Title of the study:

Dento-thalamo-cortical bundles in Friedreich's ataxia: impact of their modulation on the symptoms of Friedreich's ataxia and functional brain architecture.

Study promotor: Erasmus Hospital – ULB, Functional Neuroimaging Clinic, Nuclear Medicine Department.
Local investigators:
- principal investigator: Dr Naeije Gilles
- co-investigators: Pr De Tiège Xavier, Dr Destrebecq Virginie, Camille Comet

Information essential to your decision to participate

Introduction

You are invited to participate in a clinical study which aims to better understand the role of the connections between the cerebellum and the cerebral cortex in Friedreich's ataxia. The study of these connections will be done using cerebral magnetic resonance imaging (MRI) and magneto-encephalography (MEG) techniques before and after transcranial cerebellar electrical stimulation. Transcranial cerebellar electrical stimulation is a non-invasive technique that stimulates the cerebellum and modulates the activity of the connections between the cerebellum and the cerebral cortex. This technique has recently shown an improvement in motor and intellectual abilities in degenerative ataxias without being associated with a possible side effect.

Before you agree to participate in this study, we invite you to find out what it involves in terms of organization, advantages and possible risks, so that you can make an informed decision. This is called giving “informed consent”.

Please read these few pages of information carefully and ask any questions you wish to the investigator or the person representing him. This document consists of 3 parts: the information essential to your decision-making, your written consent and additional information (appendices) which detail certain parts of the basic information.

If you participate in this research, you should know that:

➢ This clinical study is implemented after evaluation by an ethics committee.

➢ Your participation is voluntary and must remain free of any constraint. It requires the signing of a document expressing your consent. Even after signing it, you can end your participation at any time by informing the principal investigator. Your decision not to or no longer to participate in the study will have no impact on the quality of your care.

➢ You will not be charged any fees for examinations specific to this study (examinations made necessary by the condition from which you suffer will be invoiced according to the usual terms).

➢ The data collected on this occasion is confidential and your anonymity is guaranteed when the results are published.

➢ Insurance has been taken out in case you suffer damage related to your participation in this research.

➢ You can always contact the investigator or a member of his team if you need additional information.

These points are detailed in the appendix under the heading “Rights of participants in a clinical study”.

If you participate in this research, we ask that you:

➢ To collaborate fully in its smooth running.

➢ Not to hide anything such as information about your state of health, the medications you take or the symptoms you experience.

➢ Not to present the exclusion criteria described below.

Description of the study protocol

Inclusion/exclusion criteria and duration of the examination

You have Friedreich's ataxia.

This is why we propose that you take part in this study as a patient.

Your participation in the study requires the absence of contraindications to MRI

Contraindications to MRI concern subjects with:

- intraocular metal foreign bodies (accidental or other splinters);
- pacemakers, implantable cardiac defibrillators, implanted neuro-stimulators, cochlear implants, and more generally any electronic medical equipment permanently implanted and not compatible with MRI;
- intracerebral ferromagnetic vascular clips;
- metal heart valves.

Finally, if you are pregnant or have the possibility of being pregnant, we ask that you let us know because this represents a contraindication relating to the examinations carried out.

The examinations carried out as part of this study will be carried out on a PET-MRI machine located in the Nuclear Medicine Department of the Erasmus Hospital. Certain MRI sequences may possibly be carried out separately on an MRI machine located in the Radiology Department.

The MEG exam requires half an hour of preparation before starting the exam which lasts about thirty minutes. The MRI investigation is carried out after the MEG examination and also lasts approximately 30 minutes. You will be informed beforehand orally about the practical aspects and the estimated duration of the investigations that concern you. These durations of examination(s) are provided for information purposes and may possibly be variable depending on technical hazards beyond our control.

Rationale and objectives of the study

The cerebellum is a structure of the brain of vertebrates. Anatomically, the cerebellum appears as an isolated structure, located below the cerebral hemispheres and behind the brainstem. It contributes to the coordination and synchronization of gestures, and to the precision of movements.

Recent work has highlighted the fundamental role of the cerebellum in a whole series of brain functions, ranging from movement control to language and tactile perception. The impairment of the connections between the cerebellum and the cortex is associated in Friedreich's disease with the appearance and evolution of motor symptoms as well as the alteration of certain cognitive functions such as language. We believe that modulating the activity of the connections between the cerebellum and the cortex through transcranial cerebellar electrical stimulation could significantly improve the symptoms of Friedreich's

ataxia in a non-pharmacological way. The study of cerebral activity by MEG and MRI would make it possible to understand by which mechanisms, transcranial electrical cerebellar stimulation acts.

