BMJ Open

Effects of multisession transcranial direct current stimulation as an augmentation to cognitive tasks in patients with neurocognitive disorders in Japan: a study protocol for a randomised controlled trial

Takuma Inagawa ,[1] Yuma Yokoi ,[1] Yuji Yamada,[1] Nozomi Miyagawa,[1] Takeshi Otsuka,[2] Naonori Yasuma ,[3] Yoshie Omachi,[1] Tadashi Tsukamoto,[4] Harumasa Takano,[5] Masuhiro Sakata,[1] Kazushi Maruo,[6] Mie Matsui,[7] Kazuyuki Nakagome[1]

To cite: Inagawa T, Yokoi Y, Yamada Y, *et al*. Effects of multisession transcranial direct current stimulation as an augmentation to cognitive tasks in patients with neurocognitive disorders in Japan: a study protocol for a randomised controlled trial. *BMJ Open* 2020;**10**:e037654. doi:10.1136/bmjopen-2020-037654

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-037654).

Received 14 February 2020
Revised 16 October 2020
Accepted 05 November 2020

For numbered affiliations see end of article.

Correspondence to
Dr Takuma Inagawa;
tinagawa@ncnp.go.jp

ABSTRACT

Introduction Transcranial direct current stimulation (tDCS) is a potentially novel strategy for cognitive enhancement in patients with disorders. We present a study protocol for a randomised controlled trial designed to evaluate the safety and efficacy of tDCS combined with cognitive tasks on cognition in such patients.

Method and analysis This is a two-arm, parallel-design, randomised, sham-controlled trial, in which participants and raters will be blinded at a single centre. Stratified randomisation will be conducted, and a randomisation sequence will be generated through the Electronic Data Capture system. Patients who met the Diagnostic and Statistical Manual of Mental Disorders-5 criteria for neurocognitive disorders will be recruited and randomised to receive either active (2 mA for 20 min) or sham (stimulation ramped up and down for 1 min) stimulation in 10 sessions over five consecutive days. A direct current will be transferred by a 35 cm^2 saline-soaked sponge electrode. An anode will be placed over the left dorsolateral prefrontal cortex, and a cathode will be placed over the right supraorbital cortex. Calculation tasks will be conducted in both arms as a cognitive task for 20 min during the stimulation. This task consists of basic arithmetic questions, such as single-digit addition, subtraction, multiplication and division. The primary outcome will be the mean change in the Alzheimer Disease Assessment Scale–cognition at Day 5 after baseline. Depressive symptoms, as measured by the geriatric depression scale, and quality of life, as measured by the Medical Outcomes Study 36-item Short-Form Health Survey, will also be assessed. Data will be collected at baseline, within 3 days following the final stimulation and 1 month thereafter. The estimated sample size is 46 per group based on the assumptions that an estimated mean difference is −1.61 and SD is 2.7. Mixed models for repeated measures will be used for the statistical analysis.

Ethics and dissemination The National Center of Neurology and the Psychiatry Clinical Research Review Board (CRB3180006) approved this study. The results of this study will be published in a scientific peer-reviewed journal.

Trial registration details Japan Registry of Clinical Trials jRCTs032180016.

Strengths and limitations of this study

- This study will provide an optimised protocol on the effects of transcranial direct current stimulation (tDCS) as an augmentation strategy for patients with neurocognitive disorders.
- This is the first randomised controlled trial following a priori and proper sample size calculation to assess the effects of tDCS combined with cognitive tasks for patients with neurocognitive disorders.
- A standardised cognitive battery (Repeated Battery for the Assessment of Neuropsychological Status) is used to comprehensively assess both global cognition and specific cognitive domains.
- A limitation of this study is that we could not sufficiently evaluate the long-term effects of tDCS.

