BEAT DRUGS FUND REGULAR FUNDING EXERCISE

RESEARCH REPORT

The Application of Repetitive Transcranial Magnetic Stimulation (rTMS) as an Adjunct Therapy in Reduction of Craving and Consumption of Illicit Drugs

重複經顱磁刺激(rTMS)在減少毒癮及使用非法藥物的功效研究

(Project Reference No.: BDF190052)

*[1]FONG Nai Kuen Kenneth, Professor
[1]ZHANG Jiaqi Jack, Research Assistant Professor
[1]LAU Wui Man Benson, Associate Professor
[1]CHAN Sofina, Research Associate
[2]CHAN Wai Leung, Charlie, Service Head
[3]SIU Man Hong Andrew, Reader in Occupational Therapy

[1]Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Hong Kong SAR
[2]Youth and Community Service, Caritas Hong Kong, Hong Kong SAR
[3]Department of Health Sciences, Brunel University London, United Kingdom

Principal Investigator:
Kenneth N. K. FONG
Department of Rehabilitation Sciences, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR
Email: rsnkfong@polyu.edu.hk
Contact telephone: +852 2766 6716

Amount of grant approved: $796,807.00 (including external audit fee)
Amount of grant spent: $763,880.06
Date of commencement: 15 Aug 2020
Date of completion:14 Aug 2023

Executive Summary

Background/Objective

Repetitive transcranial magnetic stimulation (rTMS) is increasingly used as an intervention for treating substance addiction. In this study, we aimed to examine the effects of high-frequency rTMS applied to the left dorsolateral prefrontal cortex (DLPFC) as an adjunct treatment of common illicit drugs addiction in Hong Kong.

Methods

We conducted a within-subject, crossover design study enrolling adults with history of using amphetamine/cocaine currently receiving counselling or rehabilitation services from the community centres. Participants were allocated to either a 6-session (3 sessions/week) real rTMS (10Hz, 2000 pulses, 100% RMT) or sham rTMS groups to the left dorsolateral prefrontal cortex in a random order, with a 2-week washout period between 2 phases. We measured outcomes including craving scores, self-reported substance consumption, executive functioning, and mood at baseline, after Phase I, start of Phase II, and end of Phase II.

Results

Forty-eight participants with illicit drugs abuse were recruited from 6 non-government organizations, 24 participants were randomly assigned to the TMS-Sham group (rTMS first, then sham) and 24 participants to the Sham-TMS group (sham first, then rTMS). There were 18 dropouts at various phases. 'Intention-to-treat' using 'last observation carried forward' was used for the missing data in the final analysis for the carry-over and treatment effects. Both real and sham rTMS significantly reduced the craving scores and improved performance in executive functional tests, however, only real rTMS significantly reduced the anxiety and depression levels in illicit drug users (P=0.020), as measured using the Depression Anxiety Stress Scales, and on increasing motivation for change ($p<0.001$).

Conclusion

Both real rTMS and sham rTMS improved craving and executive functioning showing that placebo effect of rTMS on craving and executive functioning in illicit drug users is large. Real rTMS, but not sham, appears to improve the mood and motivation for change of illicit drugs users. Future studies are required to investigate the neural mechanism underlying the therapeutic effect in substance abuse in association with rTMS as well as to determine an optimal stimulation setting for clinical application for SUD in future.

(335 words)

報告摘要

背景/研究目的

重複經顱磁刺激 (rTMS) 越來越多地被用作藥物成癮的治療方法。在本項研究中，我們旨在研究高頻 rTMS 於左側背外側前額葉皮層(dorsolateral prefrontal cortex, DLPFC) 作輔助治療對香港地區常見藥物成癮者的作用效果。

方法

本研究採用主體間交叉試驗設計，受試人群為社區接受諮詢或康復服務的有安非他明(amphetamine) (或可卡因(cocaine)濫用史的成年人。所有參與本研究的受試者會按隨機次序接受兩個治療階段的試驗，分別是應用高頻 rTMS 刺激左側 DLPFC(10Hz, 2000 脈衝, 100% RMT)及 rTMS 假刺激。每一階段共 6 次治療 (3 次/周)，兩個階段之間設定 2 周的洗脫期。在實驗開始、第一階段結束之後、第二階段開始及第二階段結束之後會分別進行結局指標評估，評估內容包括成癮渴望得分、自我報告的藥物消耗、執行功能以及情緒。

結果

本研究從 6 個非政府組織一共招募了 48 例藥物濫用者，其中 24 例先接受 rTMS 真刺激，再接受 rTMS 假刺激；另外 24 例先接受 rTMS 假刺激，再接受 rTMS 真刺激。共有 18 例受試者在不同階段退出，數據分析採用 “前一次觀察數據向後結轉(last observation carried forward, LOCF)的"意向治療”分析(Intention-to-treat)處理缺失數據。結果發現 rTMS 真刺激和 rTMS 假刺激均能顯著降低受試者的成癮渴望及改善執行功能；然而，僅 rTMS 真刺激顯著降低藥物濫用者的焦慮和抑鬱評分(Depression Anxiety Stress Scales) (P = 0.020), 並顯著增加了其尋求改變的動機(P <0.001)。

結論

rTMS 真刺激和 rTMS 假刺激均能夠顯著改善藥物濫用者的成癮渴望及執行功能，這表明 rTMS 對藥物濫用者存在較大的安慰劑效應。然而，僅 rTMS 真刺激表現出顯著改善藥物濫用者的情緒和尋求改變的動機。在未來的研究中，應就 rTMS 治療效果的神經機制對於藥物濫用者的作用及確定未來 rTMS 在藥物濫用臨床應用的最佳方案作深入探究。

BACKGROUND

Substance use disorder (SUD) is a chronic psychiatric disorder which is characterized by the continual use of substances despite significant cognitive, behavioral, and physiological symptoms. Substance use disorder leads to functional and social problems (American Psychiatric Association, 2013). The proportion of reported young abusers aged under 21 was over 10% in recent years in Hong Kong (Central Registry of Drug Abuse (CRDA), 2024). Adults aged between 21 to 40 remained to be the group with the largest proportion (58%) in 2023 of newly reported drugs abusers (Narcotics Division, Security Bureau, 2024). Current neuroscience studies suggested that there are underlying changes in brain circuits in people with drug addiction, which perpetuates relapse and impedes the effort of drug rehabilitation.

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique based on the principle of electromagnetic induction. TMS consists of an equipment that discharge high current of about 3000A that flows through an insulated stimulating coil, generating a brief magnetic pulse with field strengths up to 3 Teslas in 200ms. The coil is placed over the head, the magnetic field can only reach about 2-3 centimeters into the brain directly beneath the treatment coil but will pass through the scalp, cranial bone, meninges, and cerebrospinal fluid layer and is able to induce an electric field sufficient to depolarize superficial axons and to release neurotransmitters which activate neuronal pathways in the stimulated region (Lefaucheur et al., 2014). For Repetitive Transcranial Magnetic Stimulation (rTMS), the repetitive nature of applied pulses activates neural networks and can result in either excitatory or inhibitory after-effects (Balconi, & Finocchiaro, 2015). High-frequency (>5Hz) rTMS can increase cortex excitability by increasing regional cerebral blood flow, thus induce a long-term potentiation like effect (LTP-like effect) whereas low-frequency simulation (<5Hz) can inhibit the cortex excitability by decreasing regional cerebral blood flow, thus induce a long-term depression like effect (LTD-like effect). rTMS is a safe technique, unlike some previous forms of physical treatment like electroconvulsive therapy (ECT), rTMS does not require surgery or implantation of electrodes, require sedation with anesthesia, and it seldom causes seizures. The risk of seizure from TMS was described by Rossi et al. (2009) as very low, the general side effects are mild and transient, which may include headache, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscle, lightheadedness, hearing discomfort, etc.

