TESTING THE NEUROMODULATORY EFFECTS OF THETA BURST STIMULATION

ZHANG BINGBING

PhD

The Hong Kong Polytechnic University

2025

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Testing the neuromodulatory effects of theta burst stimulation

Zhang Bingbing

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

December 2024

CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

_ __(signed)

ZHANG Bingbing (Name of student)

ABSTRACT

Intermittent theta-burst stimulation (iTBS) is a non-invasive brain stimulation technique that enhances cortical excitability beyond the stimulation period. It has become increasingly favored as a therapeutic intervention for various neuropsychiatric disorders, such as depression, by targeting the left dorsolateral prefrontal cortex (DLPFC). However, several challenges need to be addressed, including variability in individual responses, uncertainty about the optimal stimulation intensity, and unclear effects of timing in priming protocols. Additionally, differences in head anatomy, such as scalp-to-cortex distance, may influence treatment outcomes. To tackle these issues, several experimental studies have been conducted to investigate the mechanisms of iTBS and the parameters that affect its efficacy, aiming to optimize iTBS protocols for future clinical use. Functional near-infrared spectroscopy (fNIRS) has been employed as a non-invasive neuroimaging tool to measure the effects of iTBS on brain function and aid in this investigation.

Study I: Pilot Study I (published)

Chapter 2 explores how stimulating different brain areas with iTBS affects associative learning. The results demonstrated that stimulating the DLPFC and lateral parietal cortex (LPC) produced distinct effects on brain activity patterns and associative learning, highlighting the specific roles these regions play in memory.

Study II: Pilot Study II (published)

Chapter 3 investigated the impact of varying iTBS intensity on the left DLPFC in healthy adults. Each of the twenty participants underwent iTBS sessions at 50%, 70%, and 100% of their individual resting motor threshold (RMT). The results indicated that 70% RMT is the most effective stimulation intensity and was therefore used in the main study.

Study III: Main study (under preparation)

Chapter 4 presents the main study of this thesis. This study examined how timing influences the neuromodulatory effects of priming theta burst stimulation (TBS) in individuals with depressive symptoms. The results indicated that a 10-minute interval between continuous TBS (cTBS) and iTBS optimally leveraged metaplasticity to alter hemodynamic responses. However, these neurophysiological changes did not translate into significant behavioral improvements. These findings highlight the potential of priming TBS protocols to enhance the efficacy of iTBS by optimizing stimulation timing and utilizing metaplasticity mechanisms.

Study IV: Computational study I (under preparation)

Chapter 5 explored the neurobiological sources of variability, specifically the scalp-to-cortex distance, that may influence transcranial magnetic stimulation (TMS) efficacy. The results indicated significant ethnic differences in scalp-to-cortex distance and associated electrical field (EF) strengths. The findings highlight the need to account for individual anatomical variability when designing stimulation protocols.

Study V: Computational study II (Published)

In Chapter 6, the relationship between TMS-induced EF characteristics and antidepressant effects was investigated in patients with treatment-resistant depression (TRD). The results showed that the normal component of the EF was significantly associated with symptom relief, providing insights into the neurobiological mechanisms underlying TMS efficacy in depression.

Overall, the studies presented in this thesis contribute to the optimization of iTBS protocols by addressing factors such as stimulation intensity, time interval, and individual anatomical morphology, with the goal of enhancing the therapeutic effects of TMS for future use.

LIST OF RESEARCH OUTPUT DURING THIS CANDIDATURE

A. Journal publications during the PhD study period (arising from this thesis)

1. **Zhang, B. B. B.**, Kan, R. L. D., Woo, T.-F., Chan, C. C. H., Fong, K. N. K., & Kranz, G. S. (2021). Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study. Brain Stimulation, 14(4), 924-926. https://doi.org/10.1016/j.brs.2021.05.017

2. **Zhang, B. B. B**., Kan, R. L. D., Giron, C. G., Lin, T. T. Z., Yau, S.-Y., & Kranz, G. S. (2022). Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study. Frontiers in Psychiatry, 13. https://doi.org/10.3389/fpsyt.2022.1049130

3. **Zhang, B. B. B.**, Stöhrmann, P., Godbersen, G. M., Unterholzner, J., Kasper, S., Kranz, G. S., & Lanzenberger, R. (2022). Normal component of TMS-induced electric field is correlated with depressive symptom relief in treatment-resistant depression. Brain Stimulation, 15(5), 1318-1320. https://doi.org/10.1016/j.brs.2022.09.006

4. **Zhang, B.B.B.**, Priming theta-burst stimulation: the importance of the right timing (Manuscript under preparation)

5. **Zhang, B.B.B.**, Lin, T.T.Z., Kranz, G.S. Rethinking intensity: Repetitive

transcranial magnetic stimulation across ethnic populations (Manuscript under preparation)

B. Conference publications during the PhD study period (arising from this thesis)

1. **Zhang, B. B. B.**, Stöhrmann, P., Godbersen, G., Unterholzner, J., Kasper, S., Kranz, G., & Lanzenberger, R. (2023). Which component of TMS-induced electric field contributes to the antidepressant effects? Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 16(1), 389. https://doi.org/10.1016/j.brs.2023.01.780

2. **Zhang B.B.B.**, Liu L.T., Kan R.L.D., Xia A.W.L., Jin M.X., Qin P.P., Kranz G., Impact of Time Interval on Theta Burst Stimulation Priming Effects in Healthy and Subclinical Depressed Individuals. Brain Stimulation. Accepted.

C. Conference presentations during the PhD study period (arising from this thesis)

1. **Zhang B.B.B.**, Kan R.L.D., Woo T.F., Chan C.C.H., Fong K.N.K., Kranz G.S. Boosting memory performance with brain stimulation? *12th Pan-Pacific Conference on Rehabilitation*. 27-28 November 2021, Hong Kong SAR, China. [Poster Presentation]

2. **Zhang B.B.B.**, Kan R.L.D., Giron C.G., Lin T.T.Z., Kranz G.S. The effects of iTBS on prefrontal hemodynamic response and executive function are not linear to the stimulation intensity: A TMS-fNIRS experiment. *The 33rd Hybrid World Congress of Neuropsychopharmacology*, 9-13 June 2022, Taiwan, China. [e-Oral Presentation]

3. **Zhang B.B.B.**, Kan R.L.D., Giron C.G., Lin T.T.Z., Kranz G.S. Dose-response relationship of iTBS for prefrontal activation and executive function: A TMS-fNIRS study. *Annual meeting of the Society for Functional Near-infrared Spectroscopy.* 9-12 October 2022, Boston, Massachusetts, USA. [e-Oral Presentation]

4. **Zhang B.B.B.**, Stöhrmann P, Godbersen G, Unterholzner J, Kasper S, Kranz GS, Lanzenberger R. Which component of TMS-induced electric field contributes to the antidepressant effects? *5th Brain Stimulation conference*. 18-22 February 2023, Lisbon, Portugal. [Poster Presentation]

5. **Zhang B.B.B.**, Kan R.L.D., Jin M.X., Giron C.G., Lin T.T.Z., Kranz G.S. Hypoactivity of prefrontal cortex is a trait marker of depression: an fNIRS study. *The 13th Pan-Pacific Conference on Rehabilitation*. 23-24 November 2023, Chiang Mai, Thailand. [Oral Presentation]

6. **ZHANG B.B.B.**, Liu L.T., Kan R.L.D., Jin M.X., Xia A.W.L., Qin P.P., Fong K.N.K., Kranz G.S. Priming the pump? Investigating the effects of priming theta burst stimulation in healthy and subclinically depressed groups. *The 6th Neurotechnology Innovation Forum & Founding Conference of the Basic and Translational Neuromodulation Branch of Chinese Neuroscience Society*. 26-28 April 2024, Shanghai, China. [Oral Presentation]

7. **ZHANG B.B.B.**, Liu L.T., Kan R.L.D., Jin M.X., Xia A.W.L., Qin P.P., Fong K.N.K., Kranz G.S. Investigating the effects of priming theta burst stimulation in healthy and subclinical depressed populations. *The 35th CINP World Congress of Neuropsychopharmacology*. 23-26 May 2024, Tokyo, Japan. [Poster Presentation]

8. **ZHANG B.B.B.**, Liu L.T., Kan R.L.D., Jin M.X., Xia A.W.L., Qin P.P., Fong K.N.K., Kranz G.S. Exploring brain state-dependent stimulation: time intervals' effects on priming stimulation response in subclinical depression. *1st Meeting of Neuromodulation Society in China Great Bay Area*. 7-8 June 2024, Zhuhai, China. [Oral Presentation]

9. **Zhang B.B.B.**, Bai Z.F., Kranz S.G., Zhang J.J.Q., Interindividual Variability

in TMS-Induced Electric Fields: A Computational Study of Different Cortical Motor Areas. *The Neurotechnology Innovation Forum 2024*. 12-13 October 2024, Shanghai, China. [Oral Presentation]

10. **Zhang B.B.B.**, Liu L.T., Kan R.L.D., Xia A.W.L., Jin M.X., Qin P.P., Kranz G.S. Impact of Time Interval on Theta Burst Stimulation Priming Effects in Healthy and Subclinical Depressed Individuals. *6th Brain Stimulation Conference*. 23-26 February 2025. Kobe, Japan. [Poster Presentation]

D. Journal publications during the PhD study period (not arising from this thesis):

1. Giron, C. G., Lin, T. T. Z., Kan, R. L. D., **Zhang, B. B. B.**, Yau, S. Y., & Kranz, G. S. (2022). Non-Invasive Brain Stimulation Effects on Biomarkers of Tryptophan Metabolism: A Scoping Review and Meta-Analysis. International journal of molecular sciences, 23(17). https://doi.org/10.3390/ijms23179692

2. Giron, C. G., **Zhang, B. B. B.**, Baeken, C., & Kranz, G. S. (2022). Prognostic potential of the cortisol response to therapeutic rTMS. Psychiatry Res, 317, 114859. https://doi.org/10.1016/j.psychres.2022.114859

3. Jin, M. X., Qin, P. P., Xia, A. W. L., Kan, R. L. D., **Zhang, B. B. B.**, Tang, A. H. P., Li, A. S. M., Lin, T. T. Z., Giron, C. G., Pei, J. J., & Kranz, G. S. (2024). Neurophysiological and neuroimaging markers of repetitive transcranial

magnetic stimulation treatment response in major depressive disorder: A systematic review and meta-analysis of predictive modeling studies. Neurosci Biobehav Rev, 162, 105695. https://doi.org/10.1016/j.neubiorev.2024.105695