INTRODUCTION

Dementia (major neurocognitive disorder) is characterised by cognitive decline that interferes with patients' daily living as well as caregivers' consequent quality of life and social functioning. There often exists a transitional state from normal state to dementia, called mild cognitive impairment (minor neurocognitive disorder, MND).[1 2] Currently approved pharmacotherapies, cholinesterase inhibitors and memantine are not disease-modifying and therefore cannot revert the course of the disease; however, they exhibit

slight improvements in certain cognitive scales.[3] Recent studies have gradually been identifying a few potentially modifiable factors that can help prevent dementia, such as physical inactivity, social isolation and depression.[4] Furthermore, a recent meta-analysis indicated that the overall effect of cognitive training on cognition in patients with MND was moderate (Hedges' g=0.35)—yet it was small in patients with dementia (g=0.26)[5]—while another review indicated that current evidence cannot prove the preventive effects of cognitive training. Therefore, more strategies are needed to combat cognitive decline in patients with MND. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique that involves passing a direct electrical current (usually 1 to 2 mA) through the cerebral cortex, usually via two electrodes placed on the scalp.[6] The basic mechanism is that the anodal tDCS at 1 mA increases neuronal excitability by causing a depolarisation of the resting potential, while the cathodal tDCS at 1 mA hyperpolarises the resting potential, thereby suppressing neuronal excitability.[7] However, another study indicated that both anodal and cathodal tDCS at 2 mA increases neuronal excitability by causing the depolarisation of the resting potential.[8] Furthermore, anodal tDCS at 2 mA induced neuronal excitability for a longer amount of time compared with 1 mA. Moreover, prolonged membrane polarisation by tDCS changes neuroplasticity through activating N-Methyl-D-aspartic acid (NMDA) receptors, thereby resulting in lengthening the after-effects of tDCS.[9] Although tDCS may have cognitive effects on healthy participants,[10] the specific cognitive benefits of tDCS for dementia and patients with MND remain unclear.[11] The disparity among these aforementioned results may be due to differences in electrode montage, stimulation parameters and target populations.[12] Furthermore, a randomised trial demonstrated that active tDCS (but not sham), over dorsolateral prefrontal cortex (DLPFC), combined with a working memory task exhibited greater improvements in healthy participants in terms of their performance on an attention and working memory test 1 month following a final treatment session when compared with tDCS alone.[13 14] These studies indicate the possibility of simultaneous augmentation strategies using tDCS combined with cognitive tasks in patients with neurocognitive disorders. While a recent study indicated that tDCS combined with a cognitive training may improve delayed recall and working memory in patients with MND,[15] this recent short-term trial was unable to indicate clinically meaningful benefits. However, this study selected the Alzheimer Disease Assessment Scale-cognition (ADAS-Cog) for the assessment of cognition in patients with MND, which may be affected by floor effects. Therefore, further large-scale trials with optimised tDCS protocol using appropriate cognitive outcome scales are warranted. The objectives of the proposed study will be to assess the safety and efficacy of tDCS by comparing the effects of active tDCS plus cognitive tasks with the effects of sham tDCS plus cognitive tasks on the cognitive outcomes of patients with neurocognitive disorders. Since combining tDCS with cognitive tasks may enhance the benefits of tDCS, we hypothesise that tDCS will improve cognitive functioning, particularly when administered during their engagement in cognitive tasks.

METHODS AND ANALYSIS

Trial design

A parallel, prospective, randomised, sham-controlled, confirmatory, superiority study will be conducted on 92 participants with a diagnosis of major neurocognitive disorder or mild neurocognitive disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Participants will be randomly assigned to two groups in a 1:1 ratio: an active group and sham group. The study design is in accordance with the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (online supplemental file 1).[14] This study was registered within the Japan Registry of Clinical Trials (Trial ID: jRCTs032180016).

Participants

Both inpatients and outpatients will be recruited from a single academic hospital: the National Center of Neurology and Psychiatry in Tokyo, Japan. Potential participants will be referred by their treating psychiatrists or neurologists, who will provide them with brief information on the trial using a brochure following their first appointments. After a show of interest, the principal investigators or sub-investigators will obtain participant informed consent using the Informed Consent Form (online supplemental file 2). Then, both the principal investigator and outcome assessors will arrange an appointment to explain the study design as well as its potential benefits and risks. After providing their informed consent, participants will then be screened by a treating psychiatrist to establish whether they meet the eligibility criteria (shown below).