rTMS treatment of depression and obsessive-compulsive disorders has been approved by the U.S. Food and Drug Administration (FDA) (Medicare Coverage Database,

2024). In several systematic reviews, repetitive transcranial magnetic stimulation (rTMS), including theta burst stimulation (TBS) and deep TMS (dTMS), has also emerged as a potentially useful treatment for decreasing craving in people with substance use disorder (Dunlop, Hanlon, & Downar, 2017; Enokibara, Trevizol, Shiozawa, & Cordeiro, 2016; Maiti, Mishra, & Hota, 2017). Many recently completed studies have focused on how far rTMS could reduce craving for nicotine (Li, Hartwell, Owens, LeMatty, Borckardt, Hanlon, Brady, & George, 2013), alcohol (Höppner, Broese, Wendler, Berger, & Thome, 2011), cocaine (Rachid, 2018), methamphetamine (Liu, et. al, 2017; Su et. al, 2017) and food craving in people with bulimia (Van den Eynde et. al, 2010). Many of the completed rTMS studies on substance craving focus on cocaine, and there are few or no studies on many other types of illicit drugs. Our critique of these studies revealed that many studies of rTMS on craving of cocaine were based on small samples, there were marked differences on the protocol (such as on the site of stimulation, frequency, intensity of stimulation), and outcomes measures are mostly based on self-report and Visual Analogue Scale (VAS) of craving. Drug consumption data is not often reported. Previous meta-analysis published in 2016 included eight studies, and concluded that excitatory rTMS of the right dorsolateral prefrontal cortex (DLPFC) has a significant anti-craving effect (Enokibara et al., 2016). Another meta-analysis published in 2017 based on 10 studies showed a significant anti-craving effect of excitatory rTMS of either left or right DLPFC in patients with substance dependence (Malti et al., 2017). However, our recent review (Zhang et al., 2019) showed that excitatory (facilitatory) repetitive transcranial magnetic stimulation (rTMS) of the left DLPFC significantly reduced craving (Hedges' g = -0.62; 95% CI, -0.89 to -0.35; $p< 0.0001$), compared with sham stimulation, but the overall effect was not significant for rTMS on the right DLPFC (Hedges' g = -0.60; 95% CI, -1.43 to 0.23; $p=0.158$). The rTMS on the left DLPFC may suppress the right DLPFC, which might be hyperactive after SUD, and to help on activating the left DLPFC which might be hypofunctional after SUD (Diana et al, 2017; Hanlon et al, 2018).

According to our review (Zhang et al., 2019), we noted that there are studies indicated that 5 sessions of 1Hz rTMS (Liu, et. al, 2017), 12 daily sessions of sTMS (Bolloni, et al., 2016), or even one single session (Li, et al., 2017) could decrease craving of either cocaine or methamphetamine. Therefore, this current study aims to address these research gaps in applying six sessions of rTMS using high frequency excitatory rTMS in 10Hz to the left DLPFC over two weeks aiming to reduce craving and consumption for the popular types of illicit drugs (not only cocaine) in Hong Kong. The study also

attempts to address methodological gaps in previous studies, and using appropriate outcome measures (De Sousa, 2013; Rachid, 2018).

Objectives

The research objectives of this study are: 1) To examine if rTMS can reduce craving and consumption of the most commonly used illicit drugs (amphetamine, cocaine) among people aged 18 to 55 in Hong Kong? 2) What is the association between rTMS protocol (frequency, intensity) and drug craving and consumption? 3) Would there be gains in executing functioning among participants who have received rTMS treatment? 4) Would there be reduction in depressive and anxiety symptoms among participants who have received rTMS treatment?

METHODOLOGY

Participants

Participants were: 1) aged 18 to 55 years old, 2) illicit drug users in community, 3) currently using or have used either methamphetamine (ice)/cocaine or both frequently for at least 3 times per week, 4) with Craving Visual Analogue Scale score ≥ 5 (range 0 - 10), 5) currently engaged in drug counselling or rehabilitation services. Exclusion criteria were: 1) History of seizures, 2) Severe mental disorders, 3) Brain damage from illness or injury, 4) Any metal or implanted medical devices in body, 5) Frequent or severe headaches, 6) Pregnant or thinking of becoming pregnant, 7) In pharmacological or physical treatment related to substance use disorders, and 8) Had prior treatment with rTMS in the past year.

Research design

The study was a single-blinded cross-over design with high frequency (real) rTMS treatment and sham rTMS treatment (**Figure 1**). Participants were recruited consecutively from 6 non-government organizations (NGOs): Caritas Hong Kong Hugs Centre, Hong Kong Christian Service PS33, Evergreen Lutheran Centre, Hong Kong Children & Youth Services – Sane Centre Office, Hong Kong Sheng Kung Hui – New Horizon, Hong Kong Christian Service Jockey Club Lodge of Rising Sun - outpatient service and inpatient service, and randomly assigned by drawing lots to either the TMS-Sham (rTMS first, then sham) or the Sham-TMS (sham first, then rTMS) groups. A 2-week washout period (that is, no treatment) was arranged between both treatments. After the washout period, participants who had previously been assigned to receive the rTMS and who had received the sham treatment were crossed-over and assigned the sham treatment and rTMS respectively. Informed written consent was sought from each participant after screening for eligibility and before the

recruitment. Ethical approval was obtained from the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (Ref. No.: HSEARS20210602002). All participants had to be screened using the safety screening checklist that was developed based on the guidelines in use of TMS on patients (Rossi et al., 2009).

Participants allocated to rTMS received a 6-session (3 sessions/week) real rTMS treatment (10Hz, 2000 pulses, 40 trains with 50 pulses per train, inter-train interval at 10 sec, at 100% resting motor threshold (RMT)) to the left DLPFC whereas participants in the sham rTMS treatment received the same treatment protocol as real rTMS but the intensity was reduced to 20% RMT). The left DLPFC was localized using the Beam F3 method (https://clinicalresearcher.org/F3/calculate.php). There were two trial sites in this study - the experiment for all community participants was carried out at the Assistive Technology Laboratory, ST814, of the Hong Kong Polytechnic University (**Figure 2A**). The TMS equipment used in this study was MagPro X100 (https://www.medicalexpo.com/prod/magventure/product-84839-546415.html) with a figure-of-eight dynamic cool-B65 Butterfly coil putting over the left DLPFC region (Figure 2B). Regarding participants who were resided in residential hostels, the experiment would be delivered on-site at the hostel. The TMS equipment used is much smaller and portable provided by the rental company - MagPro R30 (https://www.medicalexpo.com/prod/magventure/product-84839-546415.html) with a MC-B70 Bended Butterfly cool coil putting over the left DLPFC region (**Figure 2B**).

Outcome measures

The primary outcomes were about drug consumption, we translated and applied the 11-item Craving Experience Questionnaire, which is a theory-based and brief measure of craving for substances (May et al., 2014). We adopted the Contemplation Ladder which measures the motivation for change (Salvet et. al, 2006). We used the self-report questionnaire Set 5 of Beat Drugs Fund, which assesses drug use frequency in past 30 days (Narcotics Division, Security Bureau, 2024). Regarding the secondary outcomes, we used the anxiety and depression subscales (13 items) of DASS-18 (Oei, Sawang, Goh, & Mukhtar, 2013; a shortened version of DASS-21), for monitoring the negative emotional states of the participants. We used the computer-administered measure of sustained attention of the MATRICS Consensus Cognitive Battery (MCCB) - Continuous Performance Test (CPT)—Identical Pairs (CPT-IP) (https://www.matricsinc.org/mccb/) (August et al., 2012), and the Trail Making Test (TMT) - Part A (Gaudino et al., 1995; Reitan, 1958), to monitor potential change in

attention, as well as the Mazes test of the Neuropsychological Assessment Battery® (NAB®) (https://www.parinc.com/Products?pkey=260) to evaluate executive functioning after rTMS treatment (Gavett, 2011).

Sample size prediction

We used the assumption that significance level is 0.05, a sample size of 19 per group is needed to detect a true difference of 2 (in the craving scale) at the power of 0.90. This is estimated using sample size software PASS12 for a two-period cross-over design. Accounting for a potential attrition of 25%, it is necessary to recruit a total of 55 subjects for the clinical trial.

Statistical analysis

All statistical analyses were performed using SPSS version 23.0 (IBM SPSS Statistics). Chi-square and paired t-tests were used to measure differences in the baseline data and demographic variables between the TMS-Sham (rTMS first, then sham) and Sham-TMS (sham first, then rTMS) groups. The carryover effect considers whether the impact of both sTMS and sham treatments were still present when the participants in the rTMS commenced the sham treatment period or vice versa. This was assessed using the mean (95% confidence interval) of the difference between the evaluations at baseline and the end of the washout period. The treatment effect considers the benefit of TMS-Sham and Sham-TMS treatments, and was assessed using paired t-tests to compute the mean change pre- and post-treatment in the combined samples. Between-group differences of change scores were also investigated, using independent t-test, to compare the treatment effect of the combined rTMS treatment and combined sham treatment for the total sample. The effect size was computed using two-group Cohen's d based on between-group comparisons. The observed power was computed using G*Power. 'Intention-to-treat' using 'last observation carried forward' (LOCF) was used for the missing data in the final analysis for the carry-over and treatment effects as well as the between-group differences. For all analyses, a significant level of $p < 0.05$ was used for two-tailed tests.

RESULTS

Figure 3 showed the PRIMSA flowchart of participants. A total of 48 participants (24 TMS-sham and 24 sham-TMS groups) with illicit drugs abuse were recruited from 6 NGOs. The number of participants recruited are: Caritas Hong Kong Hugs Centre (n=7), Hong Kong Christian Service PS33 (n=4), Evergreen Lutheran Centre (n=6), Hong Kong Children & Youth Services – Sane Centre Office (n=4), Hong Kong

Sheng Kung Hui – New Horizon (n=1), Hong Kong Christian Service Jockey Club Lodge of Rising Sun - outpatient service (n=2) and inpatient service (n=24). Among the 48 participants, 30 out of 48 had completed both Phase I and Phase II (Figure 3), and there were 18 dropouts at various phases of the study, the final attrition rate was 37.5%. In our original proposal, we targeted at recruited 38 completed cases, taking into an estimated attrition (dropouts) of 25%, we aimed to recruit 55 cases in the sample at the beginning. After the study, we had achieved 87% (including dropouts) of the projected sample size. The process of participant recruitment in this study lasted 2.5 years from 2020 to 2023, much longer than expected. It would have been possible to recruit more participants to obtain the desired sample size if the participant recruitment had not been affected because of the COVID pandemic during the study period, which probably meant that many potentially eligible individuals were not recruited to participate. A final analysis on the 30 completed participants and 'intention-to-treat' was done for 18 dropouts using 'last observation carried forward' (LOCF) method for missing data at the 2 phases respectively. Since the participants from Hong Kong Christian Service Jockey Club Lodge of Rising Sun - inpatient service (n=24) did not have access to illicit drugs during the detoxification service of inpatients stay, therefore, only 22 participants from other NGO services were included in the analysis of actual drug consumption.

Table 1 shows the mean and standard deviation (SD) scores of outcome measures at each measurement occasions after LOCF imputation. **Table 2** shows the statistical results of baseline comparisons, as well as carry-over and treatment effects. Baseline comparisons between the TMS-sham and sham-TMS groups did not reveal any differences in baseline measures across all outcome variables (all *ps*>0.05). Regarding within-group analysis, carryover effects of real rTMS were observed in the DASS scores ($p<0.01$), craving scores ($p<0.01$), TMT performance ($p<0.05$), maze scores ($p<0.01$), and CPT test (3-digits) ($p<0.05$). On the other hand, carryover effects of sham-TMS were only noted in craving scores ($p<0.01$), TMT performance ($p<0.05$), and Maze score ($p<0.01$).

Regarding the treatment effects within groups, both real (n=41) and sham (n=40) rTMS significantly reduced craving scores (within-group difference: real rTMS: $p<0.001$; sham rTMS: $p=0.035$; Table 2, **Figure 4A**) and increased performance on executive functional tests, including TMT and maze scores. Only real rTMS had significant effects on increasing motivation for change ($p<0.001$; **Figure 4B**).

Regarding between-group analysis, when comparing the mean changes across the total sample between the groups, we observed a significant increase in motivation for change among individuals who received real rTMS compared when they received sham stimulation (p=0.031) (Table 2).

In addition, real rTMS, but not sham rTMS, reduced anxiety and depression levels in illicit drug users (p=0.020), as assessed by the DASS (**Figure 4C**). To note, the carryover effect in the DASS scores was only significant following the real rTMS phase (p<0.010), but not after the sham rTMS phase (**Table 2**), which also suggested that the treatment effect existed after real rTMS but not sham.

Regarding actual drug consumption, there were no significant carryover effects of rTMS or sham treatment. In terms of treatment effects for actual drug consumption within each group, both real (n=18) and sham (n=18) rTMS did not significantly change the number and type of illicit drug use or the frequency of using methamphetamine or cocaine, however, rTMS did marginally reduce the number of types of illicit drug use after intervention (p=0.056) (Table 2).

Table 2 presents the effect sizes (Cohen's d) and observed powers of all between-group comparisons (real TMS vs. sham TMS). The largest effect size (d) of real rTMS relative to sham was found in motivation for change (d=0.509), followed by craving (d=0.368) and DASS (d=0.347). However, it is important to note that post hoc power analyses indicated that all observed between-group differences were still underpowered (β <0.80).

DISCUSSION

Our study aimed to address a main question - can rTMS reduce craving and consumption of the mostly used illicit drugs - amphetamine & cocaine, among people in Hong Kong? We concluded that 6-session high-frequency excitatory rTMS to the left DLPFC can reduce craving but the reduction of actual drug consumption remains unclear in illicit drug users who are addicted to amphetamine or cocaine or both. Treatment and rehabilitation services for drug abusers is multi-modal, as it is necessary to address the volitional and functional deficits, as well as psychosocial and lifestyle issues. Many drug rehabilitation agencies provide a range of services like outreach social work, counseling, detoxification service, peer support, employment services for people who abuses drugs. At present, rTMS is not a common treatment for illicit drug users in clinics or rehabilitation centres in Hong Kong, it would be

beneficial if rTMS could be applied as an adjunct and non-invasive therapy that reduce craving for illicit drugs. Craving is a core symptom of addiction and possible reason for relapse in patients with SUD (Zhang et al., 2019). Craving is defined as a pressing, urgent, and irrepressible desire, motivated by internal and external cues associated with brain's reward in executive functioning, resulting to loss of self-control and consequently leading to an addictive behaviour (Koob & Volkow, 2016; Skinner & Aubin, 2010). According to our findings, we recommended that rTMS can be used as an adjunct treatment to reduce craving and improve their motivation for change for illicit drug users in Hong Kong in parallel with traditional pharmaceutical and psychosocial treatments.

Regarding the association between rTMS and sham treatments to drug craving and consumption, we concluded that high-frequency excitatory rTMS to the left DLPFC is better than sham rTMS treatment in reducing craving and improving motivation for change, but its effects on the reduction of actual drug consumption remains unclear because of a large portion of the participants did not have access to illicit drugs during the detoxification service of inpatients stay in our study. According to the calculated effect sizes (Cohen's d) of comparing real rTMS relative to sham rTMS, the effect size for motivation for change (d=0.509) is interpreted to be 'medium' and the effect sizes for reducing craving (d=0.368) as well as reducing depression and anxiety (d=0.347) are interpreted to be 'small to medium' (Lakens et al., 2013). Although this result is consistent with our review that excitatory rTMS of the left DLPFC significantly reduced craving but not on consumption, compared with sham stimulation (Zhang et al., 2019). The effect sizes of real TMS vs. sham TMS for reducing carving is lower than that in our calculated 'large' effect size for the immediate effect of excitatory rTMS of the left DLPFC for illicit drug dependence (Hedges' g=0.812) and 'medium' effect size for all substances (Hedges'g=0.624) in our previous meta-analysis (Zhang et al., 2019). The reason for the discrepancy is unclear but according to our previous meta-analysis, the total number of pulses was a significant predictor of the effect size ($p = 0.01$), whereas the number of sessions, pulse per session, frequency and intensity were insignificant. Another recent meta-analysis found that greater number of sessions were associated with a greater craving reduction of craving after rTMS intervention (Gay et al., 2022). In our study, we have used 10Hz, 2000 pulses in 6 sessions for the real rTMS, perhaps an increase in the number of pulses and number of sessions for treatment should be considered in further studies to determine an optimal stimulation setting for clinical application in future.

Meta-regression revealed a significant positive association between the total number of stimulation pulses and effect size among studies using excitatory left DLPFC stimulation ($p = 0.01$). Interestingly, we found that there were gains in executing functioning among participants who have received high frequency rTMS and sham rTMS. However, we found that only high frequency rTMS, but not sham, appears to improve the motivation for change of illicit drugs users. Our findings on reducing craving are closely interlinked with the improvement in executive functioning of participants after rTMS. Regarding the reason for the anti-craving effect of rTMS but not on consumption in our study findings, it was likely due to the fact that our participants were quite heterogenous because they were recruited to the study from different stages of SUD, some of them were currently using methamphetamine (ice)/cocaine or both frequently while some of them had had used either methamphetamine (ice)/cocaine or both before. Half of our participants were inpatients from the Hong Kong Christian Service Jockey Club Lodge of Rising Sun (n=24), they were prohibited of consuming any illicit drugs at the residential hostel. Therefore, the rate of consumption in our study might not reflect the true picture of our participants in reducing consumption after rTMS treatment.

The DLPFC has a crucial role in improving cognitive performance, resulting that it is the commonly used target area for the treatment of many neuropsychiatric disorders (Mikellides et al., 2021). There is also growing evidence that SUD is a disorder of the prefrontal cortex (PFC). An imbalance between the dorsal and ventral PFC network has been hypothesized as the key mechanism for maintaining SUD. The DLPFC and the dorsal anterior cingulate cortex (dACC) governs executive functioning like decision making and self-control; while the ventral PFC network, including the medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC) and ventral anterior cingulate cortex (vACC), are involved in limbic arousal and emotion processing (Goldstein & Volkow, 2011; McClure & Bickel, 2014). The hyperactivation of the ventral PFC network has been associated with craving (Hayashi, Ko, Strafella, & Dagher, 2013), leading to excessive substance use (Dunlop, Hanlon, & Downar, 2017), whereas hypoactivity of the left (Eldreth, Matochik, Cadet, & Bolla, 2004) as well as the right DLPFC (Salo, Ursu, Buonocore, Leamon, & Carter, 2009) has been observed in people with SUD while performing cognitive tasks, indicating impairments of executive functions processed by the DLPFC network. It has also been assumed that the left DLPFC processes reward-based motivation whereas the right DLPFC is more involved in withdrawal-related behaviors and self-inhibition (Balconi, Finocchiaro, & Canavesio, 2014). Therefore, the left DLPFC should be hyperactive as a result of amplified incentive salience of substance use, meanwhile, a

hemispheric asymmetry exists between the left and right DLPFC, as measured with electroencephalography, in patients with SUD (Balconi, & Finocchiaro, 2015). In fact, the left DLPFC is a prime target for many TMS applications in a variety of psychiatric disorders (Kan et al., 2023) and the DLPFC is the only target approved so far by the US American FDA to treat depression. According to a recent review, effect size for rTMS on the left DLPFC was large for craving (Hedges'g -0·803 [95% CI -1·099 to -0·507], p<0·0001; I2=82·40%), medium for depressive symptoms (-0·725 [-0·889 to -0·561], p<0·0001; I2=85·66%), small for anxiety, obsessions or compulsions, pain, global cognition, declarative memory, working memory, cognitive control, and motor coordination (Hedges'g -0·198 to -0·491) and non-significant for attention, suicidal ideation, language, walking ability, fatigue, and sleep (Kan et al., 2023).

However, we noted that placebo effect of sham rTMS treatment on craving and in drug abusers is significant. In a recent review published in Nature Mental Health (Xu et al., 2023), the placebo responses in TMS clinical trials for depression were large (d = 1.016) and increasing yearly (Z = 2.18, p = 0.029), irrespective of sham methods, assessment scales or age, however, other factors such as the trial location, number of sites, sample size, sex ratio, study quality and medication status might influence the outcome. Nevertheless, the inclusion of a placebo group is still recommended in TMS studies since it provides essential insights into the treatment-response and placebo mechanisms (Xu et al., 2023).

Our findings are consistent with our hypotheses that there was reduction in depressive and anxiety symptoms among participants who have received rTMS treatment. It is not surprised to find that high-frequency rTMS to left DLPFC, but not sham stimulation, appears to improve mood of people with illicit drugs abuse because the stimulated region for craving overlapped with depression treatment targeting left DLPFC. This is consistent with the research findings in the depression population. Anxiety and depressive symptoms are common among drug users and are mental disorders that often comorbid with drug addiction, and that rTMS is also well-known to reduce depression for unipolar and bipolar depression in previous reviews and meta-analyses (Cohen et al., 2021; Gershon et al., 2003; Mikellides et al., 2021). However, apart from self-reporting, we regret that the NGOs did not have any medical records regarding formal diagnosis of depression for the participants.

The study has few limitations. This is a cross-over study, the analysis includes combining both real rTMS and sham rTMS before and after wash-out period, the results should not be interpreted as that of a randomized controlled trial. We had an

estimated attrition (dropout rate) of 25% and that we had achieved 87% (including dropouts) of the projected sample size, and that there is a drop-out rate of 25%. It would have been possible to recruit more participants to obtain the desired sample size if our participant recruitment had not been affected because of the COVID pandemic during the study period from 2020 to 2023. In addition, we did not know any previous medical histories of depression in the participants' records from the NGOs. Moreover, half of our participants were male drug abusers aged under 35 years old receiving inpatient service newly admitted to a residential hostel for drug rehabilitation, they were prohibited of consuming any illicit drugs at the residential hostel; therefore, the actual consumption rate might not reflect the true picture after they have left the hostel and exposed to real life temptation. Last but not least, the equipment at both trial sites were different, however, there is no evidence in the literature on which stimulation coil would provide the optimal efficacy of stimulation for craving reduction.

CONCLUSION

It is recommended that rTMS can be useful as an adjunct treatment to reduce craving and improving their motivation for change for illicit drug users in Hong Kong in parallel with traditional pharmaceutical and psychosocial treatments. Future studies are required to investigate the underlying neural mechanism underlying the therapeutic effect in SUD in association with rTMS as well as to determine an optimal stimulation setting for clinical application for SUD in future.

(3,891 words)

REFERENCES

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (DSM-5®). American Psychiatric Pub.

August, S. M., Kiwanuka, J. N., McMahon, R. P., Gold, J. M. (2012). The MATRICS Consensus Cognitive Battery (MCCB): Clinical and cognitive correlates. *Schizophrenia Research*, *134*(1), 76-82. https://doi.org/10.1016/j.schres.2011.10.015.

Balconi, M., & Finocchiaro, R. (2015). Decisional impairments in cocaine addiction, reward bias, and cortical oscillation "unbalance". *Neuropsychiatric Disease and Treatment*, *11*, 777.

Balconi, M., Finocchiaro, R., & Canavesio, Y. (2014). Reward-system effect (BAS rating), left hemispheric "unbalance" (alpha band oscillations) and decisional impairments in drug addiction. *Addictive Behaviors*, *39*(6), 1026-1032.

Central Registry of Drug Abuse (CRDA) (2024). *The CRDA Annual Report*. Downloaded 9 May 2024 from Narcotics Division, Security Bureau, The Government of the Hong Kong SAR, at https://www.nd.gov.hk/pdf/report/crda_72nd/CRDA_72nd_Report_Full_Version.pdf

Cohen S.L., Bikson M., Badran B.W., George M.S. (2021). A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. *Brain Stimulation*, *15*, 73–75. https://doi.org/10.1016/j.brs.2021.11.010.

De Sousa, A. (2013). Repetitive transcranial magnetic stimulation (rTMS) in the management of alcohol dependence and other substance abuse disorders–emerging data and clinical relevance. *Basic and Clinical Neuroscience*, *4*(3), 271.

Diana, M., Raij, T., Melis, M., Nummenmaa, A., Leggio, L., & Bonci, A. (2017). Rehabilitating the addicted brain with transcranial magnetic stimulation. *Nature Reviews Neuroscience, 18*, 685–93.

Dunlop, K., Hanlon, C. A., & Downar, J. (2017). Noninvasive brain stimulation treatments for addiction and major depression. *Annals of the New York Academy of Sciences*, *1394*(1), 31.

Enokibara, M., Trevizol, A., Shiozawa, P., & Cordeiro, Q. (2016). Establishing an effective TMS protocol for craving in substance addiction: Is it possible?. *The American Journal on Addictions*, *25*(1), 28-30.

Eldreth, D. A., Matochik, J. A., Cadet, J. L., & Bolla, K. I. (2004). Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. *Neuroimage*, *23*(3), 914-920.

Gay, A., Cabe, J., De Chazeron, I., Lambert, C., Defour, M., Bhoowabul, V., Charpeaud, T., Tremey, A., Llorca, P.-M., Pereira, B., & Brousse, G. (2022). Repetitive transcranial magnetic stimulation (rTMS) as a promising treatment for craving in stimulant drugs and behavioral addiction: A meta-analysis. *Journal of Clinical Medicine*, *11*, 624. https://doi.org/10.3390/jcm11030624

Gershon, A. A., Dannon, P. N., & Grunhaus, L. (2003). Transcranial magnetic stimulation in the treatment of depression. *American Journal of Psychiatry*, *160*, 835-845.

Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, *12*(11), 652.

Gaudino, E. A., Geisler, M. W., Squires, N. K. (1995). Construct validity in the Trail Making Test: What makes Part B harder? J Clin Exp Neuropsychol., 17(4), 529-535.

Gavett, B.E. (2011). Neuropsychological Assessment Battery. In: Kreutzer, J.S., DeLuca, J., Caplan, B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_2250

Hanlon, C. A., Dowdle, L. T., & Henderson, J. S. (2018). Modulating neural circuits with transcranial magnetic stimulation: implications for addiction treatment development. *Pharmacological Reviews*, 70, 661–83.

Hayashi, T., Ko, J. H., Strafella, A. P., & Dagher, A. (2013). Dorsolateral prefrontal and orbitofrontal cortex interactions during self-control of cigarette craving. *Proceedings of the National Academy of Sciences*, *110*(11), 4422-4427.

Höppner, J., Broese, T., Wendler, L., Berger, C., & Thome, J. (2011). Repetitive transcranial magnetic stimulation (rTMS) for treatment of alcohol dependence. *The World Journal of Biological Psychiatry*, *12*(sup1), 57-62.

Kan, R.L.D., F. Padberg, C.G. Giron, T.T.Z. Lin, B.B.B. Zhang, A.R. Brunoni, and G.S. Kranz. (2023). Effects of repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex on symptom domains in neuropsychiatric disorders: a systematic review and cross-diagnostic meta-analysis. *Lancet Psychiatry*, *10*(4), 252-259.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: A neurocircuitry analysis. *Lancet Psychiatry*, *3*, 760–773.

Lakens, D. (2013). Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. *Frontiers in Psychology*, *4*, 863. https://doi.org/10.3389/fpsyg.2013.00863

Lefaucheur, J., Andre-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., et al. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology*, https://doi.org/10.1016/j.clinph.2014.05.021

Li, X., Hartwell, K. J., Owens, M., LeMatty, T., Borckardt, J. J., Hanlon, C. A., Brady, K. T., & George, M. S. (2013). Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex reduces nicotine cue craving. *Biological psychiatry*, *73*(8), 714-720.

Liu, Q., Shen, Y., Cao, X., Li, Y., Chen, Y., Yang, W., & Yuan, T. F. (2017). Either at left or right, both high and low frequency rTMS of dorsolateral prefrontal cortex decreases cue induced craving for methamphetamine. *The American Journal on Addictions*, *26*(8), 776-779.

Maiti, R., Mishra, B. R., & Hota, D. (2016). Effect of high-frequency transcranial magnetic stimulation on craving in substance use disorder: a meta-analysis. *The Journal of neuropsychiatry and clinical neurosciences*, *29*(2), 160-171.

Maiti, R., Mishra, B. R., & Hota, D. (2017). Effect of high-frequency transcranial magnetic stimulation on craving in substance use disorder: a meta-analysis. *The*

Journal of Neuropsychiatry and Clinical Neurosciences, *29*, 160–71.

May, J., Andrade, J., Kavanagh, D. J., Feeney, G. F., Gullo, M. J., Statham, D. J., Skorka-Brown, J., Connolly, J. M., Cassimatis, M., Young, R. M., & Connor, J. P. (2014). The craving experience questionnaire: a brief, theory-based measure of consummatory desire and craving. *Addiction*, *109*(5), 728-35. doi: 10.1111/add.12472. Epub 2014 Feb 16. PMID: 24400950.

McClure, S. M., & Bickel, W. K. (2014). A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training. *Annals of the New York Academy of Sciences*, *1327*, 62.

Medicare Coverage Database (2024). Local Coverage Determination (LCD): Transcranial magnetic stimulation (TMS) in the treatment of adults with major depressive disorder. Downloaded 25 Jan 2024 from https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdId=34522&ver=29#:~:text=Transcranial%20Magnetic%20Stimulation%20(TMS)%20is%20FDA%20approved%20for%20the%20treatment,depression%20and%20obsessive%2Dcompulsive%20disorders.&text=It%20is%20a%20non%2Dinvasive,region%20of%20the%20cerebral%20cortex.

Mikellides, G., Michael, P. & Tantele, M. Repetitive transcranial magnetic stimulation: an innovative medical therapy. *Psychiatriki*, *32*, 67–74 (2021).

Narcotics Division, Security Bureau, The Government of the Hong Kong Special Administrative Region (2024). Retrieved Mar 27, 2024 from: https://www.nd.gov.hk/en/statistics_list.htm

Oei, T. P., Sawang, S., Goh, Y. W., & Mukhtar, F. (2013). Using the depression anxiety stress scale 21 (DASS-21) across cultures. *International Journal of Psychology*, *48*(6), 1018-1029.

Rachid, F. (2018). Neurostimulation techniques in the treatment of cocaine dependence: A review of the literature. *Addictive behaviors*, *76*, 145-155.

Reitan, R. M. (1958). Validity of the Trail Making test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*, 271-276.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & The Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*, 2008-2039.

Salo, R., Ursu, S., Buonocore, M. H., Leamon, M. H., & Carter, C. (2009). Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biological Psychiatry*, *65*(8), 706-709.

Skinner, M. D., & Aubin, H. J. (2010). Craving's place in addiction theory: Contributions of the major models. *Neuroscience & Biobehavioral Reviews*, *34*, 606–623.

Slavet, J. D., Stein, L. A. R., Colby, S. M., Barnett, N. P., Monti, P. M., Golembeske, C., & Lebeau-Craven, R. (2006). The marijuana ladder: Measuring motivation to change marijuana use in incarcerated adolescents. *Drug and Alcohol Dependence*, *83*(1), 42-48. https://doi.org/10.1016/j.drugalcdep.2005.10.007

Su, H., Zhong, N., Gan, H., Wang, J., Han, H., Chen, T., Li, X. T., Ruan, X. L., Zhu, Y.W., Jiang, H. F. & Zhao, M. (2017). High frequency repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex for methamphetamine use disorders: A randomised clinical trial. *Drug and Alcohol Dependence*, *175*, 84-91.

Van den Eynde, F., Claudino, A. M., Mogg, A., Horrell, L., Stahl, D., Ribeiro, W., Uher, R., Campbell, I., & Schmidt, U. (2010). Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. *Biological Psychiatry*, *67*(8), 793-795.

Xu, Y., Zhang, Y., Zhao, D., Tian, Y., & Yuan, T. (2023). Growing placebo response in TMS treatment for depression: a meta-analysis of 27-year randomized sham-controlled trials. *Nature Mental Health*, *1*, 792-809. https://doi.org/10.1038/s44220-023-00118-9

Zhang, J. J. Q, Fong, K. N. K., Ouyang, R. G., Siu, A. M. H, & Kranz, G. S. (2019). Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: A systematic review and meta-analysis. *Addiction*, *114*(12), 2137-2149.

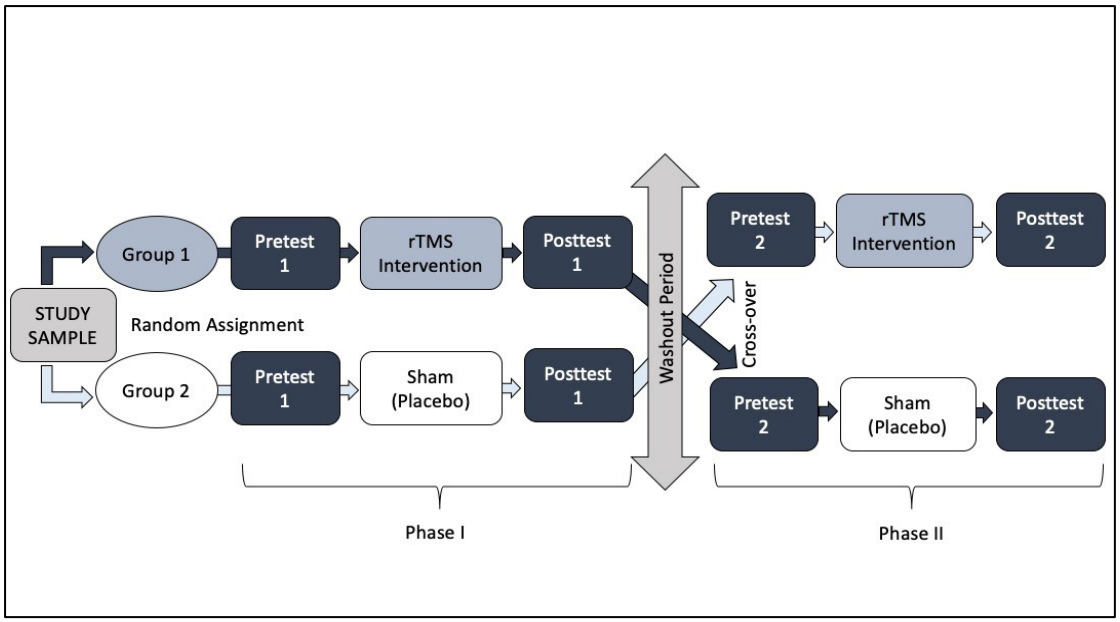
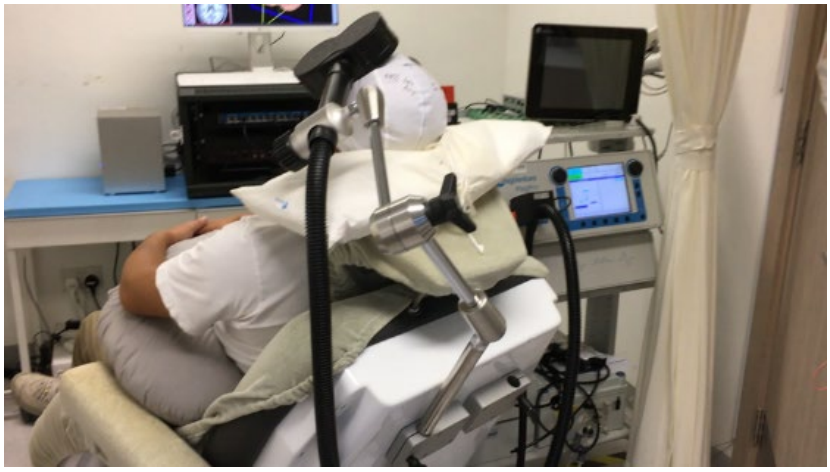
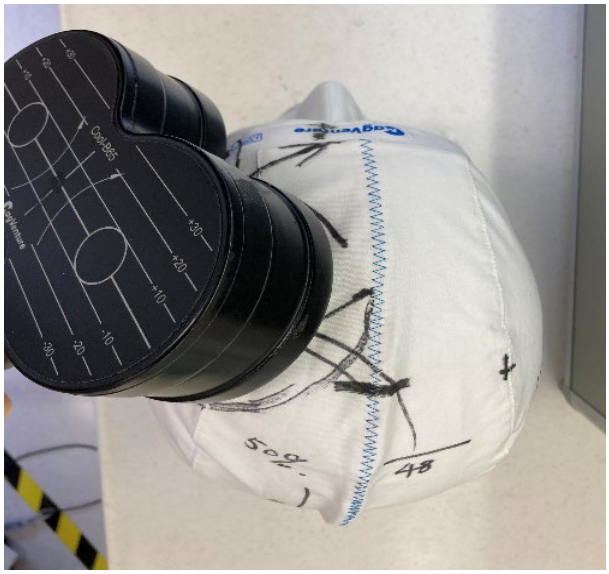


Figure 1. Research design of the study



1A) The experimental setup



1B) The location of left DLPFC for stimulation using the Beam F3 method.

