Information letter and informed consent for participants of fMRI + tDCS experiments

1 Title of the study:

Modulation of the cerebellar activity with tDCS in autism spectrum disorder patients.

2 Goal of the study:

You have been asked to participate in a study. Before you decide to participate, it is important that you understand why the study is being conducted and what the study entails. So please take the time to read the following information thoroughly and discuss it with others if you wish. We are available to answer your questions or if you require additional information.

With this study we want to delve deeper into the underlying brain mechanisms that underlie understanding social events, as well as the influence of a brain stimulation method on these brain mechanisms and social understanding. In addition, we will measure brain activity over two visits via a MRI while you are performing a computer task. During the measurements, after the brain stimulation, you will see different cartoons describing different situations on the computer screen. You will have to put the pictures in the right order. Afterwards in the next task, a face will be presented and you will have to judge which emotion was depicted. You will receive questionnaires on those days.

Each visit will take approximately 2 hours. You will receive a compensation of 80 euros for this, at the end of the last visit. The examination takes place in a department of the University Hospital Brussels.

3 Description of the study:

MRI scan

A brain scan or Magnetic resonance imaging (MRI) is a physical (magnetic) technique that makes it possible to visualize brain areas. On the one hand one can study the anatomy (shape) of the brain by means of MRI, on the other hand one can also study important aspects of the functioning of the brain, such as brain blood flow, oxygen and energy consumption.

Brain stimulation with tDCS

Brain stimulation is a technique that makes it possible to temporarily influence activity in areas of the brain in living and conscious people. Using this, one can study important aspects of the functioning of the stimulated brain parts.

Brain stimulation via transcranial direct current stimulation (tDCS) is a form of brain stimulation that is widely researched. tDCS uses a weak current that is passed to the

brain through two electrodes (anode and cathode) placed on the scalp. The electric current is "direct", so the current flows from the anode to the cathode, creating static electric field. The direct current changes the excitability of the neurons. This can continue for up to an hour after the end of the stimulation. In addition to the location of the electrons, the choice of where to place the anode and cathode also plays a role. At the neuronal level, we see that anodal stimulation causes a depolarization that leads to an increase in excitability, while cathodal stimulation causes a hyperpolarization that leads to a decrease in excitability of the neuron.

New to this research is that we want to investigate whether the way in which people with an autism spectrum disorder process and understand social events can be influenced by means of tDCS.

The expected total duration of the study is approximately 4 hours (two times 2 hours), of which 2 hours (twice 1 hour) in the scanner.

100 people will participate in this study (40 people with autism spectrum disorder and 60 neurotypical (healthy) individuals).

4 What is expected of the participant?

For the success of the study, it is extremely important that you cooperate fully with the investigator and that you follow his/her instructions carefully.

Since alcohol and caffeine affect brain activity, we ask you to stop drinking alcohol after 6 pm the evening before both visits and to stop drinking/eating caffeinated goods (coffee, tea, energy drinks, chocolate) 2 hours before the start of each visit. For this reason, you should also sleep no less than usual the night before each visit, do not engage in unusual vigorous physical activity the day before and the same day of each visit, and do not smoke 2 hours before the start of each visit.

In addition, we ask you to respect the items listed below in the procedure (6) and risks (7) below.

5 Participation and termination:

Participation in this study is voluntary.

You can refuse to participate in the study, and you can withdraw from the study at any time without giving any reason and without affecting your further relationship and/or treatment with the investigator or the treating physician.

Your participation in this study will be terminated if the investigator believes this is in your best interest. You may also be prematurely withdrawn from the study if you do not properly follow the procedures described in this information letter or if you do not respect the described items.

When you participate, you will be asked to sign the consent form.

6 Procedures:

6.1 Procedures:

First of all, a screening will take place to check whether you meet the conditions for participation in the study. This screening consists of online questionnaires of approximately 30 minutes, covering general as well as personal information about your health and state of mind.