The inclusion criteria are set as follows:

1. Subjects aged 55 to 90 years with a diagnosis of either a major neurocognitive disorder or mild neurocognitive disorder, as defined in the DSM-5.
2. Subjects taking a stable dose of antidementia medication, such as cholinesterase inhibitors or NMDA receptor antagonists, for the 2 weeks prior to enrolment.
   a. Because it is necessary to stabilise the concentration of drugs that may influence cognition.
3. Ambulant subjects with or without an aiding device, for example, canes.
   a. Because participants must be able to visit our hospital five times a week.
4. Benzodiazepines during this trial will be allowed but should be limited to a maximum dose of 20 mg per day of a diazepam equivalent, and the dosage should remain stable during the trial.
   a. Because benzodiazepines might weaken the effects of tDCS, and this follows the protocol of previous studies using the same criteria.

The exclusion criteria are set as follows:

1. Subjects with severe behavioural and psychotic symptoms, including delusion and hallucination, who require antipsychotic treatment.
   a. Because severe behavioural and psychotic symptoms are likely to heavily influence cognition. Such symptoms will affect the participants' ability to complete the cognitive task.
2. Subjects anticipated to be hospitalised within 6 weeks before the administration of tDCS due to severe depression and/or suicidal ideation.
   a. Because of the same reasons above.
3. Subjects who have a clinical contraindication to electroconvulsive therapy or tDCS.
   a. Because of safety concerns.
4. Subjects with an Mini-Mental State Examination (MMSE) score of less than 18 or a Clinical Dementia Rating (CDR)-Japan score of more than 2.
   a. Because some cognitive scales used in our study have no validity for patients with MMSE scores of less than 18 or a CDR score of more than 3.
5. Subjects who are unable to participate for more than 2 days of the trial.
6. Subjects who failed the subsets (writing a sentence or copying a figure) in the MMSE at the time of screening.
   a. To be in accordance with the criteria of our pilot study.[16]
7. Subjects deemed inadequate for participation by a physician in charge.

Intervention tDCS will be performed using a 1×1 transcranial direct current low-intensity stimulator (Model 1300A, Soterix Medical Inc, New York, USA) that delivers a direct current through two 35 cm^2 electrodes. We soaked 4 mL of saline per side (8 mL into each sponge). A recommended amount of saline has not yet been defined,[17] but a previous study recommended that approximately 6 mL of solution per side may suffice.[18] However, 6 mL sometimes causes fluid leaking across the subject. To avoid excessively wet, we selected 4 mL. The anode electrode will be placed over the left DLPFC (F3) using the electroencephalography (EEG) 10/20 placement method. The cathode will be placed over the contralateral supraorbital ridge (Fp2) using the EEG 10/20 placement method, which is in line with recent tDCS studies that improved cognitive functioning in patients with mild cognitive impairment,[19] Alzheimer's dementia[20] and schizophrenia.[21] Participants will be randomised into two groups to receive either active or sham tDCS. The participants in the active group will receive tDCS at a constant current with an intensity of 2 mA for 20 min per session, with two sessions per day for five consecutive days. If too high a resistance is set due to poor electrode contact quality, we will at times regulate the current down to be a relax amount for a participant to minimise the patients' discomfort. After this, we will record the current in three stages: 2 mA, 1 to 2 mA and less than 1 mA. During the administration of tDCS, we will attempt to increase the current to 2 mA as much as possible and will also try to minimise the patients' uncomfortable feelings. Those in the sham group will receive tDCS, but the overall active stimulation period is only 60 s, including the 30 s for both the fade-in and fade-out periods. For the other periods, the stimulator will remain active but will not generate a current for 20 min in each session. Therefore, those in the sham group usually experienced an initial itching sensation but received no current for the remainder of the session. The tDCS device will be kept out of sight so participants will be unable to see whether the device is turned on or off. The assessors and patients will be blinded to the treatment administration, and participants will be unable to communicate with each other to enhance the effect of the study blinding. Trained psychiatrists or neurologists who are not blinded will administer tDCS, but their interaction with the participants will be minimised. Also, the testers will not evaluate any of the outcome measures. Raters and participants will not be aware of their administered treatment until all participants finish their follow-up evaluations. To assess the quality of blinding, after completing Day 5, participants will be asked about which participants were in which group. All participants will be subject to calculation tasks during each 20 min stimulation session. Our calculation task is a face-to-face training task. For 20 min, patients will complete as many calculation tasks, including addition, subtraction, multiplication and division, as possible. Moreover, this calculation task is a digit-by-digit simple task, so its level of difficulty is lower than elementary school level. We will record the number of correct answers at baseline, after the treatment and at follow-up. We also assess the other cognitive tasks to assess other specific cognitive domains, including immediate memory, delayed memory, visuospatial function, attention and language through Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), to ascertain whether this procedure can improve non-trained cognitive domains. These tasks are designed to improve working memory.[22] All questions will be printed on A4 sheets of paper. The interval between sessions will be set as greater than 20 min. The participants will generally receive active or sham tDCS in two sessions per day for five consecutive days. The maximum interval between tDCS sessions is up to 72 hours. If the time interval between tDCS administrations is more than 72 hours, we will regard it as a protocol deviation.