Figure 2. The experiment setup and stimulation site

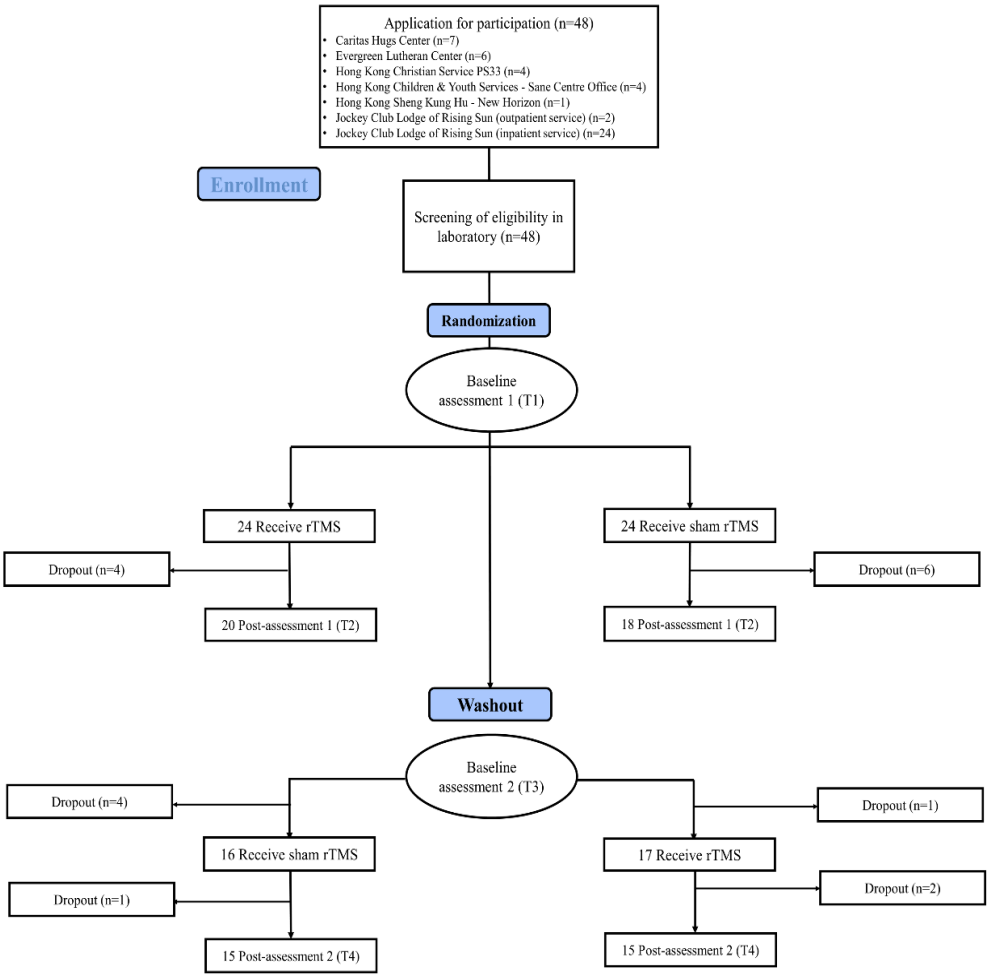
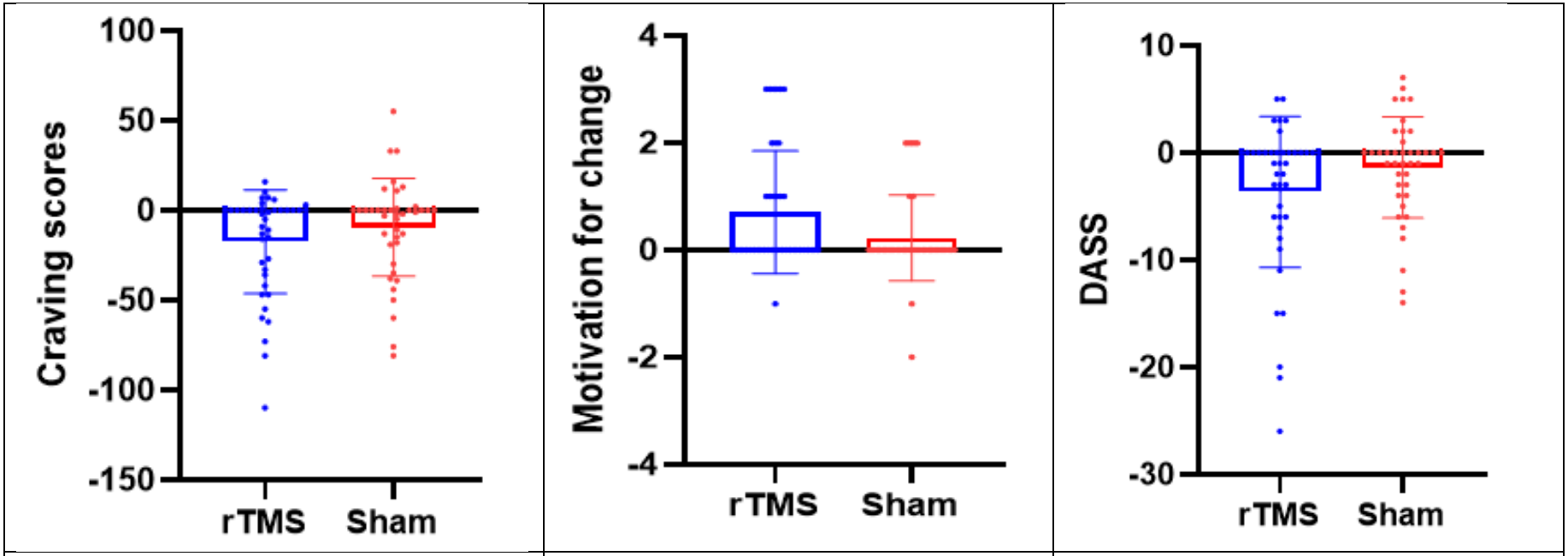


Figure 3. PRIMSA flowchart of participants



(A) Both real and sham rTMS significantly reduced craving in illicit drug users (within-group difference: $p<0.001$ vs. $p=0.035$) but only real rTMS is significant at $p<0.01$.

(B) rTMS demonstrated a higher level of effectiveness compared to sham rTMS in enhancing motivation to quit addictive behaviors among illicit drug users (between-group difference, $p = 0.031$).

(C) rTMS, but not sham rTMS, significantly improved mood in illicit drug users (within-group difference: $p=0.020$ vs. $p=0.072$).

Figure 4. Comparison of effects on real rTMS and sham rTMS in craving, motivation for change and Anxiety Depression Stress Scales-15 (DASS)

Table 1. Mean (SD) scores of outcome measures at each measurement occasions using LOCF

Variables	Baseline for two groups (n=48)		Carry-over effect between baselines and end of washout by group of order (n=33)				Treatments effect in the whole sample (n=81)			
			TMS-Sham (n=16)		Sham-TMS (n=17)		TMS (n=41)		Sham (n=40)	
	TMS-Sham (n=24)	Sham-TMS (n=24)	Baseline	Start of Sham Treatment	Baseline	Start of TMS Treatment	Start of TMS	End of TMS	Start of Sham	End of Sham
DASS	16.42 (9.72)	11.17 (10.70)	14.63 (10.91)	7.38 (7.89)	12.12 (11.77)	8.88 (12.30)	13.29 (11.36)	9.63 (10.20)	9.65 (9.75)	8.28 (10.09)
Craving	73.08 (28.93)	70.17 (32.78)	75.81 (31.05)	42.81 (34.25)	67.47 (36.40)	45.35 (34.48)	61.59 (33.88)	44.02 (35.54)	59.23 (35.63)	49.75 (33.48)
Motivation for change	7.63 (1.47)	7.75 (1.75)	7.69 (1.30)	8.38 (0.96)	7.82 (1.74)	8.47 (1.46)	7.98 (1.51)	8.68 (1.13)	8.00 (1.50)	8.23 (1.46)
TMT	29.60 (13.01)	29.22 (8.65)	25.89 (9.28)	19.26 (5.77)	28.84 (8.16)	24.07 (5.76)	27.30 (10.87)	24.81 (11.14)	25.23 (9.02)	22.94 (7.84)
Maze scores	18.17 (5.84)	18.33 (6.64)	18.56 (6.49)	22.13 (4.32)	18.88 (6.86)	23.71 (3.61)	20.46 (5.67)	22.49 (4.25)	19.85 (6.06)	21.68 (5.59)
CPT-2 digits	3.39 (0.96)	3.71 (0.75)	3.55 (0.74)	3.40 (0.78)	3.76 (0.82)	3.79 (0.59)	3.56 (0.84)	3.60 (0.87)	3.59 (0.77)	3.68 (0.67)
CPT-3 digits	2.70 (0.82)	2.69 (1.09)	2.83 (0.57)	3.51 (0.86)	2.82 (1.02)	2.94 (1.26)	2.80 (1.02)	3.02 (1.02)	3.02 (1.07)	3.09 (1.13)
CPT-4 digits	1.76 (0.83)	1.94 (1.02)	1.99 (0.81)	2.20 (1.21)	1.85 (0.83)	1.98 (0.97)	1.85 (0.89)	2.00 (0.83)	2.05 (1.09)	2.30 (1.08)
Variables	Baseline for two groups (n=22)		Carry-over effect between baselines and end of washout by group of order (n=14)				Treatments effect in the whole sample (n=36)			
			TMS-Sham (n=9)		Sham-TMS (n=5)		TMS (n=18)		Sham (n=18)	
	TMS-Sham (n=13)	Sham-TMS (n=9)	Baseline	Start of Sham Treatment	Baseline	Start of TMS Treatment	Start of TMS	End of TMS	Start of Sham	End of Sham
No. of types of illicit drugs use	1.62 (0.96)	2.56 (1.94)	1.44 (0.73)	1.00 (0.87)	2.20 (1.64)	0.60 (0.89)	1.33 (1.03)	1.06 (1.06)	1.78 (1.66)	1.33 (1.50)
Frequency of using cocaine or methamphetamine	1.92 (0.27)	1.78 (0.44)	1.89 (0.33)	1.56 (0.88)	2.00 (0.00)	0.80 (1.10)	1.61 (0.78)	1.39 (0.92)	1.67 (0.69)	1.44 (0.86)

Abbreviation: LOFC: last observation carried forward; DASS: Depression Anxiety and Stress Scale; TMT: Trail Making Test; CPT: Continuous Performance Test

Table 2. Carry-over effect and treatment effect using LOCF

Variables	Baseline comparison between TMS-sham and sham-TMS groups (n=48)		Carry-over effect: Difference between baseline and end of washout by group of order[b] (n=33) Mean [95% CI]		Treatment effect: Mean changes by two treatments in the whole sample (n=81)						
	Mean difference	*p*[a]	TMS-sham group (n=16; LOCF=1)	Sham-TMS group (n=17; LOCF=2)	TMS (n=41; LOCF=11)	*p*[c]	Sham (n=40; LOCF=10)	*p*[c]	*p*[d]	*Effect size (d)*	*Power (β)*
DASS	5.25	0.082	-7.25 [-12.16, -2.35]**	-3.24 [-7.37, 0.90]	-3.66 (7.04)	0.020*	-1.38 (4.71)	0.072	0.091	0.347	0.338
Craving	2.92	0.745	-33.00 [-51.62, -14.38]**	-22.12 [-36.27, -7.96]**	-17.56 (28.87)	<0.001***	-9.48 (27.35)	0.035*	0.200	0.368	0.373
Motivation for change	-0.13	0.790	0.67 [-0.08.1.46]	0.65 [-0.06, 1.35]	0.70 (1.15)	<0.001***	0.23 (0.80)	0.083	0.031*	0.509	0.619
TMT	0.38	0.906	-6.63 [-12.04, -1.22]*	-4.76 [-9.09, -0.46]*	-2.50 (7.48)	0.039*	-2.29 (5.37)	0.010**	0.877	0.032	0.052
Maze scores	-0.17	0.927	3.56 [1.72, 5.41]**	4.82 [2.37, 7.28]**	2.02 (3.68)	0.001**	1.83 (3.70)	0.003**	0.808	0.056	0.057
CPT-2 digits	-0.32	0.201	-0.15 [-0.71, 0.41]	0.03 [-0.42, 0.48]	0.04 (0.66)	0.696	0.09 (0.61)	0.334	0.706	0.099	0.072
CPT-3 digits	0.01	0.976	0.69 [0.16, 1.22]*	0.12 [-0.61, 0.85]	0.22 (1.07)	0.201	0.07 (0.78)	0.594	0.469	0.223	0.168
CPT-4 digits	-0.18	0.503	0.21 [-0.37, 0.79]	0.13 [-0.22, 0.48]	0.14 (0.77)	0.236	0.25 (0.76)	0.043*	0.533	0.161	0.110
Variables	Baseline comparison between TMS-sham and sham-TMS groups (n=22)		Carry-over effect: Difference between baseline and end of washout by group of order[b] (n=14) Mean [95% CI]		Treatment effect: Mean changes by two treatments in the whole sample (n=36)						
	Mean difference	*p*[a]	TMS-sham group (n=9; LOCF=0)	Sham-TMS group (n=5; LOCF=2)	TMS (n=18; LOCF=4)	*p*[c]	Sham (n=18; LOCF=4)	*p*[c]	*p*[d]	*Effect size (d)*	*Power (β)*
No. of type of illicit drugs use	-0.94	0.207	0.44 [-0.11, 1.00]	1.60 [-0.97, 4.17]	-0.28 (0.57)	0.056	-0.44 (1.29)	0.163	0.621	0.160	0.075
Frequency of using	0.15	0.353	0.33	1.20	-0.22	0.104	-0.22	0.163	0.999	0.000	0.050

cocaine or methamphetamine	[-0.21, 0.88]	[-0.16, 2.56]	(0.55)	(0.49)

Abbreviation: LOCF: last observation carried forward; DASS: Depression Anxiety and Stress Scale; TMT: Trail Making Test; CPT: Continuous Performance Test

[a]Independent t-test comparing baseline difference between TMS-Sham and Sham-TMS groups.

[b]Paired t-test analyzing carry-over effect by group of order. *p<0.05; **p<0.01,***p<0.001

[c]Paired t-test comparing pre- and post-treatments' means in combined sample.

[d]Independent t-test comparing the mean changes between groups in total sample.

(d) (β) Effect sizes and power were computed based on between-group comparisons using independent t tests.