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

(Beat Drugs Fund, Narcotics Division, Security Bureau,
Ref. No.: BDF190052)

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The team

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Other team members

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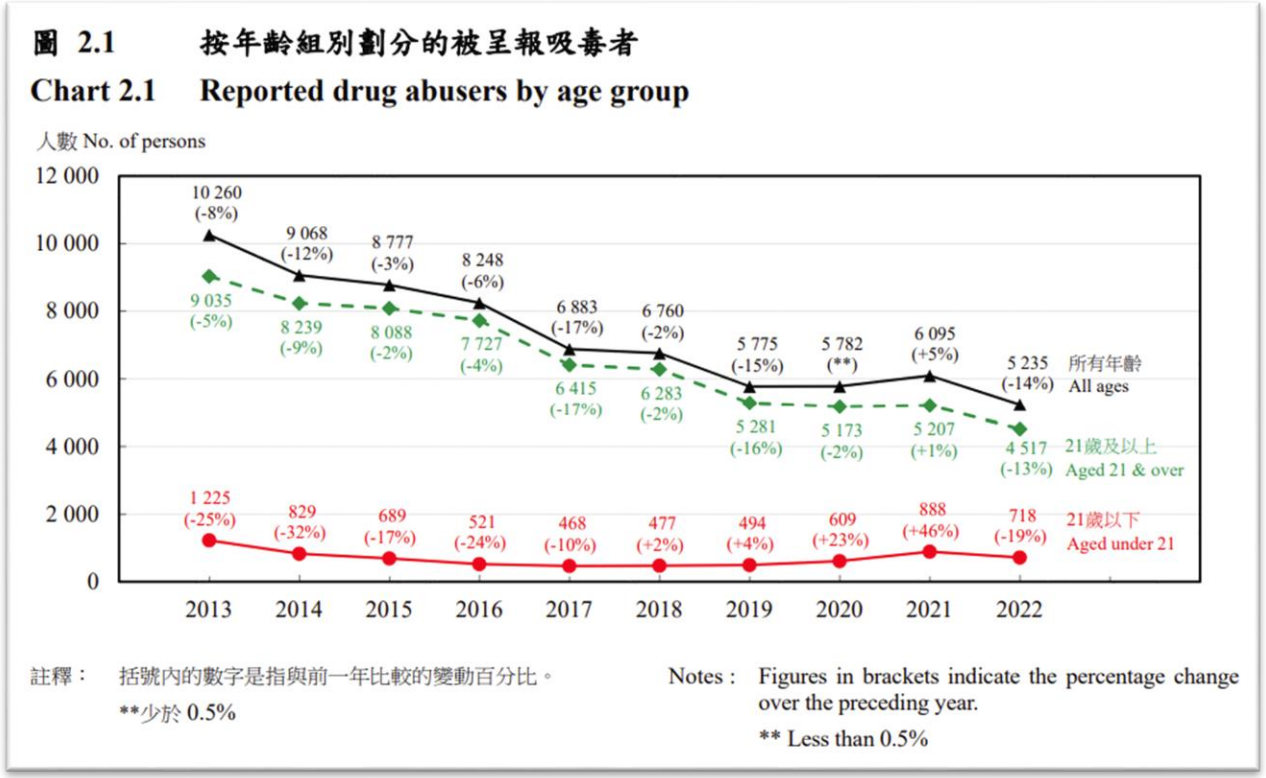
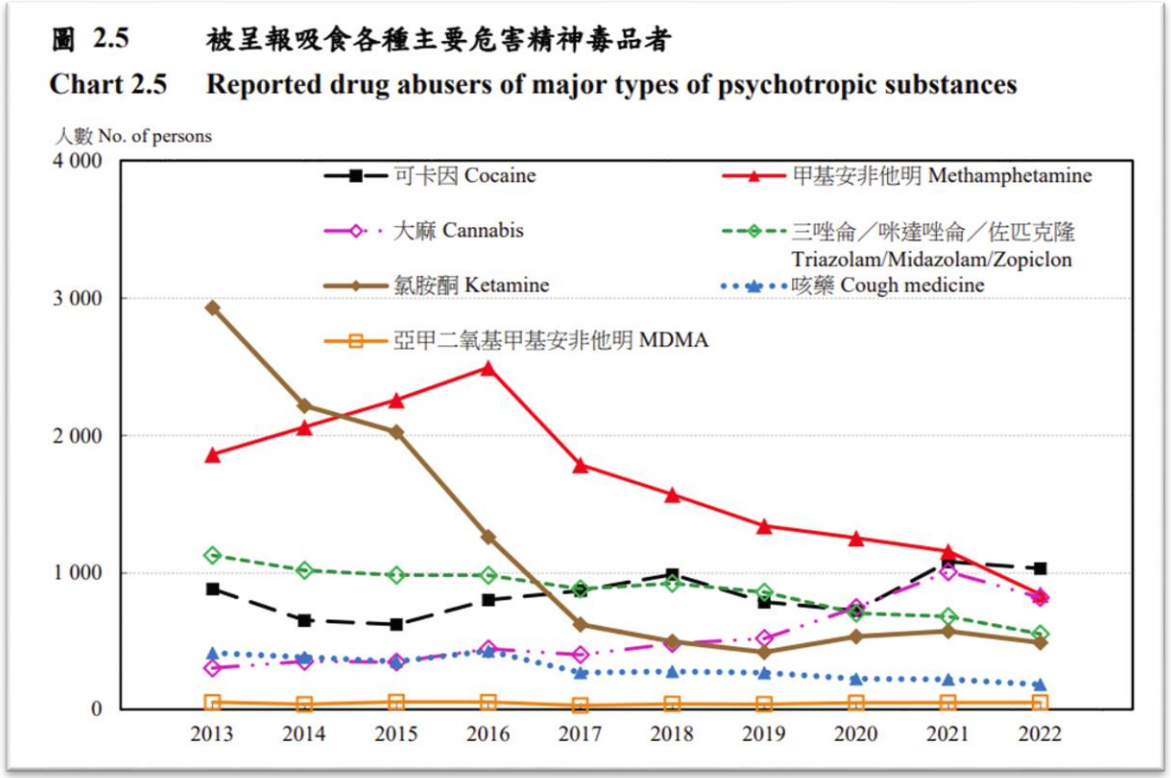
Background: Drug Addiction in Hong Kong

- **Drug addiction** is a chronic psychiatric disorder which is characterized by the continual use of illicit drugs despite significant cognitive, behavioral, and physiological symptoms (American Psychiatric Association, 2013).

Data from the Central Registry of Drug Abuse, Seventy-second Report





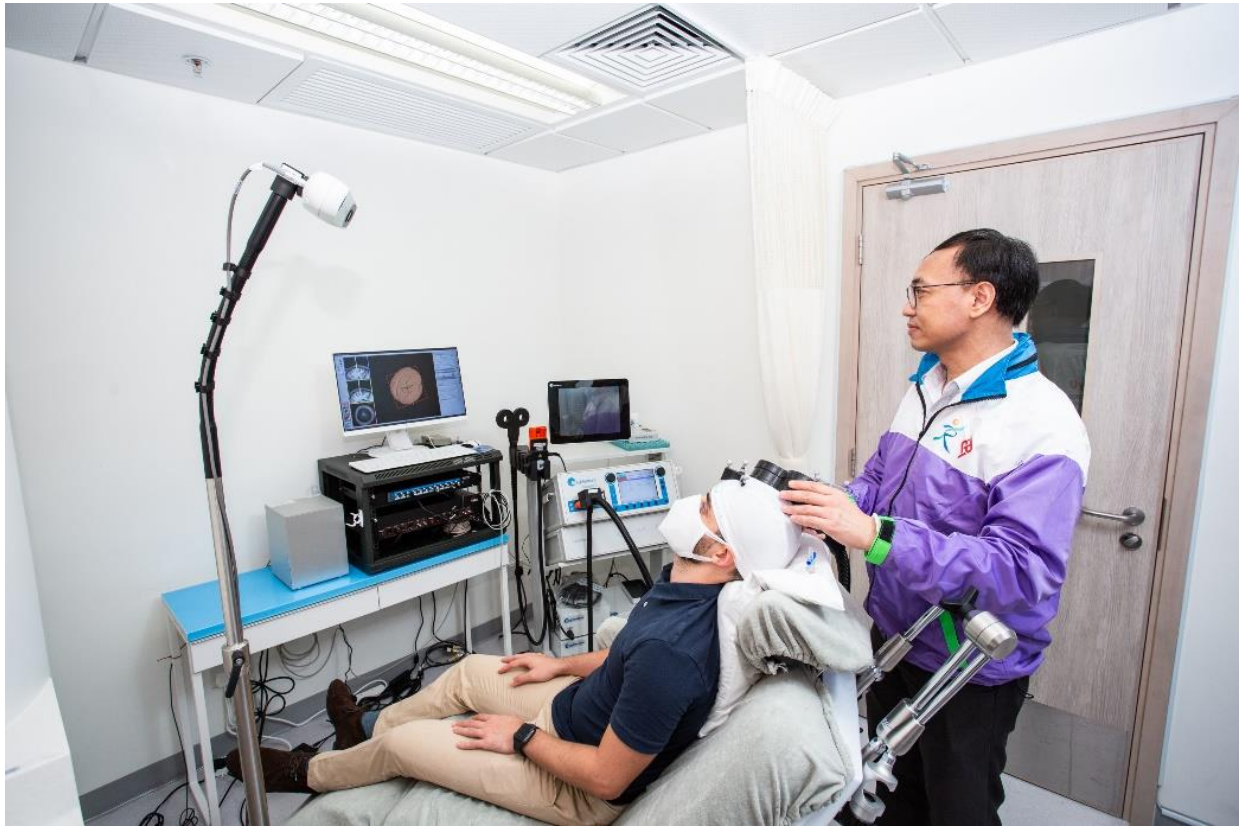
The proportion of reported young abusers aged under 21 was over 10% in recent years in Hong Kong (Central Registry of Drug Abuse (CRDA), 2024).