If you are eligible for the study, you will be asked to come to the MRI unit at the University Hospital Brussels twice, each visit will take approximately 2 hours. It is important that there are at least 1week between the visits. You will receive anodal or sham tDCS per visit. The order of type of tDCS (anodal first and then sham stimulation, or vice versa) is random and will not be announced until the end of both visits.

During both studies you will be clearly explained in advance what the experimental course entails and about the MRI recordings and brain stimulation (briefing). Some examples are also given until you feel comfortable. A standard questionnaire will be administered to rule out potential risks from scanning and stimulation.

Then, the researcher will measure your head, to determine where the electrodes of the tDCS device are placed. Then two electrodes of approximately 2.5 x 2.5cm with gel are applied to the skull and attached with a rubber band. You will then be placed in a lying position (supine) in the tube of the scanner. You do not have to undress, but all metal or magnetic objects (watches, jewelry, bank cards, etc.) must be discarded. The tube is fairly narrow, but you can see out through a mirror. The device also makes a lot of noise during the recordings so that you wear protective earplugs. If you feel unwell, you can let us know by simply pressing a button. The experiment is then immediately stopped.

In the MRI scanner, you will first be asked to look at a fixation cross for not more than 10 minutes at rest. After that, you will see a video at rest while tDCS is applied for 20 minutes. Then you will see a fixation cross for not more than 10 minutes at rest again. After this, you will perform a task in which a sequence of cartoons are presented that together represent a certain action. The cartoons are in the wrong order and it is up to you to put them in the correct order as soon as possible. This task takes 15 minutes. Afterwards you will have a second task about emotion recognition. You will be presented small clips of video depicting an emotion and you will have to identify which emotion you have seen via a press button. The facial expressions can be identified as positive, neutral or negative. This task takes 5 minutes. The fixation cross, video and task are all presented on the screen, which can be seen with the help of a special video glasses ~~mirror~~. Afterwards you will come out of the scanner, and we will discuss your impressions of the study together and give you more information about it (debriefing). You will be asked to complete a questionnaire after each visit.

The MRI technique does not require injections or medication and is completely harmless. The examination technique does require that you keep your head perfectly

still for the entire duration of the examination. It will be explained to you which strategy you should follow in order not to cause unwanted head movement while swallowing.

6.2 Flowchart:

In summary, the following will happen during the two visits:

At the beginning

- Explanation about the MRI recordings
- Standard questionnaire administration (excluding risks)
- Viewing instructions and examples

Preparation

- Remove metal or magnetic objects (watches, jewelry, bank cards ...)
- Make head measurements and set up the tDCS device
- Place supine in the scanner
- Explanation about the emergency button
- Explanation of how to avoid head movements

In the scanner

- First recording when seeing a fixation cross for a maximum of 10 minutes at rest
- Second recording for 20 minute when watching a video at rest while tDCS is applied
- Third recording when seeing a fixation cross for a maximum of 10 minutes at rest
- Fourth recording of 15 minutes when seeing the cartoons
- Fifth recording of 5 minutes while performing the emotion recognition task
- Exit the scanner

After scanning

- Extra psychological tests (small questionnaire)
- At the end of the **second** visit: we talk about your impressions and give explanation about the experiment (debriefing).

7 Risks and benefits:

The MRI technique or brain stimulation does not require any injections or medication and is completely harmless. They are not associated with benefits. No other technique is able to know so reliable where certain thought processes take place in the brain. Walking around in the strong magnetic field (3T) of the MRI scanner, some people experience a feeling of dizziness or see flashes of light. However, with a 3T device like ours, these complaints are rather exceptional. However, when you

become aware of something, it helps to walk more slowly to make the complaints go away. Outside the room of the MRI scanner, these complaints should also disappear by themselves. Due to the rapid switching of magnetic fields and the absorption of RF radiation (radio waves) during the MRI scan, you may feel slight tingling, small muscle contractions (chance <20%) or warmth (maximum heating <1 ° C). After the scan, these complaints should disappear immediately.

