Project topic:

A Randomised Controlled Trial of Concurrent Cognitive Training with online Transcranial Direct Current Stimulation (tDCS) and Cognitive Training Alone in Patients with Schizophrenia

Background:

i.Cognitive Deficits in Schizophrenia and Current Treatment Options

Schizophrenia is a disabling mental illness characterized by a wide range of impairments across multiple cognitive domains. [1-6] There is substantial evidence that cognitive deficits represent a 'glass ceiling' preventing functional recovery and impact on utilization of hospital service. [7, 8] It is expected that even small improvements in cognitive performance could facilitate their transition to independent living and working, and improve their wellbeing. Schizophrenia patients show significant cognitive deficits across all domains with the greatest deficits in working memory, visual spatial learning , attention/ vigilance and speed of processing. [9-11] It is suggested that dorsolateral prefrontal cortex (DLPFC) is responsible for the deficits in the cognitive domains based on recent functional magnetic resonance imaging studies. [12] On neurobiological level to increase DLPFC activity , current pharmacological options have shown no or only weak effects in schizophrenia. [13, 14] . Intensive training might ameliorate the cognition in modest effect size, but it has limited viability to be used on much larger scale. [15] Considering the burden, severity and functional outcome of schizophrenia including the explosion of technological advances underused in mental healthcare, new cognitive enhancement techniques to improve their wellbeing are needed.

ii.Role of tDCS in Schizophrenia

The breakthrough findings in therapeutic applications of repetitive transcranial magnetic stimulation(rTMS) have revived the popularity of exploring neuromodulation strategies. In particular, tDCS is a non-invasive brain stimulation that uses small electric current (usually 2mA) to specific areas of the brain, and alters excitability of brain cells through polarity dependent stimulation. Anodal stimulation of the brain areas generally enhances excitability, whereas cathodal stimulation reduces it. [16] Similar to rTMS, the manipulation of electrode positions and polarity would lead to different targeted effects in the brain. Nonetheless, unlike rTMS, tDCS is easier to use with behavioral techniques to enhance learning, because it is less likely to influence attention, produces less scalp sensation [17] and being portable with wide clinical utility with remote control setting. [18, 19]

In the past randomized controlled trials, it had been reported that anodal stimulation of the dorsal lateral prefrontal cortex (DLPFC) is effective in enhancing working memory.[20-22] One randomized-controlled study in 2015 showed that 5 tDCS sessions has the potential to enhance cognitive function in schizophrenia , particularly working memory[23]. However, other studies have yielded inconsistent results. In the most recent meta-analysis in 2017, it was concluded that 'due to plaucity of available data, much remains unknown regarding the clinical efficacy of tDCS in schizophrenia'.[24] Furthermore, none of these studies used the Cambridge Neuropsychological Test Automated Battery (CANTAB), which was developed at the University of Cambridge as the international standard in detecting changes in cognitive performances in schizophrenia[10]. Therefore, it is important to explore strategies that may augment and consolidate cognitive benefits of tDCS with more sensitive measurement.

iii.Role of Cognitive Training in Schizophrenia

Available evidence suggests that cognitive training is able to improve cognitive performance, at least in the domain being trained (near transfer). Specifically designed cognitive training

may have an additional role of transferrable cognitive benefits to other cognitive domains (distal transfer).[25-27] Of particular interest, recent computer-assisted cognitive rehabilitation and training studies have successfully shown improvements. [28-33] In particular, Professor Sahakian at the University of Cambridge developed a computerized cognitive training to improve cognition in schizophrenia, which is available on iOS as part of the online app ' the Peak' . It was evidenced that patients with schizophrenia improve cognitive performance after the game. [33, 34]

iv.Potential to Enhance Cognitive Training in tDCS in 'Online Mode'

Our brain is responsive to mental stimulation with enhanced function. Electrical stimulation to the brain appeared to alter neuronal activities with corresponding changes in neuroplasticity , that would modulate the neural response to mental stimulation through cognitive training. A further line of investigation has involved using tDCS to enhance the effects of cognitive training, based on the principle that anodal tDCS lowers the threshold for neuronal activation, and thus stimulation before or during the cognitive training may facilitate the activation and reinforcement of the specific neural circuits involved. [35-37].

Based on current evidence, 'online' tDCS (tDCS is applied concurrently with cognitive training) is superior to 'offline' tDCS (tDCS is applied immediately before cognitive training). It was suggested that 'online' tDCS was superior in the combination of tDCS and cognitive training protocols in cognitive rehabilitation. [36] It is postulated that the neurons involved in cognitive training are more sensitive to the polarizing effects of tDCS and potentiate the impact of tDCS. [38] There is a dearth of data on 'online' tDCS to induce cognitive improvements in schizophrenia. A single-blinded randomized-control trial in 2016 [39] explored the role of tDCS combined with cognitive training. The study included both 'online' and 'offline' tDCS, the effect size extracted from pre-post assessment suggested cognitive functions might be more modifiable with 'online' tDCS in patients with schizophrenia. However, 'online' tDCS was not the center of interest in its study design.

Therefore, the present study aims to focus on 'online' tDCS (when tDCS is administered concurrently with cognitive training) and examine the incremental gain of specific cognitive domain performance in patients with schizophrenia.

Objectives:

The primary objective of the study is to investigate the adjunct effect of online tDCS with cognitive training on specific cognitive domains in stable schizophrenia patients. (i) right after the intervention (ii) whether maintenance effect at 1 month after intervention.

The secondary objective of the study is to probe (i) any effects on affective , psychotic and negative symptoms; (ii) psychosocial functioning, cognitive insight, subjective quality of life (QOL); (iii) the motivation and enjoyment of continuing playing the computerized cognitive training; (iv) the tolerability and adverse events of tDCS among patients with schizophrenia.

Hypotheses:

1. Concurrent cognitive training with online transcranial direct current stimulation(tDCS) will result in greater incremental training effect in specific cognitive domains as compared to cognitive training alone.

2. The cognitive effect in concurrent cognitive training with online tDCS will be maintained over time.
3. tDCS will have no effect on the affective, psychotic or negative symptoms, as compared to the control group(sham stimulation).

Methodology:

Study design

It will be a parallel-group, double-blinded, randomized controlled trial. It will be a 1-week intervention (5-week observation). Subjects will be randomized into two groups:

1. The intervention group- active stimulation of tDCS in 'online' mode +cognitive training
2. The control group- sham stimulation of tDCS + cognitive training

Subjects will be blinded to the allocation with group ratio of 1:1. The schedule, environment and equipment used for both groups will be identical. The study will observe the CONSORT guideline.

Study population and recruitment

Recruitment strategies include a convenience sample of patients with stable schizophrenia who will attend Psychiatric Day Hospitals in Tai Po Hospital. Informed consent will be obtained from each eligible subject.

Inclusion criteria: aged 18-65, right handed, understand and speak in Cantonese, diagnosis of schizophrenia meeting the diagnostic criteria of the World Health Organization's 10th version of the International Statistical Classification of Disease and Related Health Problems (ICD-10). The screening of subjects will be made clinically by the study psychiatrist based on ICD-10.

Exclusion criteria: 1) History of significant head trauma; 2) active abuse of alcohol or illegal substances; 3) significant neurologic history such as dementia, stroke, seizure, Parkinson's disease, multiple sclerosis; 4) concurrent use of cognitive-enhancing medications e.g. acetylcholinesterase inhibitors ; 5) documented history of learning disability; 6) implanted with pacemakers, intracranial electrodes, defibrillators; 7) changes in medication regime over the 2 weeks before or during the study period.

Ethical consideration

The study will be performed in accordance with the Declaration of Helsinki (1964). All participants should take part in the study under voluntary basis. Written, informed consent will be obtained from all participants before inclusion in study, which will be submitted to the CUHK-NTEC Clinical Research Ethics Committee for approval. The study will be conducted in the Psychiatric Day Hospital in Tai Po Hospital. Any participant can withdraw from the study at any time point without the need of explanation. It will not affect the usual care of the participant.

Intervention

Within one week, subjects will receive 5 tDCS sessions applied concurrently with cognitive training on 5 consecutive days (a total of 5 sessions, each 20 minutes) . Participants will have 20 minutes of tDCS stimulation concurrently with 20 minutes of computerized cognitive training.

Based on the most recent metanalysis on tDCS in neuropsychological measures schizophrenia, when the number of tDCS session is not fewer than 5 sessions, no direct trend is identified between the amount of tDCS sessions and neuropsychological measures [24] .

Intervention apparatus:

tDCS Apparatus

tDCS will be applied using the StarStim 8 (NeuroElectrics, Barcelona, Spain). The StarStim8 system consists of a Neoprene head cap with marked positions for electrode placement, a wireless cap-mounted stimulator and a lap-top control computer. tDCS with strength of 2mA for 20 minutes will be applied based on similar previous studies. [40] The stimulation electrode will be applied according to international EEG system 10-20. The anode will be applied at the left dorsolateral prefrontal cortex , which is located at F3; the cathode will be applied at the right dorsolateral prefrontal cortex , which is located at F4. For electrode placement, saline-soaked , 5cm diameter sponge electrodes will be used. The intervention sessions will be conducted in dedicated consultation rooms of the psychiatric day hospital. The rooms are standard consultation rooms with satisfactory sound-proof quality and comfort.

Sham stimulation will be essentially the same setup and procedure, except that the loading protocol will be different. The electric current will ramp up and ramp down, and will stimulate at 0mA for the remainder of the stimulation time. Because it ramps up in the same way as the real stimulation for a short period of time, the subjects will find it difficult to distinguish between the active and sham tDCS. Sham stimulation is generally regarded as an effective blinding technique, especially for those who have never experienced tDCS before[41].

Cognitive Training

All subjects will have ‘online tDCS’ during computerized cognitive training. Each training session lasts for 20 minutes. Subjects will play an app ‘the Peak’ designed by Professor Sahakian with computerized cognitive training on a hand held portable iPad. The traditional Chinese version with Cantonese instructions will be selected. The progress, the errors and the sum scores will be kept track in the personal profile. Subjects will play a few exercises supplied by the computerized cognitive training in pseudorandomized order within each session.

Randomization procedure

The subjects will be randomly allocated to the intervention group or the control group by a block randomization procedure (1:1 allocation) . The randomization sequence will be generated by an online randomization tool (www.sealedenvelop.com) . A code (either ‘a’ or ‘s’) will be generated for each patient and the code corresponds to whether ‘a’ (active) or ‘s’ (sham) tDCS will be administered.

Both the assessor and the subjects will be blinded to the procedure. All subjects are assessed by the study psychiatrist who is blinded to the group allocation. Sham stimulation is generally regarded as an effective blinding technique, especially for those who have never experienced tDCS before[41]. All subjects will not be informed of the group allocation neither.

Definitions and Time Point of Measurements

At baseline(T0, at week-0), after the eligibility of the subjects are confirmed and consent to participate is obtained, the following will be assessed 1) clinical and demographic characteristics of the sample include 2) the primary outcome measure and 3) the secondary outcome measures. At completion of the intervention (T1, at week-1), and one month after the intervention (T2, at week-5), the primary and secondary outcome measures of the subjects will be measured.

i.Clinical and Demographic Characteristics

The subject characteristics include age, gender, handedness, years of education and employment status will be collected. Clinical data, including diagnosis, duration of illness, dosage of medications, daily exercise level and insight will be assessed.

ii. Primary Outcome Measure

Cambridge Neuropsychological Test Automated Battery (CANTAB) will be used as the primary outcome measure. [10] CANTAB is a computerized assessment that is automated and does not rely on the assessors' subjective assessment. It has standardized automated test delivery with systematic scoring and automated saving. Practice effects are eliminated with parallel mode and stimuli randomization. It has concurrent validity same as the MATRICS consensus cognitive battery (MCCB). Due to the sensitivity of CANTAB, it can detect effects in small effect size over shorter period of time. Test-retest reliability is > 0.7 , which is consensed opinion for cognitive evaluation in schizophrenia. Computerized CANTAB tasks on specific cognitive domains on paired associates learning, working memory, processing speeds and executive function will be selected.

iii. Secondary Outcomes Measures

Measures on Affective , Psychotic and Negative Symptoms

- Positive and Negative Syndrome Scale (PANSS) [42] is a 30-item clinician rated questionnaire to assess the symptoms in schizophrenia patient. It has 3 sub-categories of positive symptoms, negative symptoms and general psychopathology. It is shown to have good construct validity , internal reliability and inter rater reliability. [43] It is also shown to be sensitive to change. [44] The assessment time is around 40-50 minutes.

- Calgary Depression Scale for Schizophrenia [45, 46] is a 9-item clinician rated and is administered following a semi-structured interview. It has been used by other tDCS studies in schizophrenia, and it has been shown to be reliable , valid and sensitive to depressive symptoms separate from positive, negative and extrapyramidal symptoms in schizophrenia. A score above 6 has 82% specificity and 85% sensitivity for predicting the presence of a major depressive episode.

- Clinical Global Impression Scale (CGI) [47]- Schizophrenia is a 3-item clinician rated questionnaire to assess illness severity, global improvement or change, and treatment response.

Measures on Psychosocial Functioning

- Social and Occupational Functioning Assessment scale (SOFAS)[48]
- World Health Organization Five Well-Being Index (WHO-5) is a 5-item self reported questionnaire of subjective quality of life (QOL). [49, 50]

Ratings on Motivation and Enjoyment on Cognitive Training

- Visual Analog Scale to rate their motivation and enjoyment to continue playing the computerized cognitive training game (scores ranged from 0-100, with higher scores indicating enhanced enjoyment/ willingness to come)

Tolerability on tDCS

- An Adverse Effects Questionnaire associated with t-DCS administration, which is generated from a systematic review in 2011 by Brunoni. [51]

Clinical Insight

- Beck Cognitive Insight Scale Taiwanese Version is 15-tem self reported questionnaire with two subscales (nine items tapping self-reflectiveness and six on self-certainty); it is shown to have Cronbach's alpha values of >0.70 for both subscales and moderate stability.[52, 53]

Statistical Analyses:

The data will be collected according to the Intention-to-treat(ITT) protocol, with last observation carried forward (LOCF) design i.e. all subjects whose baseline date collected and performed at least 1 day of stimulation will be included in the analysis. The missing observation due to non-compliance will be imputed accordingly to the last assessment performed.

The baseline demographics and baseline clinical characteristics (T0)will be compared between the group of active tDCS and sham tDCs with Pearson's chi-square test (for categorical variables) and independent-sample t tests (for continuous variables).
Linear mixed effect models will be used for each outcome measures, using the covariates of group (tDCS versus sham) and time (T0, T1 and T2).
Pearson's correlation test will be performed to evaluate whether there will be correlation between change in cognitive performance vs demographics and baseline clinical characteristics.

Statistical significance will be referred to a two tailed p-value of less than 0.05.
All computations will be performed using SPSS for Mac OS and Microsoft for excel.

Data Management:

Raw data and electronic data will be stored in locked space and password protected computers respectively. All data will be destroyed 5 years after completion of study and submission for publication.

Sample size estimation :

The effect in difference found in the specific cognitive domains between the tDCS and sham group before and after the intervention in the similar studies was 0.31 (Smith et al., 2015), 0.21 (Lam, 2016), 0.6 (Nienow et al., 2016) represented by partial eta square. Considering the medium to large effect size of the studies, it is difficult to replicate a study with a large effect size. Hence, the rule-of-thumb medium effect size Cohen's F 0.25 was chosen as the partial eta square. Considering a power of 80% and a critical alpha of 5%, it was estimated that a total of 44 patients would be needed in total. .

Safety Consideration:

Concerning the safety profile, tDCS is generally regarded as safe for short-term administration. There is no published report that tDCS has to be discontinued for safety reasons. The adverse effects of tDCS have been reported to be minimal and its risk of inducing seizure is minimal. Meta-analysis suggested that tDCS is associated with mild adverse effects only, such as itching, tingling, mild burning or pain sensations. [51]In particular, mild burning is related to administration of electric current with higher contact impedence. In our study, we will use the StarStim 8 (NeuroElectrics, Barcelona, Spain). StarStim 8 will not operate if the contact impedance is above 20 kOhm, which is the far from the threshold for tissue damage.

Safety studies showed that the concentration of serum neuron-specific enolase, a marker of neuronal damage, is not raised immediate or 1-hour after tDCS. [54, 55]It was also shown that tDCS did not induce changes in diffusion-weighted or contrast-enhanced magnetic resonance imaging (MRI) measures[56] or electroencephalogram (EEG) [57].

The long term safety of tDCS is yet to be evaluated through systemic long term studies. Notably, there is a single case report of safe and effective use of daily to twice-daily domiciliary use of tDCS sessions for 3 years for disabling and clozapine-resistant auditory hallucinations in a patient with schizophrenia. [58]

In the unlikely event that adverse effects or complication arise during the tDCS sessions, subjects will be immediately attended by an on-site medical professional.

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