Outcomes

The primary outcome measured is the mean change in ADAS-Cog scores from baseline to Day 5. Depressive symptoms, measured by the geriatric depression scale; quality of life, measured by the MOS 36-item Short-Form Health Survey (SF-36); and cognition, measured by the MMSE (with scores ranging from 18 to 30). RBANS will also be assessed. RBANS will enable us to evaluate global cognition, immediate memory, delayed memory, visuospatial function, attention and language. All the above-mentioned outcome measures were scored by a

	STUDY PERIOD						
	baseline	Allocation	Post-allocation				Follow up
TIMEPOINT**	-14 days	0	Day1	Day2 -4	Day5	After tDCS	+28 days
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
[active tDCS + cognitive task]			X	X	X		
[sham tDCS + cognitive task]			X	X	X		
ASSESSMENTS:							
[List baseline variables]	X						
[safety questionnaire]			X	X	X	X	
ADAS-Cog	X				.	X	
RBANS	X					X	X
GDS	X					X	X
MMSE	X					X	
SF-36	X					X	X
FAST	X						
Apathy Scale	X						

Figure 1 Example template of the recommended content for the scheduling of the enrolment, interventions and assessments. The time point of post-tDCS evaluation will be allowed within 3 days after the final stimulation and that of follow-up evaluation will be allowed within 7 days before or after the final stimulation. ADAS-Cog,Alzheimer Disease Assessment Scale-cognition; FAST, Functional Assessment Staging of Alzheimer's disease; GDS, geriatric depression scale; MMSE, Mini-Mental StateExamination; RBANS, Repeatable Battery for the Assessment of NeuropsychologicalStatus; SF-36, 36-item Short-Form Health Survey; tDCS,transcranial direct current stimulation.

psychologist, who was blinded to group allocation, after a clinical interview. The outcome measures are assessed at baseline, at the end of the final stimulation and 4 weeks after the final stimulation. The psychological evaluations at the end of the final stimulation and at 4 weeks after the final stimulation are set to within 3 days and 7 days from the designed day, respectively. The schedule for enrolment, intervention and assessment is summarised in figure 1. We will record any previous history of substance use disorder, dementia, schizophrenia, mood disorder, neurological disorder, brain injury and other conditions at baseline to avoid recruiting patients with clinically contraindicated conditions.[23] Well-trained psychologists will assess the outcomes using the scales mentioned above. Adverse events are defined as any undesirable patient experience during tDCS administration. Regardless of causal relationship, all adverse events are monitored and recorded throughout the study via clinical evaluations and observations. We will follow any untreatable adverse events after trial completion. The principal investigator will be responsible for the diagnosis, treatment and explanation of any serious adverse events to the relevant patients. The sub-investigators will be responsible for reporting any information related to such adverse events to the principal investigator. The principal investigator will have to report any serious adverse events to the clinical research review board, the Ministry of Health, Labour, and Welfare, and the pharmaceutical and medical device agencies.

