Informed Consent Form
Title: The effects of transcranial direct current stimulation combined with
cognitive training on cognition in patients with major or mild neurocognitive
disorders - A randomized controlled trial

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National Center of Neurology and Psychiatry

1. Introduction.
The clinical research we are asking you to participate in this time is called "specific
clinical trial," and it applies to the following;

Research that uses unapproved or off-label* drugs and other products
Off-label refers to the use of a drug or medical device approved by the Minister of
Health, Labour and Welfare for use in Japan in a manner different from that approved
by the Minister of Health, Labour and Welfare.

This informed consent form is provided to those who are considering participating
and cooperating in this clinical research by the principal investigator or sub-researcher
in order to help them deepen their understanding of the research.

Please decide whether or not you will participate in the research after you have
received an explanation of the research and have a full understanding of the contents
of this document. We ask that you decide of your own free will whether or not you
will participate in this research. Even if you decide not to participate in this research,
we guarantee that you will not be disadvantaged in any way by this decision. Also,
although there is a possibility that the results of this research may result in patents
and other intellectual property rights in the future, please understand that these
rights do not belong to you, the research participant.

If you have any questions or concerns about the research, please do not hesitate to
ask us.

2. The name of the study and approval for its implementation
Title of the study: " The effects of transcranial direct current stimulation combined with
cognitive training on cognition in patients with major or mild neurocognitive disorders - A
randomized controlled trial ".

This study was approved by the Clinical Research Review Board of the National Center for

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Neurology and Psychiatry, which reviews specific clinical trials, and the implementation plan was submitted to the Minister of Health, Labour and Welfare. We have received approval from the head of the medical institution where the research will be conducted.

3. Purpose and significance of this study

3.1. Introduction
In dementia and mild cognitive impairment, which is said to be a precursor to dementia, the goal of treatment is to maintain and improve the quality of life of patients and caregivers, since there is no curative treatment for the core symptoms (decline in cognitive function) of the disease. Treatment with anti-dementia drugs is said to inhibit the progression of dementia, but it is said to be ineffective in treating mild cognitive impairment. Cognitive training (e.g. calculation) is one of the treatments other than anti-dementia drugs, but it has not been established that it is effective in preventing the progression to dementia or preventing the progression to dementia. As an adjuvant therapy, we believe that transcranial direct current stimulation (tDCS) may be effective.

3.2. What is transcranial direct current electrical stimulation (tDCS)?
This device is expected to support the function of cranial nerves, which are originally activated by electrical signals, by passing a very weak (2mA in this study) current through electrodes attached to the scalp, and to have various effects such as improving mental symptoms and cognitive function (see Figure 1).

3.3. Purpose of the Research
In this study, we will measure and evaluate cognitive symptoms by asking consenting patients to solve computational drills while receiving transcranial direct current electrical stimulation to determine the effectiveness of the study. If it becomes clear that cognitive symptoms improve, this will lead to the development of new methods to strengthen the effectiveness of cognitive training.

4. Method and duration of the study

4.1. Inclusion Criteria
1) The people between the ages of 55 and 90 who are attending the hospital
2) Those diagnosed with dementia or mild cognitive impairment
3) Those who have not discontinued or changed dosage of psychotropic drugs, donepezil hydrochloride (Aricept®), galantamine hydrobromide (Reminyl®), rivastigmine (Exelon Patch®, Rivastach®), or memantine hydrochloride (Memory®) for the past two weeks, or who are not taking memantine hydrochloride, or who are not taking memantine hydrochloride.
4) Those who are ambulant without the aid, or can walk with an assistive device such as a cane or walker.

4.2. Exclusion Criteria
1) Those whom their physician determines that it is necessary to use antipsychotic medication
for neuropsychiatric and behavioral symptoms of dementia, such as hallucinations, delusions and aggression.

2) Those who have depression or suicidal thoughts that require psychiatric inpatient treatment within 6 weeks, as determined by the doctor.

3) Patients who are clinically unable to perform electroconvulsive therapy or transcranial direct current electrical stimulation

4) Those who are deemed to have severe dementia as a result of the examination.

5) Unable go to the outpatient clinic every day during the examination period (except for inpatients).

6) You are unable to write sentences or copy figures.

7) Those who have had tDCS in the past.