4. Kan, R. L. D., Lin, T. T. Z., **Zhang, B. B. B.**, Giron, C. G., Jin, M., Qin, P. P. I., Xia, A. W. L., Chan, S. K. W., Chau, B. K. H., & Kranz, G. S. (2023). Moderators of stimulation-induced neural excitability in the left DLPFC: A concurrent iTBS/fNIRS case study. Brain Stimul, 16(5), 1445-1447. https://doi.org/10.1016/j.brs.2023.09.015

5. Kan, R. L. D., Mak, A. D. P., Chan, S. K. W., **Zhang, B. B. B.**, Fong, K. N. K., & Kranz, G. S. (2022). Protocol for a prospective open-label clinical trial to investigate the utility of concurrent TBS/fNIRS for antidepressant treatment optimisation. BMJ Open, 12(2), e053896. https://doi.org/10.1136/bmjopen-2021-053896

6. Kan, R. L. D., Padberg, F., Giron, C. G., Lin, T. T. Z., **Zhang, B. B. B.**, Brunoni, A. R., & Kranz, G. S. (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. https://doi.org/10.1016/s2215-0366(23)00026-3

7. Kan, R. L. D., **Zhang, B. B. B.**, Lin, T. T. Z., Tang, A. H. P., Xia, A. W. L., Qin, P. P. I., Jin, M., Fong, K. N. K., Becker, B., Yau, S. Y., & Kranz, G. S. (2024). Sex differences in brain excitability revealed by concurrent iTBS/fNIRS. Asian J Psychiatr, 96, 104043. https://doi.org/10.1016/j.ajp.2024.104043

8. Kan, R. L. D., **Zhang, B. B. B.**, Zhang, J. J. Q., & Kranz, G. S. (2020). Non-invasive brain stimulation for posttraumatic stress disorder: a systematic review and meta-analysis. Transl Psychiatry, 10(1), 168. https://doi.org/10.1038/s41398-020-0851-5

9. Kranz, G. S., **Zhang, B. B. B.**, Handschuh, P., Ritter, V., & Lanzenberger, R. (2020). Gender-affirming hormone treatment - A unique approach to study the effects of sex hormones on brain structure and function. Cortex, 129, 68-79. https://doi.org/10.1016/j.cortex.2020.04.005

10. Nam, C., **Zhang, B.**, Chow, T., Ye, F., Huang, Y., Guo, Z., Li, W., Rong, W., Hu, X., & Poon, W. (2021). Home-based self-help telerehabilitation of the upper limb assisted by an electromyography-driven wrist/hand exoneuromusculoskeleton after stroke. Journal of NeuroEngineering and Rehabilitation, 18(1), 137. https://doi.org/10.1186/s12984-021-00930-3

11. Qin, P. P., Jin, M., Xia, A. W., Li, A. S., Lin, T. T., Liu, Y., Kan, R. L., **Zhang, B. B.**, & Kranz, G. S. (2024). The effectiveness and safety of low-intensity transcranial ultrasound stimulation: A systematic review of human and animal studies. Neurosci Biobehav Rev, 156, 105501. https://doi.org/10.1016/j.neubiorev.2023.105501

12. Xia, A. W. L., Jin, M., Qin, P. P. I., Kan, R. L. D., **Zhang, B. B. B.**, Giron, C. G., Lin, T. T. Z., Li, A. S. M., & Kranz, G. S. (2024). Instantaneous effects of prefrontal transcranial magnetic stimulation on brain oxygenation: A systematic review. NeuroImage, 293, 120618. https://doi.org/10.1016/j.neuroimage.2024.120618

13. Zhang, J. J., **Zhang, B. B.** (*co-first authorship*), Bai, Z., & Fong, K. N. K. A comparative study of simulated electric fields of transcranial magnetic stimulation targeting different cortical motor regions. Bioelectromagnetics, n/a(n/a). https://doi.org/https://doi.org/10.1002/bem.22523

E. Awards to the student during the PhD study period:

1. Ernst Mach Grant, Eurasis-Pacific Uninet (award by OeAD – Austria's Agency for Education and Internationalisation). May 2021

2. Champion of the FHSS 3MT® (award by Faculty of Health and Social Science,

The Hong Kong Polytechnic University). June 2023

3. People's Choice of the FHSS 3MT® (award by Faculty of Health and Social Science, The Hong Kong Polytechnic University). June 2023

4. PolyU Outstanding Work by Students (award by The Hong Kong Polytechnic University). November 2023

5. CNSNM2024 Award for Excellence in Neuromodulation (award by The Basic and Translational Neuromodulation Branch of the Chinese Society of Neuroscience). April 2024

6. Student Encouragement Award (award by CINP 2024 conference committee). May 2024

7. Travel award of 1st Meeting of Neuromodulation Society in Great Bay Area (award by Great Bay Area Neuromodulation Society). June 2024

8. NTIF Award for Excellence in Neuromodulation (award by The Basic and Translational Neuromodulation Branch of the Chinese Society of Neuroscience). October 2024

ACKNOWLEDGEMENTS

I would like to express my deepest gratitude to my PhD supervisor, Dr. Georg S. Kranz, for his unwavering guidance and invaluable support throughout my PhD journey. His mentorship was instrumental in shaping my development, both professionally and personally, teaching me essential hard and soft skills. Dr. Kranz's dedication, integrity, and exemplary research practices have been a constant source of inspiration. This thesis would not have been possible without his assistance and his warm encouragement, which consistently bolstered my spirits during challenging times. I also extend my sincere thanks to my co-supervisor, Prof. Kenneth Fong, for his continuous guidance and insightful contributions, which greatly enriched my research.

It has been a great pleasure to work with a supportive and nice team under Dr. Kranz's leadership. I am deeply indebted to Rebecca Kan and Teng Liu for their invaluable assistance with data collection. My sincere appreciation also goes to the members of Dr. Kranz's research team: Tianze Lin, Weili Xia, Minxia Jin, Ping Qin, Alvin Tang, Xiao Wang, Wanda Chau, Nancy Shi, and Vera Lam, for their collaborative support.

I gratefully acknowledge the University Research Facility in Behavioral and Systems Neuroscience for providing the essential facilities for my experiments. I would like to especially thank Dr. Celia Dong and Dr. Tommy Lam for their prompt and invaluable technical assistance during the experiments. My sincere thanks also extend to all the participants who generously contributed to this research.

Finally, my deepest gratitude goes to my parents, family, and my boyfriend, Jack, for their unconditional love and unwavering support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

iTBS: Intermittent theta burst stimulation

DLPFC: Dorsolateral prefrontal cortex

fNIRS: Functional neal-infrared spectroscopy

LPC: Lateral parietal cortex

RMT: Resting motor threshold

TBS: Theta burst stimulation

cTBS: Continuous theta burst stimulation

VFT: Verbal fluency task

TMS: Transcranial magnetic stimulation

TRD: Treatment-resistant depression

MDD: Major depressive disorder

SSRIs: Selective serotonin reuptake inhibitors

TCAs: Tricyclic antidepressants

SNRIs: Serotonin-norepinephrine reuptake inhibitors

CBT: Cognitive-behavioral therapy

sgACC: Subgenual cingulate cortex

CNN: Cognitive control network

Rs-FC: Resting-state functional connectivity

StD: Subthreshold depression

rTMS: Repetitive transcranial magnetic stimulation

tDCS: Transcranial direct current stimulation

DBS: Deep brain stimulation

ECT: Electroconvulsive therapy

M1: Primary motor cortex

MEP: Motor evoked potential

EMG: Electromyography

LTD: Long-term depression

LTP: Long-term potentiation

MEPs: Motor evoked potentials

RCT: Randomized controlled trial

BCM: Bienenstock-Cooper-Munro

HbO: Oxygenated hemoglobin/ oxyhemoglobin

HbR: Deoxygenated hemoglobin

fMRI: Functional magnetic resonance imaging

DPF: Differential pathlength factor

BOLD: Blood-oxygen-level-dependent

HF: High-frequency

E1: First encoding period

R1: First recall period

R2: Secon recall period

New-E2: New encoding period

New-R3: New recall period

PTB-3: PsychToolbox-3

MNI: Montreal Neurological Institute

AMT: Active motor threshold

FDI: First dorsal interosseous muscle

BA: Brodmann area

OD: Optical density

ANOVA: One-way repeated measures analysis of variance

LSD: Least significant difference

EEG: Electroencephalogram

GABA: Gamma-aminobutyric acid

EPSP: Excitatory postsynaptic potential

IPSP: Inhibitory postsynaptic potential

NMDA: N-methyl-D-aspartate

ERA: Emotion recognition accuracy

BIA/BAS: Behavioral inhibition and activation systems

PHQ-9: Patient Health Questionnaire-9

I-PANAS-SF: International Positive and Negative Affect Schedule Short Form

ROI: Region of interest

BAS-RR: BAS reward responsiveness

PFC: Prefrontal cortex

EF: Electric field/Electric fields

PET: Positron emission tomography

FEM: Finite element method

GLMM: Generalized liner mixed model

Chapter 1 Introduction

1.1 Overview of depression

1.1.1 Major depressive disorder

Major depressive disorder (MDD) presents a significant global health challenge, profoundly impacting psychosocial functioning and diminishing the quality of life for millions worldwide. [1]. According to the World Health Organization, depression affects around 350 million people globally, representing approximately 4.4% of the total disease burden [2]. This pervasive disorder manifests in a range of debilitating symptoms, including persistent sadness, diminished interest or pleasure in previously enjoyed activities, profound fatigue, and pervasive feelings of worthlessness or guilt [1, 3]. The impact of MDD extends beyond these core emotional symptoms to encompass cognitive deficits, affecting attention, memory, decision-making, and executive functions [4, 5]. This cognitive impairment further compounds the challenges faced by individuals struggling with depression, hindering their ability to navigate daily life and contributing to the overall burden of the disorder.

Current first-line treatments for moderate to severe depression primarily involve pharmacological interventions, such as tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [6]. In addition, psychotherapy, especially cognitive-behavioral therapy (CBT), serves as an essential complementary option, providing strategies to manage depressive symptoms and prevent relapse [7]. Despite the availability of these treatments, a substantial proportion of individuals with MDD do not achieve remission with initial

antidepressant therapy, with estimates suggesting only about one-third experience symptom relief [8]. Furthermore, a significant percentage (around 34%) of patients [9] are classified as treatment-resistant, facing persistent and debilitating symptoms despite multiple treatment attempts [10, 11]. The limitations of current treatments are further compounded by the potential for adverse side effects associated with antidepressant medications, ranging from mild discomfort to potentially life-threatening reactions and possible long-term neurotoxic effects [12]. This combination of limited treatment efficacy and the risk of adverse reactions underscores the urgent need for the development and exploration of alternative therapeutic approaches.