Serious adverse events can be defined as any negative medical occurrence at any dose that:

1. Results in death.
2. Is life-threatening.
3. Requires inpatient hospitalisation or causes the prolongation of existing hospitalisation.
4. Results in persistent or significant disability/incapacity.
5. Is a congenital anomaly/birth defect.
6. Requires interventions to prevent permanent impairment damage.

Treating psychiatrists will record the name, occurrence date, severity, grade, intervention implemented (if any), outcome and relationship to the study medication in an electronic clinical research form (eCRF). If the symptoms already existed at baseline, and no exacerbation occurred during the study, they will not be treated as adverse events.

Adverse events are divided into three categories in the present study:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated; no effect on usual daily activities.

Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL); some effects on usual daily activities.

Severe: medically significant, life-threatening or related to death; hospitalisation or the prolongation of hospitalisation indicated; disabling; limiting self-care in ADL; significant effects on usual daily activities.

Sample size calculation

An estimated sample size is 46 in each group, which is based on the assumption that an estimated mean difference in ADAS-Cog from baseline to Day 5 is −1.61, and its SD is 2.7, which is based on the results of our pilot study.[16]

Sequence generation

Participants will be randomised at a 1:1 ratio to either the active or sham tDCS group using a computer-generated stratified sequence in the Electronic Data Capture (EDC) system. All data will be recorded in the EDC system, HOPE eACReSS (Fujitsu, Tokyo, Japan). Group allocation and other personal identification data will be stored in a computer disconnected from the Internet. This will be done to ensure a balanced allocation of diagnosis type (eg, major neurocognitive disorder or mild neurocognitive disorder). This randomisation method includes stratification according to diagnosis.

Allocation concealment mechanism

Allocation concealment will be maintained by a computer-generated method in the EDC. Participant records will be sequentially numbered, and each participant's allocation will be revealed by the principle investigator to both the participants and raters only after the study's endpoint.

Data collection methods and data management

The assessments will be conducted at baseline, immediately after the intervention and 4 weeks after the end of the intervention (figure 1). Baseline and follow-up evaluations are conducted by experienced psychologists blinded to the group assignments. The data is initially recorded on paper files, with each participant assigned to a code number. These files are stored in a locked security box. After the follow-up data is collected, the data from the paper files will be recorded in the EDC.

After that, the data will be sent to independent data managers for cleaning.

The data monitors will also oversee and review the progress of the trial. If a participant decides to withdraw their consent, they will be allowed to leave the study. We will also cease the intervention if we observe any severe adverse events (SAEs), like burning. In this pilot study, the Efficacy and Safety Assessment Committee (ESAC), which is comprised of members independent of the research from the National Center of Neurology and Psychiatry, check and assess whether this clinical trial is conducted safely and appropriately. The committee is also called on to decide whether it is possible to continue the trial or whether the research protocol must be revised in the case of either SAEs or protocol violations. The ESAC will decide whether to stop the trial if any SAEs occur.

The committee will follow this procedure by checking the trial documents during the intermediate period, during which five participants will complete or discontinue their participation in this trial. The safety questionnaire regarding adverse events will be established at this time according to the guidelines published in a recent consensus paper.[24] 'On-site' data monitoring will be conducted by a specialised psychiatrist to ensure the clinical trial is conducted adequately, all data is recorded precisely and this data is reliable.

