Brain Connectivity in Mild Cognitive Impairment and Alzheimer's Disease: A resting and task-based fMRI-MEG Study Examining Alterations in Functional Connectivity Following Treatment with Transcranial Direct Current Stimulation (tDCS)

Informed Consent Form

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NATIONAL INSTITUTE OF MENTAL HEALTH AND NEUROSCIENCES
Hosur Road,Dharmaram P.O., Bengaluru Karnataka India 560029

Informed Consent Form

For Patients with Alzheimer's Disease or Mild Cognitive Impairment

Study Title:

"Brain Connectivity in Mild Cognitive Impairment and Alzheimer's Disease: A resting and task-based fMRI-MEG Study Examining Alterations in Functional Connectivity Following Treatment with Transcranial Direct Current Stimulation (tDCS)"

Information to participants:

What is the purpose of the research study?

You are invited to participate in the above-mentioned research study, which is being carried out at the Department of Psychiatry, NIMHANS with due approval by the Institute Ethics Committee, NIMHANS. This project is funded by the Cognitive Science Research Initiative (CSRI) of the Department of Science and Technology (DST), Government of India. Please read this form carefully. If you agree to participate in this study, you are required to indicate your informed consent by signing at the appropriate place at the end of this form.

As you are aware, you have been diagnosed as having Alzheimer's Disease/Mild Cognitive Impairment and have been receiving treatment for the same. If you have earlier participated in a similar study conducted at NIMHANS, you may be familiar with some of the information given below.

Alzheimer's Disease and Mild Cognitive Impairment are typically diseases of old age. Alzheimer's Disease is a condition characterized by brain degeneration leading to progressive decline in various brain functions such as memory, language, orientation, decision making, reasoning, and planning, causing significant difficulties in daily activities. Mild cognitive impairment involves impairment in certain brain functions with only minimal impairment in activities of daily living; but it has the potential to progress into Alzheimer's disease. The underlying brain abnormalities in Alzheimer's disease has been fairly well characterized at the cellular level. However, by the time the disease is detected on MRI structural scans of the brain, the disease is fairly well-advanced and may no longer be adequately responsive to treatment. Therefore, many researchers are focussing on detecting the earliest functional changes in the brain that may precede structural changes of Alzheimer's dementia using functional brain imaging methods. Furthermore, the utility of these functional changes are also being studied in Alzheimer's disease to examine their reversal following treatment.

In this study, we are investigating the functional brain connections of participants with Alzheimer's dementia as well as mild cognitive impairment during resting state as well as during the performance of a simple memory task. Our aim is to compare the brain connectivity of persons with Alzheimer's Disease and amnestic mild cognitive impairment with those individuals who are not affected by the above conditions in order to advance our understanding of the disturbance in functional brain connections in these disorders. We will be estimating the brain connectivity using two techniques-functional Magnetic Resonance Imaging (fMRI) and Magnetoencephalography (MEG). These imaging techniques provide different aspects of brain connectivity.

If you are willing to participate in a 10-day course of treatment with transcranial direct current stimulation (tDCS), a safe and well-tolerated non-invasive treatment to enhance brain connectivity, we would then recruit you for receiving the above treatment. Following the 10-day course of treatment, we would repeat the fMRI and MEG investigations to examine the changes in brain connectivity following treatment. We would then attempt to link these connectivity changes with any measured improvement in your memory and other brain functions.

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In the following sections, we provide information regarding the various techniques / 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.

What tests will be performed in this research?

We employ 2 techniques in this study for functional imaging of the brain during resting condition and during performance of a simple memory task, viz., functional magnetic resonance imaging (fMRI) and magnetoencephalography (MEG). These investigations last 1-1 ½ hours each and would be performed on separate days. On the day of the investigations/scanning, you will be accompanied to the MRI/MEG room, where the investigation is performed. You will be shown a video of these procedures so that you can understand this better.

The MR 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. Further, you will be requested to perform certain tasks projected on to a screen in front of you, while the scan is being taken. The study coordinators and the MR 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 facilitate consultation with the appropriate specialist for obtaining the necessary guidance regarding treatment. You will be provided with a printed MRI scan report. However, the scans done in this study will not be made available to you in any form.

Though the MRI scan procedure is considered very safe, in 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 MR 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 eye liner, 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 orthopaedic 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 to notify the study coordinator if you have any of these items in your body and to avoid participating in this study.