1.1.2 Neural network dysregulation in depression

Emerging research offers a more nuanced understanding of MDD, conceptualizing it as a network disorder characterized by disruptions in the coordinated activity of various brain regions. These regions include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, medial prefrontal cortex, subgenual cingulate cortex (sgACC), thalamus, insula, hippocampus, and hypothalamus [13-16]. Among these interconnected areas, the left DLPFC and the sgACC have emerged as key players in the neurobiology of depression, exhibiting consistent abnormalities in individuals with MDD [17] (Figure 1.1). Studies have revealed a pattern of overactivity in the sgACC, with reductions in its activity correlating with positive responses to antidepressant treatment [15, 18]. Conversely, the left DLPFC often displays reduced activity in individuals experiencing depression, and enhancing its activity has been associated

with improvements in depressive symptoms [17, 19, 20]. This contrasting pattern of activity between the sgACC and the left DLPFC highlights the complex interplay of brain regions involved in the regulation of mood and cognition and provides a crucial focus for the development of targeted interventions aimed at restoring healthy brain function and alleviating the debilitating effects of MDD.

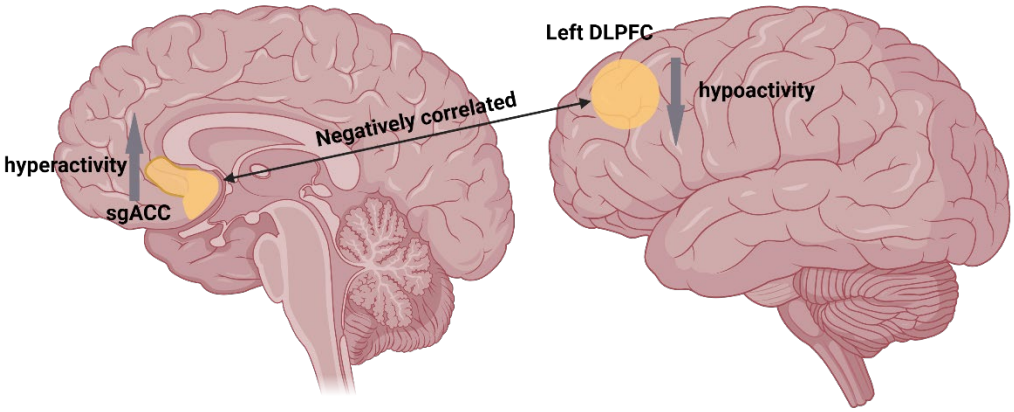

Figure 1. 1 Neural network dysregulation in the left DLPFC and sgACC in MDD. Created in https://BioRender.com.

Furthermore, the cognitive impairments associated with depression have been linked to structural and functional abnormalities within the cognitive control network (CCN) [21, 22]. The CCN, comprising frontoparietal brain areas, plays a vital role in the top-down regulation of attention and working memory [21]. Research in MDD has shown dysregulation of resting-state functional connectivity (rs-FC) within the CCN, with most studies reporting decreased connectivity. Importantly, the level of activation within the frontoparietal network appears to be correlated with clinical outcomes and can predict treatment efficacy [23]. For example, activation of this network during cognitive tasks has been shown to predict remission following antidepressant treatment [24], whereas reduced connectivity within the CCN is linked to lower remission rates and persistent depressive symptoms [25]. These findings underscore the CCN's role in the pathophysiology of depression and highlight its potential as a target for therapeutic interventions.

1.1.3 Subclinical depression

Subclinical depression (ScD) is characterized by clinically relevant depressive symptoms but fall short of meeting the diagnostic criteria for MDD [26]. Although ScD symptoms are typically less severe than those of MDD, its higher prevalence in the general population contributes to a considerable health service burden [27-29]. Moreover, individuals with ScD face a markedly higher risk of progressing to a first-lifetime episode of MDD [30], underscoring the importance of early identification and intervention. Neuroimaging studies have revealed alterations in brain connectivity in

individuals with ScD, particularly within the CCN. These alterations manifest as decreased rs-FC between the DLPFC and brain areas related to self-awareness and social cognition (temporoparietal junction and precuneus), as well as salience detection (insula). Furthermore, the connectivity strength between the DLPFC and the left temporoparietal junction has been found to correlate with the severity of depressive symptoms in ScD. [31]. This highlights the potential for early intervention in ScD to prevent the development of MDD and improve overall well-being.

1.1.4 Brain stimulation for depression treatment

The findings on neural network dysregulation in both MDD and ScD underscore the potential of brain stimulation techniques to offer promising, targeted interventions by directly modulating the activity of specific brain regions implicated in these conditions. Several brain stimulation methods have been explored as treatments for depression, such as repetitive transcranial magnetic stimulation (rTMS), [20, 32, 33], transcranial direct current stimulation (tDCS) [34, 35], deep brain stimulation (DBS) [18, 36], and electroconvulsive therapy (ECT) [37, 38]. Each of these techniques offers a unique approach to modulating brain activity, but they differ in their invasiveness, mechanisms of action, and associated side effects. Among these modalities, rTMS has garnered significant attention from both researchers and clinicians due to a combination of factors that contribute to its appeal. These include its demonstrated effectiveness in alleviating depressive symptoms, its non-invasive nature (not requiring surgery or implantation of devices), relatively low levels of discomfort during treatment, and ease

of administration in a clinical setting [39]. This combination of efficacy, safety, and practicality enhances both patient comfort and the overall usability of rTMS as a treatment option for depression.

In summary, MDD is a global health concern, and current treatments are often insufficient. Research points to neural network dysregulation, particularly in the DLPFC, sgACC, and CCN. ScD also shows altered connectivity, highlighting the need for early intervention. Brain stimulation, especially rTMS, offers a promising non-invasive approach, with the left DLPFC as a key target for modulating brain activity and improving depressive symptoms.

1.2 Neuroplasticity

The human brain possesses the remarkable capacity to reshape its structure, function, and connections in response to internal and external stimuli across the lifespan [40]. This process, known as neuroplasticity, plays a vital role in forming neural circuits and facilitating processes such as learning, adaptation, and recovery [40]. It is driven by activity-dependent modifications in the strength and efficiency of synaptic connections, allowing the brain to adapt dynamically to various experiences and challenges [41]. Neuroplasticity occurs at various levels, from molecular and cellular to systemic and behavioral levels. This remarkable adaptability highlights the brain's capacity to change structurally and functionally in response to stimulation and experience. Research evidence shows that impaired neuroplasticity can hinder this ability,

potentially contributing to the development of neuropsychiatric disorders [42-44]. Therefore, understanding the mechanisms underlying physiologically relevant synaptic plasticity is very important for advancing treatments and interventions for neurological and psychiatric conditions. Non-invasive brain stimulation has become a promising and safe technique to study neuroplasticity in humans, offering valuable insights into how the brain adapts and functions under different conditions.

1.3 Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) was first introduced in 1985 by Anthony T. Barker and colleagues as a non-invasive method for stimulating the brain [45]. TMS operates on the principle of electromagnetic induction, a phenomenon first reported by Michael Faraday [46]. In TMS, a brief electrical current is pulsed through a coil of wire, resulting in the generation of a rapidly changing magnetic field. Due to the low resistance of the skull to magnetic fields, the magnetic field passes through the skull with low attenuation. Simultaneously, an electrical field (EF) is induced perpendicular to the magnetic field within the brain, which further generates electrical currents in the conductive brain tissue. These currents influence the transmembrane potential of neurons, and when sufficient in magnitude, they can depolarize cortical neurons and generate action potentials [47, 48].

The distribution and strength of the EF induced by TMS are critically influenced by head morphology. Factors such as skull thickness, cortical folding, and the distance

between the coil and the cortical surface significantly affect the EF's magnitude and focality [49, 50]. For instance, thicker skulls or greater coil-to-cortex distances tend to attenuate the EF, while cortical folding can alter its local distribution. In addition to head morphology, TMS parameters—such as coil geometry, orientation, pulse waveform, and stimulation intensity—play a direct role in shaping the induced EF. For example, figure-of-eight coils produce more focal EFs compared to circular coils, and the orientation of the coil relative to the underlying cortical gyri can modulate the efficiency of neuronal activation [50,51].

The EF generated by TMS can be simulated using computational models that incorporate detailed head anatomy, including the scalp, skull, cerebrospinal fluid (CSF), and brain tissues. These models typically employ numerical methods such as finite element methods (FEM) to solve Maxwell's equations and predict the spatial distribution of the EF within the brain [52, 53]. By combining these computational approaches with experimental validation, researchers can optimize TMS protocols to achieve targeted and effective neuromodulation.

TMS was initially created and utilized as a diagnostic method for examining brain function. A notable example is its use on the primary motor cortex (M1), where a single TMS pulse delivered to M1 can produce a measurable muscle response, called a motor evoked potential (MEP), in the hand muscles of the contralateral side, whether relaxed or active [54] (Figure 1.2). The characteristics of MEP, such as amplitude and latency,

provide valuable insights into the excitability of the motor cortex. In addition, MEP serves as a well-established parameter for quantifying cortical excitability and determining the appropriate TMS intensity for various experimental and clinical applications.

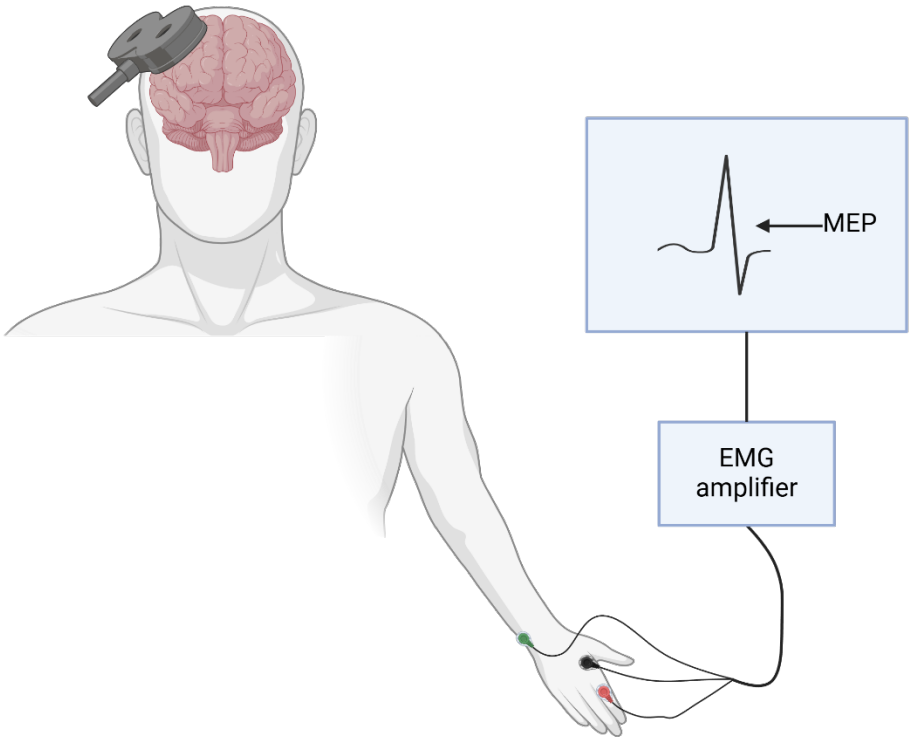

Figure 1. 2 A schematic representation of TMS. The electric current flowing through the TMS coil produces a perpendicular magnetic field perpendicular to the coil, which penetrates the scalp and induces a secondary electric field in the cortex beneath. This electric field depolarizes cortical neurons in the M1, triggering a descending signal along the corticospinal tract and eliciting a MEP in the target muscle. The MEP is recorded using electromyography (EMG). Created in https://BioRender.com.