How will the exams be conducted?

MEG exam

Magnetoencephalography (MEG) is a totally non-invasive cerebral imaging technique based on the passive detection of magnetic fields produced by the brain. Very simply, when a population of neurons activates within the brain, it emits very weak electric currents which will generate detectable magnetic fields outside the skull. The interest of studying these magnetic fields is based on the fact that they are a direct reflection of the activity of neurons and that they are not altered by the different structures that they must cross to reach the outside of the skull. (meninges, skull, skin). One can then search using computer software for the region of the brain that generated the MEG signal recorded outside the skull.

When you arrive, we will ask you to remove any metallic objects (jewelry, watch, glasses, braces, etc.) and to put on hospital clothing specially designed for MEG examinations. Then, we will put you for a few minutes in the conventional MEG in order to determine the quality of the recorded signals. If we consider that the MEG examination can be performed, we will then prepare you for the experiments that are the subject of this study. First, electrodes will be placed below your collarbones (to record the rhythm of your heart) and on either side of your eyes (to record your eye movements). A gel will be applied between the electrodes and your skin to ensure optimal electrical contact. Several hundred points will also be located on your head using a magnetic pen and special glasses to be able to project the results obtained in MEG on the MRI of your brain. This step is absolutely not dangerous or painful and will be necessary for both types of MEG.

After the preparation, we will proceed to the recordings of the MEG data. During these, we will ask you to perform different tasks (for example moving your fingers) and then, we will perform a 5-minute acquisition at rest (doing nothing for 5 minutes, eyes open). We will ask you to stay calm and not move your head. If you feel uncomfortable, the recordings can be stopped at any time during the exam. The recording will last a maximum of twenty minutes.

MRI examination

For the performance of the MRI examination, you will be placed in a supine position on a table, which will be introduced into a “tunnel” whose diameter is approximately 60-70 cm. Upon introduction into the magnet, a transient sensation of claustrophobia may be felt, despite the implementation of comfort features such as ventilation and lighting. If that's the case, it's usually enough to look (via the mirror) outside the MRI's pipe or focus on his breathing movements.

When an MRI acquires images of the brain, it makes noise. To minimize the inconvenience related to this noise, we will ask you to wear noise-canceling headphones or earplugs.

An alarm will be positioned in your hand so that you can warn us in the event of a problem during the examination while limiting your movements. There is also, in the tunnel, a microphone and loudspeakers by means of which it is possible to communicate with the nursing staff during the breaks of a few seconds that are taken between the different acquisitions or if a problem should arise from your side.

During the examination, we will ask you not to move (except for the acquisition of functional MRI data). The easiest way is to stay still with your eyes closed until you are told that the

exam is over. The slightest movement causes noise in the images that significantly affects their quality: they become too blurry to be used for the study.

Functional MRI

This will be performed using an MRI-compatible device that will allow you to move your fingers or toes passively using painless or active pneumatic stimulators.
The total duration of the exam is approximately 20 minutes. If you experience significant discomfort during the exam, we will end the exam as soon as possible. You can also decide at any time to stop the exam.

transcranial cerebellar electrical stimulation

Transcranial electrical cerebellar stimulation consists of placing a square electrode with a side of 5 cm on the back of the skull facing the cerebellum as well as a reference electrode glued to the back. These electrodes will make it possible to pass a very low intensity current (2 mA) which will stimulate the cerebellum. The established protocols for this type of stimulation consist of a stimulation duration of 20 min per day for five days.

In practice

The investigations take place over five days in two sessions separated by 12 weeks. In each session, on the first day, a clinical examination, a magnetoencephalography and a basic functional MRI are carried out before starting the transcranial electrical cerebellar stimulation sessions. Then the first session of cerebellar stimulation is carried out. The following three days, a session of 20 minutes per day of cerebellar stimulation is carried out. On the last and fifth day, the cerebellar stimulation session is followed by a clinical examination, a magnetoencephalography and a functional MRI which will be compared to the investigations that preceded the cerebellar stimulations in order to measure the effect of the cerebellar stimulations. The difference between the two sessions is that in one of the two sessions, the stimulation is ineffective. This design makes it possible to assess the presence of a placebo effect.

What are the potential benefits?

The main benefit of your participation in this study is to contribute to a better understanding of the role of modulation of the loops between the cerebellum and the cerebral cortex in the symptoms of Friedreich's ataxia and to potentially validate a neurophysiological treatment of symptoms in your disease which currently has no recognized treatment.

What are the risks?