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).

Objectives

The primary question:

- Can rTMS reduce **craving** of the mostly used illicit drugs, such as methamphetamine & cocaine, among people in Hong Kong?
- rTMS能否減少參加者對最常使用的非法藥物，如甲基苯丙胺和可卡因的渴望?



The secondary questions:

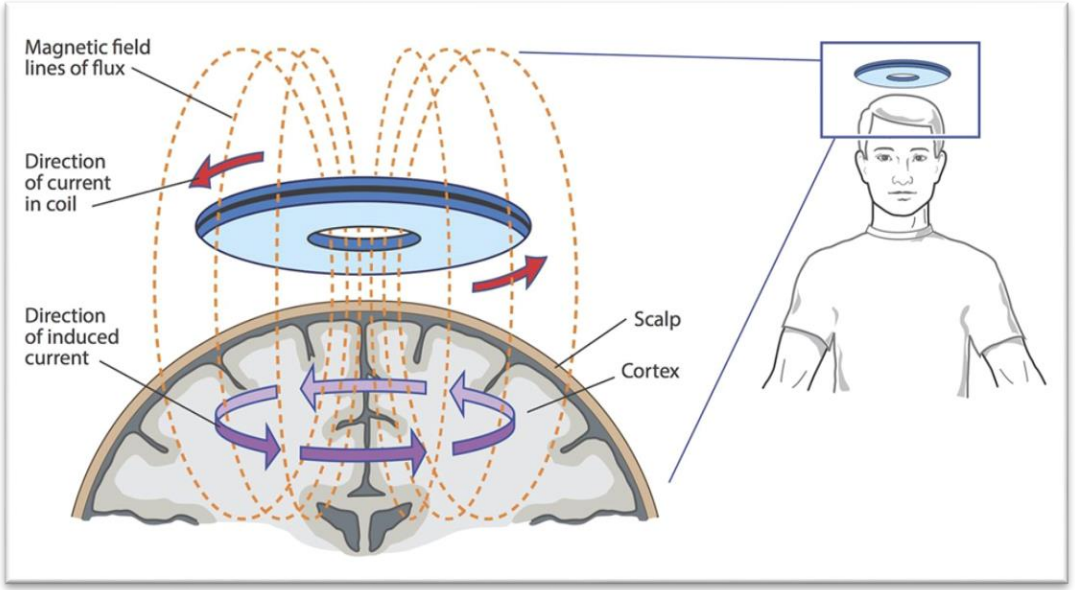
- Can rTMS provide reduction in **depressive and anxiety symptoms**?
- rTMS 可以減輕抑鬱和焦慮症狀嗎？

- Can rTMS provide any gains in **executive functioning**?
- rTMS 可以在執行功能方面提供任何改進嗎？

Background: Transcranial Magnetic Stimulation (經顱磁刺激)

- **Transcranial magnetic stimulation (TMS)** is a noninvasive form of brain stimulation in which a changing magnetic field is used to induce an electric current at a specific area of the brain through electromagnetic induction.

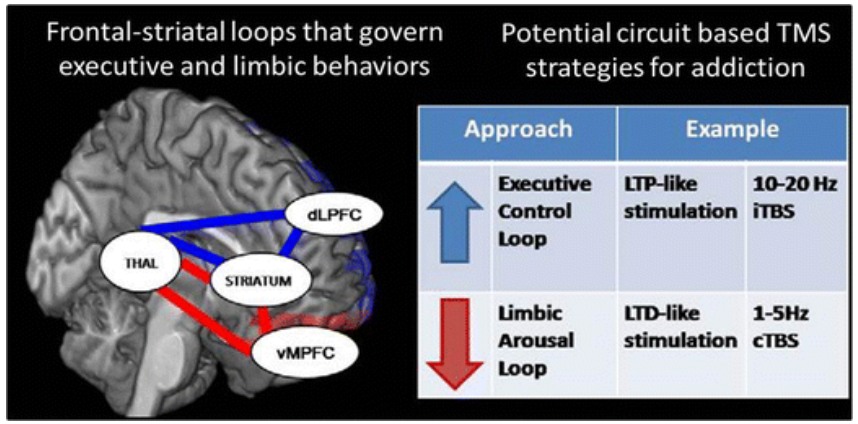
- In neuropsychiatric treatment, repetitive TMS (rTMS) has been approved by US FDA for major depressive disorders and obsessive-compulsive disorder.



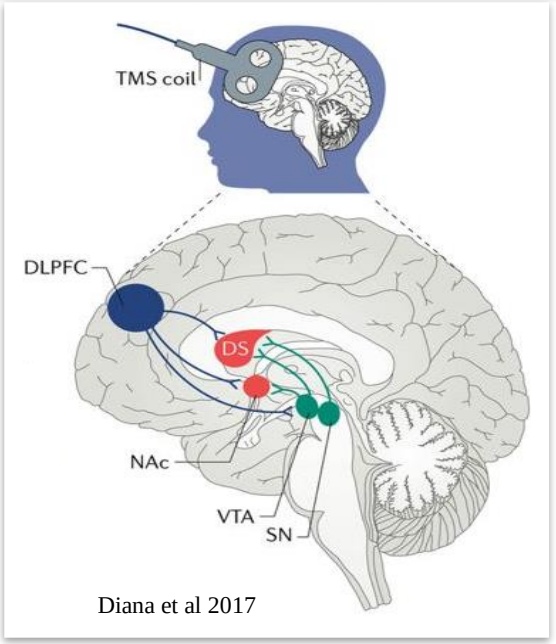
The therapeutic mechanisms of rTMS in drug addiction:

1) To rebalance the dorsolateral prefrontal cortex (DLPFC) (左背外側前額皮質) and the medial prefrontal cortex (MPFC) (fMRI evidence).