1.3.1 Repetitive transcranial magnetic stimulation

Beyond single-pulse applications, nowadays, TMS is more widely used in repetitive ways, known as rTMS. rTMS involves delivering trains of magnetic pulses at various frequencies and durations [55]. The effects of rTMS on cortical excitability depend on the frequency, intensity, and duration of the stimulation. In general, low-frequency rTMS (≤1 Hz) produces an inhibitory effect [56] similar to long-term depression (LTD) reported in basic research with electrical stimulation. Conversely, high-frequency rTMS (⩾5 Hz) produces an excitatory effect, resembling long-term potentiation (LTP) seen in similar animal experiments, and is thus described as having LTP-like effects [57-59].

1.3.2 Theta burst stimulation

A more recent form of patterned rTMS is theta burst stimulation (TBS) which was first tested in humans by Huang et al in 2005 [60]. Its popularity stems from the ability to induce lasting changes in neural plasticity with relatively brief stimulation periods and lower intensities compared to traditional rTMS protocols. This efficiency is rooted in the specific stimulation pattern of TBS, which draws inspiration from the natural firing patterns of hippocampal neurons [61]. TBS utilizes short bursts of three pulses delivered at a high frequency of 50 Hz, mirroring the complex-spike discharges of pyramidal neurons in the hippocampus [62]. These bursts are then repeated at a slower frequency of 5 Hz, reflecting the theta rhythm (around 6 Hz) that governs hippocampal excitability [63]. This design is based on animal studies showing that while high-

frequency stimulation alone can induce LTP in rats, the effect is limited. However, when combined with a theta rhythm, these high-frequency bursts produce robust and reliable LTP in the CA1 region of the hippocampus [64, 65].

TBS can be administered in two distinct modes: intermittent TBS (iTBS) and continuous TBS (cTBS) [60, 66]. These two modes produce opposing effects on cortical excitability. Both iTBS and cTBS utilize a specific burst pattern: three pulses at 50 Hz (with a 20 ms inter-pulse interval) repeated at 5 Hz (with a 200 ms inter-burst interval). Intermittent TBS, as demonstrated by Huang et al. (2005), typically increases cortical excitability, similar to the effects of high-frequency rTMS [60]. Specifically, a protocol consisting of 600 pulses of iTBS, delivered in 2-second bursts (5 Hz for 2 seconds) followed by 8-second periods of rest, has been shown to reliably induce LTP-like plasticity in the motor cortex. This protocol effectively enhances synaptic strength and facilitates neuronal communication. In contrast, cTBS delivers the same burst pattern but without the intermittent rest periods. This continuous stimulation typically decreases cortical excitability, analogous to the effects of low-frequency rTMS, and is thought to induce LTD-like plasticity [60]. The flexibility offered by these two modes of TBS allows researchers to selectively upregulate or downregulate cortical activity, providing a valuable tool for exploring the complexities of brain function and plasticity.

Since its development, iTBS has become a widely used technique in both experimental research and the treatment of neuropsychiatric disorders [20, 66-70]. In their seminal

2005 study, Huang et al. demonstrated that a single 3-minute session of iTBS (consisting of 3 pulses per burst, 10 bursts per train, and 20 trains) applied to the M1 could increase motor evoked potentials (MEPs) for up to 15 minutes, indicating a significant increase in cortical excitability [60]. Since its first adaptation in humans, a large number of studies have used this technique, and it is now generally accepted that iTBS increases excitability up to about 30 mins while cTBS decreases up to about 60 mins [71].

Beyond its effects on the motor cortex, iTBS has shown promise in modulating a range of cognitive functions. Studies have examined its capacity to improve working memory, a cognitive system vital for holding and processing information temporarily, which is necessary for complex activities such as decision-making and reasoning [67, 72]. Furthermore, research suggests that iTBS may improve executive functions, a set of higher-order cognitive processes that include planning, inhibition, and cognitive flexibility [73, 74]. Additionally, preliminary findings also indicate that iTBS could influence emotion regulation, potentially offering new avenues for treating mood disorders [75]. These diverse cognitive effects highlight the potential of iTBS to target a broad spectrum of neuropsychiatric conditions.

The therapeutic potential of iTBS has been most notably recognized in the field of depression treatment [76, 77]. In 2018, iTBS received clearance from U.S. Food and Drug Administration for the treatment of MDD [78]. This approval was based on a large

randomized controlled trial (RCT) published in 2018 by Blumberger et al, which demonstrated the efficacy of iTBS in alleviating depressive symptoms [79]. As time goes by, there is accumulating evidence demonstrating the efficacy of iTBS not only in alleviating depressive symptoms but also in improving cognitive function [77]. Beyond depression, research is ongoing to explore the potential benefits of iTBS for other conditions, including stroke rehabilitation [70, 80], aphasia [81, 82], and even neuropathic pain [83, 84]. While further research is required to better understand its mechanisms of action and optimize treatment protocols, iTBS holds considerable promise as a versatile and effective tool for modulating brain activity and treating a variety of neurological and psychiatric disorders.

While iTBS has demonstrated considerable promise in various applications, recent studies have revealed substantial interindividual variability in response to the treatment [85, 86], posing a challenge to its widespread clinical and experimental use. This variability limits the predictability and reliability of iTBS effects, making it difficult to tailor treatment protocols to individual patients. Several factors are thought to contribute to this variation, including stimulation intensity [87], the individual's brain state at the time of stimulation [88], and head morphology [89].

For example, baseline MEP amplitude has been identified as a key factor influencing iTBS response. Studies have reported an inverse relationship between baseline MEP amplitude and the subsequent change in MEP amplitude following iTBS, with

individuals exhibiting higher baseline MEPs experiencing smaller increases or even decreases in MEP amplitude after iTBS [90]. This suggests that individuals with already high levels of motor cortex excitability may have less capacity for further enhancement through iTBS.

Furthermore, research investigating the influence of stimulation intensity has revealed that subthreshold iTBS, can be more effective than suprathreshold stimulation [87, 91]. This counterintuitive finding highlights the complex, non-linear relationship between stimulation intensity and cortical excitability [87].

Adding another layer of complexity, computational modeling studies have demonstrated that individual differences in head morphology can significantly impact the dose and location of stimulation, even when the same intensity, same coil location and coil direction is applied externally [92-94]. These morphological variations can lead to substantial differences in the induced EF distribution within the brain, potentially explaining some of the observed interindividual variability in iTBS response [93, 94]. Understanding and accounting for these diverse factors is crucial for optimizing iTBS protocols and maximizing their therapeutic and experimental potential.

1.4 Metaplasticity

Metaplasticity refers to the concept that the plasticity of a synapse—the capacity for synaptic strength to change—is influenced by its prior activity. This higher-order form

of plasticity acts as a regulatory mechanism, ensuring that neural networks maintain a dynamic balance between stability and adaptability. Despite the promise of iTBS as a non-invasive treatment for depression, its overall efficacy remains inconsistent [95]. One explanation for this variability is the brain's intrinsic self-regulatory system, known as homeostatic metaplasticity, which may limit the benefits of external stimulation by maintaining synaptic activity within a functional range [96]. The Bienenstock-Cooper-Munro (BCM) theory provides a theoretical basis for understanding this phenomenon. It posits that synaptic plasticity operates on a "sliding threshold" that depends on recent neuronal activity. Specifically, a history of low neuronal activity lowers the threshold for inducing LTP, making further excitation more likely, whereas high recent neuronal activity raises this threshold, reducing the probability of additional excitation [97].

1.5 Priming stimulation

To enhance the therapeutic effects of rTMS, researchers have developed priming stimulation protocols that aim to exploit the principles of homeostatic metaplasticity [98]. These protocols involve administering an initial "priming" stimulation, followed by a break of variable duration, and then applying a secondary "test" stimulation [98-100]. Evidence supporting this approach comes from studies showing that the excitatory effects of iTBS on the motor cortex are amplified when preceded by inhibitory cTBS [101, 102]. This sequential priming approach appears to take advantage of homeostatic mechanisms by creating an optimal neural environment for

subsequent stimulation. Similarly, in the context of depression, research has demonstrated that priming with low-frequency (1 Hz) rTMS significantly enhances the antidepressant effects of standard rTMS protocols compared to protocols without priming stimulation [99]. These findings highlight the potential of priming protocols to improve the clinical efficacy of brain stimulation techniques.

The timing of priming stimulation is a critical factor in determining the nature of the resulting metaplasticity. Specifically, whether the response is homeostatic or non-homeostatic depends on the interval between the priming and test stimulations [103, 104]. Shorter intervals tend to favor non-homeostatic metaplasticity, likely due to the lingering neurophysiological effects of the initial stimulation. In contrast, longer intervals allow for a reset of neural activity, promoting homeostatic responses [105]. For example, studies have shown that a 10-minute interval between cTBS and iTBS sessions induces homeostatic effects in young adults [106]. Conversely, when no interval is provided, homeostatic effects fail to emerge, as observed in studies using tDCS [107]. These findings underscore the importance of optimizing the timing of priming protocols to effectively harness metaplasticity for therapeutic purposes.

Despite these advances, there remains a significant gap in literature. To date, no study has systematically investigated how the timing of priming TBS stimulation influences metaplasticity in the left DLPFC. This region is essential for cognitive and emotional regulation and served as a primary target for rTMS in treating depression.

Understanding the timing-dependent dynamics of metaplasticity in the DLPFC could shed light on the neurobiological mechanisms behind the antidepressant effects of rTMS and could inform the development of more effective stimulation protocols. For instance, it remains unclear whether the optimal interval for inducing homeostatic metaplasticity in the DLPFC mirrors that observed in the motor cortex or if region-specific differences in neural dynamics necessitate different timing strategies. Addressing these questions could enhance the precision and efficacy of rTMS protocols, ultimately improving treatment outcomes for individuals with depression.

