Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal
Québec

Information and consent form

Title of the research project:	Pathophysiology of narcolepsy and idiopathic hypersomnia: a multimodal neuroimaging study.
Principal investigator of the research project:	Thien Thanh Dang-Vu, M.D. Ph. D., researcher at the Research Center of the Institut universitaire de gériatrie de Montréal (CRIUGM), Montreal, Canada.
Co-investigators of the research project:	▪ Christophe Grova, Ph. D., Habib Benali, Ph. D., Jean-Paul Soucy, M.D., researchers at the Perform Center, Concordia University, Montreal, Canada ▪ Jamie Near, Ph. D., researcher at the Douglas Hospital Research Center, Montreal, Canada ▪ Hosung Kim, Ph. D., researcher at the University of Southern California, Los Angeles, USA. ▪ Sophie Schwartz, Ph. D., researcher at the University of Geneva, Geneva, Switzerland ▪ Ysbrand Van Der Werf, Ph. D., researcher at the VU University Medical Center, Amsterdam, Netherlands. ▪ Rolf Fronczek, M.D. Ph. D., Gert Jan Lammers, M.D., researchers at the Leiden University Medical Center, Leiden, Netherlands
Funding Agency :	Canadian Institutes of Health Research (CIHR)

1. Introduction.

We invite you to participate in a research project. However, before agreeing to participate in this project and signing this information and consent form, please take the time to read, understand, and carefully consider the following information.

This form may contain words that you do not understand. We encourage you to ask the principal investigator or research staff to answer any questions you may have and clarify any unclear information.

2. Nature and objectives of the research project.

The purpose of this research project is to use brain imaging techniques including magnetic resonance imaging (MRI) and electroencephalography (EEG) with a polysomnography sleep recording to understand the brain mechanisms of narcolepsy and idiopathic hypersomnia.

Narcolepsy and idiopathic hypersomnia are central disorders of hypersomnolence, characterized by excessive daytime sleepiness, which impacts sleep and daytime functioning.

To date, the mechanisms underlying central hypersomnias are poorly understood. Moreover, the precise impacts of these disorders on cognitive function (e.g., attention, memory) have not been studied thoroughly.

In order to understand better the neural mechanisms as well as the cognitive disturbances specific to each central hypersomnia disorder, this project will include several sessions of electroencephalography (EEG) and magnetic resonance imaging (MRI) during which your brain anatomy and function will be examined.

For this research project, we plan to recruit approximately 30 participants suffering from narcolepsy with cataplexy, 30 participants with narcolepsy without cataplexy, 30 participants with idiopathic hypersomnia and 30 healthy sleepers, men and women, aged 18 and above.

3. Development of the research project

3.1 Location of the research project.

This research study will take place at the Research Center of the University Institute of Geriatrics of Montreal (CRIUGM).

3.2 Breakdown of groups, duration of participation and number of visits.

This project is aimed at adult participants who are suffering from narcolepsy (with or without cataplexy) or idiopathic hypersomnia. The project will also include healthy sleepers to act as controls.

If you are a participant with central hypersomnia, your participation in this research project will include two visits separated by approximately 1 week, the first visit in the sleep laboratory for the PSG recording (screening) and the second visit for the overnight sleep session (EEG) and the MRI session. You will stay ≈24h (7 PM to 4:30 PM) at the sleep lab during both visits.

If you are a healthy control, your participation in this research project will include three visits separated by approximately 1 week. The first visit will be to the sleep laboratory for the PSG screening night, the second visit for the overnight sleep session (EEG – 8 hours sleep) and MRI session and a third visit for an overnight sleep session (EEG – 4 hours restricted sleep) and MRI session. During the first visit, you will spend the night in the sleep lab (7 PM to 8:30 AM). You will stay ≈24h (7 PM to 4:30 PM) at the sleep lab during both the second and third visits. The order of the second and third visits will be randomized for healthy controls.

All participants will undergo the same brain imaging protocol (MRI visit) during the second visit (and third visit for the healthy sleepers). The second and thirst visits will be randomized.

All participants will be completing questionnaires during one of their visits. The time of completion of these questionnaires will take on average 30 minutes.

