have so far been identified using small sample groups, but their correspondence with other hypersomnolence disorders has yet to be investigated. As distinctive features between narcolepsy type 2 and idiopathic hypersomnia have not clearly been defined and given the clinical similarities between these two disorders, the question arises whether the current third edition of the International Classification of Sleep Disorders (ICSD-3) classification addresses two

separate entities or arbitrarily splits a heterogeneous group of patients. This is further emphasized by > 50% diagnosis crossover of narcolepsy type 2 and idiopathic hypersomnia after repetition of diagnostic testing. In the future, the neural signatures of different central disorders of hypersomnolence could reveal transdiagnostic disease dimensions and help to improve classification of central disorders of hypersomnolence and potentially treatment options. The molecular exhaled breath composition will also be compared between the patient groups. If the differences in this pattern are robust and sensitive, this could substantially improve diagnostic possibilities of central disorders of hypersomnolence in the future.

Study objective

The objective is to identify non-invasive neuroimaging biomarkers and mechanisms characterizing different phenotypes of central disorders of hypersomnolence (narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia) as compared to groups of partially sleep-deprived and healthy control subjects.

Study design

Cross-sectional multi-center study with harmonized data collection across two sites (Netherlands & Canada), including three patient groups (narcolepsy type 1, narcolepsy type 2 and idiopathic hypersomnia) and one group of healthy controls. Healthy controls will undergo the study protocol twice, once with a regular sleep-wake pattern and once with a night of partial sleep deprivation (<4 hours of sleep) before MRI acquisition. The study paradigm consist of one week of actigraphy, after which all subjects will administer multiple clinical and cognitive questionnaires and undergo two MRI sessions. They will also undergo a short breathing measurement.

Study burden and risks

The participation burden will consist of:
- Signing informed consent (at home for patients and during a visit to the VUmc for control subjects, minimal burden)
- Wear an actigraphy watch and keep a sleep diary (at home for 1 week, minimal burden)
- Visiting the Spinoza Centre (total duration: ±4 hours, preparation before the MRI ±1 hour, MRI protocol including a break ±2 hours and 40 minutes). The MRI protocol will consist of 2 sessions (respectively 78 and 38 minutes), separated by a short break of an hour. During the first session simultaneous EEG-MRI will be used.

In total the study procedures will take 2-3 weeks for patients (exact duration depends on the exact date of signing the informed consent and the availability

of the MRI scanner)

Control subjects will undergo the aforementioned protocol twice (signing the informed consent form will be done once), separated by roughly 2 weeks without study procedures. Before 1 of the visits to the Spinoza Centre, the control subject will be partially sleep deprived for 1 night at home (<4 hours of sleep). In total the burden for control subjects will be: signing informed consent, 2x1 week of wearing an actigraphy watch and keeping a sleep diary, 2x4 hours visit to the Spinoza Centre and 1 night partial sleep deprivation.

In total the study procedures will take 5-6 weeks for control subjects (exact duration depends on the exact date of signing the informed consent and the availability of the MRI scanner). Study participation therefore does require a time investment from the subjects.

Possible benefits related to participation:
Besides financial compensation, subjects will not have any direct benefit from participating in the study. However, participation is expected to result in increased insight in the neurobiological background of sleep in general and central disorders of hypersomnolence.

Potential risks when participating and how we tried to minimize them:
- Temporal halt of psychoactive medication intake in patients:
Patients may experience distress, withdrawal symptoms and increase of symptom severity (depending on the type of medication mainly sleepiness, sleep duration and cataplexy rate). Clear instructions will be given to the patients on the possible effects of temporarily stopping their medication before inclusion. Patients are also allowed to continue medication directly after MRI acquisition. In previous research by our research group, patients were asked to refrain from medication intake for 14-31 days, not leading to problems. In this study we tried to minimize the period by just asking patients to stop for up to 7 days.

- Risks associated with MRI (and simultaneous EEG acquisition):
Simultaneous EEG-fMRI may potentially be a risk for patient safety, due to excess heating as a result of eddy currents. Some people may experience distress due to the claustrophobic environment of an MR scanner. Some may also experience the sound of the scanner as loud. There also is a chance that incidental brain abnormalities will be found.To avoid the potential issue of heating up subjects during EEG-fMRI we will omit the EEG electrodes during MRI sequences that produce a high SAR (specific absorption rate). Standard procedures and equipment will be used, so patient risk is negligible. For subjects who are sensitive to claustrophobia, the positioning in an MRI scanner might provoke feelings of distress or in extreme situations panic attacks. In case a subject feels uncomfortable in the scanner, it is possible to terminate the scanning session at any moment without any consequences for the participant. In case of incidental findings of abnormalities in the MRI scans,

participants will be immediately notified.

- Risks associated with partial sleep deprivation (only in the acutely sleep-deprived control group):
Acute sleep deprivation (< 4 hours sleep for 1 night) may cause distress and lead to increased sleepiness and reduced attention. Acutely sleep-deprived controls will be advised to not drive after the night with limited sleep and will be reimbursed for their (public transport) travelling costs.

Given that the this will not be an intervention study and that the risks are negligible, we believe that the potential knowledge gain on central hypersomnolence disorders in general outweighs the possible risks.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1108
Amsterdam 1081HZ
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1108
Amsterdam 1081HZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients:
- Definite narcolepsy type 1, narcolepsy type 2 or idiopathic hypersomnia, diagnosed according to the International Classification for Sleep Disorders - Third Edition (ICSD-3) criteria
- Age between 18 and 65 years old
- Normal or corrected-to-normal vision
- Capacity to provide informed consent

Healthy controls:
- Age between 18 and 65 years old
- Normal or corrected-to-normal vision
- Capacity to provide informed consent

Exclusion criteria

The following exclusion criteria will apply:

- Systemic or neurological diseases (e.g., infections, inflammatory disorders, dementia, epilepsy);

- Presence of another sleep-related disorder:
For patients:
Previous REM sleep behaviour disorder, insomnia, obstructive sleep apnoea, REM sleep behaviour disorder or Restless legs syndrome diagnosis according to the medical records

For healthy controls:
REM sleep behaviour disorder as screened by the Single-Question Screening for REM Sleep Behaviour Disorder
Restless legs syndrome as screened by the Restless Legs Syndrome Screening Questionnaire (score > 6)
High-risk for obstructive sleep apnoea according to the Stop-Bang questionnaire (score > 4)
Insomnia disorder by the Insomnia Severity Index (score > 14)
Circadian rhythm disorder

- Short sleepers (< 6 hours on average) or irregular sleep schedules
- Having worked on night shifts during the last month
- < 18 or > 65 years of age
- Major psychiatric disorder (e.g., major depression, psychotic or bipolar disorder)
- History of trauma capitis, encephalopathy, former intracranial surgery,

alcoholism or substance abuse
- Contraindications for MRI exam (e.g., claustrophobia, metallic implants)

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-08-2019
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	23-07-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2020
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2021
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	NL68388.029.18