- **To activate the DLPFC**
- **To inhibit the MPFC**



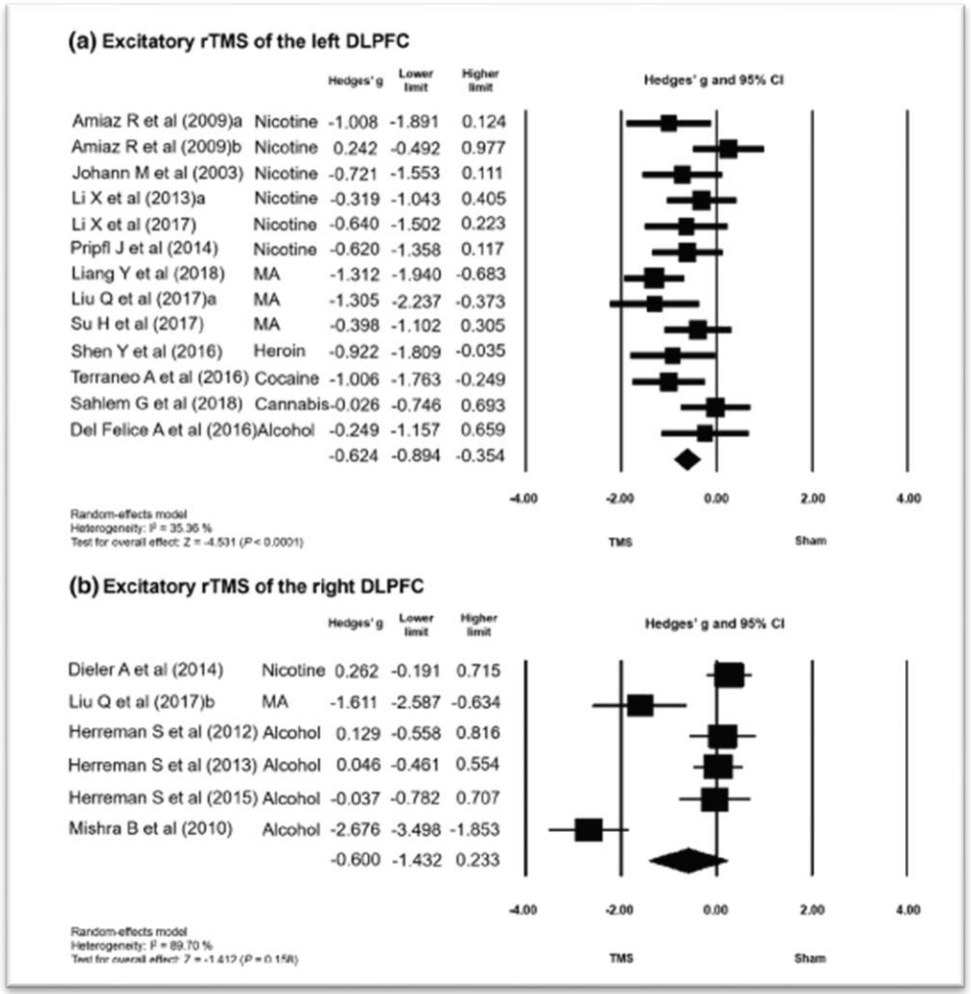
Hanlon et al 2018



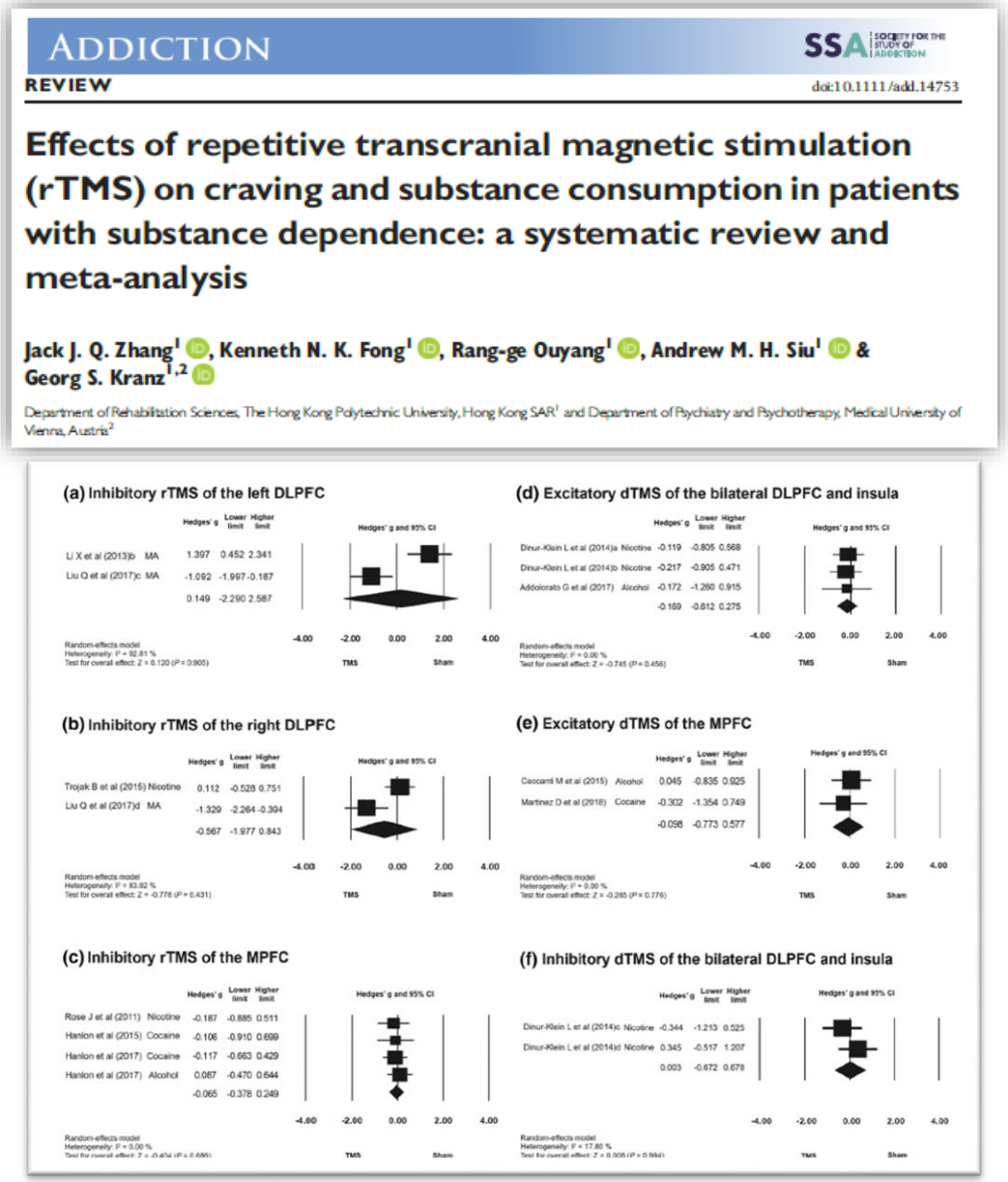
Diana et al 2017

2) To activate the dopamine pathway in the prefrontal cortex-ventral striatum (PET evidence)

Repetitive TMS in substance addiction: Clinical evidence



Meta-analysis shows that excitatory rTMS of the left DLPFC reduced craving in individuals with substance addiction (including cocaine, methamphetamine, etc.)（Hedges'g=0.62, *P* <0.001）


ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
REVIEW
doi:10.1111/add.14753

Effects of repetitive transcranial magnetic stimulation (rTMS) on craving and substance consumption in patients with substance dependence: a systematic review and meta-analysis

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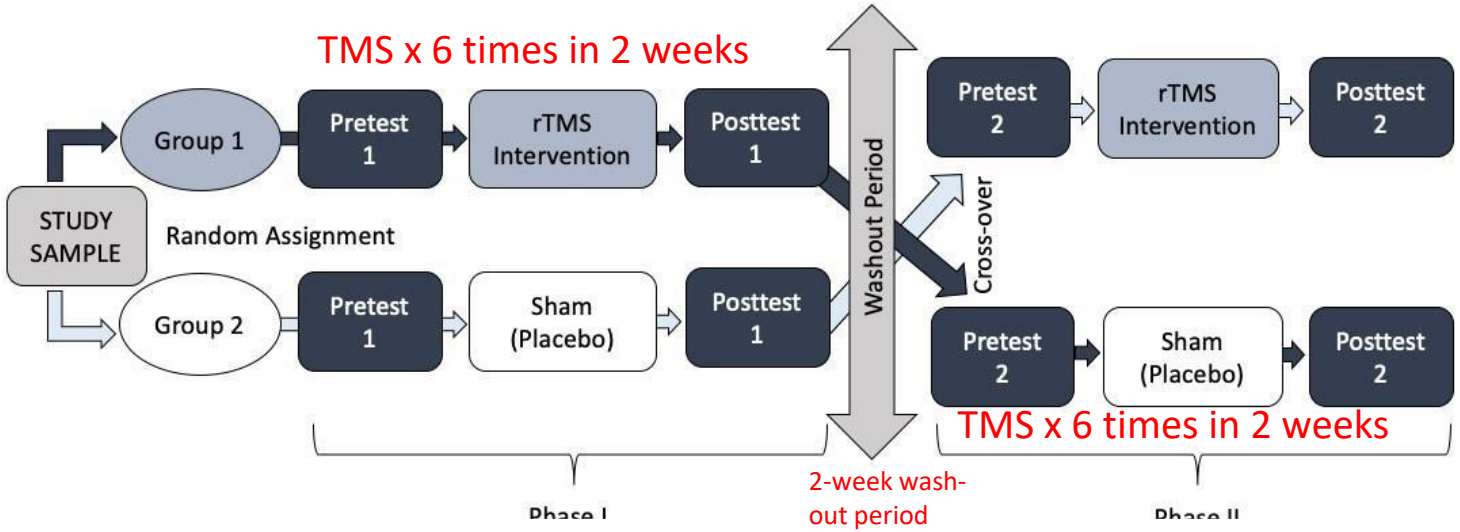
Zhang, **Fong***, Ouyang, Siu, Kranz., 2019 Addiction

Methods:

- **Study design**: A randomized, cross-over study: rTMS & sham rTMS



Group 1: TMS – sham

Group 2: Sham – TMS

Eligibility

Inclusion

- Aged 18 to 55;
- Illicit drug users in community;
- Use either methamphetamine (ice), cocaine, or both, frequently for at least 3 times per week;
- Engaged in counselling or rehabilitation services for drug abuse.

Exclusion

- History of seizures, severe mental disorders, brain damage from illness or injury;
- Frequent or severe headaches;
- Any metal or implanted medical devices in body;
- Pregnant or planning for pregnancy;
- Had prior treatment with rTMS in the past year.

Outcome measures

Primary

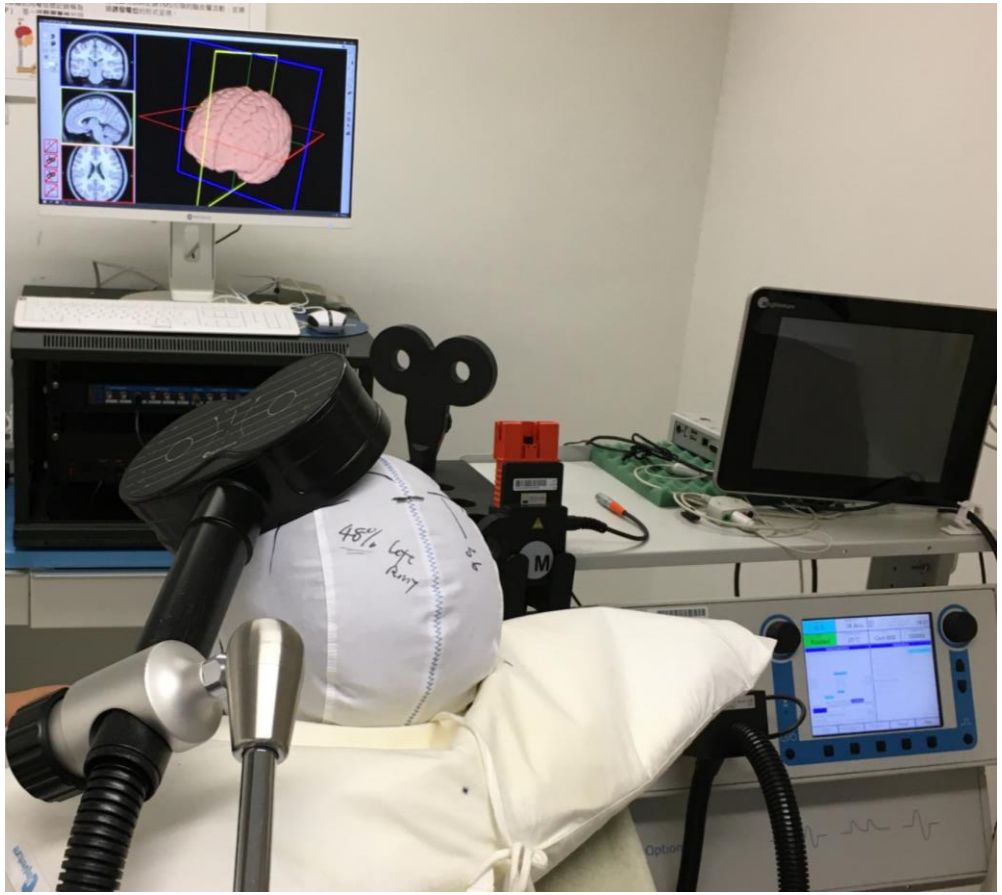
- **Drug consumption**: Self-report Questionnaire (Set 5 of Beat Drugs Fund).
- **Craving**: Craving Experience Questionnaire (CEQ) and Contemplation Ladder.

Secondary

- **Emotion**: Anxiety Depression Stress Scales-15 (DASS21).
- **Executive functioning**: MATRICS Consensus Cognitive Battery (MCCB)'s subtests for attention (CPT-IP), processing speed (TMT), reasoning and problem-solving (NAB Mazes).

Methods: rTMS protocols

Intervention: high-frequency repetitive TMS delivered to the left DLPFC



Brain target: Left DLPFC, using the Beam F3 localization method.
Parameters: 10 Hz, 2000 pulses, 40 trains with 50 pulses per train, inter-train interval at 10 sec, 100% resting motor threshold (RMT)
Sham: same as above but the intensity was reduced to 20% RMT.
Duration: 2-3 sessions per week for 2-3 weeks, 6 sessions in total.
Venue: Assistive Technology Laboratory, ST814, PolyU except for delivered on-site for residents at the hostel

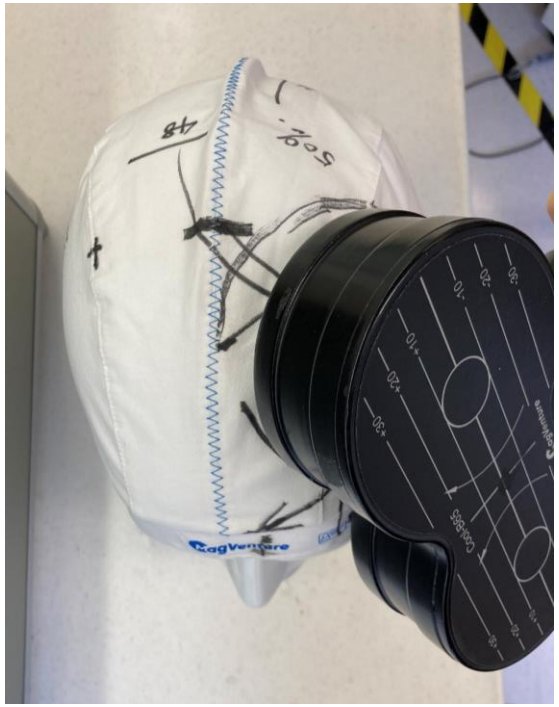


figure-of-eight cool coil

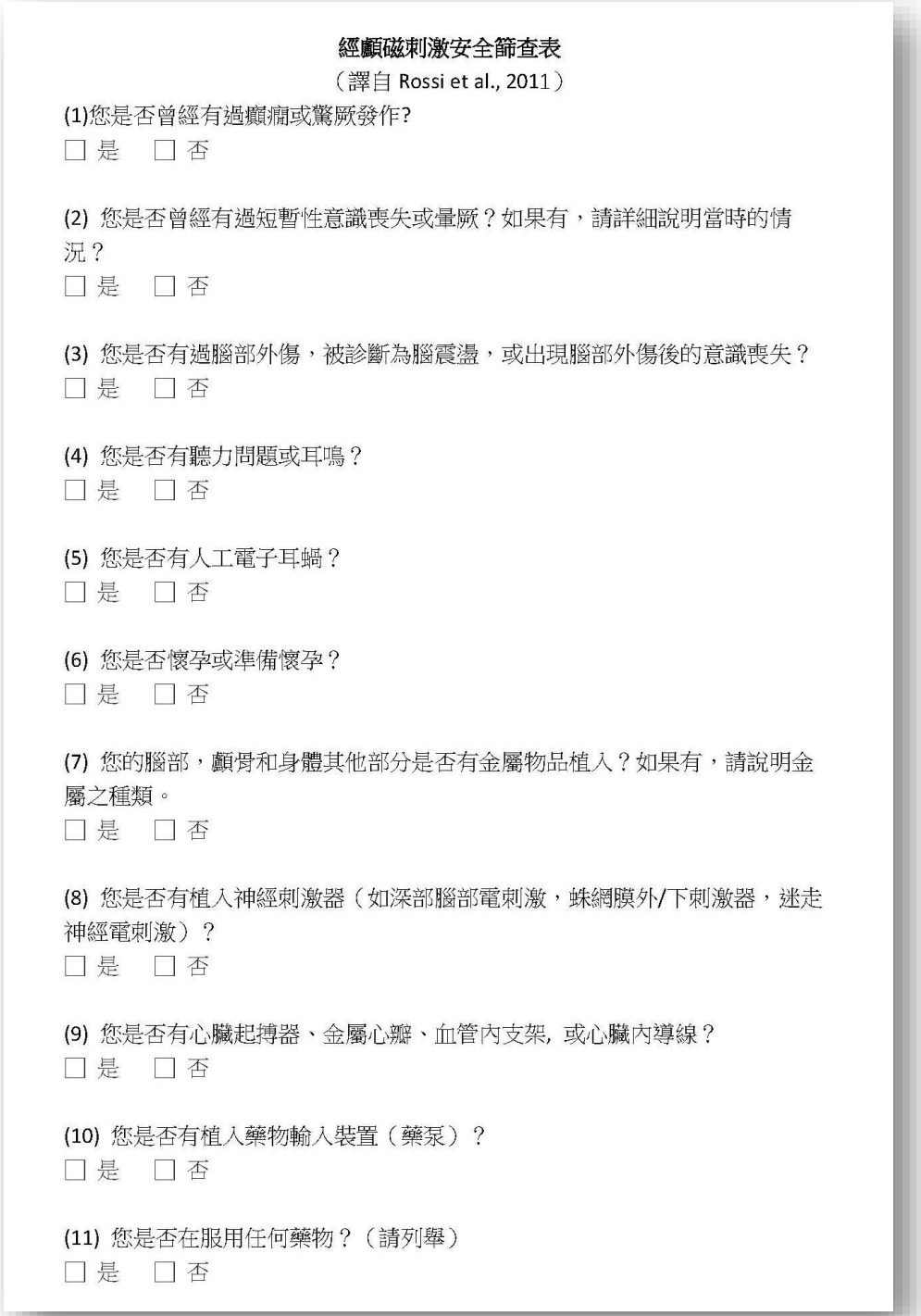
The left DLPFC was localized using the Beam F3 method (https://clinicalresearcher.org/F3/calculate.php).

Safety screening of rTMS

- According to literature, risk of seizure after TMS is less than 0.1%.
- Effect of TMS is state-dependent, with most seizures due to the state and condition of individual clients on the day, rather than any underlying neurological conditions.
- Safety screening and guidelines in use of TMS on patients (attached).

Ethical approval was obtained from the Human Subjects Ethics Sub-committee of the Hong Kong Polytechnic University (Ref. No.: HSEARS20210602002).

