Universitätsklinikum Hamburg-Eppendorf

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Information leaflet about the study "Neuronal basis of physical physical activity and pain"

Dear prospective study participant, dear prospective study participant,

Please read this information brochure carefully, it contains all the important information about this study. You are completely free to decide whether you wish to participate in the study or not, and you can end your participation at any time. If you decide not to participate, there will be no disadvantages for you. Ask the investigator to explain anything you do not understand.

The principal investigator of this study, Prof. Christian Büchel (hereinafter referred to as "principal investigator"), and the deputy principal investigator Jonas Stadler (hereinafter referred to as "deputy principal investigator") will explain the study to you as follows:

1. Objective/purpose of the study

The aim of this study is to investigate the neuronal and pharmacological basis of physical exercise and pain. For this purpose, you will be asked to perform some movement exercises during the examination and nerve fibers will be stimulated directly through the skin on the forearm with pressure stimuli. The following is a brief description of the examination procedure.

2. Procedure of the examination

The study is divided into 3 appointments on 3 days, which are always approximately one week apart.

<u>Day 1: Procedure</u>

1) Information from the study management

   First of all, we will ask for your consent to participate in the study and clarify any questions you may have in a personal interview. Before the study begins, you will

you will have enough time to raise any questions and concerns and discuss them with the study management.

2) Individual calibration of the pressure pain
   For the individual pressure pain calibration, a cuff (similar to a blood pressure cuff) will be attached to your left upper arm, through which you will receive short pressure stimulations, which you must rate in terms of pain intensity. This allows us to determine your individual pain threshold and pain tolerance.
3) Individual calibration of the heat pain
4) For the individual heat pain calibration, a thermode is attached to your left forearm, through which you receive brief heat stimulation, which you must rate in terms of pain intensity. This allows us to determine your individual pain threshold and pain tolerance.
5) FTP performance test to determine the anaerobic threshold
   We then customize the exercise equipment used in this study based on your performance in the sports test. The test lasts 1 hour.
6) Electrocardiogram (ECG)
   An ECG measurement is carried out for your safety in order to rule out the risk of cardiac arrhythmia as a side effect of the pharmacological preparation.
7) Urine sample
   As part of the study, you will have to provide a urine sample, which we will immediately test for illegal drugs such as amphetamine, cocaine, ecstasy, morphine/opiates and tetrahydrocannabinol using a rapid test. We may also carry out an alcohol saliva test. This is necessary because drug use affects the reward system and, if present, could influence the results of the experiment, ultimately rendering the results useless. If a test is positive, we will immediately exclude you from participation in the study. In this case, you will not receive any compensation.
8) Completion of

questionnaires <u>Day 2: Procedure</u>

1) Medical information on the administration of medication and declaration of consent
   One of our doctors will have a personal, one-to-one consultation with you and ask you about your medical history, your medication intake and any other questions you may have. The medical examination is important in order to rule out any health risks for you during the experiment. You will also have the opportunity to clarify any unanswered questions. If there are no objections to your participation from a medical point of view and you decide to take part in the study, we will ask you to confirm that you have read and understood this information and to sign the attached declaration of consent.
2) Instruction of the study and going through the exercise sessions
3) Administration of a pharmacological preparation by the study physician

You will then be administered the pharmacological preparation naloxone or a saline solution intravenously (as a syringe into the vein) by a study doctor. The preparation will then be administered as an infusion via an IV. These preparations are described in more detail below. The preparations will change at each appointment, so that after the second appointment each participant will have received each preparation once. Neither you nor the study leader will know which preparation you will receive at a particular appointment. Such a procedure is known as a "double-blind study" and aims to ensure that the effects of the preparations are measured as objectively as possible and without being influenced by the expectations of the participant or the investigator. However, if unexpected health reactions occur in connection with your intake, the doctor can immediately recognize which preparation you have just taken with the help of a list kept ready. The doctor or nursing staff will measure your blood pressure, pulse and oxygen saturation and assess the condition of your skin at prescribed intervals to monitor your state of health.

4) Cycling and administering pressure stimuli and heat stimuli, some of which may be painful
5) Completion of questionnaires
6) Follow-up examination
   Before you are discharged, a doctor will take your blood pressure and pulse again and have a brief discussion with you about how you are feeling. Under certain circumstances, the doctor may decide against your discharge and recommend further examinations, a longer stay at the university hospital or any necessary treatment. You are not bound by these recommendations, but it is your own responsibility if you do not follow the doctor's recommendations.
7) Finally, you will be warned not to drive a vehicle, operate machinery or carry out any other dangerous activities on the day of the examination.
8) Financial compensation

<u>Day 3: Procedure (same as day 2)</u>

Details of the study procedure:
Each examination appointment lasts a total of approx. 3 hours. The study appointments should always take place at approximately the same time.

The actual study on day 2 and day 3 consists of short movement exercises of varying intensity on one. You will then receive alternating heat and pressure stimuli. To do this, we attach a type of cuff to your upper arm and a Thermode to your forearm and apply a series of different pressure and heat stimuli using a pressure stimulation device (the so-called pressure algometer) or Thermode. You will be asked to rate each of these stimuli as to whether you find it painful or not.

We will then t a k e a second blood sample, measure your pain sensitivity again and ask you to complete further questionnaires.

3. Description of the procedures used

Pressure stimulation

You will receive repeated pressure stimuli on your upper arm via a so-called pressure algometer. You yourself can influence the strength of the stimulation, as it is individually adjusted to your pain sensation at the beginning of the measurement. The stimulation lasts about 15 seconds. During the stimulation and afterwards, you are asked to rate the stimulation on various scales.

Thermal stimulation

During the experiment, you will receive multiple heat stimuli on your forearm via the thermode. You yourself can influence the intensity of the stimulation, as it is individually adjusted to your pain sensation at the beginning of the measurement. The stimulation lasts about two minutes. During the stimulation and afterwards, you are asked to rate the stimulation on various scales.

Skin conductivity measurement

We measure your skin conductivity using two active electrodes attached to the palm of your hand. The electrodes may be fixed in place with adhesive tape. The measurement is not perceptible.

Pulse measurement

We measure your pulse using a clip attached to your fingertip. The measurement is not perceptible.

Pharmacological preparations

As described above, you will receive naloxone on one appointment and saline solution o n the other. The following forms of administration and dosages are planned:

Naloxone will be administered to you intravenously (as a syringe into the vein) in the form of an injection solution from the company Ratiopharm. The solution for injection contains a single dose of 0.15 mg/kg body weight followed by an infusion of 0.00337 mg/kg body weight/minute of the substance naloxone. Naloxone is an active substance for the regulation of so-called opioids, which also occur in the body and play a role primarily in the perception of pain. Naloxone serves to reduce the activity of this endogenous opioid system.

Naloxone solution for injection is approved in Germany for the treatment of opioid overdoses (e.g. in narcotics to counteract these effects). These applications and approvals also include neonates and infants. The standard dosage for adults is to be adjusted individually and is between 0.1 and 2 mg.

A very common side effect (more than 10%) is nausea; frequent (1-10%) side effects include dizziness, headache, vomiting and an effect on blood pressure (increased or decreased blood pressure) or a faster heartbeat. Occasionally (0.01% - 1%) increased sweating, trembling, dry mouth, a slower heartbeat, an irregular heartbeat, accelerated breathing or local irritation of the injection site may occur. Rarely (0.01%-0.001%), seizures, the entry of water in the lungs, suspension of the heartbeat, or cardiac arrhythmia (ventricular flutter) occur.

cardiac arrhythmias (ventricular fibrillation). Very rare (less than 0.001%) are allergic reactions.

The preparation must not be used in case of hypersensitivity to the active substance naloxone or other components of the medication.

Possible complications of an injection include the risk of bruising (common), infection (rare) or permanent nerve damage (rare).

Saline is often used as a carrier solution for drugs administered intravenously, but has no medical efficacy itself. In this study, saline is used as a comparator and is therefore also administered intravenously (injected into a vein).

4. Assessment of the benefits and risks of participating in the study

4.1 Assessment of the benefits

This study is a basic science study that aims to expand our knowledge of pain and the control of human behavior. While it is possible that a better understanding of these mechanisms will provide us with new therapeutic options for treating disorders in the future, this study will not have any immediate clinical benefit. Nor will it provide any therapeutic benefit to you personally. The benefit of this study is to increase our knowledge of how the human brain works.

4.2 Assessment of the risks

The risks of the study can be assessed as low overall if the exclusion criteria are applied correctly.

Pressure stimulation

Pain stimulation with pressure stimuli has no long-term side effects. In the short term, however, in addition to the sensation of pain itself, anaemia is triggered in the stimulated extremity, which can lead to **a temporary loss of sensitivity and discoloration of the skin**. These side effects are harmless and subside after a few minutes. The stimuli are adjusted to your individual sensitivity in careful preliminary examinations so that you are within a tolerable range.

Thermal stimulation

Apart from **temporary reddening of the skin**, pain stimulation with heat stimuli has no side effects. Nevertheless, the examiner will only place the thermode on healthy, intact skin and will refrain from stimulation if the skin surface is not intact. The stimuli are adjusted to your individual sensitivity in careful preliminary examinations.

Skin conductivity measurement

Skin conductance measurement has no side effects.

Pulse measurement

Pulse measurement has no side effects.

Pharmacological preparations

In order to assess the risks that may arise from your participation in the study, we discuss the intake of pharmacological preparations. The possible risks are therefore described again below and related to everyday clinical practice.

With regard to the use of the preparations, it should be noted that both preparations used have been approved in Germany and Europe for decades and are in everyday clinical use. Furthermore, only healthy persons and persons with no contraindications are permitted to participate in the study. A list of inclusion and exclusion criteria to ensure this can be found below. It is essential that you provide honest and complete information during the telephone conversation prior to the study, during the medical examination as part of the informed consent discussion and also during the course of the study in order to avoid uncontrollable risks.

The frequent and occasional side effects (e.g. influence on blood pressure or heartbeat, nausea, dry mouth) are checked by a doctor immediately after administration of the preparation so that immediate intervention can be made if necessary. The likelihood of serious side effects is rare to very rare, and people with a history of these illnesses or side effects are excluded from the study. Naloxone is broken down very quickly in the body, so that a short course of possible undesirable side effects can also be expected.

When making a final assessment of the risks of taking the preparations, it should also be taken into account that both preparations have been used in clinics for decades and that there is a great deal of experience in the effects and side effects of these active substances. You will be under medical observation during and after taking the preparation and various safety parameters (blood pressure, pulse, oxygen saturation, skin condition and movement) will be measured at fixed intervals. In addition, emergency medical care is provided directly at the University Medical Center Hamburg-Eppendorf or at another hospital closer to your home at all times.

Taking into account the risks and countermeasures discussed, we consider the risks to you from taking one of the preparations in our study to be low. Please follow our instructions not to drive or operate dangerous machinery or participate in road traffic on the day you take the preparation.

5. Information on insurance cover

All participants in the study are covered by the University Hospital's public liability insurance in accordance with the principle of fault-based liability (i.e. for damage culpably caused by us). The insurance cover does not extend to damage on the way to or from the place of study.

6. Inclusion and exclusion criteria

Inclusion criteria

- Healthy, adult participants who have full legal capacity and the ability to provide information and who are able to carry out the pain rating reliably
- Age: 18 to 45 years
- Body mass index: 18 to 30

Exclusion criteria

- Acute or chronic pain (including sore muscles)
- Presence of acute or chronic somatic or psychiatric illnesses (based on self-report or routine examination)
- Participation in studies with medication, or regular use of medication (except thyroid, allergy medication, occasional use of painkillers, contraceptives)
- Taking painkillers within the last 24 hours before the start of the examination
- Pregnancy or breastfeeding
- Acute skin disease or injury in the areas to be stimulated
- Acute respiratory illness or symptoms
- No past or current physical opioid dependence
- No cardiovascular disease
- No disease of the nervous system
- No disease of the immune system
- No disease of the gastrointestinal tract
- No intake of cardiotoxic drugs/substances (e.g. cocaine, metamphetamine, cyclic antidepressants, calcium antagonists, beta blockers, digoxin)

7. Data protection

The personal data collected in the course of the study are covered by the duty of confidentiality of the study director and his representative and are protected in accordance with data protection regulations.

The storage and processing of your personal data is pseudonymized[1], i.e. in a form that is not identifiable by name. This means that the data will only be used with a pseudonym assigned to you, e.g. VP5 for subject no. 5. The pseudonymization of the other data is carried out by the study director and is only known to him and his deputy. The data will not be stored with your name or initials, neither during data collection nor during the evaluation, but only with the assigned pseudonym. In order to be able to use improved evaluation programs, the measurement data may be evaluated in collaboration with scientists from other working groups, but only in pseudonymized or anonymized form.

[1] **Pseudonymization** is the replacement of the name and other identifying features with an identifier for the purpose of excluding or significantly complicating the identification of the data subject (Section 3 (6a) of the Federal Data Protection Act).

anonymized[2]form, so that other scientists without exception are not aware of the person to whom the analyzed data belongs.

Study results are published anonymously. You can obtain information about the stored data that has not yet been anonymized at any time.

In accordance with data protection regulations, we require your consent to store and use the data. We have separate forms for your declaration of consent:

Type of data	**Study-specific data**
Sheet	A2
Behavioral data	• Behavioral data, such as pain ratings • Physiological data, such as for example skin conductivity
Location of storage location	Institute for Systemic Neurosciences
Pseudonymization	Yes
Access to the pseudonymization key key	Deputy study director
Access to the data	Deputy study director
Responsible person	Head of study Deputy Director of Studies

You can contact the person(s) responsible for storing your data (study director and deputy study director) at

Institute for Systemic Neuroscience University Medical
Center Hamburg-Eppendorf, Building W34 Martinistraße 52
20246 Hamburg
Phone +49 (0) 40 7410-59899
E-mail: sysneuro@uke.de

If you have any complaints, please contact one of the above-mentioned persons responsible or the data protection officer of the University Medical Center Hamburg-Eppendorf:

Matthias Jaster
Martinistraße 52
20246 Hamburg
Phone +49 (0) 40 7410 - 56890
Email: m.jaster@uke.de

[2] **Anonymization** is the alteration of personal data in such a way that the individual details of personal or factual circumstances can no longer be attributed to an identified or identifiable natural person, or only with a disproportionate amount of time, cost and effort (Section 3 (6) of the Federal Data Protection Act)

Or to the State Data Protection Commissioner:

The Hamburg Commissioner for Data Protection and Freedom of
Information Ludwig-Erhard-Straße 22
20459 Hamburg
Tel +49 (0) 40 42854-4040
Fax +49 (0) 40 4279-11811
E-mail:mailbox@datenschutz.hamburg.de
www.datenschutz-hamburg.de.

8. Voluntary participation/withdrawal from the study

Your participation in this study is voluntary. You have the right to terminate your participation in the study at any time and without giving reasons. You have the right to ask questions at any time about possible or known risks that may exist in this study. Please use this right extensively (also during the study) until you feel fully informed. If you have any questions about your rights regarding your participation in this study, please contact the principal investigator or the deputy principal investigator.

The principal investigator or deputy principal investigator may decide to terminate your participation in the study prematurely. Reasons for this may be a recognizable medical risk, a failure to fulfill your obligations to us or a violation of the study protocol. The study director may also decide to discontinue the entire study.

9. Compensation for expenses

For participating in this study, you will receive an expense allowance of €162 for an expected total study duration of 3 days of 3 hours each. After successful participation, the expense allowance will be transferred to a German bank account specified by you.

10. General information

This study has been advised by the independent ethics committee of the Hamburg Medical Association with regard to its medical, legal and ethical justifiability. However, the responsibility for the conduct of the study remains with the principal investigator.

In the declaration of consent for this study, you are asked to confirm with your signature that you have carefully read and understood this information brochure. This brochure and a copy of the signed consent form are intended for your records. Please keep them in a safe place.