3.3. Neuroimaging techniques

3.3.1 Magnetic resonance imaging (MRI)

Magnetic resonance imaging (MRI) in research provides images of the brain's anatomy and its functioning. Functional magnetic resonance imaging (fMRI) enables us to see the areas of the brain that become active when someone is asked to perform a task. Specifically, when an individual undergoing an fMRI performs a task there is an increase in blood flow in the brain regions that control the activity related to the task. This increased blood flow causes the brain to emit signals that are subsequently detected by the MRI scanner.

Participants will not be injected with any substances. You will simply be asked to lie on a mattress that will slowly slide into a large tube. The tube is open at both ends. An intercom system will enable you to communicate with the medical imaging technologists as needed. For your comfort, we will ask you to wear either a headset or protective caps that will be installed in your ears. This is to reduce the volume of the noises emitted by the MRI scanner. While the scanner is working, it is important to remain immobile. A cushion will be placed around your head to help you remain immobile.

3.3.2 Electroencephalography (EEG)

Electroencephalography (EEG) is a non-invasive technique, which measures bioelectrical brain activity using electrodes placed on the scalp. A gel will be applied under each electrode to enable conductive contact between the electrodes and the scalp. We are simply measuring the spontaneous electrical signal from your brain; we will not induce any current, therefore, you will not feel anything.

3.3.3 Polysomnography (PSG)

Polysomnographic recording (PSG) is a technique used to accurately measure and detect the different stages of sleep. It is used mostly to diagnose sleep disorders. This method is non-invasive and without risk to your health. It allows for measurement of brain activity, blood oxygen levels, heartbeat, breathing rate and eye and leg movements.

The recording of these data will be performed using the EEG described above along with additional measures: electrooculography (EOG) to measure eye movements, electromyography (EMG) to measure muscle tone, a nasal-

oral thermocouple airflow and finger pulse oximeter to measure breathing and blood oxygenation.

3.4 Description of your participation.

3.4.1. Participation to the entire project

- Determination of eligibility.

First, we will determine whether you apply to the criteria of inclusion or exclusion. Indeed, you might not be able to participate to the project for various reasons. This first step of admission will be performed by telephone. If you meet all the criteria of inclusion, you will be invited to the first visit.

- First visit.

You will be invited to spend the night at the sleep laboratory at CRIUGM. You will arrive in the evening after your dinner, you will be prepared with the PSG equipment (electrodes hookup), and then you will spend the night in a private bedroom. When you wake up the next morning, you will receive a breakfast. Healthy controls will be free to go when they wake up the next morning. Participants with central hypersomnia will be asked to stay during the day after they wake up, in order to undergo a test consisting of five 20 min-naps every 2 hours until 4:30 PM. The naps will also be monitored by PSG recording.

- Second visit.

One week later, you will be asked to come back to the sleep laboratory at CRIUGM to stay for the EEG night before the MRI session. On the following day, we will collect saliva samples to analyze markers related to your sleepiness. In particular, we will be analyzing a marker called HLA-DQB1*0602, which is very often found in patients with narcolepsy. Please note that, in order to analyze this marker, your saliva samples will be sent to the Stanford Center for Narcolepsy at Dr. Emmanuel Mignot lab, California, US, a world reference center for this analysis, and will be destroyed once the analyses have been completed.

Then, the MRI imaging session will take place and last approximately 3 hours, including a 60 min-break. All the participants will be required to stay in the morning in the lab until the MRI session begins. Before the MRI session, we will place an EEG cap on your scalp in order to monitor your vigilance and sleep in the MRI. During the MRI session, we will ask you to lie down calmly on the mattress, relax while remaining as immobile as possible, and follow the technician's instructions. During this session, the anatomy and functional activity of your brain will be examined in several different ways. You will also be asked to participate in various tasks such as memorizing sequences of images or text as well as responding as fast as possible to images appearing on a screen. During these tasks, you will be asked to respond by pressing a button on a keypad.

The MRI session will include the following steps:

1. Attention task: You will be instructed to press a button as fast as possible when certain images appear on the screen. The task will last 9 minutes.

2. Memory task: You will be asked to memorize a series of items and recall them. The initial phase of the task will last 15 min, while the recall session will last 7 minutes.

3. Nap: You will be asked to relax and try to sleep in the MRI. This step will last maximum 30 minutes.

4. Repeated Tasks: You will be asked to repeat the attention task and the recall phase of the memory task.

5. Resting-state segment: You will be asked to remain still, awake, with eyes open. This part will last 7 minutes.

6. Break of 60 min outside the MRI scanner

7. Anatomy segment: You will be asked to remain still for a total 30 minutes (with a few breaks to reposition yourself). You will be given the possibility to sleep or watch images on a screen during that segment.

Prior to the MRI session, you will be asked to wear a special watch for at least 7 days. This watch will record your movements and will allow researchers to assess the quality of your sleep at home during the week.

- Third visit (for healthy sleepers only).

A week later, healthy sleepers will be invited to the sleep laboratory at CRIUGM to undergo another EEG session during the night. This time you will be restricted to 4 hours sleep during the night and you will stay in the lab the next morning until MRI session begins. You will undergo same MRI procedure, including cognitive tasks, as described above.

As mentioned before, the order of the second and third visits will be randomized for healthy controls.

3.4.2. Participation to the pilot of the project

In order to test the feasibility of the project, several participants will be invited to participate to a preliminary phase (pilot) of the project. If it concerns you, you will be invited to participate to one or multiple sessions of the project:

- Cognitive tasks

You will also be asked to participate in various tasks such as memorizing sequences of images or text as well as responding as fast as possible to images appearing on a screen. During these tasks, you will be asked to respond by pressing a button on a keypad.

- Sleep session

You will be invited to spend the night at the sleep laboratory at CRIUGM. You will arrive in the evening after your dinner, you will be prepared with the PSG equipment (electrodes hookup), and then you will spend the night in a private bedroom. When you wake up the next morning, you will receive a breakfast.

- MRI session

The MRI imaging session will last approximately 2 to 3 hours, which may include a 60 min-break. Before the MRI session, we will place an EEG cap on your scalp in order to monitor your vigilance and sleep in the MRI. During the MRI session, we will ask you to lie down calmly on the mattress, relax while remaining as immobile as possible, and follow the technician's instructions. During this session, the anatomy and functional activity of your brain will be examined in several different ways. You will also be asked to participate in various tasks such as memorizing sequences of images or text as well as responding as fast as possible to images appearing on a screen. During these tasks, you will be asked to respond by pressing a button on a keypad.

The MRI session may include the following steps:

1. Attention task: You will be instructed to press a button as fast as possible when certain images appear on the screen. The task will last 9 minutes.

2. Memory task: You will be asked to memorize a series of items and recall them. The initial phase of the task will last 12 min, while the recall session will last 6 minutes.

3. Nap: You may be asked to relax and try to sleep in the MRI. This step will last maximum 30 minutes.

4. Repeated Tasks: You will be asked to repeat the attention task and the recall phase of the memory task.

5. Resting-state segment: You will be asked to remain still, awake, with eyes open. This part will last 7 minutes.

6. Break of 60 min outside the MRI scanner

7. Anatomy segment: You will be asked to remain still for a total 30 minutes (with a few breaks to reposition yourself). You will be given the possibility to sleep or watch images on a screen during that segment.

4. Incidental findings.

Although you will not be subjected to any formal medical assessment, the results of all tests, tasks, and procedures entailed by your participation in this project may lead to the detection of previously unknown health problems. This is what we call an incidental finding. Should an abnormality be detected, you will be informed by the principal investigator.

5. Benefits associated with the research project.

You will not obtain a personal benefit from your participation in this research project. Nonetheless, results obtained from this study will contribute to the advancement of scientific knowledge in this area of research.