There exist the following auditing standards for field work: Based on the Clinical Research Act, if any of the following criteria are met, audits will be conducted in this study. First, at least two SAEs are reported that can be causally related to the medical device. Second, at least two severe protocol deviations are found. Third, multicentre clinical trials are initiated. Fourth, potential severe conflict of interest are found that deviate from the prespecified plan for conflicts of interest. When we conduct any necessary protocol modifications, we will report the protocol amendments and the outcomes to both the clinical research review board and the Ministry of Health, Labour, and Welfare for registration in the Japan registry of clinical trials website. After finishing the trial, we will write an original article to share the results of the data.

Patient and public involvement

None.

Statistical analysis

We will conduct an intention-to-treat analysis for patients who were randomised into either the active or sham group; in addition, we will summarise the demographic data of all the patients. Per-protocol set analysis will also

be conducted after excluding all cases with any protocol deviations as sensitivity analyses. In order to evaluate the mean treatment effect, we will conduct a mixed model for repeated measures (MMRM) analysis to detect changes in ADAS-Cog, MMSE, RBANS, Geriatric Depression Scale (GDS) and SF-36 values from baseline to Day 5 and follow-up as secondary outcomes. The MMRM analysis models will include the fixed effects of group, time point (Day 5 and follow-up), group-by-time interaction, baseline and disease (major or mild neurocognitive disorders), which are the stratification factors of dynamic allocation. As the primary statistical test, a t-test for the difference of the adjusted means of ADAS-Cog between the groups at Day 5 will be conducted. T-tests for the follow-up period and/or the other outcomes will also be conducted. As a sensitivity analysis, the baseline score will impute the missing data. A Fisher's exact test will be used to assess the integrity of the blinding. Further, we evaluated the demographics of the patients and used this data to provide descriptive characteristics of the population. We will evaluate whether any differences in the baseline characteristics between the two groups were found by a two-sample t-test or Fisher's exact test will be used to assess after calculating the mean, standard difference and frequency of each baseline characteristic. We will also use the Pearson's correlation coefficient to evaluate whether the baseline characteristics, ADAS-Cog, RBANS, GDS, Apathy scale or SF-36 correlate with the cognitive outcomes at Day 5 and follow-up. Moreover, we will use Stata 16 (StataCorp LP, College Station, Texas) and SAS V.9.4 to conduct the statistical analysis. The results will be significant at $p<0.05$, and statistical tests will be conducted for two-tailed hypotheses.

DISCUSSION

Many tDCS studies for neurocognitive disorders, including our study, have targeted DLPFC, and tDCS was administered in combination with a cognitive task.[10] Our current study will include calculation tasks only, so the results obtained from this study will be more generalisable regardless of participant cultural differences and will provide meaningful information that can help determine the optimal protocol for tDCS trials in patients with neurocognitive disorders. However, a recent tDCS protocol for apathy in Alzheimer's disease focussed on bilateral prefrontal, temporal and parietal targets, whose Cognitive Training consists of multiple tasks involving working memory, language and visuospatial function.[25] Novel protocol may optimise the cognitive effects of tDCS in the future.

Strengths and limitations of this study

The advantage of this study is its appropriate sample size calculation for global cognition based on our previous pilot study[16] when compared with most other previous studies that lacked proper sample size calculations. Trial adherence strategies include reducing the number of hospital visits. Our current trial will only include calculation tasks, so the results obtained from this study will be more generalisable regardless of cultural differences.

We recognise some limitations of this study. First, this study is planned to be conducted at a single site, which might limit the external validity of this result. Second, the long-term cognitive benefits of tDCS cannot be assessed. Our pilot study[16] indicated the short-term effects of tDCS on cognition in 10 sessions. Because the long-term cognitive effects of tDCS are uncertain, no large-scale trials have assessed these effects. In this study, it is difficult to re-assess at 6 months after the final tDCS session due to the increasing burdens of the assessors and participants. Third, we did not choose age and sex as covariates to ensure a balanced allocation, because our pilot study[15] indicated that too many factors will unbalance the group allocation. On the other hand, if age and sex were unbalanced in the groups, the results may also be unbalanced. In this study, we adopt stratified permuted block randomisation with the stratification factor of disease. We believe that the randomisation procedure in itself will also balance the factors mentioned above.