In summary, metaplasticity represents a critical factor in understanding and optimizing the effects of brain stimulation techniques. Homeostatic metaplasticity, in particular, offers a promising framework for enhancing the therapeutic efficacy of rTMS by leveraging the brain's inherent capacity for self-regulation. However, research is needed to elucidate the complex interplay between timing, stimulation parameters, and regional neural dynamics, particularly in the context of the DLPFC.

1.6 Functional near-infrared spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging tool used to measure brain activity by detecting changes in blood oxygenation [108]. This technique works by emitting near-infrared light with wavelengths between 700-1000 nm through the scalp and skull. These wavelengths are specifically chosen because biological tissue, including bone, is relatively transparent to them, allowing the light to

penetrate deeper into the brain (Figure 1.3) [109]. By measuring the amount of light absorbed by the tissue, fNIRS quantifies changes in the concentrations of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR). While similar to functional magnetic resonance imaging (fMRI) in its reliance on blood flow changes to infer brain activity, fNIRS does not measure neuronal activity directly. Instead, it monitors the hemodynamic response, which reflects the coupling between neuronal activity and vascular changes—a phenomenon known as neurovascular coupling [110].

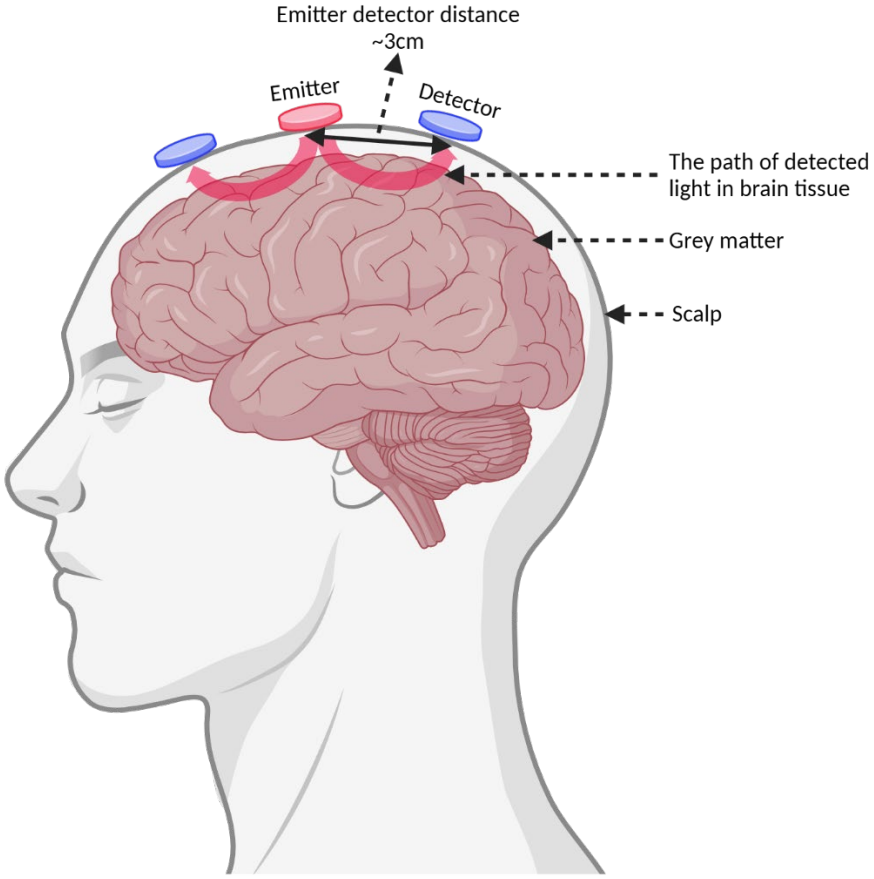

Figure 1. 3 Illustration of fNIRS Measurement of Brain Activity. Emitters generate near-infrared light that penetrates the scalp and brain tissue, following banana-shaped paths. Detectors collect the residual light after it has traversed these paths. Created in BioRender. Zhang, B. (2024) https://BioRender.com/t59c377.

When neurons in a specific brain region become active, they consume oxygen to support their increased energy demands. This leads to a temporary depletion of oxygen in the surrounding blood. To compensate, blood vessels in the area dilate in a process called vasodilation, increasing blood flow to the active region. This response, known as functional hyperemia, overcompensates for the oxygen demand and results in an increase in HbO and a decrease in HbR levels. Once neuronal activity subsides, blood flow and oxygen levels gradually return to their baseline state. These fluctuations in blood oxygenation and flow are collectively referred to as the hemodynamic response, which forms the basis of fNIRS measurements [111].

The ability of fNIRS to detect these changes is grounded in the modified Beer-Lambert law, which describes the relationship between light attenuation through a substance and the concentration of absorbing molecules in that substance [112]. In the context of fNIRS, this law is used to calculate changes in HbO and HbR concentrations based on variations in light intensity detected by the system. However, because biological tissues scatter light, photons travel a longer and more complex path than the direct distance between the light source and detector. To account for this scattering, the modified Beer-Lambert law incorporates a differential pathlength factor (DPF), which estimates the average distance traveled by photons. The DPF is specific to the type of tissue being studied and the wavelength of light used, making it a critical factor in accurately quantifying hemoglobin concentration changes [112].

One of the key strengths of fNIRS is its excellent temporal resolution, typically in the range of milliseconds, which allows researchers to track the hemodynamic response with high precision [113]. However, its spatial resolution is comparatively limited, typically in the order of centimeters. This limitation arises from the distance between the light emitter and receiver as well as the scattering properties of biological tissue, which reduces the precision of locating specific brain activity. Despite this limitation, fNIRS is especially well-suited to studying the frontal lobe, including the prefrontal cortex, due to the superficial location of these regions and the ease of placing light sources and detectors on the scalp [114, 115].

The reliability and validity of fNIRS as a neuroimaging method have been extensively validated [113, 116]. Research has shown a strong correlation between fNIRS signals and the blood-oxygen-level-dependent (BOLD) signals measured by fMRI, supporting its use as a robust measure of brain activity [117, 118]. Furthermore, fNIRS exhibits strong test-retest reliability, consistently producing reproducible results across multiple sessions [119, 120]. Importantly, fNIRS has also emerged as a valuable method for investigating the effects of TMS on brain activity and plasticity. By monitoring changes in hemodynamic responses before, during, and after TMS, researchers can gain valuable insights into how TMS influences neural activity, brain connectivity, and plasticity mechanisms [121].

fNIRS has a wide range of applications in cognitive neuroscience research, particularly

in investigating brain regions associated with language, executive function, and other higher-order cognitive processes [115]. One widely used paradigm is the verbal fluency task (VFT), in which participants are asked to generate as many words as they can within a specific category (e.g., animals) within a limited time frame [122]. This task reliably activates the frontal cortex, particularly the DLPFC, a region critical for executive functions. The ability of fNIRS to measure activity in this region makes it an invaluable tool for investigating the neural mechanisms underlying executive function and language. Moreover, combining fNIRS with TMS allows researchers to investigate how TMS-induced changes in brain plasticity affect task performance, providing deeper insights into the relationship between brain stimulation, neural activity, and behavior.

In summary, fNIRS is a valuable neuroimaging technique that offers unique advantages in studying brain function. While it may not match the spatial precision of fMRI, its exceptional temporal resolution, ease of use, and adaptability to diverse research settings make it an indispensable tool in neuroscience. Its ability to reliably measure activity in specific brain regions, such as the frontal cortex, combined with its integration with other methods like TMS, positions fNIRS as a critical tool for deepening our knowledge of brain activity, plasticity, and cognitive function across a wide range of tasks and populations.

1.7 Research gaps

Several key questions remain unanswered regarding the effective application of iTBS.

First, the underlying mechanisms of iTBS remain unclear. Second, the optimal stimulation intensity for therapeutic use is still unknown. Third, while priming iTBS with cTBS appears promising, the ideal timing between cTBS and iTBS delivery is yet to be determined. Fourth, individual anatomical variations, particularly scalp-to-cortex distance, influence the dose of stimulation reaching the brain and require further investigation. Finally, the relationship between the characteristics of the TMS-induced electric field and treatment response in depression, particularly treatment-resistant depression, requires clarification.

This thesis addresses these gaps through a series of studies. The research explores the mechanisms of iTBS and investigates the relationship between stimulation intensity and its effects. Furthermore, the influence of timing on the neuromodulatory effects of priming TBS protocols in individuals with depressive symptoms is examined. Finally, computational modeling is employed to explore the impact of individual anatomical differences on TMS dose delivery and to investigate the relationship between the TMS-induced electric field and antidepressant effects in treatment-resistant depression.

1.8 An Outline of This Thesis

1.8.1 Chapter 2 Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study

This chapter introduces a published study conducted by the author that explored the

mechanisms of iTBS in associative learning.

1.8.2 Chapter 3 Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study

This chapter describes a published pilot study conducted by the author that investigated the impact of varying iTBS intensity (50% RMT, 70% RMT and 100% RMT) on the left DLPFC in healthy adults.

1.8.3 Chapter 4 Priming theta-burst stimulation: the importance of the right timing

Chapter 4 presents the main experiment of the author's PhD study. This study examined how timing influences the neuromodulatory effects of priming TBS in individuals with depressive symptoms.

1.8.4 Chapter 5 Rethinking intensity: Repetitive transcranial magnetic stimulation across ethnic populations

In Chapter 5, the author investigated the neurobiological sources of variability, with a focus on scalp-to-cortex distance, and explores their potential influence on the actual dose of TMS delivered to the brain across diverse ethnic groups.

1.8.5 Chapter 6 Normal component of TMS-induced electric field is correlated with depressive symptom relief in treatment-resistant

depression

Chapter 6 presents a published study conducted by the author that investigated the relationship between TMS-induced EF characteristics and antidepressant effects in patients with TRD.

1.8.6 Chapter 7 Conclusion

In Chapter 7, the author summarizes the clinical applications as well as the limitations of the included studies, while also discussing potential directions for future research.