The tDCS sessions can in rare cases be accompanied by a few discomforts, the main ones being mild headache, dizziness and nausea. These complaints are always responsive to a normal painkiller (eg: paracetamol, aspirin…) and usually disappear within half an hour. During the start of the tDCS, a mild skin irritation may occur under the electrodes, but it will disappear fairly quickly. Another point of attention is the prevention of an epilepsy attack. However, these are very rare when the tDCS session is performed according to current security guidelines. Also for this reason, your doctor will ask for a clear history of epilepsy in yourself and in your family. In very exceptional cases, minor skin burns are found.

Are not allowed to participate (the existence of possible risk factors will be verified before the study).

- ***fMRI scan***

If you have one or more of the following contraindications, you may not participate in this study:

- Carrier of **prostheses** and **artificial implant**
- Carrier of **dental braces** or other important **dental prostheses**
- If you are **claustrophobic**,
- If you are (think you are) **pregnant**, **breast-feeding** or cannot guarantee adequate contraceptive measures for the duration of the study. Are you sure you are not pregnant? If there is any doubt, it is better not to participate in the study.

- ***Brain stimulation with tDCS***

If you have one or more of the following contraindications, you may not participate in this study:

- Recent neurosurgical procedures
- Pacemaker or other electronic implants
- Inner ear prosthesis
- Metallic objects or magnetic objects in the brain
- Heart, respiratory, or neurological problems / conditions
- Pregnancy
- Unstable medical condition
- A current or past psychiatric disorder (for healthy participants)
- The use of psychotropic drugs (for healthy participants)
- Skin disorders of the head
- Skin disorders of the head
- Because highly changing visual information is displayed, there is a very small risk of triggering an **epileptic** seizure during the visual stimulation. This risk is increased if you or a family member has epilepsy, if you are taking medication that increases the risk of epilepsy (such as some antidepressants, high doses of neuroleptics, cocaine and stimulants, if you are sleep deprived in the 24

hours before the test, or during excessively use or withdrawal of alcohol). Persons belonging to one of these groups are not allowed to participate in this study.

There is no known permanent risk associated with this study. All tests that are administered are completely painless and harmless. No injections or oral medications are given. The only drawback of this research is the additional burden it may cause you. This is fundamental scientific research and so there is no direct additional benefit.

fMRI scan:
An anatomical scan of your brain will also be taken as part of this examination. These scans will be screened by a neuroradiologist. If an unexpected brain disorder manifests itself on this scan that requires medical attention, the researchers are obliged to let you know this. If you do not want this, you cannot participate in the study.

You have the right to ask questions at any time about the possible and/or known risks, disadvantages of this study. If any information comes to light in the course of the study that could affect your willingness to continue participating in this study, you will be notified. Should you experience any disadvantage as a result of your participation, you will receive appropriate treatment.

This study was approved by an independent Medical Ethics Committee connected to this hospital and is being conducted in accordance with the guidelines for good clinical practice (ICH/GCP) and the Declaration of Helsinki issued to protect people participating in clinical studies. Under no circumstances should you consider the approval by the Medical Ethics Committee as an encouragement to participate in this study.

8 Costs:

Your participation in this study does not entail any additional costs for you.

9 Compensation:

For your cooperation, you will receive a compensation of 80 euros for two visits.

10 Confidentiality:

In accordance with the General Data Protection Regulation (or GDPR) (EU) 2016/679 of April 27, 2016, your privacy will be respected, and you will have access to the collected data. Any incorrect information can be corrected at your request. Your consent to participate in the study means that we process your data for the purpose of the study. The processing of data is legally provided on the basis of article § 1, (b), (e) or (f) and article 9, § 2(j) of the General Data Protection Regulation.

All information collected during the study will be pseudonymized (your data can still be linked back to your personal file). In the case of pseudonymization the key to those codes will only be accessible for the examining and treating doctor or the replacement appointed by him. Only the pseudonymized data will be used for documentation, reports or publications (in medical journals or conferences) about the study. Personal information and information concerning your health will be processed and are kept for at least 20 years. The controller of the data is principal investigator, Prof. Dr. Chris Baeken. The research team of the principal investigator will get access to the personal data. The Data Protection Officer can provide you, if desired, with more information about the protection of you personal data. Contact details: privacy@ugent.be.

