The Therapeutic Effect of Transcranial Direct Current Stimulation on Depression in Parkinson's Disease
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Research project's background and goals:

As one of the most common neurodegenerative diseases worldwide, Parkinson's disease (PD) has affected 1% of the population older than 60 years [1, 2]. Despite of major motor symptoms, psychopathological disturbance including mood disorders, hallucinations, anxiety, and cognitive impairment with negative impact on life quality are often observed [3], among which depression reveals as one of the most common non-motor symptoms [4, 5]. It is also observed that PD patients have higher risk to develop depression as compared to the age-matched population [6, 7]. The prevalence of depression in PD has been estimated between 30-50% [8-10], although this may differ due to the nature of the patient groups and the subjectivity of diagnostic criteria. The depressive symptoms include anhedonia (inability to experience pleasure), feeling of incapability, reduced action to emotion stimuli, and social withdraw, while PD-related symptoms such as raised dysphoria and irritability, pessimism about the future, low level of inadequacy, together with a sense of guilt, sorrow, and shame are also observed [11]. Moreover, the depressive symptoms in PD are associated with cognitive dysfunction such as impairment with attention, intellectuality, executive function, and working memory [12-15]. The underlying mechanisms of depression in PD remain unclear, although it has been linked to the degeneration of NA locus coelueus and serotonin (5-HT) raphe neurons, which is related to dopaminergic dysfunction [16, 17]. However, it is also argued that depressive symptoms might be due to psychosocial factors or secondary to motor impairment [17].

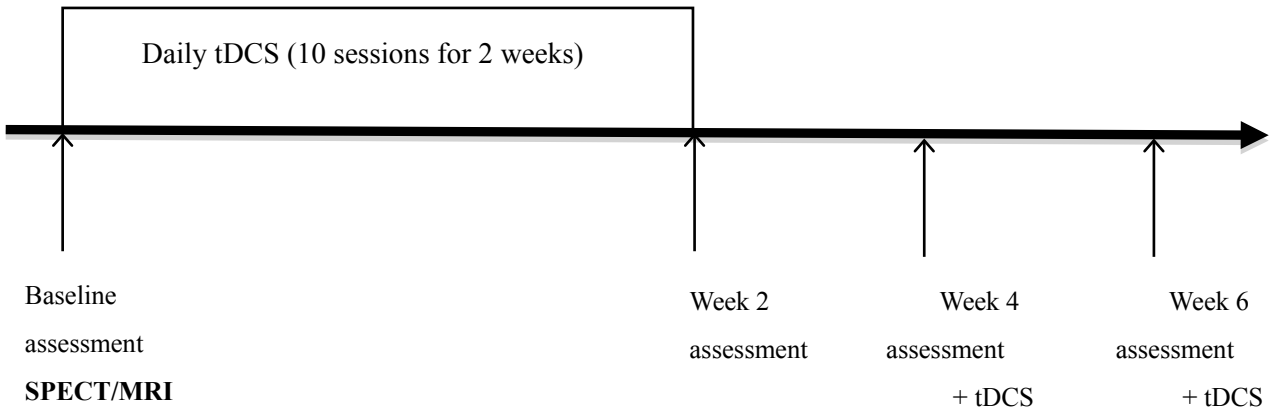
Despite the crucial influence of depression in PD on the quality of life, it is often undiagnosed and untreated. In a study where 23,000 PD patients were investigated, only 26% were treated with antidepressants which were 59% selective serotonin reuptake inhibitors (SSRIs) and 41% tricyclic antidepressant drugs (TCA) [18]. In reality, SSRI remains the most common prescribed medication for the depressive symptoms in PD, although in some studies the effects revealed no superior to placebo [17]. Electroconvulsive therapy (ECT), which is effective for idiopathic major depression, is also applied to treat depression in PD patients especially who do not respond to any antidepressants, since it's beneficial effect might be the strong stimulation of several major neurotransmitter systems including 5-HT, dopamine, and noradrenaline [17, 19, 20]. However, it should be consider only for PD patients with moderate to severe depression due to the adverse effects such as memory impairment or delirium. Alternatively, non-invasive brain stimulation such as repetitive transcranial magnetic stimulation (rTMS) also showed antidepressive effect [21] and has been demonstrated to improve depressive symptoms in PD [22], although its application might be limited by the cost and accessibility.