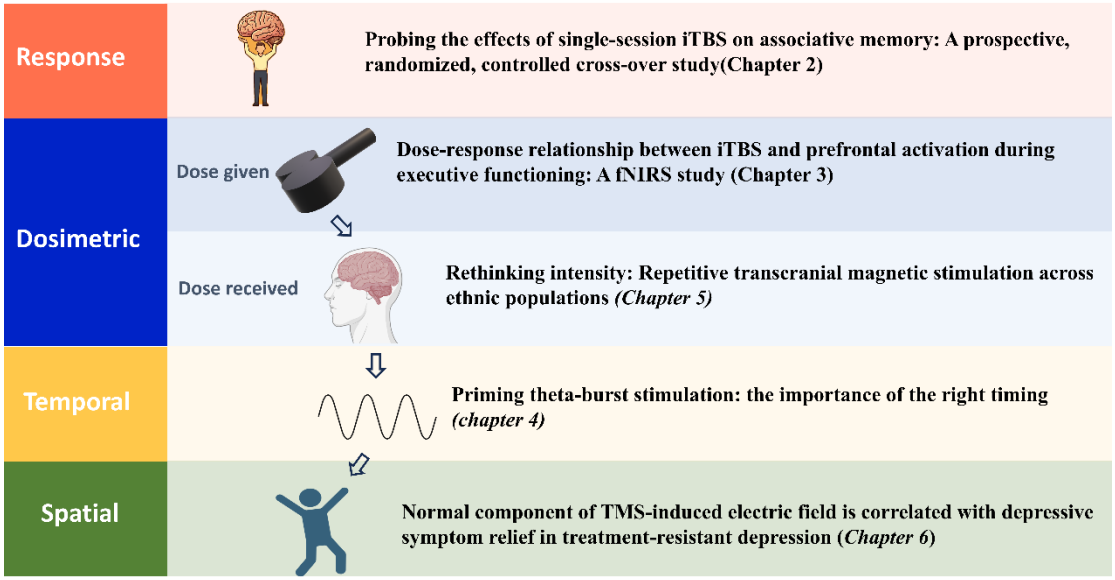

Figure 1. 4 An outline of this thesis

1.9 References

1. Malhi, G.S. and J.J. Mann, Depression. Lancet, 2018. 392(10161): p. 2299-2312.
2. World Health, O., Depression and other common mental disorders: global health estimates. 2017, World Health Organization: Geneva.
3. Williams, L.M., Precision psychiatry: a neural circuit taxonomy for depression and anxiety. The Lancet Psychiatry, 2016. 3(5): p. 472-480.
4. Lam, R.W., et al., Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. Can J Psychiatry, 2014. 59(12): p. 649-54.
5. Rock, P.L., et al., Cognitive impairment in depression: a systematic review and meta-analysis. Psychological Medicine, 2014. 44(10): p. 2029-2040.
6. Kupfer, D.J., The pharmacological management of depression. Dialogues Clin Neurosci, 2005. 7(3): p. 191-205.
7. Psychotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Health Technology Assessment. Ont Health Technol Assess Ser, 2017. 17(15): p. 1-167.
8. Trivedi, M.H., et al., Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry, 2006. 163(1): p. 28-40.
9. Rush, A.J., et al., Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry, 2006. 163(11): p. 1905-17.

10. Wijeratne, C. and P. Sachdev, Treatment-Resistant Depression: Critique of Current Approaches. Australian & New Zealand Journal of Psychiatry, 2008. 42(9): p. 751-762.

11. Fava, M., Diagnosis and definition of treatment-resistant depression. Biological Psychiatry, 2003. 53(8): p. 649-659.

12. Riggs, L.M. and T.D. Gould, Ketamine and the Future of Rapid-Acting Antidepressants. Annu Rev Clin Psychol, 2021. 17: p. 207-231.

13. Schmaal, L., et al., Cortical abnormalities in adults and adolescents with major depression based on brain scans from 20 cohorts worldwide in the ENIGMA Major Depressive Disorder Working Group. Molecular Psychiatry, 2017. 22(6): p. 900-909.

14. Baxter, L.R., Jr., et al., Reduction of prefrontal cortex glucose metabolism common to three types of depression. Arch Gen Psychiatry, 1989. 46(3): p. 243-50.

15. Drevets, W.C., J. Savitz, and M. Trimble, The subgenual anterior cingulate cortex in mood disorders. CNS Spectr, 2008. 13(8): p. 663-81.

16. Drevets, W.C., J.L. Price, and M.L. Furey, Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct Funct, 2008. 213(1-2): p. 93-118.

17. Koenigs, M. and J. Grafman, The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. Behav Brain Res, 2009. 201(2): p. 239-43.

18. Figee, M., et al., Deep Brain Stimulation for Depression. Neurotherapeutics, 2022. 19(4): p. 1229-1245.

19. Kan, R.L.D., et al., 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, 2023. 10(4): p. 252-259.

20. Brunoni, A.R., et al., Repetitive Transcranial Magnetic Stimulation for the Acute Treatment of Major Depressive Episodes: A Systematic Review With Network Meta-analysis. JAMA Psychiatry, 2017. 74(2): p. 143-152.

21. Sheline, Y.I., et al., Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc Natl Acad Sci U S A, 2010. 107(24): p. 11020-5.

22. Fales, C.L., et al., Altered emotional interference processing in affective and cognitive-control brain circuitry in major depression. Biol Psychiatry, 2008. 63(4): p. 377-84.

23. Kaiser, R.H., et al., Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry, 2015. 72(6): p. 603-11.

24. Gyurak, A., et al., Frontoparietal Activation During Response Inhibition Predicts Remission to Antidepressants in Patients With Major Depression. Biological Psychiatry, 2016. 79(4): p. 274-281.

25. Alexopoulos, G.S., et al., Functional connectivity in the cognitive control

network and the default mode network in late-life depression. J Affect Disord, 2012. 139(1): p. 56-65.

26. Cuijpers, P. and F. Smit, Subthreshold depression as a risk indicator for major depressive disorder: a systematic review of prospective studies. Acta Psychiatr Scand, 2004. 109(5): p. 325-31.

27. Cuijpers, P., et al., Differential mortality rates in major and subthreshold depression: meta-analysis of studies that measured both. Br J Psychiatry, 2013. 202(1): p. 22-7.

28. Horwath, E., et al., What are the public health implications of subclinical depressive symptoms? Psychiatr Q, 1994. 65(4): p. 323-37.

29. Johnson, J., M.M. Weissman, and G.L. Klerman, Service utilization and social morbidity associated with depressive symptoms in the community. Jama, 1992. 267(11): p. 1478-83.

30. Fogel, J., W.W. Eaton, and D.E. Ford, Minor depression as a predictor of the first onset of major depressive disorder over a 15-year follow-up. Acta Psychiatr Scand, 2006. 113(1): p. 36-43.

31. Hwang, J.W., et al., Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. Translational Psychiatry, 2015. 5(11): p. e683-e683.

32. John, P.O.R., et al., Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. Biological Psychiatry, 2007.

33. George, M.S., et al., Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry, 2010. 67(5): p. 507-16.

34. Nitsche, M.A., et al., Treatment of depression with transcranial direct current stimulation (tDCS): A Review. Experimental Neurology, 2009. 219(1): p. 14-19.

35. Brunoni, A.R., et al., Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. Br J Psychiatry, 2016. 208(6): p. 522-31.

36. Delaloye, S. and P.E. Holtzheimer, Deep brain stimulation in the treatment of depression. Dialogues in Clinical Neuroscience, 2014. 16(1): p. 83-91.

37. Pagnin, D., et al., Efficacy of ECT in Depression: A Meta-Analytic Review. Focus, 2008. 6(1): p. 155-162.

38. Lisanby, S.H., Electroconvulsive Therapy for Depression. New England Journal of Medicine, 2007. 357(19): p. 1939-1945.

39. Mishra, B.R., et al., Repetitive transcranial magnetic stimulation in psychiatry. Ann Indian Acad Neurol, 2011. 14(4): p. 245-51.

40. Costandi, M., Neuroplasticity. 2016.

41. Butz, M., F. Wörgötter, and A. van Ooyen, Activity-dependent structural plasticity. Brain Research Reviews, 2009. 60(2): p. 287-305.

42. Price, R.B. and R. Duman, Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. Mol Psychiatry, 2020. 25(3):

p. 530-543.

43. Pittenger, C., Disorders of memory and plasticity in psychiatric disease. Dialogues Clin Neurosci, 2013. 15(4): p. 455-63.

44. Appelbaum, L.G., et al., Synaptic plasticity and mental health: methods, challenges and opportunities. Neuropsychopharmacology, 2023. 48(1): p. 113-120.

45. Barker, A.T., R. Jalinous, and I.L. Freeston, Non-invasive magnetic stimulation of human motor cortex. Lancet, 1985. 1(8437): p. 1106-7.

46. Faraday, M., Experimental Researches in Electricity. Philosophical transactions of the Royal Society of London, 1832. 122: p. 125-162.

47. Terao, Y. and Y. Ugawa, Basic mechanisms of TMS. Journal of clinical neurophysiology, 2002. 19(4): p. 322-343.

48. Klomjai, W., R. Katz, and A. Lackmy-Vallée, Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med, 2015. 58(4): p. 208-213.

49. Laakso, I., et al., Where and what TMS activates: Experiments and modeling. Brain Stimulation, 2018. 11(1): p. 166-174.

50. Thielscher, A., A. Opitz, and M. Windhoff, Impact of the gyral geometry on the electric field induced by transcranial magnetic stimulation. NeuroImage, 2011. 54(1): p. 234-243.

51. Deng, Z.D., S.H. Lisanby, and A.V. Peterchev, Electric field depth-focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil

designs. Brain Stimul, 2013. 6(1): p. 1-13.

52. Saturnino, G.B., et al., SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation, in Brain and Human Body Modeling: Computational Human Modeling at EMBC 2018, S. Makarov, M. Horner, and G. Noetscher, Editors. 2019, Springer Copyright 2019, The Author(s). Cham (CH). p. 3-25.

53. Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.

54. Rossini, P.M., et al., Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalography and clinical neurophysiology, 1994. 91(2): p. 79-92.

55. Hoogendam, J.M., G.M. Ramakers, and V. Di Lazzaro, Physiology of repetitive transcranial magnetic stimulation of the human brain. Brain stimulation, 2010. 3(2): p. 95-118.

56. Chen, R., et al., Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology, 1997. 48(5): p. 1398-403.

57. Berardelli, A., et al., Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Exp Brain Res, 1998. 122(1): p. 79-84.

58. Bliss, T.V. and A.R. Gardner-Medwin, Long-lasting potentiation of synaptic

transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. J Physiol, 1973. 232(2): p. 357-74.

59. Bliss, T.V.P. and T. Lømo, Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. The Journal of Physiology, 1973. 232(2): p. 331-356.

60. Huang, Y.-Z., et al., Theta Burst Stimulation of the Human Motor Cortex. Neuron, 2005. 45(2): p. 201-206.

61. Larson, J. and E. Munkácsy, Theta-burst LTP. Brain research, 2015. 1621: p. 38-50.

62. Ranck, J.B., Jr., Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. I. Behavioral correlates and firing repertoires. Exp Neurol, 1973. 41(2): p. 461-531.

63. Rudell, A.P., S.E. Fox, and J.B. Ranck, Hippocampal excitability phase-locked to the theta rhythm in walking rats. Experimental Neurology, 1980. 68(1): p. 87-96.