6. Risks associated with the research project.

6.1 Magnetic resonance imaging.

Based on current medical knowledge, undergoing magnetic resonance imaging does not pose any medical risks if you do not have any contraindications. However, due to the power of the magnetic field emitted by the MRI scanner, it is necessary to take certain precautions. Therefore, you will be asked to complete a detailed questionnaire to detect any contraindications, including: the presence of a pacemaker, an aneurysm clip, a metal prosthesis, a prosthetic heart valve, presence of metal in the eye or on the body, tattoos, piercings, dental braces, or if you suffer from claustrophobia. The medical imaging technologist sin charge will be rigorous in detecting the possible presence of any contraindications.

Lastly, participants may experience mild discomfort or stress during the MRI session due to the noise generated by the machine and the need to remain immobile.

6.2 Electroencephalography (EEG) and polysomnography (PSG).

Although negative effects are rare, you may feel a slight irritation on your skin, following the setup of the electrodes (EEG, EOG, EMG). This irritation, if it occurs, will be only slight and temporary and will not cause any risk to your health.

6.3 Partial sleep deprivation – sleep duration restricted to 4h maximum – only for controls.

The partial sleep deprivation imposed during this period will not put you in medical risk. You might feel the effects of lack of sleep such as drowsiness and decrease in vigilance but these effects will dissipate after a night of sleep.
Note that you will not be authorize to drive home after the second visit. Hence, you should be accompanied by someone or go home in taxi or with public transportation.

6.4 Stopped medications use.

For this study, we ask our participants to stop stimulants 48 hours before their first visit and until their participation is complete.

We also ask to stop antidepressants that are used for Narcolepsy and Hypersomnia 2 weeks before the first visit and for the duration of the participation to the study.

In case participants are using a CBD oil, they will be asked to stop it 2 weeks before the first visit and not re-start the usage until their participation is complete.

All participants will be asked to consult with their physician before stopping these medications, to ensure medical approval and appropriate counselling about the withdrawal.

7. Risks associated with pregnancy.

Participation in this research project may involve known or unknown risks, for pregnant women, unborn children, and breast-fed infants. Therefore, pregnant and breastfeeding women cannot participate in this project.

Women who may become pregnant should be tested for pregnancy before undergoing a MRI session and may participate in this project only if the pregnancy test result is negative.

8. Voluntary participation and possibility of withdrawal.

Your participation in this research project is voluntary. You are therefore free to refuse to participate. You may also withdraw from this project at any time, without explanation, simply by notifying the principal investigator or a member of the research staff.

Your participation may be terminated without your consent by the principal investigator, the Comité d'éthique de la

recherche vieillissement-neuroimagerie, or the granting agency, should new information arise indicating that participation in the project is contrary to your best interest; if you do not respect the instructions of the research project; or if administrative concerns preclude your participation.

If you withdraw or are withdrawn from the project, any data already collected under this project will be retained, analyzed or used to comply with the regulatory requirements.

Any new information that arises throughout the course of the project that may affect your decision to continue to participate will be communicated to you without delay.

9. Confidentiality.

Throughout your participation in this project, the principal investigator and members of the research team will gather certain information about you in a research file. Only information pertaining to the scientific objectives of this project will be collected.

The information gathered in your research file may include your past and present health status, information regarding your lifestyle, the results of all tests, examinations and procedures performed in the context of this study. It may also include others information such as your name, gender, date of birth and ethnicity.

All information collected will remain confidential to the extent permitted by the law. In order to protect your privacy and the confidentiality of any information collected, you will only be identified by a participant ID. The code key linking your name to your participant ID will be securely stored by the principal investigator.

The coded data of the project will be transmitted in the United-Sates and in Europe by the principal investigator to collaborating co-researchers. The principal investigator and the collaborating researchers who will obtain the data from the project are required to respect the confidentiality rules applicable in Quebec, and Canada, regardless of the location of the collaborating researchers.

The information collected will be retained for at least 5 years by the principal investigator of this research project.

Research data may be published or be the subject of scientific discussions, but it will not be possible to identify you.

For monitoring and control purposes, your research file may be consulted by a person appointed by the Comité d'éthique de la recherche vieillissement-neuroimagerie or by an authorized person by authorized public organizations. All these individuals and organizations adhere to a privacy policy.

You have the right to consult your research file to verify the information collected and to have it corrected if necessary.

