Clinical Research Centre for Neuromodulation in Psychiatry

Research Project – 3 Information Booklet

Clinical Efficacy & Neurobiological Correlates of sequential treatment with cathodal tDCS primed iTBS and ECT in Treatment-Resistant Depression

Introduction

This research study is being carried out at the Departments of Psychiatry at (1) NIMHANS, Bengaluru; (2) Central Institute of Psychiatry (CIP), Ranchi and (3) Kasturba Medical College, Manipal with due approval by the respective Institute Ethics Committees. This multi-center research project is funded by the Wellcome Trust – Department of Biotechnology India Alliance.

Why am I being approached for participation in this research?

We are conducting research to examine the effect of a method of treatment called Cathodal transcranial direct current stimulation (c-tDCS) primed Intermittent Theta Burst Stimulation (iTBS) in individuals with depression who have not experienced improvement with earlier treatment with two different antidepressant medicines (treatment-resistant depression) or are unable to tolerate antidepressant medicines. We understand that you have been suffering from depression and your symptoms have not improved to a satisfactory extent despite receiving two different antidepressant medicines or the doctors cannot give you an optimal dose of antidepressant medicines due to side effects. We are requesting you to participate in this study in this background.

What is the purpose of the study?

The main purpose of this study is to examine clinical benefits and mechanisms of two steps of treating individuals with depression who have not responded well to earlier treatment. The first step of treatment uses neuromodulation therapies like iTBS and cTDCS (see below for details). The second step of treatment is with electroconvulsive therapy or ECT, when there is insufficient response in the first step. Previous research studies have shown that individuals with treatment-resistant depression/intolerance to antidepressant medications may respond to a brain stimulation technique called “intermittent theta-burst stimulation (iTBS)” – an advance type of Transcranial Magnetic Stimulation (TMS). However, patients respond differently (i.e., some individuals respond well, and some do not) to these neuromodulation treatments and currently, we are unable to predict which patient will respond to iTBS treatment. Also, combining iTBS with another neuromodulation technique called “cathodal transcranial Direct Current Stimulation (c-tDCS)” might result in a better treatment response.

The purpose of this research study is to compare iTBS treatment (i.e. iTBS alone) with iTBS combined with c-tDCS treatment (i.e. iTBS + c-tDCS) in terms of their efficacy in improving the depression as well as identify predictors of response to either of these treatments or to ECT using research techniques (details provided below). These research studies may, in turn, may potentially help us offer better treatment in the future. In addition, this research might help us to understand the mechanism by which such improvement occurs (through techniques/tests as described below).
What are these Neuromodulation treatment techniques (i.e. iTBS and tDCS)?

**Transcranial Magnetic Stimulation (TMS)**

Transcranial Magnetic Stimulation (TMS) is a magnetic energy-based brain stimulation technique that will involve a trained researcher placing the TMS coil on the appropriate position against your head and a current being fed to it (the current stays within the coil, which is electrically isolated). Through electromagnetic induction, this current generates a magnetic field that in turn creates a small electric field across part of your brain, slightly influencing activity at that location. This influence is very localized and slightly enhances or reduces brain activity. In this study, we will use an advanced type of TMS technique namely the intermittent theta-burst stimulation (iTBS) – this is known to enhance underlying brain activity. Here, bursts (triplet pulses) are given in an intermittent fashion – 2s on and 8s off, thus enabling the delivery of a larger number of pulses within a shorter duration of time. This technique has reduced the session-time for TMS treatment from 30 minutes to 3 minutes. You will remain conscious throughout the treatment session.

**Transcranial Direct Current Stimulation (tDCS)**

tDCS has been used as a safe and non-invasive form of treatment for various psychiatric and neurological conditions. tDCS is a safe, well-tolerated, non-invasive procedure for the stimulation of specific regions of the brain by the application of weak electric current using battery. tDCS procedure involves the application of weak direct current (2 mA) through electrodes covered with saline-soaked sponges positioned on specific parts of the head (scalp) and held in place with a rubber strap. Please note that the batteries are part of the equipment and will not be placed on the subjects.

Electroconvulsive therapy or ECT: You may learn more about ECT in the information booklet that has been provided to you; we are also going to explain to you about it in more detail. In short, in this treatment, we provide anesthesia to a patient and then induce seizures for a few seconds using a small dose of electric current.

**How many days do I need to take this neuromodulation treatment?**

As part of this research, in part-1, you will be required to participate in once-daily sessions for 20 days. In part-2 you will be given at least six or more sessions of ECT as determined by your treatment response, given every alternate day (three days a week).

**What tests will be performed in this research?**

In the following sections, we provide information regarding the various research investigations/tests that are employed in this research which we hope would address most of the questions that you may want clarity on before deciding to participate in this study. In addition to the information provided in these sections, you will be shown a video of all these procedures (TMS, tDCS as well as all other research techniques) so that you can understand them better.

**Research Investigations**

The research investigations that will be done in this study include: Magnetic Resonance Imaging (MRI), electroencephalography (EEG), electrocardiography (ECG), neuromodulation tests, detailed clinical assessments and blood sample collection. These investigations will take about 5
hours altogether. They will be done with adequate breaks & refreshments over a period of 1 or 2 days to ensure your comfort.

**Magnetic Resonance Imaging (MRI)**

MRI scan tests will help us to understand the structure (structural MRI), activation (functional MRI), connections (diffusion tensor imaging), and chemical nature (magnetic resonance spectroscopy) of the brain. We will be doing some related scanning procedures to make sure that you do not have any neurological disease as well as to meet the needs of specialized research studies. The duration of the MRI scan will be for about 1 hour.

The MRI scan uses a large magnet to obtain the scans and does not use radiation like X-rays. During the recording, you will be asked to lie on your back on a table with your head positioned in a padded headrest. The study coordinators and the MRI technicians will provide you with the necessary instructions and help during the recording.

If we notice any obvious brain structural abnormalities in your scan, we will inform you regarding the same and counsel you about the options for further treatment. If you so wish, we would refer you for consultation with the appropriate specialist for obtaining the necessary guidance regarding treatment. You will be provided with a printed report on structural MRI scan findings. Decisions would be taken in consultation with your treating team.

Though the MRI scan procedure is considered very safe, in extremely rare situations, there may be certain risks and discomforts associated with the same. Some people may get muscle aches and pains from lying on their back. This will be minimized by providing cushions at pressure points and beneath the knees as required. Earplugs or headphones will be used to dampen the sound inside the MRI room. You may feel nervous about being in a small space when you are in the MRI scanner; however, you will be able to communicate with us throughout the scan and can tell us whenever you want the scan to be stopped or interrupted.

The following items may interfere with MRI scans and some can be potentially hazardous: E.g., Cardiac pacemaker, aneurysm clips, implanted insulin/drug pump, neurostimulator (TENS unit), biostimulator/bone growth stimulator, hearing aid/cochlear implant, Gianturco coil (embolus coil), vascular clips, surgical clip or staples, heart valve prosthesis, Greenfield vena cava filter, middle ear implant, penile prosthesis, shrapnel or bullet, wire sutures, tattooed eyeliner, any type of dental item held in place by a magnet, any other implanted item not mentioned, diaphragm/Intra-Uterine Device, intraventricular shunt, wire mesh, artificial limb or joint, any orthopedic item (e.g., pins, rods, screws, nails, clips, plates, wire, etc.), dentures, dental braces or any type of removable dental items. If you have any of these items in your body, participation in the study could cause serious harm. Therefore, it is very important for you to notify the researcher if you have any of these items in your body and to avoid participating in this study. Please be reassured that we will also be examining you thoroughly to make sure that you do not have these items in your body.
**Electroencephalography (EEG)**

An electroencephalography (EEG) (or brain wave test) measures the electrical activity in the brain (brain waves) using electrodes (small metal discs or sensors) placed on the head with gel. The test does not hurt and usually takes about an hour. During EEG recording, you would be made to lie down comfortably. We would fix a net outside your head comprising of EEG recording electrodes which would be connected to the EEG amplifier. You will remain awake throughout the duration of the EEG recording. We will be doing some related EEG procedures (for example photic stimulation using flickering light) to make sure that you do not have any neurological disease.

**Electrocardiography (ECG)**

An electrocardiography (ECG) is a test that gives us a measure of the heart's electrical activity. You will be asked to lie flat on a table and several small electrode pads (like stickers) will be placed on the body. This test takes about 10 minutes. At the same time of EEG recording, your ECG will also be recorded. Like MRI, EEG as well as ECG also are absolutely safe procedures and do not involve any radioactive or other significant risks.

**Neuromodulation Tests**

Neuromodulation tests are performed to understand the reactivity of brain cells (neurons). We will do the neuromodulation tests using non-invasive and safe brain stimulation techniques namely – Transcranial Magnetic Stimulation (TMS) and transcranial Direct Current Stimulation (tDCS).

**Transcranial Magnetic Stimulation (TMS):** In this method, the brain is stimulated using a magnetic field through a coil attached to a machine. The person sits comfortably on a chair. The magnetic coil will be placed on the head (scalp) to stimulate the brain region that represents your right thumb and the activity levels of right thumb muscle will be recorded using electromyography (EMG) leads placed on the right hand. The coil makes a ticking sound every time the brain is stimulated. The person remains awake and alert during the session.

**Transcranial Direct Current Stimulation (tDCS):** tDCS procedure involves the application of weak, battery delivered direct current (2 mA) through electrodes on specific parts of the head (scalp). Please note that the batteries are part of the equipment and will not be placed on the subjects.

**Details of Neuromodulation Tests Procedure:**
The neuromodulation tests will take approximately 1 hour with adequate breaks in between to ensure your comfort. You will remain alert and awake during the whole session. The procedural details of these tests are as below:

- You will sit comfortably on a chair with hands rested on hand-rests. 3 electrodes will be attached to different areas of your right hand to record muscle activity. The TMS coil will be placed on the left side of your head and some brain reactivity recordings will be done. There will be twitches on your hand.
- After this, active or inactive tDCS will be used to stimulate your brain for 20 minutes. After this, the same brain recordings which we have done using TMS coil earlier will be done again.
Please note that after the neuromodulation tests session, you will be able to leave immediately and do all the activities including driving.

**Clinical Assessments**
In addition to the above investigations, we shall carry out a detailed evaluation of your medical, neurological and psychiatric status by examining you as well as by interviewing you in detail. We may seek additional information from other close relatives (e.g., spouse or children or other caregivers) as well as from your previous medical records. The study will involve you doing some computerized and paper-pencil tests for assessment of brain functions such as attention, concentration, memory, planning, and reasoning. All these assessments & tests will take about 2 hours.

**Blood Sample Collection**
A 15 ml sample of blood (about 3 teaspoons) will be collected for clinical blood investigations as well as research studies involving genetics and other assays. If any abnormality is found in clinical blood investigations, we will suggest the required treatment / refer you to another specialist doctor as appropriate. The blood sample (serum, plasma, and DNA) will be stored and utilized for genetic tests of this project as well as for future research assays, that will be conducted after due approvals from the Institutional Ethics Committee.

**What are the risks associated with these research investigations?**

All the investigations/tests planned in this study are found to be mostly safe and are not commonly associated with any significant risks or adverse effects. This safety of these investigations is established through previous observations from numerous research studies conducted by us as well as other researchers internationally.

MRI: This does not involve any risk apart from tolerable discomfort during procedures.

EEG: The gel used to put the discs on your head is sometimes sticky and the discs may scratch a little bit.

ECG: The test may occasionally cause some redness or itching where the pads are placed. These effects (redness/itching), if it happens, will disappear after some time.

TMS: During stimulation with TMS, you may experience mild pain over your scalp. Most people tolerate this well. However, if you find it intolerable, let us know. We will take appropriate measures. Extremely rarely, TMS has caused individuals to experience seizures. International professional bodies have provided guidelines to minimize the risk of seizure and we would strictly adhere to these. Moreover, we would have done other tests as part of this study and ruled out risk factors for seizures in your case. Please be reassured that our lab has required medicines and expertise to treat seizures immediately if it occurs in spite of these precautions.

tDCS: Sometimes, during the tDCS, you may experience mild and tolerable tingling/itching in the place where the tDCS electrodes are positioned near / on your scalp. However, these sensations are tolerable and most often transient – i.e. will disappear within 2 or 3 minutes. At the maximum, these tolerable sensations will be present usually only during the period of administration of tDCS.
Very rarely, you may get mild headache or discomfort. In such situations, the required medical help will be provided.

ECT: The risks involved in ECT treatment are elaborated in the accompanying information leaflet.

Blood Sample Collection: The collection of the blood sample is expected to be minimally painful. All aseptic precautions will be taken during the procedure.

What will happen in this research study if I take part?

As mentioned earlier, there are two parts to this study:
In the first part, you will be assessed with questionnaires and research investigations (cognitive function tests, MRI brain scan, electroencephalography (EEG) & electrocardiography (ECG), TMS based tests as well as blood sample collection). After that, you will be given one of the two treatments: iTBS combined with true c-tDCS or iTBS combined with sham c-tDCS as predetermined by computer-generated choice. You will have an equal chance of receiving either of these. We would administer one of these two treatments for four weeks (5-days per week). We will monitor your symptoms and adverse effects after each session of treatment. We may reduce the frequency of sessions if we observe a significant problem with your concentration, memory and other mental abilities. We will terminate the treatment earlier than this in any of the following situations: (1) whenever you wish; (2) if there is no improvement after 12 consecutive sessions; (3) there are significant adverse effects and you are therefore unable to tolerate the treatment; (4) complete improvement of your condition. We will be reassessing you with questionnaires & all tests except blood sample collection after terminating the treatment. If you improve significantly after this, your participation in this research will be completed. If you do not experience adequate improvement, then you will have the option to participate in the second part of the study. Please note that during the first part of the study, you will not know the exact type of treatment (i.e. iTBS combined with true c-tDCS or iTBS combined with sham c-tDCS) that you have been offered. We do this in order to reduce the effect of your expectations on the effects and adverse effects of the two treatments.

During the second part of the study, we will treat you with at least 6 sessions of ECT given on alternate days (three times a week). As stated above, you may learn more about ECT in the leaflet provided to you. We will clarify further if you have any questions. ECT will be provided under anesthesia. During anaesthesia, the anaesthesiologist will provide general anaesthesia by administering medicines through your veins to keep you unconscious, in addition to medicines that relax your muscles. During the procedure, your vital signs like heart rate, heart rhythm, blood pressure, and oxygen level will be monitored. Additional monitoring may be performed based on your medical condition. The anaesthesiologist will perform a pre-anaesthesia check prior to the procedure. Anesthesia will be administered only if you are found to be fit enough to receive anaesthesia. If you are suffering from any other co-existing illness or your blood investigations are found to be abnormal, you will be referred to a suitable physician for evaluation and optimization of your condition to facilitate safe anaesthesia. Anaesthetic drugs can interact with your existing medications and may occasionally lead to side effects.