64. Larson, J., D. Wong, and G. Lynch, Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Research, 1986. 368(2): p. 347-350.

65. Larson, J. and G. Lynch, Induction of Synaptic Potentiation in Hippocampus by Patterned Stimulation Involves Two Events. Science, 1986. 232(4753): p. 985-988.

66. Chung, S.W., et al., Use of theta-burst stimulation in changing excitability of

motor cortex: A systematic review and meta-analysis. Neurosci Biobehav Rev, 2016. 63: p. 43-64.

67. Pabst, A., et al., A systematic review and meta-analysis of the efficacy of intermittent theta burst stimulation (iTBS) on cognitive enhancement. Neurosci Biobehav Rev, 2022. 135: p. 104587.

68. Zavorotnyy, M., et al., Intermittent theta-burst stimulation moderates interaction between increment of N-Acetyl-Aspartate in anterior cingulate and improvement of unipolar depression. Brain Stimul, 2020. 13(4): p. 943-952.

69. Bulteau, S., et al., Efficacy of intermittent Theta Burst Stimulation (iTBS) and 10-Hz high-frequency repetitive transcranial magnetic stimulation (rTMS) in treatment-resistant unipolar depression: study protocol for a randomised controlled trial. Trials, 2017. 18(1): p. 17.

70. Zhang, J.J., Z. Bai, and K.N.K. Fong, Priming Intermittent Theta Burst Stimulation for Hemiparetic Upper Limb After Stroke: A Randomized Controlled Trial. Stroke, 2022. 53(7): p. 2171-2181.

71. Wischnewski, M. and D.J. Schutter, Efficacy and Time Course of Theta Burst Stimulation in Healthy Humans. Brain Stimul, 2015. 8(4): p. 685-92.

72. Zheng, B., et al., The effect of intermittent theta burst stimulation for cognitive dysfunction: a meta-analysis. Brain Injury, 2024: p. 1-12.

73. Demeter, E., Enhancing cognition with theta burst stimulation. Current Behavioral Neuroscience Reports, 2016. 3: p. 87-94.

74. Grossheinrich, N., et al., Theta burst stimulation of the prefrontal cortex: safety

and impact on cognition, mood, and resting electroencephalogram. Biological psychiatry, 2009. 65(9): p. 778-784.

75. Chou, P.-H., et al., Bilateral theta-burst stimulation on emotional processing in major depressive disorder: A functional neuroimaging study from a randomized, double-blind, sham-controlled trial. Psychiatry and Clinical Neurosciences, 2023. 77(4): p. 233-240.

76. Chung, S.W., K.E. Hoy, and P.B. Fitzgerald, Theta-burst stimulation: a new form of TMS treatment for depression? Depress Anxiety, 2015. 32(3): p. 182-92.

77. Cheng, C.M., C.T. Li, and S.J. Tsai, Current Updates on Newer Forms of Transcranial Magnetic Stimulation in Major Depression. Adv Exp Med Biol, 2021. 1305: p. 333-349.

78. Cohen, S.L., et al., A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 2022. 15(1): p. 73-75.

79. Blumberger, D.M., et al., Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet, 2018. 391(10131): p. 1683-1692.

80. Huang, W., et al., The Effectiveness of Intermittent Theta Burst Stimulation for Stroke Patients With Upper Limb Impairments: A Systematic Review and Meta-Analysis. Front Neurol, 2022. 13: p. 896651.

81. Szaflarski, J.P., et al., Intermittent Theta Burst Stimulation (iTBS) for Treatment of Chronic Post-Stroke Aphasia: Results of a Pilot Randomized, Double-Blind, Sham-Controlled Trial. Med Sci Monit, 2021. 27: p. e931468.

82. Li, H., et al., Intermittent theta-burst stimulation in aphasia caused by right side cerebral lesions after stroke: A case report with 2-year follow-up. Heliyon, 2024. 10(15): p. e35206.

83. Yang, C., et al., Effects of different transcranial magnetic stimulations on neuropathic pain after spinal cord injury. Front Neurol, 2023. 14: p. 1141973.

84. Kohútová, B., et al., Theta burst stimulation in the treatment of chronic orofacial pain: a randomized controlled trial. Physiol Res, 2017. 66(6): p. 1041-1047.

85. Schilberg, L., T. Schuhmann, and A.T. Sack, Interindividual Variability and Intraindividual Reliability of Intermittent Theta Burst Stimulation-induced Neuroplasticity Mechanisms in the Healthy Brain. J Cogn Neurosci, 2017. 29(6): p. 1022-1032.

86. Suppa, A., et al., Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects. Brain Stimulation, 2016. 9(3): p. 323-335.

87. Chung, S.W., et al., Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum Brain Mapp, 2018. 39(2): p. 783-802.

88. Sack, A.T., et al., Target Engagement and Brain State Dependence of Transcranial Magnetic Stimulation: Implications for Clinical Practice. Biol

Psychiatry, 2024. 95(6): p. 536-544.

89. Aberra, A.S., et al., Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain Stimul, 2020. 13(1): p. 175-189.

90. Corp, D.T., et al., Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'. Brain Stimulation, 2020. 13(5): p. 1476-1488.

91. Lee, J.C., et al., Subthreshold stimulation intensity is associated with greater clinical efficacy of intermittent theta-burst stimulation priming for Major Depressive Disorder. Brain Stimul, 2021. 14(4): p. 1015-1021.

92. Siebner, H.R., et al., Transcranial magnetic stimulation of the brain: What is stimulated? – A consensus and critical position paper. Clinical Neurophysiology, 2022. 140: p. 59-97.

93. Saturnino, G.B., et al., SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation, in Brain and Human Body Modeling: Computational Human Modeling at EMBC 2018, S. Makarov, M. Horner, and G. Noetscher, Editors. 2019, Springer Copyright 2019, The Author(s). Cham (CH). p. 3-25.

94. Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.

95. Hsu, J.H., et al., Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression. Brain Stimul, 2019. 12(6): p. 1553-1555.

96. Müller-Dahlhaus, F. and U. Ziemann, Metaplasticity in human cortex. Neuroscientist, 2015. 21(2): p. 185-202.

97. Cooper, L.N. and M.F. Bear, The BCM theory of synapse modification at 30: interaction of theory with experiment. Nat Rev Neurosci, 2012. 13(11): p. 798-810.

98. Iyer, M.B., N. Schleper, and E.M. Wassermann, Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci, 2003. 23(34): p. 10867-72.

99. Fitzgerald, P.B., et al., Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. J Clin Psychopharmacol, 2008. 28(1): p. 52-8.

100. Zhang, J.J., Z. Bai, and K.N.K. Fong, Priming Intermittent Theta Burst Stimulation for Hemiparetic Upper Limb After Stroke: A Randomized Controlled Trial. Stroke (1970), 2022. 53(7): p. 2171-2181.

101. Murakami, T., et al., Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol, 2012. 590(22): p. 5765-81.

102. Mastroeni, C., et al., Brain-Derived Neurotrophic Factor – A Major Player in Stimulation-Induced Homeostatic Metaplasticity of Human Motor Cortex?

PLOS ONE, 2013. 8(2): p. e57957.

103. Goldsworthy, M.R., J.B. Pitcher, and M.C. Ridding, Spaced Noninvasive Brain Stimulation: Prospects for Inducing Long-Lasting Human Cortical Plasticity. Neurorehabil Neural Repair, 2015. 29(8): p. 714-21.

104. Karabanov, A., et al., Consensus Paper: Probing Homeostatic Plasticity of Human Cortex With Non-invasive Transcranial Brain Stimulation. Brain Stimulation, 2015. 8(3): p. 442-454.

105. Monte-Silva, K., et al., Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol, 2010. 103(4): p. 1735-40.

106. Opie, G.M., et al., Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. Brain Stimulation, 2017. 10(2): p. 298-304.

107. Fricke, K., et al., Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. J Neurophysiol, 2011. 105(3): p. 1141-9.

108. Jöbsis, F.F., Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science, 1977. 198(4323): p. 1264-7.

109. Ferrari, M. and V. Quaresima, A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. Neuroimage, 2012. 63(2): p. 921-35.

110. Scholkmann, F., et al., A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology. Neuroimage, 2014. 85 Pt 1: p. 6-27.

111. Wolf, M., et al., Different Time Evolution of Oxyhemoglobin and Deoxyhemoglobin Concentration Changes in the Visual and Motor Cortices during Functional Stimulation: A Near-Infrared Spectroscopy Study. NeuroImage, 2002. 16(3, Part A): p. 704-712.

112. Kocsis, L., P. Herman, and A. Eke, The modified Beer-Lambert law revisited. Phys Med Biol, 2006. 51(5): p. N91-8.

113. Boas, D.A., et al., Twenty years of functional near-infrared spectroscopy: introduction for the special issue. NeuroImage, 2014. 85: p. 1-5.

114. Ferrari, M. and V. Quaresima, A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. NeuroImage, 2012. 63(2): p. 921-935.

115. Kim, H.Y., et al., Application of Functional Near-Infrared Spectroscopy to the Study of Brain Function in Humans and Animal Models. Mol Cells, 2017. 40(8): p. 523-532.

116. Cui, X., et al., A quantitative comparison of NIRS and fMRI across multiple cognitive tasks. Neuroimage, 2011. 54(4): p. 2808-2821.

117. Scarapicchia, V., et al., Functional Magnetic Resonance Imaging and Functional Near-Infrared Spectroscopy: Insights from Combined Recording Studies. Front Hum Neurosci, 2017. 11: p. 419.

118. Klein, F., et al., fMRI-based validation of continuous-wave fNIRS of supplementary motor area activation during motor execution and motor imagery. Scientific Reports, 2022. 12(1): p. 3570.

119. de Rond, V., et al., Test-retest reliability of functional near-infrared spectroscopy during a finger-tapping and postural task in healthy older adults. Neurophotonics, 2023. 10(2): p. 025010.

120. Niu, H., et al., Test-retest reliability of graph metrics in functional brain networks: a resting-state fNIRS study. PLoS One, 2013. 8(9): p. e72425.

121. Curtin, A., et al., A Systematic Review of Integrated Functional Near-Infrared Spectroscopy (fNIRS) and Transcranial Magnetic Stimulation (TMS) Studies. Frontiers in Neuroscience, 2019. 13.

122. Yeung, M.K. and J. Lin, Probing depression, schizophrenia, and other psychiatric disorders using fNIRS and the verbal fluency test: A systematic review and meta-analysis. J Psychiatr Res, 2021. 140: p. 416-435.

Chapter 2 Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study

This work has been published by the author of this thesis as an article in the journal "*Brain Stimulation*" in 2021.

This work was presented as a poster at the *12th Pan-Pacific Conference on Rehabilitation*, held from November 27-28, 2021, in Hong Kong SAR, China.