During magnetoencephalography (MEG) recording, you would be comfortably seated below the MEG hood and MEG would be recorded during resting condition as well as during the performance of the simple memory task as in the case of fMRI. For simultaneous recording of electroencephalogram (EEG) along with MEG, we would fix a net outside your head comprising of EEG recording electrodes which would be connected to the EEG amplifier. Like MRI, MEG and EEG also are absolutely safe procedures and do not involve any radioactive or other risks.

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If you agree to participate in the tDCS treatment procedure, we would repeat the fMRI, MEG and brain function assessments following completion of the 10-day treatment programme. Repeating the assessments following the treatment would enable us to determine whether there are any benefits of undergoing the treatment as well as the brain changes that lead to the improvement in symptoms. Your participation in the study for an additional 3 ½ to 4 hours would be required for carrying out the repeat assessments.

What is Trans-cranial direct current stimulation (tDCS)?

tDCS is a non-invasive brain modulation technique which utilizes a small strength of battery delivered current that is applied using rubber electrodes wrapped in saline-soaked sponge. You will be shown a video of this procedure so that you can understand this better.

For what purpose is the tDCS used?

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 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. You will be shown a video of this procedure so that you can understand this better.

tDCS has been used as a safe and non-invasive form of treatment for various psychiatric and neurological conditions. However, its use in the treatment of dementia including Alzheimer's Disease and mild cognitive impairment is limited till date. We are trying here to study whether tDCS has the potential to provide the benefits in those with Alzheimer's Disease and amnestic mild cognitive impairment, and also to understand the mechanism by which such improvement occurs (through techniques / tests as described above).

tDCS treatment will be given as once daily 20-minute sessions for 10 consecutive days. tDCS is not commonly associated with any risks. Sometimes, it is possible that the application of tDCS may lead to some mild and tolerable tingling / itching in the place where the electrodes are positioned on your scalp. However, these sensations are tolerable and will be present usually only during the period of administration of tDCS and not beyond that. Very rarely, you may get mild headache or discomfort. In such situations, the required medical help will be provided.

How long do I need to undergo tDCS?

As part of this research, you will be required to participate in once daily session of tDCS for 20 minutes for 10 consecutive days.

What are the potential benefits of undergoing this treatment while participating in the research?

Participating in this research will not offer you any benefits.

What are the possible risks in these procedures?

Taking part in this study does not involve any risk apart from tolerable discomfort during the MRI/MEG procedures. It is possible that the application of tDCS may lead to some mild and tolerable tingling / itching in the place where the electrodes are positioned on your scalp. Very rarely, you may get mild headache or discomfort. In such situations, the required medical help will be provided. Collection of the blood sample for routine investigations is expected to be minimally painful. All aseptic precautions will be taken during the procedure.

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What if I feel uncomfortable during the procedures?

In case you develop any discomfort (though this is very unlikely), we will immediately stop the procedure.

How long will these procedures take?

MRI & MEG procedure will take about 1 – 1½ hours each.

tDCS treatment will be given as once daily 20-minute sessions for 10 consecutive days

How many times these tests will be performed?

If you are participating in the research involving tDCS, these tests will be performed twice, once before and once after the tDCS sessions. If you are not participating in the tDCS research, these tests will be done only once.

Are any other assessments going to be done as a part of this study?

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/ your relative in detail. If any abnormality is found in biochemical tests (for example thyroid dysfunction / vitamin B12 deficiency), you may be excluded from the study. If required we may seek additional information from other close relatives as well (e.g., spouse or children or other care givers). The study will involve you doing some paper-pencil tests for assessment of brain functions such as attention, concentration, memory, planning and reasoning. These tests would last approximately 1 to 1 ½ hours. A 10 ml sample of blood (about 2 tea spoons) will be collected for routine blood investigations.

Is it compulsory to participate in this study?

Please be informed that you have every right to refuse to participation in this study at any point in time.

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 tDCS is being given independently of other treatments and we will not make any changes in the current medications that you are prescribed.

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 to, without providing any justification.

Do I have the choice to withdraw my choice of participation at any time of the study? Do I have to justify or give reasons for the same?

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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.

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 confidentiality and will be reviewed only by the investigators, Ethics Committee or regulatory bodies.

What are the steps taken to minimize risk of infection during my participation in the research study, in view of the on-going COVID-19 pandemic?

We have taken all possible measures to avoid/minimise your exposure to infection while participating in this study in the midst of the on-going COVID-19 pandemic. All the study procedures will be performed following the safety measures detailed in the document attached for your reference. We shall educate you regarding these safety precautions prior to your consent for participation in this study. However, it is still possible that you may get exposed to the infection during the process of your participation in the study due to factors beyond our control. In the event of such unforeseen circumstances, you are required to contact the designated government agencies and officials for the necessary advice regarding further testing and treatment. The investigators of this study or NIMHANS will not undertake responsibility for the same or for the treatment of the condition.

<u>Undertaking by the investigator</u>

Your consent to participate in this investigation is solicited. You have the right to refuse consent or withdraw the same at any time during the study. In such an event, you will still receive appropriate treatment as would be required for your condition without prejudice. Strict confidentiality would be maintained about the information that you provide us as part of this study, except the information that is mandatory to be revealed to the Institute Ethics Committee, Government authorities or your treating physicians/psychiatrists as warranted. The MRI scans and the blood sample collected from you will be preserved and may be used currently and in future solely for research purposes, maintaining strict confidentiality of your personal details. We might also store your MRI and other

data, acquired during the study, in online databases without disclosing your personal information. This data may be made available to the research community for the purpose of carrying out studies to advance our understanding of these disorders. The results of this study may be presented at meetings or in publications; however, your identity will not be disclosed in those presentations or publications.

You will be informed of any new findings during the study that may have a bearing on your willingness to continue in the study. Moreover, the investigator will inform you if it is deemed that your further participation in the study could adversely affect your psychiatric/medical condition or its treatment. In such a situation, following discussion with you, the investigator would withdraw you from further participation in the study. If you have any questions or concerns regarding this study, or if any problems arise during your participation in the study, you may call the principal investigator, Dr. John P John or any of the co-investigators of the project whose names and contact numbers are provided below:

Dr. John P John, Professor of Psychiatry, NIMHANS, Tel- 08026995329
Dr. Sanjib Sinha, Professor of Neurology, NIMHANS, Tel-08026995843
Dr. Venkatasubramanian G, Professor of Psychiatry, NIMHANS, Tel- 08026995366
Dr. Mathew Varghese, Professor of Psychiatry, NIMHANS, Tel- 08026995369
Dr. Jitender Saini, Additional Professor of Neuroimaging and Interventional Radiology, NIMAHNS, Tel-08026995424
Dr. P T Sivakumar, Professor of Psychiatry, NIMHANS, Tel- 08026995260
Dr. Keshav Kumar J, Professor of Clinical Psychology, NIMHANS, Tel- 08026995190
Dr. Suvarna Alladi, Professor of Neurology, NIMHANS, Tel-08026995150
Dr. Preeti Sinha, Associate Professor of Psychiatry, NIMHANS, Tel- 08026995273
Dr. N Mariyappa, Senior Scientific Officer (on contract) of Neurology, NIMHANS, Tel-08026995844

Consent:

I have read this consent form and have been informed about the procedures involved in this study titled “Brain Connectivity in Mild Cognitive Impairment and Alzheimer’s Disease: A resting and task-based fMRI-MEG Study Examining Alterations in Functional Connectivity Following Treatment with Transcranial Direct Current Stimulation (tDCS)”. I have also been given a chance to ask questions and clarify my doubts regarding my participation in the study.

I understand that as part of this study, I will undergo MRI, MEG/EEG and brain function assessments. I understand that a sample of blood will be collected. I also understand that my medical and psychiatric status will be assessed and that the entire procedure may last approximately for 5 hours spread over two separate days (clinical assessments and MRI on day 1 and MEG on day 2). Furthermore, I understand that for participating in the tDCS treatment part of the study, I would need to attend once daily 20-minute tDCS treatment sessions for 10 consecutive days, followed by repeat assessments as above lasting approximately 5 hours spread over two separate days (clinical assessments and MRI on day 1 and MEG on day 2).

I understand that I have the right to refuse my consent or withdraw it at any time during the study without adversely affecting my treatment. I have been assured that I will be given a signed copy of this consent form for my records. Furthermore, for participating in this study, I am aware that I will have to give more time for the assessments by the research team and that, I may not stand to benefit directly through my participation in this research project.

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I, ……. ……, (name of the participant) the undersigned, give my consent for participation in this research project.

This consent includes/ does not include (strike off which is not applicable) the part of the study involving administration of tDCS treatment.

Signature/ Thumb Impression of the participant

Name and address:

Place:
Date:

Signature/ Thumb Impression of the witness

Name and address:

Place:
Date:

Signature of the investigator

Name and Designation-

Place:

Date:

Approved by NIMHANS [IEC Ref. No. NIMHANS/EC(BEH.SC.DIV.) 14th MEETING/2018] dated 27/10/2018