What keeps the brain alert? - A magnetic resonance study into the neural correlates of vigilance in narcolepsy patients

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

Summary

ID

NL-OMON40453

Source
ToetsingOnline

Brief title
Vigilance and sleep resistance in the narcoleptic brain

Condition

- Sleep disturbances (incl subtypes)

Synonym
sleep disorder; hypersomnia

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Persoonlijk budget van Dr. G.J. Lammers

Intervention

Keyword: cataplexy, fMRI, narcolepsy, vigilance

Outcome measures

Primary outcome

All raw vigilance test data will be stored, but main outcome measures for the SART will be total errors of omission and total errors of commission. The comparison between patients and controls will be analysed using a multiple regression models including the number of trials.

Spatiotemporal independent component analysis for the resting state activation using fMRI and GLM (general linear modelling: multivariate regression analyses) for the data-driven fMRI data using the software packages SPM5 (Wellcome Department of Cognitive Neurology, London, UK) and FSL (FMRIB laboratory, Oxford University, UK). Appropriate corrections for multiple comparisons will be performed (Bonferroni, family-wise error, cluster correction).

Secondary outcome

During the study day the subjects will undergo (verbal) IQ assessment using the National Adult Reading Test (NART) and assessment of daytime sleepiness by means of the Epworth Sleepiness Scale (ESS). These two measures will not be utilised to categorically subdivide study groups, but rather to base the later-stage final analysis on the performance on the ESS and the NART.

Study description

Background summary

Narcolepsy with cataplexy is a primary sleep disorder caused by a loss of hypocretin (orexin)-producing neurons in the lateral hypothalamus and the perifornical area. Hypocretin-producing neurons project to brain regions involved in attention, cognition and the regulation of sleep-wake behaviour, such as the locus coeruleus, the raphe and tuberomammillary nuclei and basal forebrain regions. Reduction in activity in these regions due to loss of hypocretin signalling causes the characteristic excessive daytime sleepiness (EDS, tendency to fall asleep), and other symptoms such as the cataplexy (a sudden bilateral loss of muscle tone with retention of consciousness provoked by strong emotions). Several studies have shown that EDS may lead to severely impaired daytime performance. This can lead to dangerous situations in the working environment of the patients, or in similarly demanding situations, such as in traffic.

- Brain anatomy -
By means of neuroimaging techniques, no consistent structural brain abnormalities have yet been found in narcoleptic patients compared to healthy control subjects. Studies using magnetic resonance (MR)-based voxel-based morphometry, which allows statistical comparisons of local tissue composition (both grey and white matter) across the whole brain, have yielded mixed results. Whereas several studies found grey matter volume-decreases in the hypothalamus, thalamus, nucleus accumbens and fronto-temporal cortices, others could find no differences between patients and controls at all, or only in part of the aforementioned brain areas.

Diffusion tensor imaging (DTI) provides insight in yet another modality of the brain anatomy. This relatively quick scan reveals the diffusion direction of water, which usually is greater parallel to the axon than perpendicular to the axon, and this therefore believed to reflect the degree of tissue (white matter) organisation or alignment. In one study full brain DTI has been performed on patients with idiopathic narcolepsy, with a field strength of 1.5 T, revealing widespread abnormalities in brain regions thought to be involved in the pathophysiology of idiopathic narcolepsy. Another, complementary study objectively identified abnormalities in the hypothalamus, consistent with the hypocretin neuron loss, and the targets of these neurons. A third, recent study compared shows morphological abnormalities in the left amygdala, the left inferior frontal gyrus and the left postcentral gyrus in NC patients.

- Brain function -
There is only a limited number of recent studies that have investigated the resting, awake brain of NC patients at the functional level. Two positron emission tomography (PET) studies investigated glucose metabolism and provide us with mixed results. First, a study with 24 NC patients and an equal number of control subjects indicated hypometabolism in the hypothalamus and thalamus,

in line with the anatomical findings discussed earlier. The other group of investigators, however, reported a lack of this hypometabolism and instead suggested an increase of metabolism in the cingulate and visual association cortices of NC patients compared to controls. In addition, a single photon emission computed tomography (SPECT) study showed decreased blood flow by in the hypothalamus and thalamus, in accordance with the first PET study, further supplemented by decreased blood flow in other brain areas mostly overlapping structural changes, as reviewed recently.

An additional technique, magnetic resonance spectroscopy (MRS), provides the ability to analyse the chemical composition of living brain matter non-invasively. Only a fairly small number of studies using this technique have been published over the last two decades. After the first study, the investigators had to conclude that, in narcolepsy patients, there is no evidence of neuron loss or *gross biochemical abnormality* in the pontomedullary junction. It was not until six years later that another group reported loss or damage of neurons in the hypothalamus in NC patients compared to controls. Whereas in these studies the analyses have only been performed on one particular region of interest, a third MRS paper appeared, publishing the results of a more integrative approach by investigating metabolic changes in multiple regions of interest. Fourteen NC patients and an equivalent number of matched, healthy controls were subjected to the MRS protocol. The results indicated that the metabolic rate in the right amygdala was decreased in NC patients, which supposedly is caused by a loss of integrity of hypothalamic neurons (indicating that the neurons are damaged in one or another way).

Study objective

No studies have yet investigated brain activity in NC patients in relation to alertness and sleep resistance. The aim of the current study is to obtain more insight into the regulatory mechanisms controlling alertness and sleep resistance in patients with narcolepsy with cataplexy. To this aim, we will for the first time, perform combined EEG/fMRI recordings in narcolepsy patients and matched control subjects.

Study design

Following telephone screening for inclusion and exclusion criteria, the patients and controls will receive information about the purpose and the methods of this study. If the subjects agree to participate informed consent will be acquired.

The subjects that meet the criteria and have given informed consent will be invited to come to the Spinoza Centre for Neuroimaging. The patients are required to refrain from medication for at least 14 days prior to the study day. Furthermore, all subjects are not allowed to use caffeine-containing

beverages in the 24 hours preceding the appointment.

The subjects will be tested in the afternoon. Upon arrival, the subjects will be provided more information on the techniques, if desired. Furthermore, the subjects will undergo (verbal) IQ assessment using the National Adult Reading Test (NART) and assessment of daytime sleepiness by means of the Epworth Sleepiness Scale (ESS). Additionally, the Edinburgh Handedness score will be assessed, determining whether the particular subject is left- or right handed. Then, after equipping the subjects with the EEG electrodes, they will be placed in the MR scanner, and the study protocol will be initiated.

- fMRI and EEG measurements -
Subjects will be scanned using a 3 T Philips MR scanner. This system includes a computer to generate visual and auditory stimuli and to record the participants* responses, a beamer to project visual stimuli in the MR room, an MR-compatible headphone for auditory stimulation, a screen to display visual stimuli and response boxes for the registration of the manual responses. Blood oxygenation levels dependent (BOLD) responses will be recorded by the MR scanner. The electroencephalogram (EEG) will be recorded using an MR-compatible system. Sleep will be assessed according to the 2007 American Academy of Sleep Medicine criteria, with sleep stages scored in 30-second epochs according to the current guidelines. Eyetracking will be used to assess whether subjects have their eyes open or closed and whether patients* eyes are wandering or focussed.
Scanning will be initiated with 5 minutes of structural scanning, followed by a resting state scan (5 minutes) and scanning during the experiment (approximately 25 minutes), respectively. Furthermore, the white matter structure will be assessed (DTI, 6 minutes) and the neurotransmitter content of both amygdalae and the hypothalamus will be determined by MRS (specifically GABA and glutamate).

- Sustained Attention to Response Task (SART) -
Before and after SART administration a blank screen with a white dot in the centre will be shown to the subject. The SART is administered comprising blocks of approximately 30 seconds (27 stimuli in one block with 1150 ms per stimulus, yielding 31.05 s per block) with two different difficulty levels and blocks of equal length during which no action is required. Each of the nine target digits will be shown in an equal number of times in a predetermined quasi-random order, so that the identical target digits are not clustered. The font size will be chosen at random from 52, 72 or 144 points. In the easy blocks, each digit is presented for 250 ms, followed by a blank screen that lasts for 900 ms. A second difficulty level will be constructed and added to the SART to enable analysis of not just baseline performance and activity-correlates, but to add the possibility of analysing the changes in activity patterns in response to an increase of difficulty. In the second difficulty level the target will be presented for 100 ms. The subjects have the same 900 ms to respond. Furthermore, the difference between the presentation lengths will be