Representatives of the sponsor, auditors, the Medical Ethics Committee and the appropriate authorities, all bound by professional secrecy, have direct access to your medical records to verify study procedures and/or data, without violating confidentiality. This is only possible within the limits permitted by the relevant laws. By signing the consent form, after prior explanation, you agree to this access.
You have the right to file a complaint about how your information is used, at the Belgian supervisory authority responsible for enforcing data protection law:

Data protection law (DPL)
Drukpersstraat 35 – 1000 Brussel
Tel. +32 2 274 48 00
E-mail: contact@apd-gba.be
Website: www.gegevensbeschermingsautoriteit.be

11 Injuries as a result of study participation:

The researcher provides compensation and/or medical treatment in case of damage and/or injury as a result of participation in the study. For this purpose, a no-fault insurance policy has been taken out in accordance with the law on experiments on the human person of 7 May 2004. At that time your data may be passed on to the insurer.

12 Contact persons:

If an injury occurs as a result of the study, or if you would like additional information about the study or about your rights and obligations, you can contact at any time during the course of the study:

MSc. B. P. Catoira, Department of Psychiatry, University Hospital Brussels, Beatriz.Catoira@vub.be

- Nathalie Vanderbruggen, Afdeling Psychiatrie UZ Brussel, nathalie.vanderbruggen@uzbrussel.be - tel: 02/ 476.35.99
- Beatriz Catoira, Beatriz.catoira@vub.be tel 0456267472

- Prof. Dr. C. Baeken, Department of Pyschiatry, University Hospital Brussels, 024766425
- Prof. Dr. F. Van Overwalle, Psychologist, Free University Brussels, 0499 62 26 49

Informed consent

I, _____ have read the document "Information letter and informed consent for participants of experiments" with footnote "Informed Consent dd. 08-07-09 last adapted dd. 08-02-2022, pages 1 to 8 and received a copy. I agree with the content of the document and also agree to participate in the study.

I have received a copy of this signed and dated "Informed consent" form. I received an explanation about the nature, purpose, duration and foreseeable effects of the study and about what is expected of me. I was explained about the potential risks and benefits of the study. I have been given the opportunity and time to ask questions about the study, and I have received satisfactory answers to all my questions.

I agree to cooperate fully with the supervising investigator. I will notify him/her if I experience any unexpected or unusual symptoms.

I was informed about the existence of an insurance policy in the event of injury attributable to the study procedures.

I am aware that this study has been approved by the independent Medical Ethics Committee connected to the UZ Brussel and that this study will be conducted in accordance with the guidelines for good clinical practice (ICH/GCP) and the Declaration of Helsinki, defined to protect people participating in experiments. This approval was in no way to promote the decision to participate in this study.

I may withdraw from the study at any time without giving any reason for this decision and without affecting my further relationship with the researcher in any way.

I have been informed that both personal data and data regarding my health will be processed and stored for at least 20 years. I agree and am aware that I have the right to access and correct this data. Since these data are processed for medical scientific purposes, I understand that access to my data can be postponed until after the end of the research. If I want access to my data, I will contact the supervising researcher responsible for the processing.

I understand that auditors, representatives of the client, the Medical Ethics Committee, or appropriate authorities, may wish to inspect my records to verify the information collected. By signing this document, I consent to this check. In addition, I am aware that certain data is passed on to the client. I give my consent for this, even if this means that my data will be transferred to a country outside the European Union. My privacy will be respected at all times.

I am willing to participate in this study on a voluntary basis.

Name volunteer:

_____

Date:

_____

Signature:

I confirm that I have explained the nature, purpose, and foreseeable effects of the study to the above volunteer.

The volunteer agreed to participate by placing his/her personally dated signature.

Name of the person that has given preliminary explanation:

_____

Date:

_____

Signature: