Study Protocol

List of Abbreviations:
ANOVA – Analysis of variance EEG - Electroencephalogram
DLPFC – Dorsolateral prefrontal cortex
DSM-5 – Diagnostic Statistical Manual version 5
FTND – Fagerstrom Test for Nicotine Dependence
MNWS – Minnesota Nicotine Withdrawal Scale
tDCS – Transcranial direct current stimulation

1.1: Title
The Effects of Transcranial Direct Current Stimulation on EEG changes in Nicotine use disorder patients: An Exploratory Study

1.2: Protocol number and date
Protocol number: MUM-RP-tDCSN-VER01-31JAN24
Protocol date: 31/01/2024

1.3: Name and address of sponsor
Research Grant Sponsor: Monash University Malaysia
Address: School of Medicine and Health Science
Monash University Malaysia,
Jalan Lagoon Selatan, Bandar Baru Sunway,
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1.4: Name of institution and investigators
Principle investigator
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1.5: Study site
Hospital Permai, Johor Bahru, Malaysia.

1.6: Expertise of study's team members
The study's team members are from leading institutions whose experts include universities professors, psychiatrists, neurologists, and neuroscientists.

1.7: Conflict of interest

Please refer to the Conflict-of-Interest form.

2.1: Literature Reviews

Cigarette smoking is recognized as the leading preventable cause of death worldwide, surpassing other factors [5]. The smoke produced by cigarettes, originating from the heating or combustion of tobacco leaves, contains a blend of chemicals that are known for their oncogenic, teratogenic, cytotoxic, and mutagenic properties [6]. Globally in 2019, smoking tobacco use accounted for 7.69 million (7.16–8.20) deaths and 200 million (185–214) disability-adjusted life-years and was the leading risk factor for death among males (20.2% [19.3–21.1] of male deaths). 6.68 million [86.9%] of 7.69 million deaths attributable to smoking tobacco use were among current smokers.[7]. Despite these well-documented risks nearly half of the male population in Malaysia, are engaged in smoking. Furthermore, in Malaysia alone, smoking-related diseases are responsible for the deaths of up to 27000 individuals each year [8]. In 2023, Malaysia spent an estimated RM16 billion annually on treating smoking-related illnesses such as cardiovascular disease and lung cancer [8, 9].

The harmful health effects observed are likely due to nicotine addiction, a condition marked by an inability to resist compulsive drug-seeking behavior despite negative consequences [10, 11]. Neuroimaging studies have shown that the dorsolateral prefrontal cortex (DLPFC) plays a vital role in controlling the urge and reward sensations associated with smoking [2]. This suggests its involvement in maintaining abstinence and managing cue-induced cravings [2]. In smoking cessation research, the main areas of focus are craving, drug-seeking behavior, expectation-related aspects, and relapse. Although targeting smoking cue reactivity through brain stimulation has proven effective, cravings during abstinence have been found to be more reliable predictors of relapse than those induced by external cues [12]

Transcranial direct current stimulation (tDCS) is a non-invasive, painless brain stimulation method that uses direct electrical currents to target specific brain regions [13]. This technique involves applying a low-intensity current (1-2 mA) to the scalp using anodal and cathodal electrodes. Anodal polarization results in depolarization of the resting membrane potential, increasing neural excitability, while cathodal polarization leads to hyperpolarization, decreasing neural activity [13]. The type and duration of these changes in neural excitability depend on factors such as the polarity, intensity, and duration of the stimulus. The lasting effects of the stimulus depend on the duration of its application [13]. Recent research by Mangia et al. has provided valuable insights into the immediate neurophysiological changes induced by tDCS[14]. In their study, EEG activity was measured in ten healthy subjects during and after a session of anodal stimulation of the postero-parietal cortex. This approach was aimed at detecting tDCS-induced alterations in brain activity. The study revealed several key findings: firstly, there was an increase in theta band activity observed during the initial minutes of stimulation. Secondly, enhancements in alpha and beta power were noted both during and after the stimulation period. Lastly, the study reported a widespread activation across several brain regions [14].

Smoking addiction involves multiple brain regions, including the insula, ventral tegmental area, prefrontal cortex, and hippocampus. Altering the activity in these areas by applying anodal tDCS has been shown to influence smoking behavior [13]. Applying anodal tDCS to the DLPFC, which causes neuronal depolarization, reduces cravings in

response to smoking cues. This discovery that non-invasive stimulation can alter cue-induced cravings provides significant insights into the mechanisms of addiction and relapse. Another study by Verveer, Remmerswaal [15] showed that these immediate EEG changes suggest a complex pattern of neural modulation, which could underlie the observed long-term benefits in cognitive functions such as selective attention and motor inhibition.

The primary goal of this study is to assess whether transcranial direct current stimulation, a powerful form of non-invasive brain stimulation, can focus on the dorsolateral prefrontal cortex (DLPFC), a critical region involved in cognitive control over smoking cravings and behaviors. The study uses Electroencephalography (EEG) to track changes in brain activity, aiming to understand the effects of tDCS on brain functions in individuals with nicotine dependence.

References

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2.2: Risk and benefit to study participants

Potential adverse events:

1. Itching (39.3%) [3]
2. Tingling sensation in the first few seconds of tDCS stimulation (22.2%) [3]
3. Headache (14.8%) [3]
4. Burning sensation (8.7%) [3]
5. Retinal phosphenes [4]
6. Nausea and insomnia (2.9%) [4]
7. Brainstem stimulation (extremely rare – one case reported) [2]
8. Seizure (extremely rare – one case reported) [3]
9. Electrochemically produced toxic brain products (unlikely as electrodes not in direct contact with brain tissue) [2]
10. Metallic electrode dissolution products caused by electrode-tissue interface (unlikely as electrodes not in direct contact with brain tissue) [2]
11. Skin damage at the interface due to heat production (unlikely with the protocol used) [2]
12. Neuronal hyperactivity and tissue heating (protocol induce moderate cortical excitability as 50% of total charge enters brain which causes subthreshold production of action potential, damage from heat could be ruled out) [2]

Safety criteria

1. Non-metallic, conductive rubber electrodes soaked in saline are used to potential adverse events 9, 10 and 11 [2]
2. Current density below 25mA/cm^2 does not cause tissue damage even at higher frequency over a few hours (study would use 2mA with current density of 0.03-0.08 mA/cm^2 for 20 minutes per session) [2]
3. Current protocol would not cause heating effect and would not increase serum neuron-specific enlase (marker for neuronal damage) [1,2]. Protocol would not cause changes in diffusion-weighted or contrast enhanced MRI [2]
4. This method would also not produce permanent or structural cortical changes [2]
5. Ramping up current to prevent retinal phosphenes [4]
6. Device giving out current density that does not fluctuate [2]. This study hopes to reduce the number of cigarettes smoked from baseline and thus propelling tDCS to constitute a treatment modality for nicotine addiction.

References

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2.2.1: Justification acceptable risk

As stated in the literature above, there are no serious side effects known to be caused by tDCS. The study procedure follows methodology that has been outlined by other safety, ethical, legal regulatory and application guideline papers.
The potential adverse events are listed in order of rarity and safety criteria to minimize or prevent these effects.

3.1: Study value and outcome

This research explores the use of transcranial Direct Current Stimulation (tDCS) in treating nicotine addiction, with a focus on changes in Electroencephalogram (EEG) patterns. The study aims to assess tDCS's effectiveness as a treatment and anticipates publishing the findings in leading biomedical engineering and clinical psychiatry journals.
The research also considers the broader implications of tDCS in addiction treatment, offering innovative strategies and exploring future therapeutic interventions. A significant outcome will be a comprehensive thesis by a Ph.D. student, contributing significantly to existing knowledge.
The study serves as a foundation for larger-scale investigations, potentially extending into a pilot study and seeking substantial funding like the Fundamental Research Grant Scheme (FRGS). This approach aims to broaden the research's scope and impact, translating scientific discoveries into practical applications. The study's comprehensive nature reflects a strategic approach towards advancing understanding and treatment of nicotine addiction.

3.2: Study objectives

1) To investigate the EEG changes (alpha, beta delta and theta wave at different region, includes prefrontal lateral lobe) before and after tDCS in nicotine use disorder subjects.
2) To explore the efficacy of tDCS in the treatment of nicotine withdrawal.

4.1: Ethical issue

The research will adhere to ethical principles as outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guidelines. In addition to obtaining approval

from the National Medical Research Register (NMRR), the study will also seek approval from the Monash University Human Research Ethics Committee (MUHREC).

5.1: Study endpoint

Completed the steps as indicated in the research protocol.

5.2: Study design

Study Design

This exploratory research is focused on examining the impact of transcranial Direct Current Stimulation (tDCS) on subjects diagnosed with nicotine use disorder. The study primarily utilizes Electroencephalography (EEG) to monitor and analyze changes in cortical activities resulting from the tDCS intervention. The objective is to understand how tDCS influences brain function in individuals affected by nicotine dependence.

Participant Selection and Recruitment:

For this exploratory study, participant recruitment will be carried out through various social media platforms. The eligibility criteria for participation include a confirmed diagnosis of nicotine use disorder, as defined by the DSM-5 criteria. Additionally, candidates should generally be in good health. While details such as age and gender will be recorded for each participant, they will not serve as exclusionary factors for the study. Given the exploratory nature of this research, the recruitment will be limited to a total of ten subjects.

Intervention:

Transcranial Direct Current Stimulation (tDCS) Participants will receive tDCS intervention lasting 20 minutes per session. These sessions will occur 5 days a week, spanning two weeks. The tDCS will be delivered following standardized protocols to ensure safety and uniformity across treatments.

Electroencephalography (EEG) Assessments:

EEG recordings will be conducted at three key time points: initially at baseline (T0), then after one week of the intervention (T1), and finally, six weeks following the conclusion of the intervention (T6). These EEG assessments will focus on tracking changes in alpha, beta, delta, and theta brain waves across different regions, with a specific emphasis on the Dorsolateral prefrontal cortex. This targeted approach is designed to effectively evaluate the impact of the tDCS intervention on brain activity.

Assessment of Nicotine Dependence and Withdrawal symptoms:

The Fagerstrom Test for Nicotine Dependence (FTND) and the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes & Hatsukami, 1986) will be employed to assess nicotine addiction and withdrawal symptoms at T0, T1, and T6. These scales measure symptoms such as craving, irritability, anxiety, difficulty concentrating, restlessness, headaches, drowsiness, and gastrointestinal disturbances.

Data Analysis:

will be conducted using SPSS version 29, employing a combination of Analysis of Variance (ANOVA) and paired t-tests, along with two-way repeated measures of covariates. ANOVA will be utilized to assess the overall impact of the tDCS

intervention across three time points—baseline, after one week of intervention, and six weeks post-intervention. Paired t-tests will further analyze changes from baseline at each subsequent time point. A critical aspect of the analysis will be the focus on changes in alpha, beta, delta, and theta brain waves, nicotine dependence and withdrawal symptoms, measured by the Fagerstrom Test for Nicotine Dependence (FTND) and the Minnesota Nicotine Withdrawal Scale (MNWS). The criterion for statistical significance is set at $p < 0.05$ for all tests to ensure the reliability and validity of the findings.

5.5: Intervention group distribution

There is no specific distribution group as it's an exploratory study in which only one group is involved.

5.6: Expected duration of subject participation

The study expected subjects to be participated in for 6 weeks duration.

5.7: Sequence of participation duration

2 weeks of active tDCS intervention (20 minutes per session, 5 days a week for consequent 2 weeks). Then in week 6th subjects need to come back for EEG recording.

5.8: Procedural accountability

There will be a group of experts presented in the data collection site to responsible for the intervention procedure, safety to subjects, and the monitoring of compliance with the intervention.

5.12: Criteria for termination of study

The sponsor may decide to terminate the study at any time. Subjects will be informed if the study is terminated, and follow-up visits will be arranged if necessary.

6.1: Study Population

Age above 18-55 years old, both male and female subjects.

6.2: Sample size

10 subjects will be enrolled. The small sample size is typical to an exploratory study.

6.3: Inclusive and exclusive criteria

Inclusion criteria

1) Age from 18-55 years old, and
2) Diagnosed with nicotine used disorder as defined by DSM-5, and
3) Healthy subject with no history of seizure/epilepsy/head trauma/head surgery.

Exclusion criteria

1) Concomitant psychiatric disorder, or
2) Polysubstance disorder/uses, or
3) On psychotropic treatment.

6.4: Informed consent process

Informed consent will be obtained before or on the first day of the intervention and

assessment start. Informed consent will be taken on the study site.

6.5: Subject withdrawal criteria

1) Subject who want to withdraw under their will, or
2) Subject who are unable to tolerate the procedure, or
3) Subject who develop serious side effects.

6.5.1: Withdrawal procedures

Subjects can withdraw from the study at any time they wish. The number of drop-offs will be replaced to fulfill the targeted sample size.

7.1: Concomitant interventions

Generally, the subjects of the study are diagnosed with nicotine used disorder but otherwise diseases.

7.2: Rescue medication/procedure

In the occurrence of extremely rare complications, anti-epileptic and other medication will be prepared during the intervention of tDCS.

8.1: Output measures

EEG, FTND, MNWS.

9.1: Safety assessment

Safety assessment will be carried out after each session of intervention.

9.2: Adverse effects follow-up

Adverse effects are followed up throughout the study period.

10.1: Statistical plan

ANOVA analysis, paired t-tests.

10.2: Data selection for analysis

All data from the taken subjects will be included in analysis, accept incomplete data. The incomplete data will be replaced by enrollment of new subject.

11.0: Privacy and confidentiality

Subject's names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. Single-blinded procedure will be implemented, the blinding procedure involves the identification of each subject blind from the data analyzers. All data will be entered into a computer and Google Drive that is password protected. On completion of the study, data in the computer will be copied to Google Drive that is password protected and the data in the computer erased. Hardcopy data will be stored in a locked office of the investigators and maintained for

a minimum of three years after the completion of study. The data would be destroyed after that period of storage. Participants will not be able to view their personal study data, as the data will be consolidated into a database. The subject can write to the investigators to request access to study findings but not the data collected.

12.1: Finance and insurance

Insurance or indemnity letter will be issued by the sponsor.

13.1: Publication policy

The results of the study for publication will exclude subjects' identification and personal information.

Prepared by: K. L. Soo. March 20, 2024.