The risks and potential complications during anaesthesia for ECT include, but are not limited to: frequent/minor - nausea, vomiting, confusion, headache, body ache, muscle stiffness, memory problems, airway secretions, changes in heart rate and blood pressure. Rare/major problems include – awareness of procedure, inability to breathe or difficulty in breathing, lip/tongue/teeth
injury, delayed recovery, aspiration pneumonia, anaphylaxis (potentially fatal allergic reaction),
organ failure (heart, lung, liver, and kidney) and very rarely, death can occur due to unanticipated
complications during anaesthetic procedure. Complications may also arise as a result of the
patient's condition. All or any of these factors may lead to a decline in medical status. In the event
of any complication, physicians and staff of NIMHANS will administer all necessary treatment,
including cardiopulmonary resuscitation if needed. The severity of complications may warrant
transfer to ward/casualty/ICU to continue the necessary care. We will monitor your symptoms and
adverse effects after each session of treatment. We may reduce the frequency of sessions if we
observe a significant problem with your concentration, memory and other mental abilities. We will
terminate the ECT course if there is no change in your symptoms from the previous session for
three consecutive sessions (CGI) after the 6th ECT. Irrespective of the number of sessions, we will
terminate ECT in any of the following situations: (1) if you experience complete improvement; (2)
if you experience significant problem with your concentration, memory and other mental abilities
despite reducing the frequency of ECT; (3) if you develop any medical condition that makes ECT
unsafe; (4) any time you wish us to terminate it for whatever reason. As happened during the first
part of the study, all the above-mentioned research investigations (except blood sample collection)
will be repeated after ECT.

As we have mentioned earlier, you will have the freedom to withdraw your consent at any time
during the study. Moreover, we will be requesting your consent again before starting the second
part of the study.

What are the potential benefits and risks of participating in the research?
If you do not take part in this study, your doctors may suggest different treatments to you, which
may include ECT. In case if you improve with one of the treatments in the first part of the study,
you may not have to undergo ECT which is a relatively more invasive treatment. If you take part
in this study and if you end up receiving ECT, your treatment would be the same as you would
have received otherwise. Please keep in mind that you may not experience improvement with
any of these treatments.

What will happen if I benefit from one of the treatments?
After the completion of these treatments, this research study will be completed. However, in
consultation with your treating doctors, we would decide about the future course of your treatment.
It may or may not include ECT.

What will happen if any of the treatments do not help me?
After the completion of these treatments, this research study will be completed. However, in
consultation with your treating doctors, we would decide about the future course of your treatment.
Since you would not have improved with ECT, your future treatment may not include ECT.

What if I feel uncomfortable during the treatment procedure?
In case you develop discomfort to the level that you wish us to discontinue it, we would oblige and
stop the procedure.

How long will these procedures take?
MRI, EEG, ECG and TMS tests will altogether take about 3 hours. Part-1: Neuromodulation
treatment (iTBS) will be given as once-daily sessions for 20 days. Each session of iTBS will take
less than 5 minutes of preparation and 3 minutes of stimulation. Each combined c-tDCS+iTBS
session will take about 30 minutes (including the preparation time for positioning the coils / electrodes respectively for iTBS / tDCS). Part-2: The time taken for ECT procedures is provided in the leaflet.

**How often will these tests be performed?**
During the first part of the study these tests will be done twice (i.e. before and after the neuromodulatory treatment); In case you are participating in part-2 of this study, the tests will be repeated once more after the completion of ECT.

**Is it compulsory for me to take part in this research?**
Participation in this research is optional and it is voluntary, meaning that the decision to take part in this study will be as per your wish. You will be given a copy of this information sheet and have an adequate time to read through, think and ask any questions before deciding. If you do decide to take part, you will be asked to sign a consent form and given a signed copy of the consent form to keep. If you decide to take part, you are still free to withdraw at any time during the study without giving a reason. A decision to withdraw or not to take part, will not affect in any way your routine medical care here.

**Would my denial to participate in the study hinder me from receiving regular treatment?**
Your refusal to take part in this study would be duly respected by us and, irrespective of your participation in this study, you would continue to receive the best possible treatment from your doctor without any prejudice.

**Will there be any modifications made in the current treatment that I have been prescribed for my symptoms?**
The treatments will be administered independently of other treatments and will not influence the treatments that you are prescribed by your treating team.

**Will my treating doctors be informed about my condition?**
We will consult your doctors whenever we take any important decisions. E.g., if you develop any complications / significant worsening of your condition/termination from the study, etc

**Will I be obligated to complete my participation in this study once I agree to sign the informed consent?**
No. There is no obligation of any kind. Even if you have agreed and signed the informed consent, you are free to withdraw whenever you wish too, with no justification required.

**Do I have the choice to withdraw my choice of participation at any time of the study? If I withdraw, do I have to justify or give reasons for the same?**
Yes, you can withdraw anytime you wish to. You can willingly share with us your concerns and reasons for backing out of the study. But you are not obligated to tell us your reasons. If you do not wish to confide in us, no questions will be asked.

**Can I ask, enquire or question any doubts I have during the entire time of my participation in the study?**
Anytime during the study, you are free to clarify your doubts and questions with respect to the research procedure.
Do I have to pay anything from my side for the tests or procedures that are a part of the study?
As you are participating in the study, all your tests and procedures are carried out for the research purpose. You do not have to pay anything from your side.

Will there be any reimbursement for my travel expenses?
Yes. Incidental expenses related to research participation (travel expenses, refreshment costs) will be reimbursed.

How likely is that I might suffer from any injury attributable to my participation in the research procedures? If any such injury happens, will I be compensated?
We will implement all the research procedures taking the utmost care to avoid any injury or adverse event. In the unlikely event that you suffer any injury attributable to your participation in the research procedures of this project, you will be compensated financially as per the National Ethical Guidelines for Biomedical and Health Research involving Human Participants by the Indian Council of Medical Research.

Will the test results obtained in the study be made available to others? Will my participation confidentiality be maintained?
Your identity will be completely protected. All information from the study will be stored under code to maintain strict confidentiality and will be reviewed only by the investigators, ethics committee or regulatory bodies. This coded and de-identified data (and its copies) will be stored in an encrypted format with password protected and secured access control in a database of computer servers at NIMHANS, collaborating institutes, cloud storage and any other storage media like CDs, DVDs, hard drives / similar others. This data will be used for further advanced analyses as well as future research studies. If you agree, as per the guidelines of scientific organizations and with the approval of relevant regulatory bodies, your data (in coded and de-identified format) will be shared with interested national and international researchers/collaborators, working on similar/related research ideas to foster greater understanding of the results; this, in turn, may lead to the larger good of patients suffering from depression and other diseases as well as scientific advances worldwide.
Flow Chart: Sequence of Research Procedures

Project-3: Clinical Efficacy & Neurobiological Correlates of sequential treatment with cathodal tDCS primed iTBS and ECT in Treatment-Resistant Depression

I am interested to take part in the study

I will be explained about the study procedures in detail

If I agree, I will sign the consent form

Part-1
Detailed Interview, Blood sample collection, MRI, EEG, Neuromodulation (NM) Tests & ECG will be done

I will receive a course of Part-1 treatment i.e., either cathodal tDCS primed iTBS or sham tDCS primed iTBS

After finishing the treatment course, I will be interviewed in detail; MRI, EEG, NM Tests and ECG will be done

If I have improved substantially, I will be out of the study. My doctors will discuss with me about my future treatment

Part-2
If I have NOT experienced substantial improvement, I will be offered participation in Part-2 of the study that is to receive ECT

I will be explained about the study procedures in detail; if I agree to take part in the study, I will sign the consent form again

I will receive a course of Part-2 treatment i.e., ECT

After finishing ECT, I will be interviewed in detail; MRI, EEG, NM Tests and ECG will be done

Study ends and my doctors will discuss with me about my future treatment

Note:
You may withdraw from the study any time.
We will discuss with you and your doctors about future course of your treatment if you wish so.