In addition to these, your doctor will determine from the results of your examination and tests whether you are eligible to participate. In some cases, you may not be able to participate in the study even after you have given your consent. Please note that if your doctor determines that you would not be able to participate in the study even after you have agreed to participate, your participation in the study may be terminated.

4.3. Drugs/medical devices/treatments to be used in research

The current study will use tDCS (transcranial direct current stimulation, or transcranial direct current stimulation). It will be performed five times a week, twice a day, for 20 minutes at 2 mA each time. For the purposes of the tDCS vs. sham study, patients will be automatically assigned to either the tDCS or sham group upon their acceptance to participate. In the sham group, only the first 30 seconds and the last 30 seconds of the sham stimulation are used to simulate the actual stimulation.

Figure 1: The tDCS device

a) tDCS device
b) anode
c) cathode
d) strap
e) rubber pads
The following is how it is conducted

(1) First, the individual is interviewed and assessed for past and present medical conditions and functioning (this is a "screening" in the table below).

2) Once participation is confirmed, the computer automatically assigns the individual to a group to receive tDCS or a sham stimulation of tDCS. Participants and the evaluators conducting the psychological assessment will not be informed of which group they have been assigned to until the end of the study.

(3) On the first day of t-DCS or sham stimulation, the "At the start" test is administered as shown in the table below.

(4) The tDCS will be performed twice a day, five days a week. You will meet in the afternoon every day to receive cognitive training (calculation) while the tDCS or sham stimulus is being performed.

(5) The following tests will be performed according to the schedule. Stimulation ends when 10 stimulation sessions are completed. At the end of stimulation, you will also be tested for cognitive function and adverse events, as shown in the table below. You will come back to the hospital four weeks later and we will ask you how you are doing after that. At that time, we will also perform cognitive function tests, adverse event checks, life skills assessments, and a comprehensive evaluation, as shown in the table below.

Figure 2: Scheme of this study

4.4. Research period and schedule
The study will last approximately five weeks. During this time, we will not only test the efficacy of tDCS, but we will also confirm that your condition is safe and that you are in good health.

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<tr>
<th></th>
<th>Screening</th>
<th>Baseline</th>
<th>After interventions</th>
<th>Follow-up</th>
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<tbody>
<tr>
<td>Consent</td>
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<tr>
<td>Body height and weight</td>
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<td>Background information</td>
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<td>Medical examination</td>
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<td>Cognitive examination</td>
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<tr>
<td>Adverse events</td>
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<td>🚫</td>
<td>📹</td>
<td>⬤</td>
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<tr>
<td>Functional examination</td>
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<td>Global clinical impression</td>
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4.5. What to do after the research is completed?

TDCS cannot be used as a treatment after the study is completed because it is not approved as a medical device.

Please note that:

- If you cannot come to the hospital on the day of your visit, please be sure to contact us.
- Please contact the principal investigator or co-investigators before you change the medication you are taking or the treatment you are currently receiving from doctors.
- You should not use any medication purchased from a pharmacy or the Internet while participating in this clinical trial before consulting with the principal investigator or co-investigator.

4.6. Tests and scales to be performed

- ADAS-Cog (Alzheimer’s disease assessment scale cognitive): This test is used to assess cognitive function. It takes about 30 minutes to complete the test.
- RBANS (Repeatable Battery for the Assessment of Neuropsychological Status): This test is a more specific assessment of cognitive function. It takes about 20 minutes to complete the test.
- MMSE-J (Mini Mental State Examination): This test is designed to screen for cognitive function. It takes about 10 minutes.
- SF-36 (MOS 36-Item Short-Form Health Survey): This test is designed to assess your quality of life. You will be assessed by your family and others.
- FAST (Functional Assessment Staging): This test is one of the behavioral scales for dementia that assesses patients by observing their daily life.
5. the burdens, risks and benefits that may arise from participation in research

5.1. Burden and risk that may arise

5.1.1. Illness or failure

Under the Clinical Trial Act, "illness or disease" means a disease, disorder or death, or infection that is suspected to have been caused by a malfunction of a medical device in the course of participation in specific clinical research. In the event of a disease or illness, the principal investigator is required to report to the administrator of the medical institution, notify the principal investigator and report to other principal investigators.