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2011). Screening questionnaire before TMS: an update. *Clin Neurophysiol*, *122*(8), 1686. doi:10.1016/j.clinph.2010.12.037



經顱磁刺激安全篩查表

（譯自 Rossi et al., 2011）

(1)您是否曾經有過癲癇或驚厥發作?

☐ 是 ☐ 否

(2) 您是否曾經有過短暫性意識喪失或暈厥？如果有，請詳細說明當時的情況？

☐ 是 ☐ 否

(3) 您是否有過腦部外傷，被診斷為腦震盪，或出現腦部外傷後的意識喪失？

☐ 是 ☐ 否

(4) 您是否有聽力問題或耳鳴？

☐ 是 ☐ 否

(5) 您是否有人工電子耳蝸？

☐ 是 ☐ 否

(6) 您是否懷孕或準備懷孕？

☐ 是 ☐ 否

(7) 您的腦部，顱骨和身體其他部分是否有金屬物品植入？如果有，請說明金屬之種類。

☐ 是 ☐ 否

(8) 您是否有植入神經刺激器（如深部腦部電刺激，蛛網膜外/下刺激器，迷走神經電刺激）？

☐ 是 ☐ 否

(9) 您是否有心臟起搏器、金屬心瓣、血管內支架，或心臟內導線？

☐ 是 ☐ 否

(10) 您是否有植入藥物輸入裝置（藥泵）？

☐ 是 ☐ 否

(11) 您是否在服用任何藥物？（請列舉）

☐ 是 ☐ 否

Primary outcome

Drug consumption: Self-report Questionnaire (藥物消耗:自我報告問卷)
(Set 5 of Beat Drugs Fund) (Narcotics Division, Security Bureau, 2024)

請細心閱讀各題，填上你認為最適合的答案。所有答案將完全保密。

1. 在過去 7 日內，你有多少次：	過去 7 日內		
	從來沒有	間中有	經常有
A. 吸食大麻	☐	試過_____次	每日_____次 / 每星期_____次
B. 吸食白粉（海洛英）	☐	試過_____次	每日_____次 / 每星期_____次
C. 服食 Fing 頭丸（亞甲二氧基甲基安非他明）	☐	試過_____次	每日_____次 / 每星期_____次
D. 吸食 K 仔（氯胺酮）	☐	試過_____次	每日_____次 / 每星期_____次
E. 吸食冰（甲基安非他明）	☐	試過_____次	每日_____次 / 每星期_____次
F. 服食忽得	☐	試過_____次	每日_____次 / 每星期_____次
G. 服食五仔	☐	試過_____次	每日_____次 / 每星期_____次
H. 服食藍精靈	☐	試過_____次	每日_____次 / 每星期_____次
I. 服食白瓜子	☐	試過_____次	每日_____次 / 每星期_____次
J. 吸食可卡因	☐	試過_____次	每日_____次 / 每星期_____次
K. 服食咳藥水	☐	試過_____次	每日_____次 / 每星期_____次
L. 吸食有機溶劑（天拿水）	☐	試過_____次	每日_____次 / 每星期_____次
M. 服食其他毒品〔不包括吸煙或飲酒〕請註明：_____	☐	試過_____次	每日_____次 / 每星期_____次

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

Primary outcome

Craving Experience Questionnaire (渴望體驗問卷) (CEQ) (May et al., 2014)

Today's Date: _____/_____/_____ #_____ **CEQ-11**

Think about the time in the LAST ---------- you MOST WANTED it.

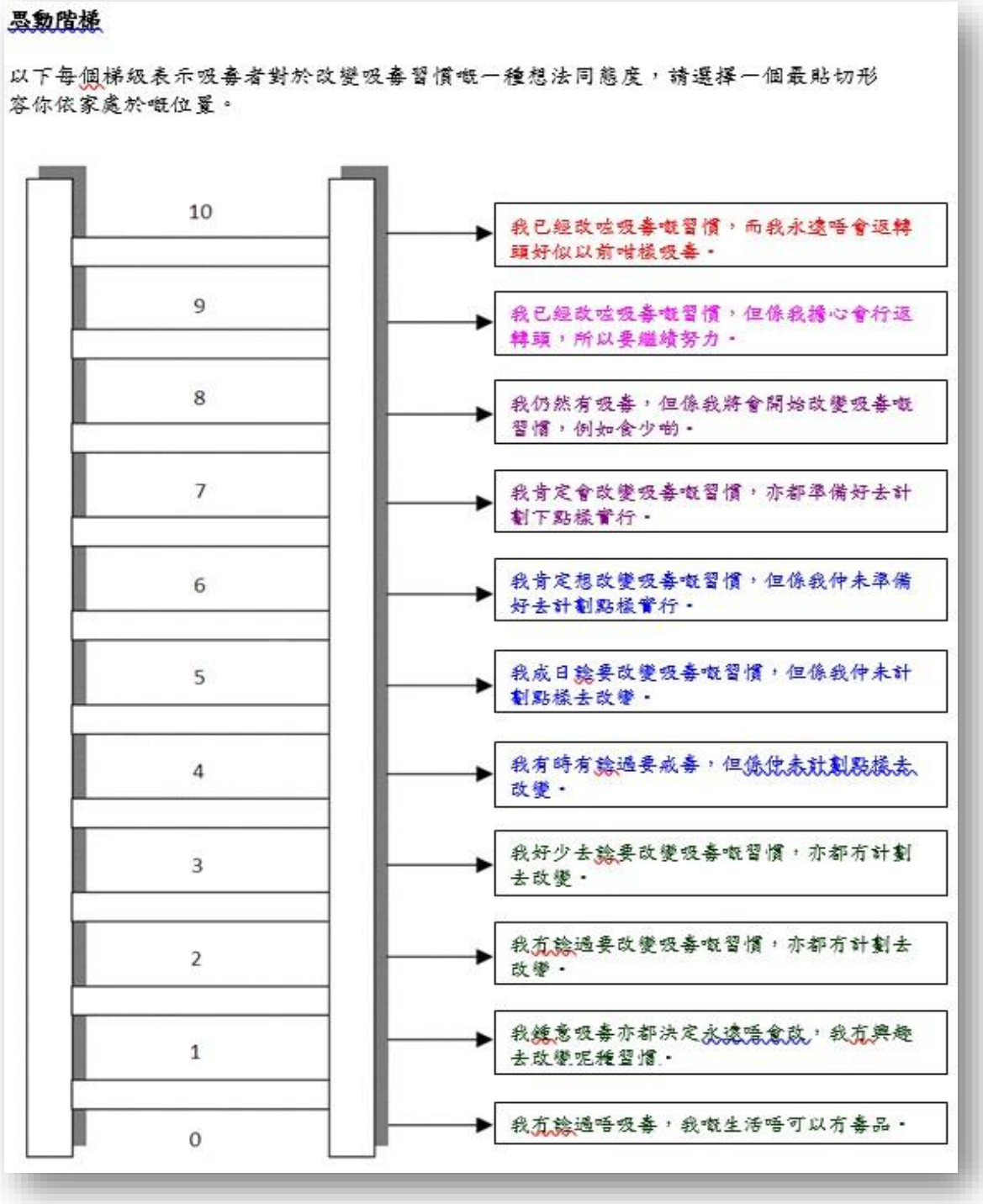
For each item, mark an X in a box to make your rating.

	0	1	2	3	4	5	6	7	8	9	10	
At that time…												
…how much did you want it?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…how much did you need it?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…how strong was the urge to have it?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
At that time, how vividly did you…												
…picture it?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…imagine its taste?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…imagine its smell?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…imagine what it would feel like in your mouth or throat?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…imagine how your body would feel?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
At that time…												
…how hard were you trying not to think about it?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…how intrusive were the thoughts?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely
…how hard was it to think about anything else?	Not at all	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Extremely

Please TURN OVER

May J, Andrade J, Kavanagh DJ, Feeney GF, Gullo MJ, Statham DJ, Skorka-Brown J, Connolly JM, Cassimatis M, Young RM, Connor JP. The craving experience questionnaire: a brief, theory-based measure of consummatory desire and craving. Addiction. 2014 May;109(5):728-35. doi: 10.1111/add.12472. Epub 2014 Feb 16. PMID: 24400950.