ETHICS AND DISSEMINATION

The protocol V.1.2 has been presented to an institutional review board for approval by the National Center of Neurology and the Psychiatry Clinical Research Review Board (CRB3180006), performed according to the Declaration of Helsinki and based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Following initial review and approval (6 August 2018), the institutional clinical research review board will review the protocol at least annually. The principal investigator will submit safety and progress reports to the review board at least annually, and the investigator will submit reports within 3 months following study termination or completion. These reports will include the total number of patients enrolled, severe and non-severe adverse events that occurred, and summaries of the safety and monitoring board's review. When SAEs occur, the principle investigator will immediately report the details of the incidence to the clinical research review board and the Ministry of Health, Labour, and Welfare. This study has been registered with the Japan Registry of Clinical Trials based on the Clinical Trials Act. The principal investigator, the research coordinator or the research assistant will be responsible for conducting the informed consent process with all study participants. All subjects must give consent to participate in the trial. Patients will be assessed after being informed of the objectives of the study and giving their informed consent to participate. Any relevant changes in the study protocol and/or the informed consent will be sent to the clinical research review board as a protocol amendment. If any participants need to receive medical treatment due to moderate or severe adverse events directly caused by the medical device, they will receive all their medical funding from the clinical

trial insurance. The data will be curated by the end of January in 2024. The results will be published after the end of March 2024. The data will be kept for 5 years after the study finished.

Author affiliations
[1]Department of Psychiatry, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[2]Department of Behavioral Medicine, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[3]Department of Mental Health, Graduate School of Medicine, The University of Tokyo, Bunkyo-ku, Japan
[4]Department of Neurology, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[5]Department of Clinical Neuroimaging, Integrative Brain Imaging Center, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan
[6]Department of Biostatistics, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[7]Clinical Cognitive Neuroscience, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Ishikawa, Japan

Acknowledgements The financial support of the KAKENHI and NCNP made it possible to begin this trial. These entities are gratefully acknowledged.

Contributors TI and YY developed the original concept for the trial. KN advised and reviewed the design and methodology. KM advised a statistical analysis plan for the original protocol, and TI established the protocol. MM helped TI use RBANS in this study. YY, NM, NY, TO and TI will administer tDCS. TI, TT, HT, MS and YO will recruit the participants. TI wrote the manuscript, and all other authors reviewed and commented on the subsequent drafts. All authors read and approved the final manuscript.

Funding This study received funding support from a grants-in-aid for scientific research (KAKENHI) from the Japan Society for the Promotion of Science and the Ministry of Education, Culture, Sports, Science and Technology, Japan (Grant-in-Aid for Young Scientists B, 26 860 958 and that for Early-Career Scientists, Basic Section 52030: Psychiatry-related) as well as an intramural research grant (28-W2) for Neurological and Psychiatric Disorders from the National Center of Neurology and Psychiatry.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Takuma Inagawa http://orcid.org/0000-0001-6147-5008
Yuma Yokoi http://orcid.org/0000-0002-4405-8322
Naonori Yasuma http://orcid.org/0000-0002-1216-7639