Symptoms that can occur with tDCS have been reported, including the following symptoms:

<table>
<thead>
<tr>
<th>Adverse events reported in more than 5% of cases</th>
<th>Skin redness</th>
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<td>itch</td>
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<td></td>
<td>Tingling sensation in the scalp</td>
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<td></td>
<td>Drowsiness/Hypersomnia</td>
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<td>Burning scalp</td>
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<td>headache</td>
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<td>Scalp pain</td>
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<td>neck pain</td>
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<td></td>
<td>dizziness</td>
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<td>Sudden mood swings</td>
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<table>
<thead>
<tr>
<th>Adverse events reported in less than 5% of cases</th>
<th>Fatigue</th>
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<tr>
<td></td>
<td>difficulty in concentrating</td>
</tr>
<tr>
<td></td>
<td>nausea</td>
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<tr>
<td></td>
<td>diarrhea</td>
</tr>
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<td></td>
<td>delirium</td>
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</table>

If such symptoms occur, your doctor will take appropriate action. In terms of skin symptoms, previous studies have shown that they are often temporary and often improve at the time of the next day's stimulation with no effect. tDCS has been reported to cause 1-2% of study discontinuation due to symptoms caused by tDCS, but a preliminary study conducted at our hospital showed that there have been no discontinuations due to symptoms caused by tDCS. Although no deaths have been reported, less than 5% of patients have experienced manic outbursts or delirium as serious adverse events. If you experience any of these serious symptoms, your doctor will take appropriate action. We have administered at least 380 stimulation sessions to 37 subjects as of May 5, 2018, with no adverse events requiring treatment.

5.1.2. Other burdens and disadvantages

If you participate in the study, you will have more visits (1 week + 2 days) and more time in the hospital compared to general practice treatment. For this, a burden reduction fee of 3,000 yen
will be paid.

5.2. Projected profits
We conducted a preliminary study of 19 patients with dementia and mild cognitive impairment who underwent tDCS (same as this one) while undergoing cognitive training. Cognitive function as assessed by the Alzheimer's disease assessment scale showed that, there was a trend of improvement in the group with actual stimulation compared to the group with sham stimulation of tDCS. This study provides knowledge about whether the intervention really works.

5.3. When to stop the study.
(1) If, after participating in the research, it is discovered that you should not be allowed to participate in the research
(2) In the event that you request to withdraw from participation in this research
(3) If you withdraw your consent to participate in this study
(4) When the principal investigator or sub-doctoral researcher judges that it is medically necessary to discontinue the research.
(5) If you are unable to come to the hospital due to a change of address or hospital transfer
(6) If the principal investigator decides to discontinue the entire study.

6. Withdrawal of consent after participation in research
Your participation or continuation in this study is at your own discretion. You will not be disadvantaged in any way if you refuse to participate in this study. You may discontinue participation in this research at any time, and you will not be disadvantaged in any way, even if you have agreed to participate and have started the research.

7. Disclosure of research-related information
An overview of this research will be registered in a public database* maintained by the Ministry of Health, Labour and Welfare (MHLW) prior to starting the research, and will be updated as the research protocol is changed and as the research progresses. When the research is completed, the results of the research will be registered in the database. The results of this research will be published only in academic venues such as conference presentations and papers. Personal information will be anonymized and the results will be presented in such a way that individuals cannot be identified.

*jRCT (Japan Registry of Clinical Trials) https://jrct.niph.go.jp/

8. To obtain or view materials related to the research proposal and research methods
The research protocol and materials related to the research methods may be viewed to the extent that it does not interfere with protecting the personal information of other research participants and ensuring the originality of the research in question. If you wish to view these materials, please contact us at the address listed at the end of this document.
9. Handling of Personal Information
If you participate in this study, the data relating to this study, such as specimens and medical information provided by you, will be maintained by a number, coded in a non-personally identifiable format. Although a correspondence list will be created to match the coded numbers with the individual information, this and other information related to this research, including personal information, will be strictly managed and stored in the hospital in accordance with the Clinical Research Act (Act No. 16 of 2017) and under a management system approved by the Accredited Clinical Research Review Committee of our center.