Primary outcome
Contemplation Ladder (思動階梯) (Salvet et. al, 2006)



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

Secondary outcome

Depression Anxiety Stress Scales-18 (DASS-18)
(抑鬱焦慮壓力量表)
(Oei, Sawang, Goh, & Mukhtar, 2013)

DASS

姓名:　　日期:

請小心閱讀以下每一個句子，並在其右方圈上一數字，表示「過往一個星期」如何適用於你。答案並無對錯之分。請不要花太多時間在某一句子上。

0＝不適用
1＝頗適用，或間中適用
2＝很適用，或經常適用
3＝最適用，或常常適用

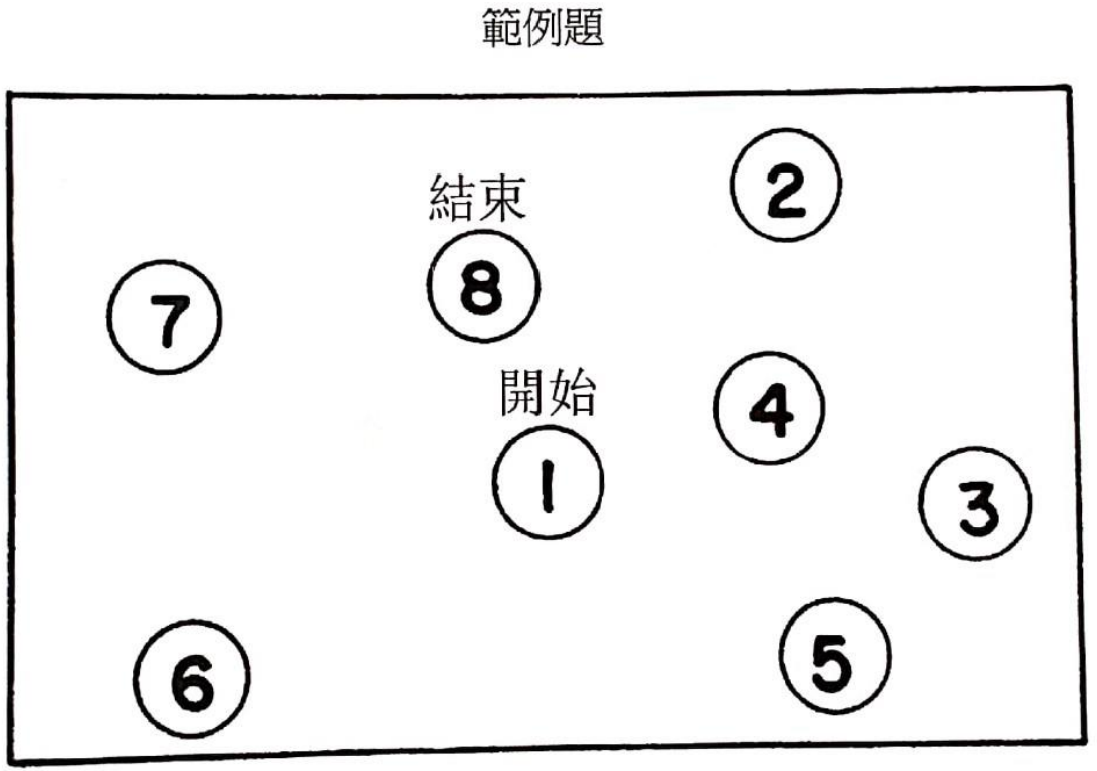
1	我覺得很難讓自己安靜下來	0	1	2	3
2	我感到口乾	0	1	2	3
3	我好像不能再有任何愉快、舒暢的感覺	0	1	2	3
4	我感到呼吸困難（例如不是做運動時也感到氣促或透不過氣來）	0	1	2	3
5	我感到很難自動去開始工作	0	1	2	3
6	我感到顫抖（例如手震）	0	1	2	3
7	我憂慮一些令自己恐慌或出醜的場合	0	1	2	3
8	我覺得自己對將來沒有甚麼可盼望	0	1	2	3
9	我感到憂鬱沮喪	0	1	2	3
10	我感到快要恐慌了	0	1	2	3
11	我對任何事也不能熱衷	0	1	2	3
12	我覺得自己不怎麼配做人	0	1	2	3
13	我察覺自己在沒有明顯的體力勞動時，也感到心律不正常	0	1	2	3
14	我無緣無故地感到害怕	0	1	2	3
15	我感到生命毫無意義	0	1	2	3

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.

Secondary outcome

MATRICS Consensus Cognitive Battery (MCCB)'s subtests in attention (CPT-IP) MATRICS (共識認知注意力測試)
(https://www.matricsinc.org/mccb/) (August et al., 2012)

Trail Making Test (TMT) - Part A
(Trail 測試)

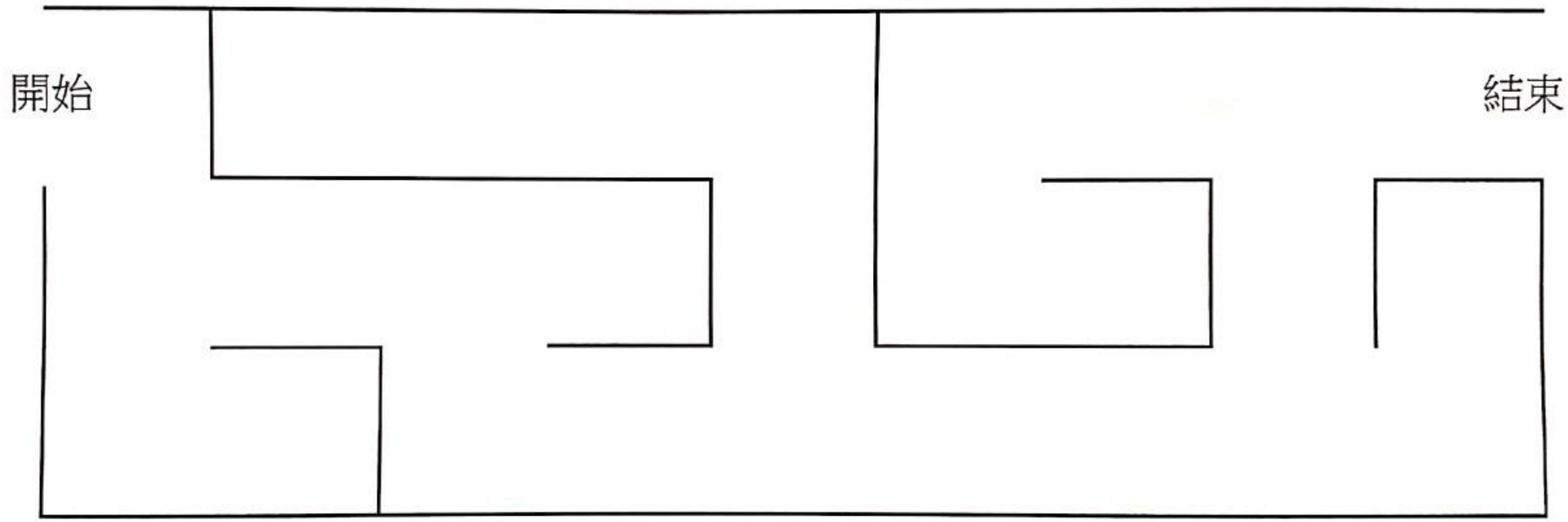


August, S. M., Kiwanuka, J. N., McMahon, R. P., Gold, J. M. (2012). The MATRICS Consensus Cognitive Battery (MCCB): Clinical and cognitive correlates. *Schizophrenia Research*, *134*(1), 76-82. https://doi.org/10.1016/j.schres.2011.10.015.

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

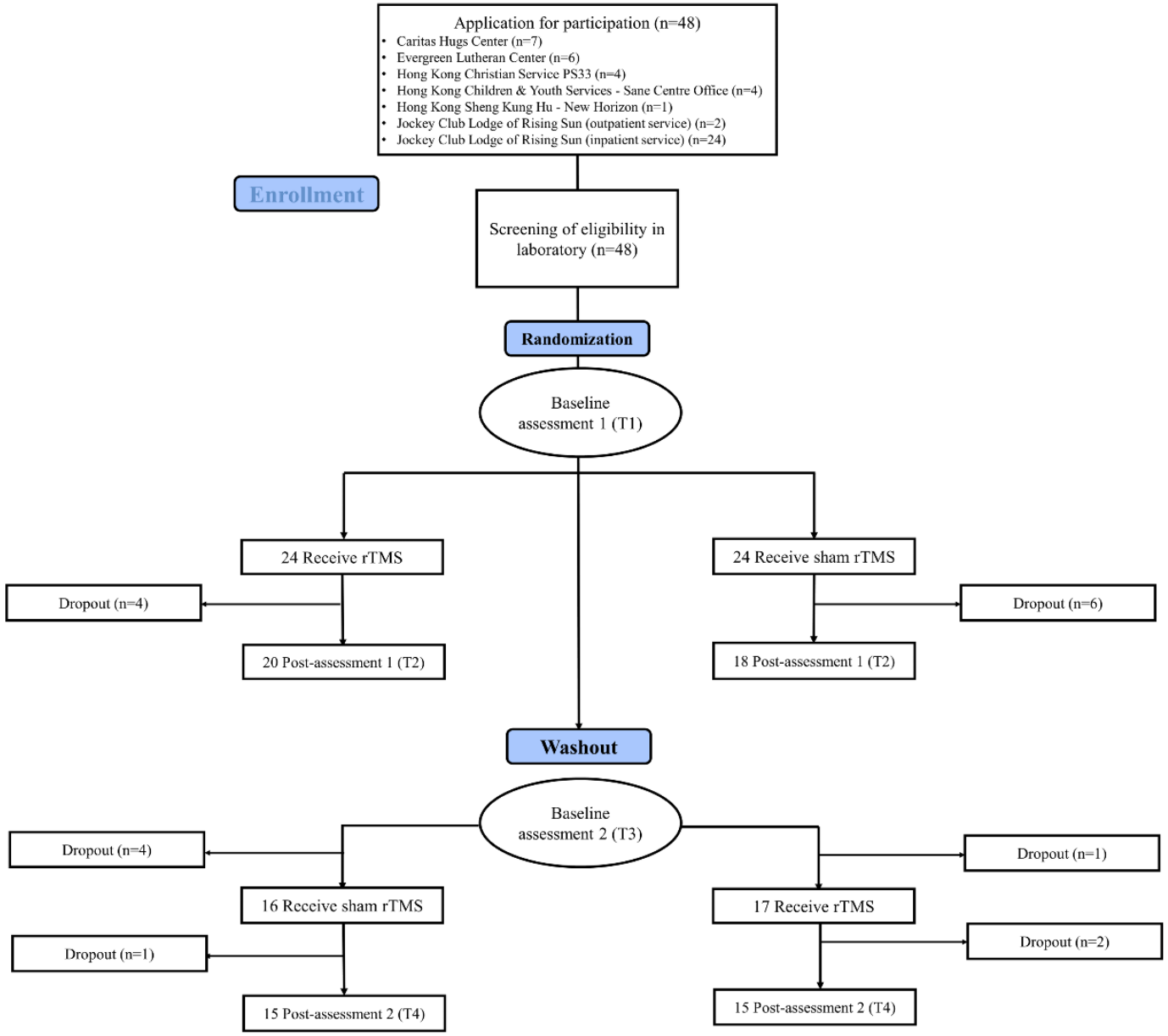
Secondary outcome

Neuropsychological Assessment Battery Mazes (NAB®)
(神經心理學評估迷宮)
(https://www.parinc.com/Products?pkey=260) (Gavett, 2011)



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

Results



- Participants were recruited consecutively from 6 NGOs:
- 香港明愛明愛容圃中心
- 香港基督教服務處 PS33
- 路德會青怡中心
- 香港青少年服務處– Sane Centre 辦事處
- 香港聖公會 – New Horizon
- 香港基督教服務處賽馬會日出山莊- 門診及住院服務

- A total of 48 participants with illicit drugs abuse were randomly assigned to TMS-sham (n=24) and sham-TMS (n=24) groups.

- Sample size prediction: 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 at p=0.05, 55 subjects are needed for a potential attrition of 25%.

Results

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]
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
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
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***
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
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
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
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
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

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

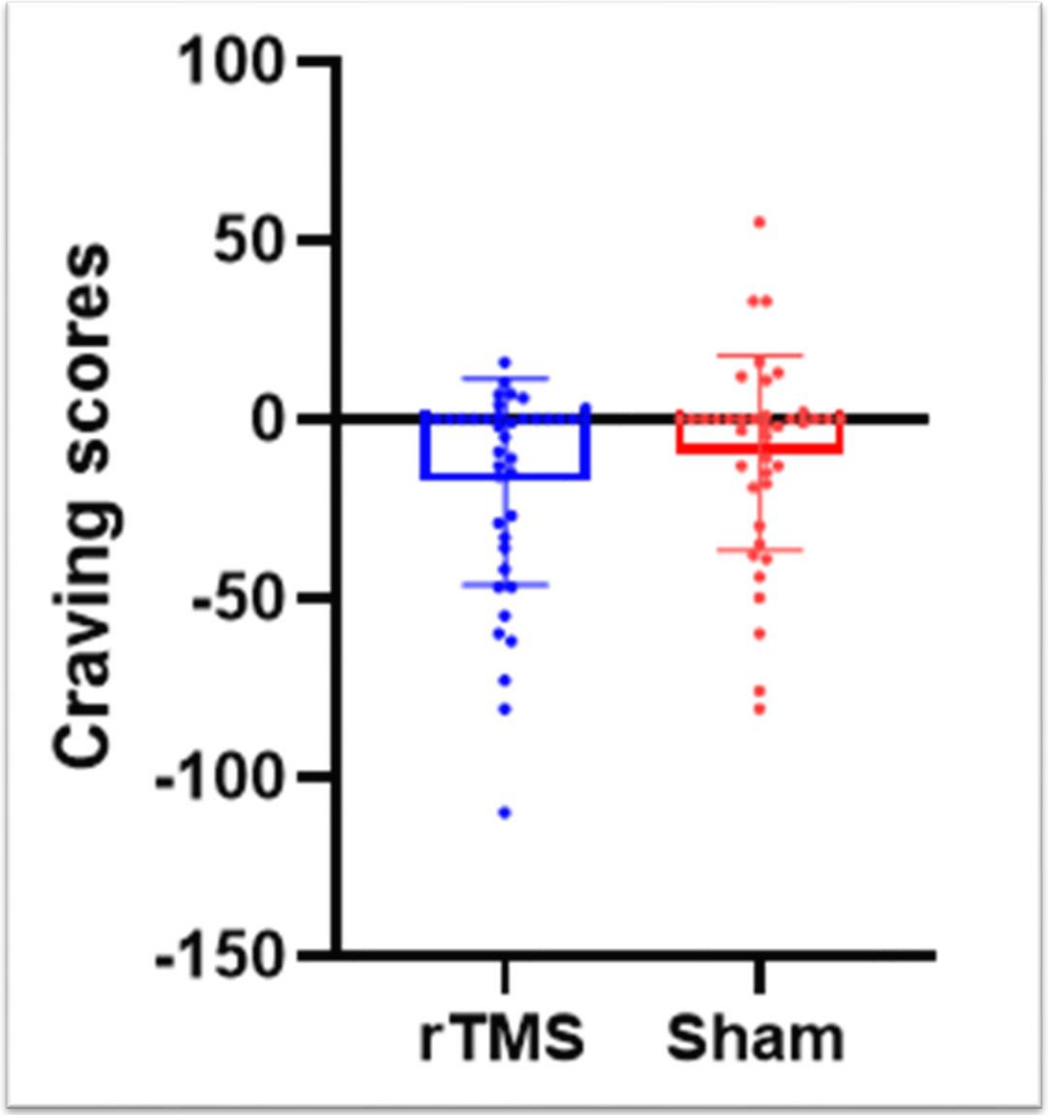
[a]Independent t-test comparing baseline difference between TMS-Sham and Sham-TMS groups.

[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.

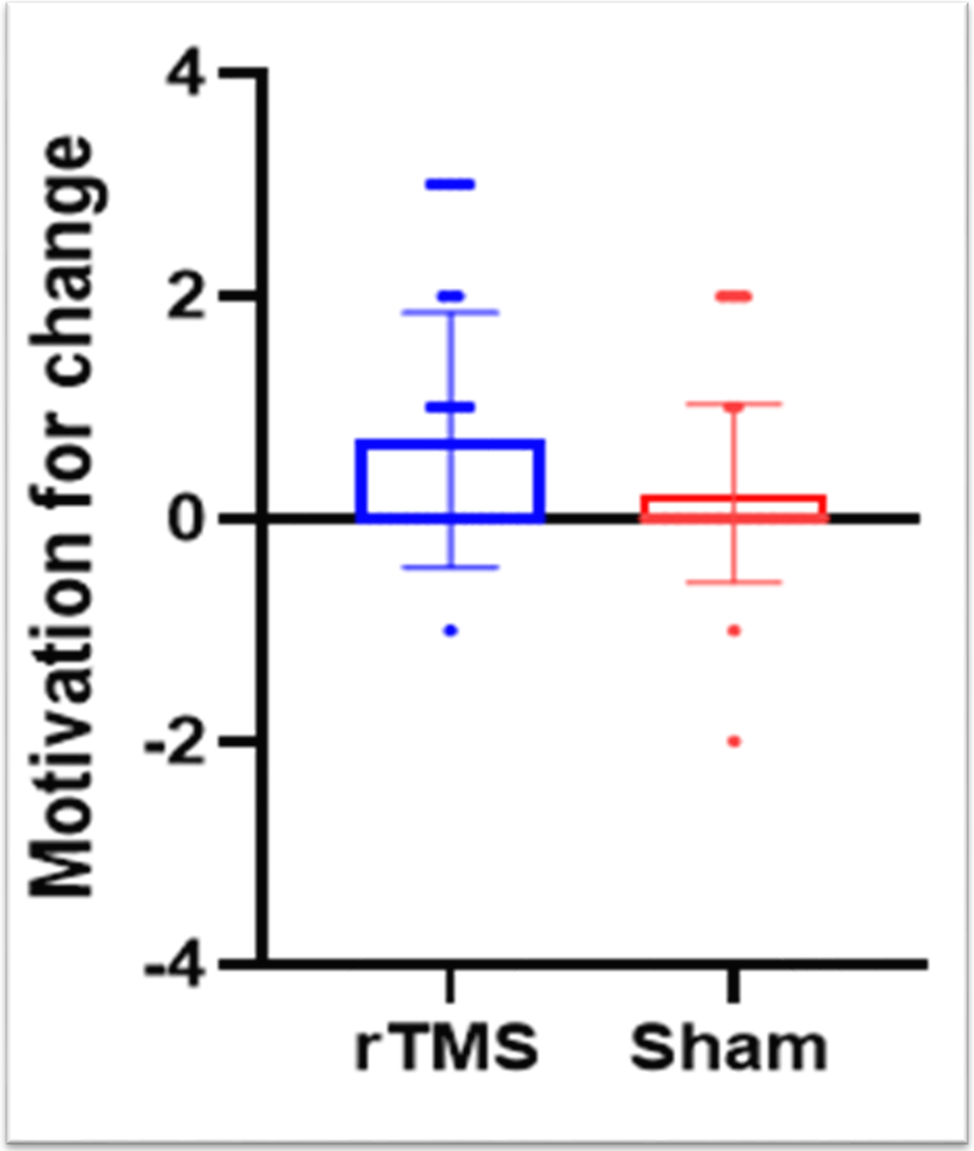
[d]Independent t-test comparing the mean changes between groups in total sample.

Results: Craving (primary outcome)



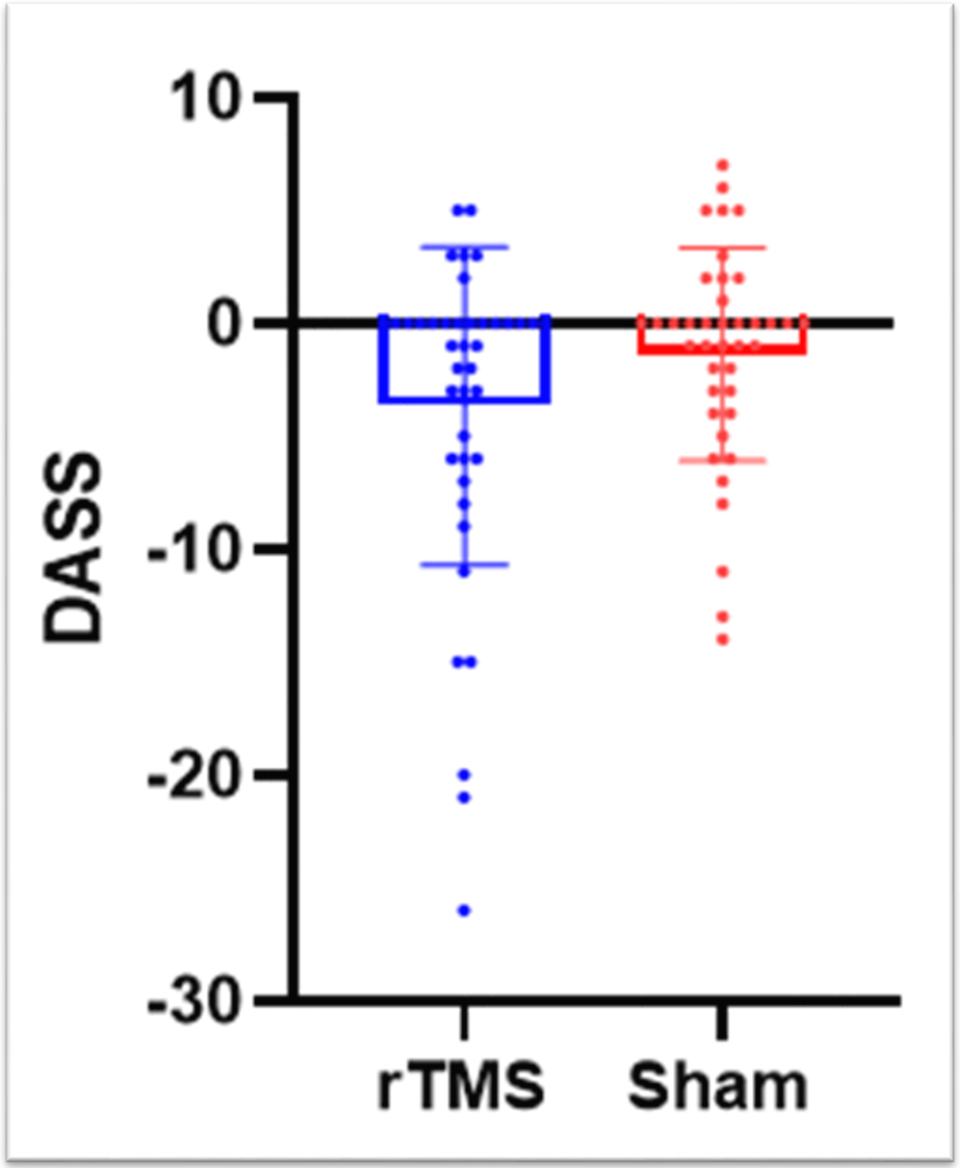
- Both real and sham rTMS significantly reduced **craving** in illicit drug users (within-group difference: $p<0.001$ vs. $p=0.035$) but only real rTMS is significant at $p<0.01$.

Results: Motivation to change



- 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).

Results: Anxiety and depression



Depression Anxiety Stress Scales (DASS)

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

Discussion

Summary of findings:

- High-frequency excitatory rTMS to the left DLPFC is better than sham rTMS treatment in reducing **craving** and improving **motivation for change**, as well as **mood** in drug abusers in Hong Kong.

- According to the calculated effect sizes of comparing real rTMS with sham rTMS, the effect size for **motivation for change** is interpreted to be **‘medium’** and the effect sizes for reducing **craving** as well as reducing **depression and anxiety** are interpreted to be **‘small to medium’.**

- However, its effects on the reduction of actual drug consumption remains unclear.

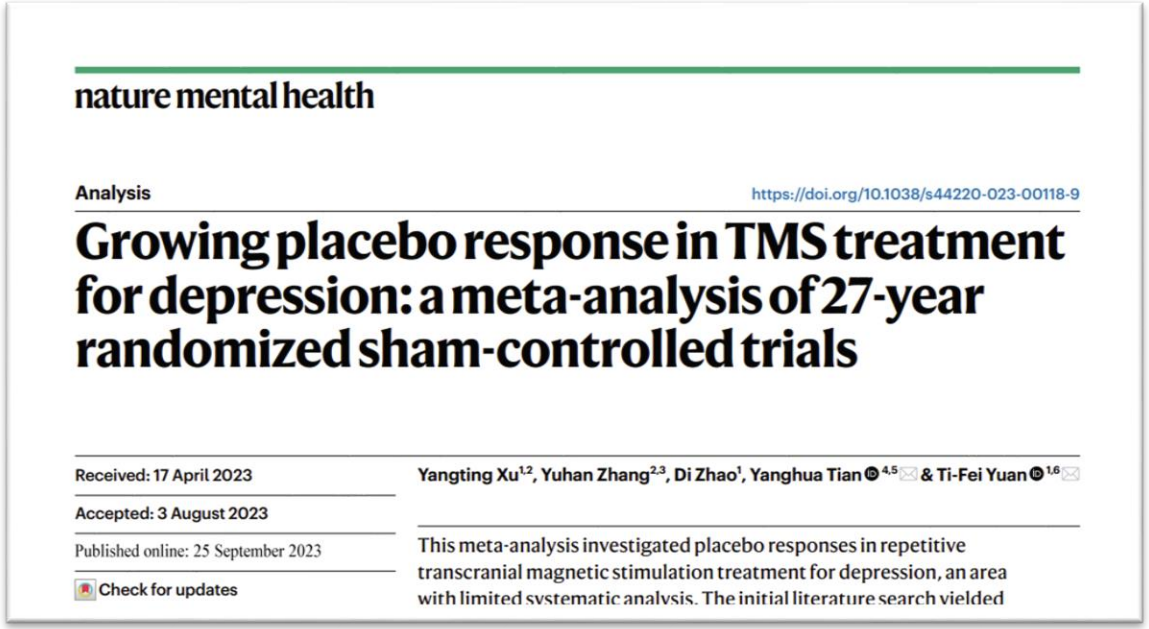
Discussion

Craving:

- High-frequency excitatory rTMS to the left DLPFC is better than sham rTMS treatment in reducing craving , however, we noted that **placebo effect** of sham rTMS treatment on craving and in drug abusers is also **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).

- 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).



nature mental health

Analysis

https://doi.org/10.1038/s44220-023-00118-9

Growing placebo response in TMS treatment for depression: a meta-analysis of 27-year randomized sham-controlled trials

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Check for updates

Yangting Xu[1,2], Yuhan Zhang[2,3], Di Zhao[1], Yanghua Tian[4,5] & Ti-Fei Yuan[1,6]

This meta-analysis investigated placebo responses in repetitive transcranial magnetic stimulation treatment for depression, an area with limited systematic analysis. The initial literature search yielded

Discussion

Mood:

- 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 TMS research findings in the **depression** population.

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%.

- 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**.

Conclusion

- It is recommended that **rTMS can be a useful therapeutic option to reduce craving and improving their motivation for change for illicit drug users in Hong Kong** if traditional pharmaceutical and psychosocial treatments were not successful.

- Future studies are required to investigate the underlying neural mechanism underlying the therapeutic effect in substance addiction in association with rTMS.

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Thank you for your attention
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