REFERENCES

1 Petersen RC, Smith GE, Waring SC, *et al*. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999;56:303–8.
2 Gauthier S, Reisberg B, Zaudig M, *et al*. Mild cognitive impairment. *Lancet* 2006;367:1262–70.
3 Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev* 2006;1:CD005593.
4 Livingston G, Sommerlad A, Orgeta V, *et al*. Dementia prevention, intervention, and care. *Lancet* 2017;390:2673–734.
5 Hill NTM, Mowszowski L, Naismith SL, *et al*. Computerized cognitive training in older adults with mild cognitive impairment or dementia: a systematic review and meta-analysis. *Am J Psychiatry* 2017;174:329–40.
6 Yokoi Y, Narita Z, Sumiyoshi T. Transcranial direct current stimulation in depression and psychosis: a systematic review. *Clin EEG Neurosci* 2018;49:93–102.
7 Nitsche MA, Fricke K, Henschke U, *et al*. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J Physiol* 2003;553:293–301.
8 Batsikadze G, Moliadze V, Paulus W, *et al*. Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol* 2013;591:1987–2000.
9 Dedoncker J, Brunoni AR, Baeken C, *et al*. A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimul* 2016;9:501–17.
10 Inagawa T, Narita Z, Sugawara N, *et al*. A meta-analysis of the effect of multisession transcranial direct current stimulation on cognition in dementia and mild cognitive impairment. *Clin EEG Neurosci* 2019;50:1550059418800889:273–82.
11 Liu CS, Rau A, Gallagher D, *et al*. Using transcranial direct current stimulation to treat symptoms in mild cognitive impairment and Alzheimer's disease. *Neurodegener Dis Manag* 2017;7:317–29.
12 Hsu W-Y, Ku Y, Zanto TP, *et al*. Effects of noninvasive brain stimulation on cognitive function in healthy aging and Alzheimer's disease: a systematic review and meta-analysis. *Neurobiol Aging* 2015;36:2348–59.
13 Martin DM, Liu R, Alonzo A, *et al*. Can transcranial direct current stimulation enhance outcomes from cognitive training? A randomized controlled trial in healthy participants. *Int J Neuropsychopharmacol* 2013;16:1927–36.
14 Chan A-W, Tetzlaff JM, Altman DG, *et al*. Spirit 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200–7.
15 Lu H, Chan SSM, Chan WC, *et al*. Randomized controlled trial of tDCS on cognition in 201 seniors with mild neurocognitive disorder. *Ann Clin Transl Neurol* 2019;6:1938–48.
16 Inagawa T, Yokoi Y, Narita Z, *et al*. Safety and feasibility of transcranial direct current stimulation for cognitive rehabilitation in patients with mild or major neurocognitive disorders: a randomized sham-controlled pilot study. *Front Hum Neurosci* 2019;13:273.
17 Lefaucheur J-P, Antal A, Ayache SS, *et al*. Evidence-Based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017;128:56–92.
18 DaSilva AF, Volz MS, Bikson M, *et al*. Electrode positioning and Montage in transcranial direct current stimulation. *J Vis Exp* 2011;51:2744.
19 Manenti R, Brambilla M, Benussi A, *et al*. Mild cognitive impairment in Parkinson's disease is improved by transcranial direct current stimulation combined with physical therapy. *Mov Disord.* 2016;31:715–24.
20 Khedr EM, Gamal NFE, El-Fetoh NA, *et al*. A double-blind randomized clinical trial on the efficacy of cortical direct current stimulation for the treatment of Alzheimer's disease. *Front Aging Neurosci* 2014;6:275.
21 Narita Z, Inagawa T, Sueyoshi K, *et al*. Possible facilitative effects of repeated anodal transcranial direct current stimulation on functional outcome 1 month later in schizophrenia: an open trial. *Front Psychiatry* 2017;8:184.
22 Cragg L, Richardson S, Hubber PJ, *et al*. When is working memory important for arithmetic? the impact of strategy and age. *PLoS One* 2017;12:e0188693.
23 Thair H, Holloway AL, Newport R, *et al*. Transcranial direct current stimulation (tDCS): a beginner's guide for design and implementation. *Front Neurosci* 2017;11:641.
24 Brunoni AR, Amadera J, Berbel B, *et al*. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *Int J Neuropsychopharmacol* 2011;14:1133–45.
25 Nguyen J-P, Boutoleau-Bretonniere C, Lefaucheur J-P, *et al*. Efficacy of transcranial direct current stimulation combined with cognitive training in the treatment of apathy in patients with Alzheimer's disease: study protocol for a randomized trial. *Rev Recent Clin Trials* 2018;13:319–27.