10. Storage, disposal and secondary use of specimens and information
The samples and information obtained in this study will be anonymized with a unique code and stored at the center for 5 years. The final data will be attributed to the principal investigator. Samples and information obtained from this study will be destroyed at the end of the study, ensuring that no personal information about you is included in the study. It may be used in the future for research other than this study. Such potential studies will be further broken down by individual age, gender, disease name, etc., completely unaware of your personal information, and combined with data from other national and international studies to statistically determine which patients are best served by tDCS. Such a method is called individual data meta-analysis and will be done within five years of the publication of the study to doctors at unspecified national and international research institutions. When such research is conducted, it will be reviewed again by the Center's Ethics Committee or Clinical Research Review Committee, and will be carried out only after obtaining the approval of the Center and confirming our willingness to cooperate in the research through re-consent or disclosure of information regarding the conduct of another study.

11. Conflicts of interest related to research funding sources and researchers
A "conflict of interest" is a situation in which a third party may be concerned that the research is not being conducted fairly and appropriately, such as falsification of research data, favoritism of a particular company, or continuation of research when it should be stopped, due to financial or other reasons.

This study was funded by the Research and Development Fund for Psychiatric Disorders, "Transcranial Direct Current Electrical Stimulation for Cognitive Function in Dementia and Mild Cognitive Impairment - This Study" (Principal Investigator, Dr. Takuma Inagawa, Period: April 1, 2018 - March 31, 2019) and the Grant-in-Aid for Scientific Research, "Development of New Augmentation Therapy for Neurocognitive Impairment. This study is being conducted as a blinded, randomized, comparative study of transcranial direct current electrical stimulation (Principal Investigator: Takuma Inagawa (Research Period: April 1, 2019 - March 31, 2022) and has not been funded by any specific company. All researchers and their family members, including spouses, have no financial interest in the
Soterix Medical company, which manufactures the 1x1 Transcranial Direct Current Low-Intensity Stimulator Model 1300A used in this study. There is no relationship or employment relationship. Therefore, the research is planned and conducted by the investigators independently of the company, and Soterix Medical has no influence on the results or analysis of the study.

The researcher's conflict of interest management plan for the study has been reviewed by a clinical research review board and is appropriately managed by the principal investigator.

12. If you have any questions about this research
If you or your family have any questions or concerns about this study, please do not hesitate to contact us at the contact point at the end of this explanatory document. Please note that we may not be able to respond to you or answer your questions due to reasons such as protection of the personal information of other research participants or intellectual property rights of the researcher.

If you wish to file a complaint, such as a complaint about any inconvenience caused by the implementation of this research, please contact the Complaints Office.

13. Financial burden of participation in this research
Participation in this study will not cover the cost of administering tDCS, booklets and stationery needed for cognitive training, or any other costs related to psychological testing. If you wish, you can take the booklets used during training home after the study. In addition, in order to reduce the cost of coming to our clinic, we will pay a fee of 3,000 yen for 9 days to an account at a bank or other financial institution of your choice to reduce the cost of coming to the clinic.

14. Other treatment methods
Treatment for cognitive function in dementia and mild cognitive impairment includes cholinesterase inhibitors for Alzheimer's disease and Lewy body dementia to inhibit the progression of dementia. For cognitive function in moderate to severe Alzheimer's disease, a drug called memantine may also be used. However, no curative treatment exists and there is no insurance-approved treatment for cognitive function in mild cognitive impairment.

15. Provision of medical care after research
After the study is completed, you will be given the right treatment for your condition. Please note that even if the results of the study turn out to be good and you conclude that one of the treatments is better than the other, you will not be able to continue the treatment used in the study because the study will be conducted using unapproved equipment. You will be offered other options that you feel are best for you.

16. handling of research results from participants in the study
In conducting this study, important findings may be obtained regarding your health status. The
results obtained in this study will be made public during the study period after the completion of the intervention with regard to psychological test results, and all the results of the allocation will be documented and communicated to you after the data are fixed.

17. compensation for health problems caused by participation in the study
Establishing new medical technologies for drugs (and medical devices) through clinical research is essential for the development of medicine and medicine. However, even if clinical research is carried out correctly and with all due care, it is difficult to completely prevent health hazards caused by drugs (and medical devices) from occurring. In recent years, from the perspective of protecting those who have cooperated in research with good intentions for the development of medicine and medical care from the occurrence of health hazards, there has been an increased emphasis on the response to health hazards caused by drugs and medical devices.