Another brain stimulation technique, transcranial direct current stimulation (tDCS) has therefore drawn more attention for the treatment of neuropsychiatric diseases [23]. This simple, non-invasive method can induce long-lasting cortical plasticity via weak, direct current through relatively large electrodes, with current intensity 1~2 mA and stimulation time about 30 minutes [24]. Anodal tDCS enhances cortical excitability, while cathodal stimulation diminishes it, and the plastic effects are mediated by *N*-methyl-D-asparate (NMDA) receptors [25]. For major depression disorder, tDCS over dorsal lateral prefrontal cortex DLPFC) showed the therapeutic effects, of which the mechanism may base on the increased excitability of pathologically hypoactive PFC [26, 27].

Recent clinical study also revealed an additive effect via the combination of DLPFC tDCS and

antidepressant sertraline for depression treatment with relative few side effects[28]. Furthermore, the efficacy and the safety of the tDCS on patients with Parkinson disease have been published [29]. Another study using tDCS found that anodal M1 stimulation increased cortical excitability and cathodal stimulation decreased cortical excitability in PD[30], and the neurplasticity would be modulated in PD patients after tDCS management[31]. However, the effects of tDCS treatment for PD with depressive disorders are still unclear. In this proposed study, we will assess the safety and efficacy of tDCS on PD patients with depression. It is hypothesized that tDCS combined with sertraline will improve the depressive symptoms and show greater effects than each intervention alone. We will further establish an effective stimulation protocol for the future application to reduce the disease impact and to improve the quality of life on PD patients with depression.

Study design



This study is a factorial randomized, placebo-control trial, including 2 groups: 'sertraline only' (sertraline + sham tDCS), and 'combined treatment' (sertraline + active tDCS). It is planned to recruit 20 subjects for each group, which results in all together 40 participants. Patients will take 12 tDCS sessions (30min for each session): first 10 consecutive sessions for two weeks (Monday to Friday), and then 2 follow-up sessions scheduled 2 and 4 weeks after the initial treatment. Both pharmacological and tDCS intervention will be started simultaneously on the first day of the treatment.

Subjects

Inclusion Criteria:

(1) In the opinion of the investigator, the participant is capable of understanding and complying with protocol requirements.
(2) The participant or, when applicable, the participant's legally acceptable representative signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
(3) Suffers from Parkinson's disease fulfill the Parkinson's Disease Society Brain Bank clinical criteria with insidious 2 or more PD symptoms (bradykinesia, tremor, or rigidity).
(4) Suffers from "DSM-IV major depressive disorder, single episode" or "DSM-IV major depressive disorder, recurrent" according to Diagnostic & Statistical Manual of Mental Disorders, 4th Edition - Text Revision (DSM-IV-TR) criteria.
(5) Reported duration of the current episode is ≥4 weeks and has not been treated with antidepressants.

(6) Has a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥20 at the screening (baseline) visit.
(7) **Is a man or woman aged 18 to 85 years, inclusive**.

Exclusion criteria:
(1) Subjects known to have allergies to sertraline and pimozide.
(2) Subjects showed any signs of substantial risk of suicide during the trial.
(3) Subjects ever received electroconvulsive treatment.
(4) Subjects co-morbid with other major mental disorders or with substance/alcohol dependence or abuse in the past 6 months per DSM-IV criteria.
(5) Nursing women, pregnant women or patients suspected pregnant.
(6) History or presence of clinically significant hepatic, cardiovascular or renal disease, or other serious medical disease that might compromise the study.
(7) History of seizure disorder or need to taking medications that increase the risk of seizure.
(8) History or presence of dementia and any previous history of brain tumor, brain arteriovenous malformation, encephalitis or meningitis.
(9) Subjects ever received or plan to receive brain surgery during the trial.
(10) Subjects with pacemaker or are contraindicated for MRI.

Interventions

Subjects will take Sertraline hydrochloride 50mg daily, 2hrs prior to tDCS. In each session, tDCS (StarStim, Neuroelectrics) is applied with the rubber electrodes embedded in 25 cm^2 saline-soaked sponges, and with montage of anode-F3 and cathode-F4 corresponding to left- and right- DLPFC respectively, according to the International 10-20 EEG system. The stimulation will last for 30 min/session with 30-sec ramping, and the current intensity will be set at 2mA (current density: 0.80 A/m^2). For sham tDCS, the current will ramp up to 2mA and then ramp down to 0 mA in the first 2 min, which is previously reported as reliable blinding protocol [32]. The subjects will also be asked at the end point to guess whether they receive real or sham stimulation and to rate their confidence, in order to assess the effectiveness of blinding. The trial will use one tDCS equipment (StarStim, Neuroelectrics).

Assessments

(1) Parkinson's Disease

1) *The modified-Unified Parkinson Disease (MDS-UPDRS):* Designed to monitor PD disability and impairment. The modified UPDRS retains the four-scale structure with a reorganization of the various subscales. The scales are now titled; (1) nonmotor experiences of daily living (13 items), (2) motor experiences of daily living (13 items), (3) motor examination (18 items), and (4) motor complications (six items). Each subscale now has 0-4 ratings, where 0 = normal, 1 = slight, 2 = mild, 3 = moderate, and 4 = severe [33].
2) *The Hoehn and Yahr scale:* Provides a global assessment of severity in PD based on clinical findings and functional disability.

Stage	Modified Hoehn and Yahr Scale
1	Unilateral involvement only
2	Bilateral involvement without impairment of balance
3	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severe disability; still able to walk or stand unassisted
5	Wheelchair bound or bedridden unless aided

(2) Mood symptoms

The outcome measures include Montgomery-Asberg Drepression Rating Scale (MADRS), 17-item Hamilton Depression Rating Scale, clinician-rated Clinical Global Impression-Severity of Illness scale, and Beck Depression Inventory. Clinical response (categorical, defined as >50% reduction of baseline MADRS score) and clinical remission (categorical, defined as MADRS score ≤10) are also calculated and compared. Assessments take place before the 10-day tDCS sessions as baseline, and then at the end of the 10 sessions, 2 and 4 weeks after, for the efficacy evaluation. The patients and raters were blind to treatment, but the clinician administering the tDCS was aware of the treatment group.

(3) Neuropsychological assessment

1) Continuous Performance Test (CPT)

The CPT is a psychological test for humans that primarily measure attention [34-37]. CPT is a vigilance task requiring the monitoring of rapid information processing, and the detection of briefly presented target stimuli. A higher processing-load version of the CPT has been proven useful for measuring visual information processing and attentive capacity. During the test, numbers from 0 to 9 were randomly presented for 50 msec each, at a rate of one per second. Each subject undertook two sessions: the non-masked 1-9 task and the 25% masked 1-9 task, in which subjects will be asked to respond whenever the number "9" preceded by the number "1" appeared on the screen. A total of 331 trials, 34 (10%) of which are target stimuli, are presented over 5 minutes for each session. During the masked session, a pattern of snow will be used to toggle background and foreground so that the image was visually distorted. Each test session began with 2 minutes of practice (repeated if subjects required) to make sure that they knew how to press the button correctly. The masked CPT is more sensitive to detect cognitive deficits than non-masked CPT because patients need to pay more attention and must possess a higher capacity for information processing to perform this task. In this study, subject responses will be recorded automatically on a diskette using the CPT machine (Sunrise Systems, version 2.20, Pembroke, MA, USA) [38]. The rater monitors each subject’s performance through the computer monitor.

3) Finger-Tapping Test (FTT)

The FTT consists of tapping with the index finger on a computer mouse as many times as possible within 10 s. The test will be repeated three consecutive times and performed randomly across subjects, and the order was kept constant in each subject at each session. The average number of taps will be then calculated [39].

4) Wechsler Memory Scale-Revise（WMS-R）

Trained psychologists with master degree will perform the WMS-R test. The WMS-R comprises a series of 13 brief subtests (1) information and orientation questions, 2) mental control, 3) figure memory, 4) logical memory I, 5) visual paired associates I, 6) verbal paired associates I, 7) visual reproduction I, 8) digit span, 9) visual memory span, 10) logical memory II, 11) visual paired associates II, 12) verbal paired associates II, and 13) visual reproduction II), each measuring a different facet of memory. Subtests 3-9 subtests measure immediate learning while the latter four measure the recall of the material learned in the previous subtests. All subtests except information and mental control measure episodic learning of both verbal and figural materials.

The first nine subtests are immediately will be followed by delayed-recall trials for four of the subtests. Two of these four subtests (logical memory II and verbal paired associates II) test the retention of verbal material, and other two (visual paired associates II and visual reproduction II) test the retention of visual material. For both the verbal and visual delayed-recall trials, one task measures the retention of paired associates learned earlier in the examination, while the other assesses the retention of more meaningful and integrated material. The four delayed recall subtests contribute to a separate delayed recall composite intended to measure how much of the material learned has been retained over a half-hour period [40-42]. Directions of time-contextual information for trials of delayed recall composite will be given to participants, as described in the WMS-R manual.

5) Wisconsin Card-Sorting Test (WCST)

The WCST is conducted by an experienced clinical neuropsychologist. There are 64 cards in the test. All definitions of the indices are as described in the WCST manual [43]. Using a computerized version of the WCST, the patients will be required to match response cards to four stimulus cards along one of three dimensions (color, form, or number) on the basis of sign feedback (correct or wrong). The subjects are not given any information about the dimensions. After sorting a series of ten cards in one category, the subject will be asked to sort the cards again in a different category. We will examine every index of WCST, including the index of preservative errors and completed categories, which are the most commonly-used index [44, 45].

(4) SPECT Imaging for dopaminergic activity

The imaging procedure will be identical to our previous study. For brain imaging, each subject will be intravenously administered 740 MBq (20 mCi) [^{99m}Tc] TRODAT-1 (a radio-labeled form of tropan derivative for the selective labeling of DAT) in a quiet environment about ten minutes after insertion of an intravenous line. The SPECT data are obtained using an energy window of 15% centered on 140 keV for [^{99m}Tc]. Imaging of [^{99m}Tc] TRODAT-1 are initiated approximately 240 minutes after injection, and SPECT images will be acquired over a circular 360° rotation in 120 steps, 50 seconds per step, in a 128×128×16 matrix. The images are then reconstructed using Butterworth and Ramp filters (cut-off frequency = 0.3 Nyquist; power factor = 7)

with attenuations by Chang's method, and the reconstructed transverse images are realigned parallel to the canthomeatal line. The slice thickness of each transverse image will be 2.89 mm. In addition, all subjects undergo magnetic resonance imaging (Signa CV-I, 1.5 Tesla, GE Medical Systems, Milwaukee, WI, USA). Using the commercial software PMOD (PMOD Technologies, Zurich, Switzerland), each subject's SPECT image wil be co-registered with the corresponding T2-weighted MRI image automatically and are then finely-adjusted manually by an experienced nuclear medicine physician. The MRI image is used as a reference, so the slice thickness of the co-registered images was the thickness of the T2-weighted MRI images (3.3 mm). For co-registration, rigid transformations are defined by 6 parameters, the rotation angles and translation distances in the three spatial directions. The interpolation method will be trilinear. On the co-registered images, the two contiguous transverse slices that contain the most intense striatal radioactivity will be further examined in order to ascertain whether the SPECT and MRI images will be co-registered accurately and whether the striatum is best seen on the two slices of the MRI images. If that is not the case, further adjustment of co-registration was performed manually until a satisfactory outcome will be achieved. Regions of interest (ROIs), including the striatum and occipital cortex, are then drawn on the two contiguous MRI transverse slices, and these ROIs will be projected onto the co-registered SPECT images. The ratio of the radioactivity [the (St-Oc)/Oc ratio] is then derived by dividing the difference between the average activity in the striatum (St) and the average activity in the occipital cortex (Oc) by the average activity in the occipital cortex (Oc).

(5)MRI of the brain

T-1 weighted MRI will be obtained on the same day in axial planes on a Megaton 1.5 Tesla scanner. The MRI images are registered using internal markers.

Withdrawal criteria

When a subject is withdrawn from the trial, the investigator or subinvestigator will fully evaluate the reason and record it on the subject's source documents and case report form.

When a subject is withdrawn from the trial due to the occurrence of an adverse event, the name of the adverse event shall be recorded as the reason for withdrawal.

All subjects have the right to withdraw consent to participate in the trial at any time during the trial without prejudice. The investigator or subinvestigator can discontinue a subject's participation in the trial at any time if medically necessary. In addition, subjects meeting the following criteria after the start of treatment with the tDCS must be withdrawn from the trial:

1) If a subject requests withdrawal from the trial
2) If an adverse event has occurred that makes continuation of trial participation difficult
3) If symptom of the primary disease worsen and continuation of trial participation is considered to be inappropriate in the opinion of the investigator or subinvestigator
4) lf symptom switch to manic symptoms
5) If the investigator or subinvestigator considers the risk of suicide high based on the clinical symptoms of the subject
6) If it has become clear that the subject has conflicted with the inclusion or exclusion criteria
7) If major non-compliance with treatment is observed (if the drug compliance rate during the period

between the previous visit and the present visit is less than 65%)

8) If a prohibited concomitant drug/therapy is used or the usage is considered necessary
9) If the continuation of trial participation is impossible because of the subject's circumstances, such as change of residence, relocation, or his/her schedule being busy
10) If the subject becomes pregnant
11) If the subject becomes unable to comply with the protocol for a reason other than those listed above or if the investigator or subinvestigator judges the withdrawal of the subject from this trial to be necessary

Adverse side effects and the possible management

tDCS is non-invasive brain stimulation treatment and previous studies has proved as a relative safe techachque. A systemic review have pointed out several side effects, including itching, tingling, headache, burning sensation and discomfort[46]. Most discomfort would spontaneous recover soon after finishing the tDCS treatment. There are also few neuro-cognotive side effects even after 6 weeks of tDCS[47]. If the discomfort persists, the PI would assess the subjects' conditions, and the trial might be stopped if the side effects are intolerable. Immediate hospital visit for further evaluation may be needed if the discomfort persists and even become more severe .

Data analysis

Clinical and demographic characteristics between groups at baseline will be compared with one-way ANOVA and $\chi 2$ test for continuous and categorical variables. For the outcome evaluation, we apply repeated-measures ANOVA with the outcome measures as dependent within-subject variables, time course as within-subject variable, and treatment group as between-subject variable. Significant difference/ effect is defined as p-value <0.05.

Appendix I

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tDCS CONSENT

I have read (or have had read to me) the information contained in this consent form abouttDCS therapy and its potential risks and benefits for the treatment of my diagnosis of _____. I acknowledge that Dr._____ has explained the purpose of the procedure, the potential risks and benefits of the procedure, and the alternatives to tDCS. All my questions regarding the procedure have been answered to my satisfaction. I understand there are other treatment options for my condition available to me and this has also been discussed with me.

If during the course of treatment other conditions arise which, in the best judgment of the medical staff, require emergency treatment, I authorize and request the said treatment be performed. I further understand that no guarantee of any results has been made.

I consent to the admission of medical students and other authorized observers during the treatments, in accordance with ordinary practices of the hospital. I therefore authorize and request the staff of NCKUH to administer a course of tDCS treatments to me.

I have read carefully, and I understand, the foregoing.

_____ _____ _____

Signature of Patient: Signature of Witness: Date:

_____

Signature of Physician/Health Care Provider Securing Consent:

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