accounted for by adding 100 ms between the end of the reaction time and the initiation of the next stimulus. This way, the temporal aspect of the cycle remains identical in both difficulty levels.
The subjects have to respond to the appearance of each digit by pressing a button before the next digit appears, except when the digit *3* is shown. They will be instructed to pay equal attention to speed as to accuracy. The SART error score consist of the total number of errors, expressed as the cumulative number of times the button is pressed when a *3* is shown and the number of times that the button is not pressed when it should have been.

- Sleep resistance -
After the SART the subjects will be asked to fight sleep and to rest quietly in alternating 30-second blocks while keeping their eyes closed, adding up to 5 minutes. Before every *fighting-sleep*-block, subjects will be woken when asleep. After the last block, subjects are free to fall asleep and may continue to sleep for 15 minutes. The presence and staging of sleep will be assessed using the MR-compatible EEG recording.

- DTI -
In addition to the standard anatomical scan that will be performed before the resting state scan (as described above) we will analyse the white matter microstructure by performing diffusion tensor imaging (DTI). In the current study, data acquisition will be performed at a field strength of 3 T, which enables us to analyse the white matter organisation in much more detail than the previous studies managed to do. Furthermore, performing DTI in this study provides the additional opportunity to use task performance as a regressor in the DTI analyses. Whole brain DTI in human subjects will cover approximately 6 minutes of scanning time.

- MRS -
Magnetic resonance spectroscopy (MRS) is a technique that allows us to determine the brain (voxel) content of a particular substance. We would like to assess the levels of GABA and glutamate in both amygdalae and the hypothalamus, and to identify potential correlations between vigilance and emotion regulatory processes and the content of these two important classes of neurotransmitters. These data will be acquired with a voxel volume of 1 cm^3 (3 voxels in total) and will take 15-20 minutes.

Study burden and risks

All subjects will be subjected to a functional MR scan. This scan will take around half an hour to be completed. There are no risks connected to MR scanning. There is, however, a chance that the researcher detects anomalies in the anatomical scan, in which case the attending doctor will be notified.

Preferably non-medicated patients will be included, which abolishes the burden of treatment cessation. Those patients that will be asked to stop their

treatment for at least 14 days will experience a temporary fall-back in their symptoms and performance.
All subjects will be asked to fill out a few short questionnaires prior to scanning. All subjects will be equipped with a net of EEG electrodes and will undergo MR scanning. These methods bring the burdens of laying still for half an hour and washing out the gel underneath the EEG electrodes.

The profit for the patients is that more insight will be gained in the neurobiology of attention and vigilance of in narcolepsy-cataplexy patients that have the extra burden of poor daytime performance, which might eventually lead to successive investigations for alternative or additive medication/treatments improving the quality of life of these patients.

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

For patients:
- definite narcolepsy with cataplexy, diagnosed according to the International Classification for Sleep Disorders * Second Edition (ICSD 2) criteria;
- confirmed hypocretin deficienct;
- age between 18 and 65 years old;
- treatment-naïve or stopping medication at least 14 days prior to the study start;
- normal or corrected-to-normal vision;
- informed consent.;For healthy controls:
- age between 18 and 65 years old;
- normal or corrected-to-normal vision;
- matched to narcolepsy-cataplexy patients regarding age and gender;
- informed consent.

Exclusion criteria

- use of hypnotics or other sleep-wake active drugs;
- younger than 18 or older than 65 years of age;
- diagnosis of uncorrected visual problems (myopia/presbyopia, peripheral vision problems or legal blindness), or cylindrical corrections stronger than -1 dpt or any prismatic visual correction
- current diagnosis of generalised anxiety disorder, depression or other psychiatric illness;
- acute, unstable medical conditions or serious chronic diagnoses;
- contra-indications for MR imaging studies.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-09-2014
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	05-06-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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	NL46982.058.14