Although this study is scientifically designed and carefully conducted, please inform your physician immediately if you experience any unusual symptoms or physical condition during your participation in this study. We will immediately provide you with appropriate treatment and assistance. You will be required to pay for the cost of the examination and treatment using your health insurance as well as your normal medical practice.

In addition, in the unlikely event that serious health problems ("death, grade 1-2 permanent disability (in accordance with the adverse drug reaction relief system)") arise as a result of this research. In the unlikely event that serious health damage ("death or permanent disability grade 1 to 2 (in accordance with the adverse drug reaction compensation system)") occurs as a result of this research, compensation will be paid by the non-life insurance related to the clinical research. However, if the health damage was caused by other causes or other factors unrelated to this research, or if the cause and effect of the health damage can be clearly explained elsewhere, or if your health damage was caused by a false declaration or if you were intentionally or grossly negligent in failing to follow your doctor’s instructions. We may not be able to pay you compensation or the amount of compensation may be limited. Please note that understanding the contents of this explanatory document and agreeing to participate in this clinical study does not mean that you are waiving your right to claim compensation for health problems.

18. Handling of the collected samples and information (possibility of future use)
Not applicable.

19. The system of this study, the name of the medical institution and the name of the principal investigator
Sponsor: National Center of Neurology and Psychiatry
Principal Investigator: Takuma Inagawa, MD, PhD (Department of Psychiatry)

20. Inquiries about this research
20.1. Contact for inquiries about this research
Takuma Inagawa, MD, PhD
Department of Psychiatry,
National Center of Neurology and Psychiatry
4-1-1, Ogawahitashicho, Kodaira, Tokyo, 187-8551, Japan
Tel: 042-341-2712 (ext. 3083)

20.2. Complaints desk
Office of the Ethics Committee
National Center of Neurology and Psychiatry
4-1-1, Ogawahitashicho, Kodaira, Tokyo, 187-8551, Japan
Email: rinri-jimu@ncnp.go.jp
Consent form for research participation

To Dr. Takuma Inagawa, Principal Investigator

I have been fully briefed and understand the following regarding the "Research Project Title: A blinded, randomized comparison of the effects of transcranial direct current electrical stimulation on cognitive function in dementia and mild cognitive impairment", using a written explanation. I am participating in this study of my own free will.

Items explained and understood

- □1 Purpose and Significance of the Study (Explanatory Document, Item 3)
- □2 Method and period of participation in this study (Explanatory document, Item 4)
- □3 The burdens, risks, and benefits that may arise from participation in the research (Explanatory Memorandum, Item 5)
- □4 The Voluntary Nature of Research Participation and the Withdrawal of Consent after Participation in Research (Explanatory Document, Item 6)
  - □4-1 Consent to participate in this study, but may withdraw at any time.
  - □4-2 Not to receive any therapeutic disadvantage if you do not participate in the study or if you withdraw your consent.
- □5 Disclosure of Information on Research (Explanatory Document, Item 7)
- □6 If you wish to obtain or view materials related to the research protocol and research methods (Explanatory Document, Item 8)
- □7 Handling of Personal Information, etc. (Explanatory Document, Item 9)
- □8 Storage and Disposal of Samples and Information, and Secondary Use of the Products (Explanatory Document, Item 10)
- □9 Conflict of interest regarding the source of funding for the research and the researcher, etc. (Explanatory document, Item 11)
- □10 Financial Burden of Participation in Research (Explanatory Memorandum, Item 13)
- □11 Other Treatment Options (Explanatory Document, Item 14)
Provision of Medical Care After Research (Explanatory Document, Item 15)

Handling of Research Results from Research Participants (Explanatory Document, Item 16)
Provide information when a non-negligible health finding is accidentally discovered or an important finding is made.

Hope □ Do not hope

Compensation for Health Damage Caused by Research Participation (Explanatory Memorandum, Item 17)

Handling of the Received Samples and Information (Possibility of Future Use) (Explanatory Document, Item 18)

<Participants>
Date of Agreement:
Signature:

<The proxy or caregiver>
Date of Agreement:
Signature:

I have explained this study in accordance with the explanatory document, when obtaining the consent of the research subjects.
Date of explanation:
Signature of Physician: