Effects of Cerebellar Transcranial Direct Current Stimulation on Upper Limb Motor Function After Stroke: Study Protocol for the Pilot of a Randomized Controlled Trial

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Study Protocol

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Abstract

Background: Transcranial direct current stimulation (tDCS) is a technique that can noninvasively modulate neural states in a targeted brain region. As cerebellar activity levels are associated with upper limb motor improvement after stroke, the cerebellum is a plausible target of tDCS. However, the effect of tDCS remains unclear. Here, we designed a pilot study to assess: 1) the feasibility of a study that aims to examine the effects of cerebellar tDCS combined with an intensive rehabilitation approach based on the concept of constraint-induced movement therapy (CIMT), and 2) the preliminary outcome of the combined approach on upper limb motor function in patients with stroke in the chronic stage.

Methods: This pilot study has a double-blind randomized controlled design. Twenty-four chronic stroke patients with mild to moderate levels of upper limb motor impairment will be randomly assigned to an active or sham tDCS group. The participants will receive 20 min of active or sham tDCS to the contralesional cerebellum at the commencement of 4 hours of daily intensive training, repeatedly for 5 days per week for 2 weeks. The primary outcome is upper limb motor function which will be evaluated using the Action Research Arm Test. Secondary outcomes comprise scores of the Fugl-Meyer Assessment for the upper extremity and the Motor Activity Log. Additionally, neurophysiological and neuroanatomical assessments of the cerebellum will be performed using transcranial magnetic stimulation and magnetic resonance imaging. These assessments will be conducted before, at the middle, and after the 2-week intervention, and finally 1 month after the intervention. Any adverse events that occur during the study will be recorded.

Discussion: Cerebellar tDCS combined with intensive upper limb training may increase the gains of motor improvement when compared to the sham condition. The present study should provide valuable evidence regarding the feasibility of the design and the efficacy of cerebellar tDCS for upper limb motor function in patients with stroke before a future large trial is conducted.

Trial registration: This study has been registered at the Japan Registry of Clinical Trials (jRCTs042200078; <https://jrct.niph.go.jp/en-latest-detail/jRCTs042200078>). Registered 17 December 2020

Background

Functional recovery of the upper limb is one of the primary goals in those who suffer stroke. In the last two decades, transcranial direct current stimulation (tDCS) has been widely investigated as a noninvasive brain stimulation technique that can enhance rehabilitation outcomes along with the modulation of brain activity [1]. Several studies using functional magnetic resonance imaging (MRI) [2,3] or transcranial magnetic stimulation (TMS) [4–7] have shown that tDCS has the potential to enhance neural plasticity. Many studies have attempted to facilitate motor recovery after stroke by applying tDCS to the primary motor cortex (M1) [8,9]. However, there is no consensus among systematic reviews regarding the effectiveness of tDCS for motor function after stroke. For instance, a recent review suggested that tDCS has significant effects on upper limb motor function in patients with stroke in the chronic stage [8]. However, a network meta-analysis, which synthesized the effects of multiple interventions (i.e., anodal, cathodal, and bilateral tDCS), showed that only cathodal tDCS had moderate effects on levels of activities of daily living, while no significant effects on the upper limb motor function were noted [9].

Recently, the neuromodulation of the cerebellum has gained increased attention. The cerebellum has multiple connections with motor and non-motor cerebral cortices and plays an important role as a hub of the brain network [10,11]. Among a wide range of cerebellar functions, its contribution to the motor domain, especially the learning processes, would be essential to patients after stroke [12,13]. Several imaging studies have suggested that increased cerebellar activity is associated with motor function improvement after stroke [14–18]. On the other hand, cerebellar inactivity such as crossed cerebellar diaschisis, which is caused by decreased blood flow and metabolism in the cerebellar hemisphere due to decreased neural inputs after stroke, is associated with functional impairments [19,20]. Furthermore, it has been reported that functional connectivity between M1 and the cerebellum [11,21] and the structural integrity of the cortico-cerebellar tract [17,18] seem to be related to motor recovery after stroke. These findings demonstrate the importance of the cerebellum and its functional connectivity to motor cortices, indicating that upregulating cerebellar neural activity would be beneficial for motor recovery after stroke [22,23]. Supporting this hypothesis, animal studies reported that, compared to sham stimulation, applying deep brain stimulation to the cerebellum in stroke-model rats resulted in superior motor improvement in association with neuroplastic changes in the area around a lesion [24–26]. Considering these findings, the cerebellum is a promising target for neuromodulation to facilitate improvements in motor function after stroke.

In stroke rehabilitation, intensive task-oriented training is crucial for facilitating motor recovery. Constraint-induced movement therapy (CIMT) is a well-known approach for improving upper limb motor function after stroke. The key element in CIMT is that it encourages the use of the affected arm through intensive functionally oriented tasks [27,28]. Although it is generally accepted that neural and functional recovery reaches a plateau around 6 months after stroke onset [29], reviews have shown the effectiveness of CIMT in post-stroke survivors in the chronic stage [30,31]. In addition, several stroke guidelines highly recommend CIMT as a beneficial approach for improving upper limb motor function and activity especially in the chronic stage [32,33]. Furthermore, studies reported that CIMT combined with tDCS [34,35] or combined with tDCS and the peripheral electrical stimulation [36] of motor-related cerebral regions induced greater effects on upper limb motor function compared to CIMT alone.

In view of these, we hypothesized that a combination of cerebellar tDCS and intensive movement therapy would further facilitate the improvement of motor function in stroke patients in the chronic stage. To clarify this hypothesis, we designed the present study to assess: 1) the feasibility of a study that will examine the effects of cerebellar tDCS combined with intensive upper limb training, and 2) the preliminary effects of this combined approach on upper limb motor function. The present study details a pilot trial that will be conducted before a large-scale randomized controlled trial.

Methods/design

Study design

This study is a double-blind randomized controlled pilot trial and was designed according to the Consolidated Standards of Reporting Trials (CONSORT) extension to pilot trials [37]. The study flowchart is shown in Fig. 1. Twenty-four stroke patients will be enrolled and randomly allocated to an active or sham tDCS group. This study will be conducted in Fujita Health University Hospital, Aichi, Japan. All participants will provide written informed consent before participation according to the Declaration of Helsinki of 1964, as revised in 2013. This study has been approved by the Certified Review Board at Fujita Health University (approval No. CR21-029) and registered at the Japan Registry of Clinical Trials (jRCTs042200078).

Participants

The inclusion criteria are as follows: (1) age 40–79 years, (2) first-ever unilateral supratentorial ischemic or hemorrhagic stroke, (3) time exceeding 6 months after stroke onset, (4) mild to moderate upper limb hemiparesis [able to perform at least one component of the Action Research Arm Test (ARAT) in the grasp, grip, or pinch subscales; score of 10–51 on ARAT], and (5) independent walking ability [score of ≥ 6 on the Functional Independence Measure (FIM) for walk]. The exclusion criteria are as follows: (1) unstable physical condition, (2) inability to communicate due to severe language impairment, (3) neurological disorders other than stroke, (4) facial sensory deficits, (5) inability to perform training because of psychological disorders or cognitive dysfunction, (6) cognitive impairments [Mini-Mental State Examination (MMSE) < 24] [38,39], (7) inability to perform training because of musculoskeletal disorders, (8) botulinum toxin injections into the arm within the last 6 months, and (9) any contraindications to tDCS, TMS, and MRI such as a history of epilepsy, metallic implants, cardiac pacemaker, drug or alcohol abuse, or pregnancy.

Recruitment

Potential participants will be identified from the outpatient clinic of the University Hospital and the local community. The advertisement for the study is open to the public via our department website to allow patients in the local community to access relevant information. Individuals who are interested in this study will be required to make an appointment for screening. The eligibility of potential participants will first be carefully assessed by a physician. They will then be screened for motor and cognitive functions using the ARAT and MMSE by a trained occupational therapist. Written informed consent will be obtained from those who fulfill the criteria and are willing to take part in this study.

Randomization

Participants will be stratified according to age and ARAT score, and randomly allocated to either the active tDCS or sham tDCS group using a computer-generated, permuted block randomization method with permuted block sizes of 2 and 4. The random allocation will

be conducted using the Research Electronic Data Capture (REDCap) tools [40] by independent researchers who will not be involved in any intervention and assessments.

Interventions

A time schedule of this study is shown in Fig. 2A. The participants will be admitted to Fujita Health University Hospital. The participants will undergo intensive upper limb training for 4 hours per day (2 hours per half-day) and receive cerebellar tDCS (active or sham) for 20 min at the beginning of the intensive training (Fig. 2B), considering that the effects of tDCS on the neural excitability of a targeted brain region last for 30–120 min [2,5–7]. This will be repeated for 5 consecutive days per week for 2 weeks (i.e., 10 days of intervention). During the intervention period, botulinum toxin injections and any changes of medications that could affect spasticity will not be allowed.

tDCS

The stimulation will be delivered using DC STIMULATOR PLUS (NeuroConn, GmbH, Ilmenau, Germany). The anode (5 × 5 cm) will be placed on the cerebellar hemisphere on the contralesional side. Specifically, lobule VI, one of the subregions contributing to motor control of the upper limb [41], will be a focal target of the stimulation. Conventionally, the anode is placed at the fixed position 3 cm lateral to the inion [42]; however, in the present study, the optimal location for targeting the lobule VI will be determined for each individual using computational simulation (see *Computational modeling* subsection). The cathode (5 × 5 cm) will be placed on the cheek on the contralesional side.

The detailed time course of active and sham tDCS is shown in Fig. 2C. The ‘study mode’ of the NeuroConn stimulator will be used to successfully implement double-blinding using 5-digit codes that activate the active or sham stimulation. Only the independent researchers that conduct the random allocation can access the code list. The experimenter will remain blinded to the information regarding which code belongs to the active or sham stimulation. In the active tDCS group, 1 mA constant current will be delivered for 20 min, whereas in the sham tDCS group, 1 mA constant current will be delivered for 40 s to induce similar scalp sensations. In both groups, the current will be ramped up to 1 mA and ramped down over 15 s at the start and end of the stimulation [43]. During the sham tDCS condition, only a weak current of 110 μ A will be delivered every 550 ms after the ramped-down periods to test the electrode impedance. Only the impedance level and stimulation duration will be displayed in both conditions, which facilitates the blinding of the experimenter. The sham procedure is commonly used in tDCS research and at least 30-s active stimulation with slow ramp up and down are recommended for effective blinding during sham sessions [44]. The participants will not be given any information about stimulation parameters.

Intensive upper limb training

Intensive upper limb training based on the concept of CIMT will be provided by trained occupational therapists who will be blinded to the intervention allocation. CIMT is a therapeutic package that consists of repetitive and task-oriented training, behavioral methods for transferring the use of the affected arm in life situations, and constraining the use of the less affected arm to achieve participants’ specific goals [45]. Since previous studies have reported that physical restraint has no significant effects on the outcome of CIMT [46,47], no restraints will be applied to the unaffected arm of the participants in this study. Another difference compared to the original CIMT is with respect to the training hours per day, with 4 hours in this study compared to 6 hours in the original [27]. To accomplish sufficient training, participants will be encouraged to use their affected arm in activities of daily living. Additionally, the participants will engage in self-training programmed by the occupational therapists for 2 hours per day (Fig. 2B). If necessary, functional electrical stimulation will be provided to enhance muscle contractions and perform functional tasks, but rehabilitative robots will not be allowed.

Computational modeling

Fig. 3 shows the method that will be used to optimize the location of the tDCS montage at the individual level. First, the head model will be treated as a passive volume conductor constructed from 3D T1- and T2-weighted MRI of each participant before the experiment. The computational method has been reported in detail in a previous report [48,49]. It involves using the scalar potential

finite difference method with fast computational techniques to accelerate the computational assessment before the intervention [50,51]. The computational model estimates the individualized electric field intensity and distribution on the cerebellar region applying a bipolar montage throughout the electrodes (5 × 5 cm) with an injection current of 1 mA, as used in the experiment. The cathode will be fixed on the buccinator muscle on the cheek on the contralesional side to avoid high electric currents flowing on the cerebrum. The anode will be placed on a grid (13 × 11, size of grid = 10 mm) centered on the inion to identify the position that generates the highest electric field strength (maximum and average values), with lobule VI as the target area. The optimal electrode location will be determined based on a reference landmark (10–20 system) and the Montreal Neurological Institute coordinates for confirmation.

Outcomes

The schedule of data collection is summarized in SPIRIT figure (Fig. 4). Clinical assessments of the upper limb and neurophysiological and neuroanatomical assessments will be conducted prior to the intervention (baseline, t_0), at the middle of the intervention [middle, t_1 (ARAT only)], immediately after the intervention (post, t_2), and 1 month after the intervention (follow-up, t_3).

Clinical assessments

The primary outcome in this study is the ARAT score. ARAT is a clinical measurement that consists of 19 tests with 4 subscales: grasp, grip, pinch, and gross movement, which assess upper limb motor function [52,53]. The quality of movement is scored on an ordinal 4-point scale, ranging from 0 to 3 in each test, with a maximum score of 57 [52]. ARAT is classified as an outcome measurement of activity capacity [54,55] based on the International Classification of Functioning framework [56], and it shows excellent validity and reliability in chronic stroke patients [57].

Secondary outcomes include the Fugl-Meyer Assessment for the upper extremity (FMA) and Motor Activity Log-14 (MAL-14). FMA is classified as an outcome measurement of body functions [55] based on the International Classification of Functioning framework [56]. FMA for the upper extremity consists of 33 items including reflex testing, movement observation, grasp testing, and coordination assessment. The score ranges from 0 to 66. FMA shows excellent validity and reliability in chronic stroke patients [58,59]. MAL-14 is a structured interview to assess how much (amount of use: AOU) and how well (quality of movement: QOM) a patient uses the paretic hand and arm during activities of daily living [60,61]. For the AOU assessment, the score ranges from 0 (never uses the arm) to 5 (uses the arm as often as before the stroke), while for the QOM assessment, the score ranges from 0 (never uses the arm) to 5 (uses the arm as well as before the stroke). MAL-14 is classified as an outcome measurement of activity performance [54,55] based on the International Classification of Functioning framework [56], and it shows excellent validity and reliability in chronic stroke patients [62].

ARAT and FMA will be video-recorded [63], and video-based assessments will be conducted by two trained occupational therapists who will be blinded to the allocation and will not be involved in the interventions. In addition, the following participant baseline characteristics will be collected: age, affected side of the brain, time since onset, and FIM and MMSE scores.

Neurophysiological assessments

As an index of cerebellar excitability, we will assess the magnitude of cerebellar inhibition (CBI) to the contralateral M1 using a paired-pulse TMS paradigm (Magstim 200², Magstim Company, Whitland, UK) (Fig. 5). CBI will be measured by delivering a conditioning stimulus (CS) over the cerebellum for 5 ms prior to a test stimulus (TS) over M1, resulting in the reduction of motor evoked potential (MEP) elicited by TS over M1 [64]. CBI is thought to be driven by inhibitory outputs from the cerebellar cortex to the deep cerebellar nuclei that have excitatory outputs to the contralateral M1 [65]. Therefore, changes in CBI magnitude can be interpreted as cerebellar excitability changes [66,67]. We will assess the cerebellar excitability changes with the assumption that cerebellar plasticity may underlie the intervention effects.

The CS will be delivered to the contralesional side of the cerebellum using a double-cone coil which will be centered at the same location determined by the computation modeling, while the TS will be delivered to the ipsilesional side of M1 using the figure-of-eight coil over the optimal stimulation site ("hot spot") of the first dorsal interosseous (FDI) muscle (Fig. 5). To determine the intensity of the cerebellar CS, we will first test the brainstem active motor threshold for the pyramidal tract by delivering stimuli over the inion using a single pulse with the double-cone coil. The brainstem active motor threshold is defined as the nearest 5% maximum stimulator output

(MSO) that elicits MEPs exceeding 50 μV from the FDI muscle in the affected hand in at least 5 of 10 successive stimuli [68]. The cerebellar CS intensity will be set at 5% below the brainstem active motor threshold [64,69,70]. If the threshold is not observed below 80% of MSO, 70% of MSO will be used for the cerebellar CS. For the intensity of TS over M1, we will first assess the resting motor threshold (rMT) of the FDI muscle which is determined as the lowest intensity that evokes an MEP amplitude greater than 50 μV in at least 5 of 10 successive stimuli [68]. Thereafter, the TS intensity will be set at 125% of rMT. For the CBI assessment, in a set of 30 TS, 15 TS will be combined with the preceding CS (conditioned TS), while the other 15 TS will be delivered without CS (unconditioned TS). The inter-stimulus interval for TS will be 4–6 s, and the order of conditioned and unconditioned TS will be randomized. The position of the TS over M1 will be tracked using a neuronavigation system (Brainsight, Rogue Research, Montreal, Canada). CBI will be calculated as the ratio of the mean amplitude of conditioned MEP over the unconditioned MEP.

We will also assess M1 excitability by delivering single-pulse TMS over the ipsilesional M1 as a separate measurement set to confirm that potential CBI changes will not be accompanied by M1 excitability changes. For this purpose, 15 stimuli with an intensity of 125% of rMT will be applied with the inter-stimulus interval of 4–6 s. The mean amplitude will be used as a proxy for M1 excitability.

Surface electromyography will be recorded using a biosignal recording system (Nuropack X1 MEB-2312; Nihon Kohden Corporation, Tokyo, Japan) at the frequency of 5 kHz, with a bandpass filter of 10 Hz to 10 kHz. Recorded analog data will be digitized with a micro 1401 AD converter (Cambridge Electronic Design, Cambridge, UK) and stored on a computer (Signal Software, Cambridge Electronic Design, Cambridge, UK) for offline analysis.

MRI

To identify structural characteristics of the individual brain, MR images will be acquired prior to the intervention (baseline, t_0) and after the intervention (post, t_2). The brain MRI will be conducted using a 3-T scanner (Vantage Centurian 3T; Canon Medical Systems, Tochigi, Japan). For brain tissue segmentation, 3D T1- and T2-weighted images with high resolution (voxel size: $0.8 \times 0.8 \times 0.8 \text{ mm}^3$) will be acquired [71]. In addition, to identify functional and structural connectivity between widespread brain areas, resting-state functional MRI and diffusion tensor imaging will be obtained [72]. The 3D T1- and T2-weighted images will be used for the computational modeling (see *Computational Modeling* subsection).

Safety evaluation

To evaluate the safety of the intervention and overall protocol, we will record adverse events such as burns to the skin, prolonged abnormal cutaneous sensation, dizziness, fatigue, pain related to overuse of the affected arm, etc. To monitor the existence of the temporary side effects, especially of the tDCS, we will provide participants with a questionnaire [73] after every 20 min of active or sham tDCS intervention. The questionnaire consists of 14 items regarding symptoms which will enable us to determine if the participants are experiencing severe symptoms. The score ranges from 1 to 10, from absent to severe symptoms.

Feasibility criteria

We created the feasibility criteria based on the suggested reasons for conducting a pilot study [74,75]. We adapted the criteria to our study settings as follows: (1) rates of eligible participants during the screening, (2) retention and follow-up rates throughout the study, (3) adherence rate to the study protocol (amount of total training hours of each participant), and (4) validity of the data collection schedule.

Sample size

A previous study proposed the rules of thumb for estimating the sample size of a pilot study based on the anticipated effect size of the future main trial [76]. According to the proposal, if the future main trial is designed around medium to large effect with 80% power and a two-sided 5% significance, a sample size for the pilot trial is set at 10 in each group [76]. Allowing for a 20% of drop-out rate, we will recruit 12 participants in each group.

Blinding

Participants, assessors, occupational therapists providing intensive upper limb training, experimenter applying the tDCS, and a researcher analyzing the data will be all blinded to group allocation. Independent researchers who will conduct the random allocation will not be blinded. A researcher who is in charge of patients' safety and risk management can access the group allocation via the REDCap if necessary.

Analytical methods

The active and sham tDCS groups will be compared with regard to demographic variables to assess group differences using the Student *t*-test or Mann-Whitney *U*-test for continuous variables and the χ^2 test for categorical variables. Group differences of the primary (ARAT score) and secondary (FMA, MAL-14, and neurophysiological measures) outcomes will be analyzed using multivariable regression analyses and compared at each assessment time point. Furthermore, adverse events and their frequency and the questionnaire score will be reported to evaluate the safety of the procedure.

Discussion

Neuromodulatory intervention for the cerebellum has been suggested to improve motor function of stroke survivors in the chronic stage. Our pilot trial aims to assess the feasibility of the proposed study (e.g., outcome measures, adverse effects, and follow-up rates, etc.) and the efficacy (i.e., effect size) of the application of tDCS to the cerebellum on upper limb motor function in patients after stroke. A future large-scale randomized controlled trial will be performed based on the results of the present study.

The present study has some potential limitations. First, the study aims to enroll patients with mild to moderate hemiparesis since intensive upper limb training requires voluntary movements of the affected hand to some extent. Therefore, the findings need to be carefully translated into clinical practice especially when considering the intervention effects in severe cases. Second, in conventional cerebellar tDCS, the anode is placed at a fixed position 3 cm lateral to the inion [42], whereas in the present study, the optimal electrode location will be determined for each individual using computational simulation. However, it remains unclear whether this personalized tDCS maneuver will improve outcomes regarding upper limb motor function compared to conventional tDCS. This question should be addressed in another future study.

To our knowledge, this is the first series of studies to evaluate the effects of cerebellar tDCS combined with intensive training on upper limb motor function in chronic stroke patients. We believe that cerebellar tDCS will improve the effect of intensive upper limb training. The comprehensive results from the present study and the forthcoming large-scale trial should provide significant evidence regarding cerebellar tDCS to determine whether it can be a beneficial intervention for stroke patients.

Abbreviations

AOU, amount of use; ARAT, Action Research Arm Test; CBI, cerebellar brain inhibition; CIMT, constraint-induced movement therapy; CS, conditioning stimulus; FDI, first dorsal interosseous; FIM, functional independence measure; FMA, Fugl-Meyer assessment for the upper extremity; M1, primary motor cortex; MAL-14, Motor Activity Log-14; MEP, motor-evoked potential; MMSE, Mini-Mental State Examination; MR/MRI, magnetic resonance / magnetic resonance imaging; MSO, maximum stimulator output; QOM, quality of movement; tDCS, transcranial direct current stimulation; TMS, transcranial magnetic stimulation; TS, test stimulus

Declarations

Ethics approval and consent to participate

Approval was obtained from the Certified Review Board at Fujita Health University (approval No. CR21-029). The study was registered at the Japan Registry of Clinical Trials (jRCTs042200078). Participants will be required to provide informed consent before inclusion into the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

YO, SU, and AH conceived the study. AY, SU, and YO established the detailed protocol. TT and KU contributed to the refinement of the study protocol. AY, SU, GJ, and TT wrote the manuscript. YO supervised the project. All authors read and approved the final manuscript.

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Figures

Figure 1

Study flowchart.

Figure 2

Study protocol. (A) Schedule of the study. The intensive upper limb training and tDCS interventions will be repeated for 5 consecutive days per week for 2 weeks (i.e., 10 days of intervention). During the middle 2 days, the participants will engage only in the intensive training. Assessments will be conducted prior to the intervention (t0, baseline), at the middle of the intervention (t1, middle), immediately after the intervention (t2, post), and 1 month after the intervention (t3, follow-up). (B) Training schedule per day. Participants will undergo intensive upper limb training for 4 hours per day (2 hours per half-day) and receive cerebellar tDCS (active or sham) for 20 min during the beginning of the training. (C) Time course of active (upper panel) and sham (bottom panel) tDCS conditions.

Figure 3

Computational method to determine the optimal individualized position of the tDCS montage. (A) Head model segmentation. Volume conductor of the head model of each patient will be constructed from the segmentation of MRI data. (B) Computational modeling of a representative example. The individualized electric field on the cerebellum using a bipolar montage (anode in yellow and cathode in blue) will be simulated. (C) Optimal montage position. The optimal location of the anode that maximizes the electric field strength (maximum and average) on the region of interest (lobule VI) is selected from a grid of 13×11 positions.

	STUDY PERIOD				
	Enrolment	Baseline	Post-allocation		Follow-up
TIMEPOINT	$-t_1$	t_0	t_1	t_2	t_3
ENROLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Active or sham tDCS
Intensive upper limb training
ASSESSMENTS:					
Demographic data collection	X				
MMSE	X				
FIM	X				
ARAT	X	X	X	X	X
FMA		X		X	X
MAL-14		X		X	X
CBI · MEP		X		X	X
MRI		X		X	
Safety

Figure 4

SPIRIT figure. tDCS, transcranial direct current stimulation; MMSE, Mini-Mental State Examination; FIM, functional independence measure; ARAT, Action Research Arm Test; FMA, Fugl-Meyer assessment for the upper extremity; MAL-14, Motor Activity Log-14; CBI, cerebellar brain inhibition; MEP, motor-evoked potential; MRI, magnetic resonance imaging

Figure 5

Position of the TMS coils for measuring CBI and MEP. A figure-of-eight coil will be placed over the ipsilesional side of M1 to deliver the test stimuli for eliciting MEP in the FDI muscle. A double-cone coil will be placed over the contralesional side of the cerebellum to deliver the CS. The CS will be delivered 5 ms prior to the TS. CBI will be calculated as the ratio between the peak-to-peak amplitude of the conditioned MEP (black line) and the unconditioned test MEP (grey line). MEP, motor-evoked potential; FDI, first dorsal

interosseous; TS, test stimulation; CS, conditioning stimulation; M1, primary motor cortex; CBI, cerebellar brain inhibition; CB, cerebellum