In the current state of knowledge, we believe that, if you have no contraindications to MRI, examinations performed by MRI do not involve any risk or danger for you.
The MEG examination is safe for you. Similarly, transcranial stimulation of the cerebellum is a process that has already been studied and the protocol for performing the stimulation is now well known. The rare reported side effects occur during stimulation and consist of a metallic taste and an itching or tingling sensation under the electrodes. To remedy these

effects we plan to leave sugary drinks and menthol pastilles. For tingling we plan to make cool compresses available.

Contact

If you need additional information, but also in case of problem or concern, you can contact one of the study investigators Dr Destrebecq or Dr Naeije Gilles at the following telephone number (02/555- 4622).

Under the GDPR, you have a number of rights regarding the processing of your data (see Privacy guarantees). If you have any other questions on this subject, you can contact your investigating doctor. The data protection officer of the study center is also at your disposal. Here are his contact details: dpo@erasme.ulb.ac.be

Similarly, if you wish to inquire or file a complaint about a problem concerning a possible breach of the protection of your personal data, you can do so at the government data protection service via the following link: https://www. dataprotectionauthority.be/citizen/act/submit-a-complaint

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Informed consent

I, the undersigned ……., declare that I have read the information relating to the study offered to me.

I had enough time to think about it and talk about it with a person of my choice like my general practitioner or a member of my family.

I had the opportunity to ask all the questions that came to my mind and I got a satisfactory answer to my questions.

The investigators told me that I was free to accept or refuse; this will have no consequences on my relations with the therapeutic team in charge of my health.

I accept, yes / no (circle the valid answer), that the research data collected for the purposes of this study may be further processed provided that this processing is limited to the context of the present study and subject to approval of the ethics committee.

I consent to the processing of my personal data according to the methods described in the section dealing with confidentiality guarantees (appendix “Rights and protection of the participant”).

I have received a copy of the Participant Information and Informed Consent.

I accept / do not accept (delete as appropriate) that my general practitioner or other medical specialists in charge of my health be informed of my participation in this clinical study.

Participant's first and last name: _____ _____

Date: ____ / ____ / _____

Signature: _____

Investigator

I, the undersigned, ……., investigator, confirm that I have provided the necessary information about the study orally and have provided a copy of the information document to the participant.

I confirm that no pressure was exerted for the patient to agree to participate in the study and that I am ready to answer any additional questions, if necessary.

I confirm that I work in accordance with the ethical principles set out in the "Declaration of Helsinki", in the "Good Clinical Practices" and in the Belgian law of May 7, 2004, relating to experiments on the human person.

Surname and first name of the investigator: _____ _____

(or the investigator's representative: _____ _____)

Date: ___ / ___ / _____

Signature: _____

Voies dentato-thalamo-corticales dans l'ataxie de Friedreich : impact de sa modulation sur les symptômes de l'ataxie de Friedreich et l'architecture fonctionnelle du cerveau.

Annex "Additional information"

MRI

MRI is a radiological technique that provides non-invasive (non-hazardous and non-painful) anatomical or functional images of high quality using a very powerful magnetic field and radiofrequency waves; in your case, anatomical or functional images of the brain. Depending on the technical parameters used, it is possible to obtain varied and complementary information on the anatomy or cerebral functioning. Therefore, a brain MRI examination usually includes several MRI "sequences".

Motor fMRI, coupled with (conventional) anatomical MRI sequences, makes it possible to locate the regions of the brain responsible for movement and to specify their relationship with a given cerebral lesion. In particular, this cerebral imaging method makes it possible to identify the regions of the brain where blood flow increases following the activation of populations of neurons involved in motricity. To do this, the patients must proceed in the MRI of the movements (generally of the hand or the foot) making it possible to locate the regions of the brain involved in the movement.

In order to minimize individual differences in task performance, motor fMRI can be performed not through the performance of motor tasks but using a stimulator that will passively move the fingers or toes. of the patient. This is called “passive” motor fMRI. The fmotor MRI will be performed as part of this study and will be “passive”.

The "non-conventional" MRI sequences (carried out specifically within the framework of this study and "in addition" to a standard preoperative examination) that will be used will be as follows:

Resting state fMRI: explores cerebral activity in resting conditions, i.e. when the patient is calmly installed in the MRI and is not subjected to a given task. The patient should then relax and not move. This examination makes it possible to estimate the integrity of the organization of the brain into neural networks, which is very reproducible from one human being to another. It also provides another way to study the impact of brain damage on neurovascular coupling by indirectly providing information on alterations in spontaneous (as opposed to task-related) fluctuations in cerebral vasculature

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Annex "Rights and protection of the participant"

Ethics committee

This study was evaluated by an independent Ethics Committee, namely the Erasme-ULB Ethics Committee, which issued a favorable opinion. Ethics Committees have the task of protecting the people who take part in a clinical study. They ensure that your rights as a patient and as a participant in a clinical study are respected, that in the light of current knowledge, the balance between risks and benefits remains favorable to the participants, that the study is scientifically relevant and ethics.

Under no circumstances should you take the favorable opinion of the Ethics Committee as an incentive to participate in this study.

Voluntary participation and costs associated with your participation

Before signing, do not hesitate to ask all the questions you deem useful. Take the time to talk to someone you trust if you wish.

Your participation in the study is voluntary and must remain free of any constraint: this means that you have the right not to participate or to withdraw without justification even if you had previously agreed to participate. Your decision will in no way affect your relationship with the team in charge of continuing your therapeutic care.

If you agree to participate in this study, you will sign the informed consent form. The investigator will also sign this form and thus confirm that he has provided you with the necessary information about the study. You will receive the copy intended for you.

If you decide to participate in this study, there will be no additional costs for you or your insurer. You will only be charged the usual treatment costs for your clinical situation. The following examinations or procedures are the responsibility of the sponsor: PET with FDG and MRI sequences complementary to the standard clinical course.

You will not be paid for your participation.

Privacy Guarantee

Your participation in the study means that you have chosen that the investigator can collect data about you and use them for research purposes.

You have the right to ask the investigator what data is collected about you and how useful it is for the study. You have a right to inspect this data and the right to make corrections in the event that it is incorrect.

The investigator has a duty of confidentiality with regard to the data collected.

This means that he undertakes not only never to divulge your name within the framework of a publication or a conference, but also that he will take all the necessary measures to protect your data (protection of source documents, identification code, password protection of created databases). The personal data collected will not contain any combination of elements that could nevertheless allow you to be identified. The investigator and his team will be the only ones who can make the link between the research data and your identity.

To check the quality of the study, your medical file may be reviewed by third parties (ethics committee, study sponsor, external auditors). In any event, this could only be done under the responsibility of the investigator or one of his collaborators and by persons subject to the obligation of professional secrecy.

The investigator will use the data collected as part of the study in which you are participating but also wishes to be able to use it in the context of other research carried out in the same context (example: using your data as a control group).
If you decide to take part in this study, it is desirable that your general practitioner or other medical specialists in charge of your health be informed of your participation in this study. We will ask you to confirm your agreement but will respect your possible wish not to inform them.
If you withdraw your consent to participate in the study, in order to guarantee the validity of the research, the data coded up to the moment of your interruption will be retained. No new data can be transmitted to the promoter.

These rights are guaranteed to you by the law of July 30, 2018 in application of regulation 2016/679 relating to the processing of personal data, and by the rights of patients defined by the law of August 22, 2002.
In practice, it will constitute 2 different databases. One will contain identifying data such as your surname, first name, telephone number, hospital file number and an identification code that it will create. The investigator or a member of his team will be the only holders of this first database. Your identification code will be used in the 2nd database against all experimental results collected during your participation in the study. This 2nd database can be retained indefinitely. These 2 databases will be kept separately and will be protected by a password. If the investigator entrusts your data for statistical processing, only the second database will be entrusted to this third party.
The database containing the results of the study will therefore not contain any association of elements such as your initials, your gender and your full date of birth (dd/mm/yyyy).
Integrity in scientific research presupposes that the results of research can be verified, even after the results have been published. It is recommended that the link between the research data and the identity of the participant be kept for at least 5 years after the publication of the results. For clinical trials (drug studies), the law requires that this link be kept for 20 years

Assurance

Any participation in a clinical study involves a risk, however small. The promoter assumes, even in the absence of fault, the responsibility for the damage caused to the participant (or to his successors in title) and linked directly or indirectly to the experiments carried out. The promoter has taken out an insurance contract for this liability (Ethias Insurance).

You are therefore invited to report any new health problem to the investigator. He will be able to give you additional information concerning the possible treatments. If he considers that a link with the study is possible (the insurance does not cover the natural evolution of your disease or the known side effects of your usual treatment), he will inform the sponsor of the study which will be responsible for initiating the insurance declaration procedure. The latter will appoint - if it deems it necessary - an expert to judge the link between your new health problems and the study.

In the event of a disagreement either with the investigator or with the expert appointed by the insurance company, and whenever you deem it useful, you or your heirs (your family) can sue the insurer directly in Belgium.