10. Secondary use of your research data

Do you consent to your research data being used by the principal investigator to carry out other research projects in the field of neuroscience of aging or health care promotion by the principal investigator?

These research projects will be evaluated and approved by the Comité d'éthique de la recherche vieillissement-neuroimagerie prior to their completion. Moreover, the Research Ethics Board will follow-up on the development of this study. Your research data will be stored securely on servers in CRIUGM. In order to conceal your identity and preserve the confidentiality of your data, you will only be identified by a code number.

Your research data will be retained for as long as it can be useful for the advancement of scientific knowledge. When they are no longer needed, your research data will be destroyed. Please note that at any time you may request that your research data be not used by contacting the researcher responsible for this research project.

Do you consent to having your research data used under these conditions? □ **Yes** □ **No**

11. Participation in further studies

Do you consent to the principal investigators of this project or members of the research staff contacting you to suggest your participation in other research projects? Please note that you would be free to accept or refuse to participate in the proposed research projects. □ **Yes** □ **No**

12. Funding of the research project

The principal investigators received funding from the granting agency to carry out this research project.

13. Compensation

All participants will receive a compensation amount that will vary depending on the number of sessions performed and the performance at the memory task. You will receive $50 per PSG, MSLT and EEG sleep session (at the sleep lab), hence you will receive up to $150 in total for the sleep part. In addition, depending on your performance at the memory task, you will receive from $5 to $50 per MRI session.

If you withdraw or are withdrawn from this project before it is completed, you will receive an amount proportional to the number of visits you attended.

For participants who will need to travel from another province or country to participate in this project, we will be able to reimburse travel (transportation) expenses for up to $500 CAD per participant upon receipt of travel tickets (e.g., flight, train, bus, taxi). Accommodations within the period of the study can be provided at a nearby hotel if needed and will be booked by the research coordinator.

14. In case of injury

If you suffer any injury as a result of your participation in the research project, you will receive all the care and services required by your state of health.

By agreeing to participate in this research project, you are not waiving any of your rights, nor are you releasing the principal investigator, the granting agency or the hospital, from their civil and professional accountability.

15. Medical Emergency Procedures

Please note that the Institut universitaire de gériatrie de Montréal is not a healthcare facility that provides short-term emergency services and that relies on the presence of a doctor on duty 24 hours a day. Therefore, in the event of a medical condition requiring immediate care, first aid will be provided by the present staff and, if necessary, arrangements will be made to transport you to the emergency room of a nearby hospital.

16. Identification of Contacts

If you have questions about the research project or if you have a problem that you believe is related to your participation in the research project, you can contact the principal investigators at the following numbers: (514) 340-3540 ext. 3991

If you have any questions regarding your rights as a participant in this research project or if you have any complaints or comments, you may contact the complaints and service quality commissioner of the CIUSSS Centre-Sud-de-l'Île-de-Montréal at 514.593.3600.

17. Monitoring the ethical aspects of the research project

The Comité d'éthique de la recherche vieillissement-neuroimagerie has approved and monitors this research project. For any information, please contact, the Comité d'éthique de la recherche vieillissement-neuroimagerie by phone at 514.527.9565, ext. 3223 or by email at the following address: karima.bekhiti.iugm@ssss.gouv.qc.ca

Consent

Title of the research project: Pathophysiology of narcolepsy and idiopathic hypersomnia: a multimodal neuroimaging study

1. Participant's consent

I have read the consent form. I acknowledge that the project was explained to me, that my questions were answered, and that I was given the time to make a decision.

Upon reflection, I agree to participate in this research project under the conditions set out.

Signature of participant Date

2. Signature of the person who obtained the consent if different from the researcher in charge of the research project.

I explained the terms of this consent form to the participant and answered the questions he/she asked me.

Signature of person obtaining the consent Date

3. Signature and commitment of the researcher responsible for the research project

I certify that the terms and conditions of this consent form have been explained to the participant, that their questions have been answered, and that we have clearly indicated that they can terminate their participation without prejudice.

I agree, with the research team, to respect what has been agreed in this consent form and to provide a signed and dated copy to the participant.

2022-01-28

Signature of researcher responsible for the research project Date