2.1 Abstract

Background: Recent animal research indicates that excitatory brain stimulation opens a time window for enhanced neuroplasticity that permits remodeling of neural representations. Intermittent theta-burst stimulation (iTBS) may thus facilitate associative memory of new associations introduced after iTBS by reducing proactive interference from previously learned associations.

Objective: We aimed to investigate the effects of iTBS on left dorsolateral prefrontal cortex (DLPFC) or left lateral parietal cortex (lPC) on influencing associative memory processes, two brain regions centrally involved in memory.

Methods: 75 healthy participants underwent either iTBS of the DLPFC (n=30) or the lPC (n=30) compared to sham stimulation (vertex), or no stimulation (n=15) in a randomized controlled cross-over design. Participants underwent an associative memory test (face-word associations) consisting of an encoding period before and after stimulation. Face-cued word recall was evaluated before and after stimulation for the initially encoded associations, as well as after stimulation for the newly encoded associations.

Results: Performance significantly increased for newly compared to previously encoded associations in all experimental conditions. Contrary to our expectation, performance increases were not significantly more substantial for either of the two active stimulations than sham stimulation. Instead, lPC stimulation significantly decreased performance for newly encoded associations compared to sham stimulation. In addition, DLPFC stimulation reduced recall of previously encoded associations

immediately after stimulation.

Conclusions: Stimulation-induced loosening of neural associations and permissiveness for change, as observed in animals, does not translate to the realm of human association learning. Instead, lPC stimulation impedes recall of newly acquired association memory, indicating increased proactive interference.

2.2 Introduction

A large corpus of research demonstrated that high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) of the human cortex exhibits neuroplastic effects similar to long-term potentiation (LTP)-inducing electrical stimulation in animal experiments [1, 2]. Intermittent theta burst stimulation (iTBS), a potent form of patterned rTMS, was also shown to have excitatory effects akin to LTP [3], although probably via a different cellular mechanism compared to standard rTMS [4, 5]. However, recent evidence provides a crucial extension to the proposed mechanism of action of rTMS. In a study by Kozyrev, et al., [6], authors investigated the effect of 30 minutes of HF rTMS over the primary visual cortex of anesthetized cats. They showed that stimulation opened a time window in which the neural substrate is permissive to reorganization and remodeling. Using voltage-sensitive dye imaging, they measured visual orientation maps in the submillimeter range. Before stimulation, these maps exhibited a regular preference of different orientation angles. Directly after the stimulation, the authors observed a reduction of orientation preferences and increased response variability. In addition, prolonged visual exposure to a single orientation following the stimulation led to a reorganization of maps, showing the domination of the newly acquired orientation preference. These results indicate that rTMS destabilizes previously acquired representations and opens a time window of increased permissiveness to change and remodeling neural representations. The potential therapeutic relevance of the results from Kozyrev et al. for neuropsychiatric disorders cannot be overstated. However, whether findings can be translated to the realm of

human cognition awaits to be investigated.

Associative memory is a function of a distributed neural network including prefrontal, medial temporal, and parietal cortices [7]. Especially left lateralized frontal and parietal regions engage during executive monitoring processes necessary for memory retrieval, as evidenced for face-name associations [7, 8]. To infer causal interpretations, several studies investigated the effect of rTMS of left dorsolateral prefrontal [9] and parietal [10-12] targets on associative memory. Of note, Wang et al. [11] demonstrated significant improvements in face-cued word recall accuracy following five days of HF rTMS to the left lateral parietal cortex. Enhancements in associative memory were also observed after a single session of theta-burst stimulation (TBS) [13], a potent form of patterned rTMS. Besides, recent research showed that neurofeedback training-induced increases of frontal-midline theta activity enhanced memory by reducing proactive interference [14]. This result substantiates the importance of theta oscillations for memory encoding and retrieval.

We therefore set out to conduct an experiment that probes stimulation induced destabilization of acquired representations, followed by a remodeling of neural representations corresponding to newly acquired information in the context of associative memory. We hypothesized that 1) active iTBS compared to control stimulation will reduce recall capacity directly after the stimulation due to increased neural excitability and loosening of neural associations, as evidenced by Kozyrev et al.

[6]. We further hypothesized that 2) active iTBS compared to control stimulation will increase recall capacity of the newly learned associations after the stimulation, due to facilitated neural reorganization and an associated reduction in proactive interference.

2.3 Materials and methods

2.3.1 Participants

A total of 75 healthy right-handed volunteers, aged 24.8±3.5 (mean±SD) participated in the current study. Participants were recruited through convenience sampling at the Hong Kong Polytechnic University from May 2019 to December 2020. Participants were included if they were aged 18-35 years, had an education level of primary six or above, were right-handed, as assessed using The Edinburgh Handedness Inventory [15, 16], had a normal or corrected-to-normal vision, and had effective command of the English language. Exclusion criteria were a history of any psychiatric or neurological disease, a history of a seizure, or any contraindications to TMS as screened by a TMS safety screening questionnaire [17]. Further exclusion criteria were substance abuse or intake of any medication influencing the central nervous system. All participants provided written informed consent prior to enrollment. The study was approved by the Human Subjects Ethics Sub-Committee of The Hong Kong Polytechnic University and performed following the Declaration of Helsinki. The study was registered on ClinicalTrials.gov (NCT03756584).

2.3.2 Study design and experimental setup

We used a prospective, randomized, parallel, counterbalanced cross-over design with repeated measures. The study was divided into three consecutive phases (Phase I, II and III, see Figure 2.1). In Phase I and Phase II, 30 participants each (15 females) were randomized to receive a single session of active and control iTBS on two visits, separated by at least one weak (7-9 days). In Phase I, participants received either active iTBS of the left lPC (n=15) or control stimulation (vertex, n=15) on the first visit, with a cross-over on the second visit. In Phase II, another 30 participants received either active iTBS of the left DLPFC (n=15) or control stimulation (n=15), with a cross-over on the second visit. Phase III consisted of the same experimental setup as in Phase I and II, except that participants (n=15) were not subjected to any stimulation. First and second visits were separated by at least one week in all three study phases.

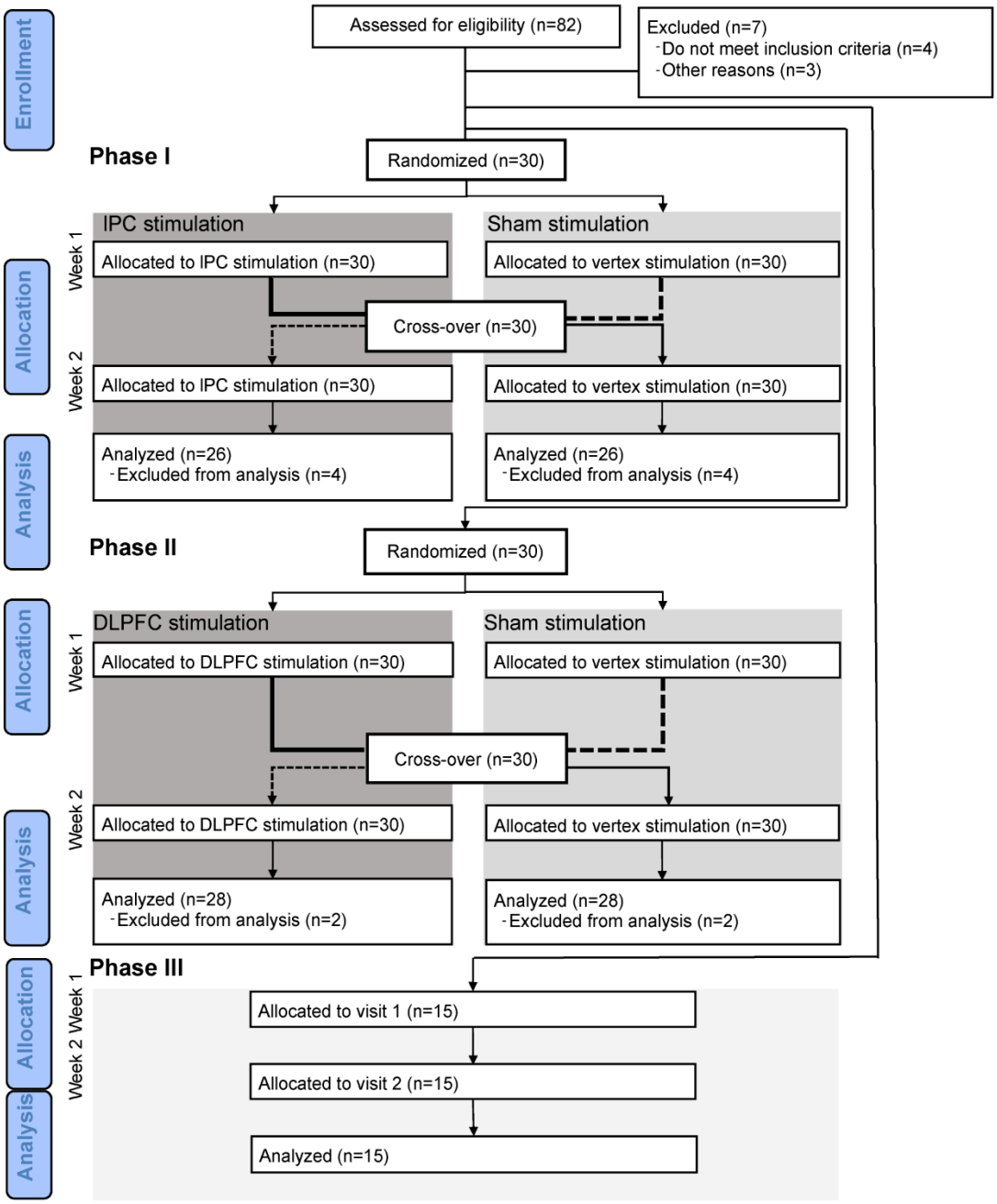

Figure 2. 1 Flow diagram of the study.

On each visit in all study phases, participants performed an associative memory test consisting of encoding and recall periods in which they had to memorize and recall word-face associations (face-cued word recall), respectively. Before the stimulation, participants underwent a first encoding period (E1), followed by a first recall period (R1). Immediately after stimulation, they underwent a second recall period (R2). This was followed by a resting period of about five minutes. Participants viewed a distraction video (Tom & Jerry) and were told that no retention of the associations learned in E1 was required. Following the resting period, participants underwent a new encoding period (New-E2) which consisted of new combinations of associations assembled using the same stimuli as in E1. The new encoding period was followed by a new recall period (New-R3) (Figure 2.2). Different sets of stimuli were used for the two visits (matched for face gender, word concreteness and frequency). The sequence of sets was randomized and counterbalanced among all participants.

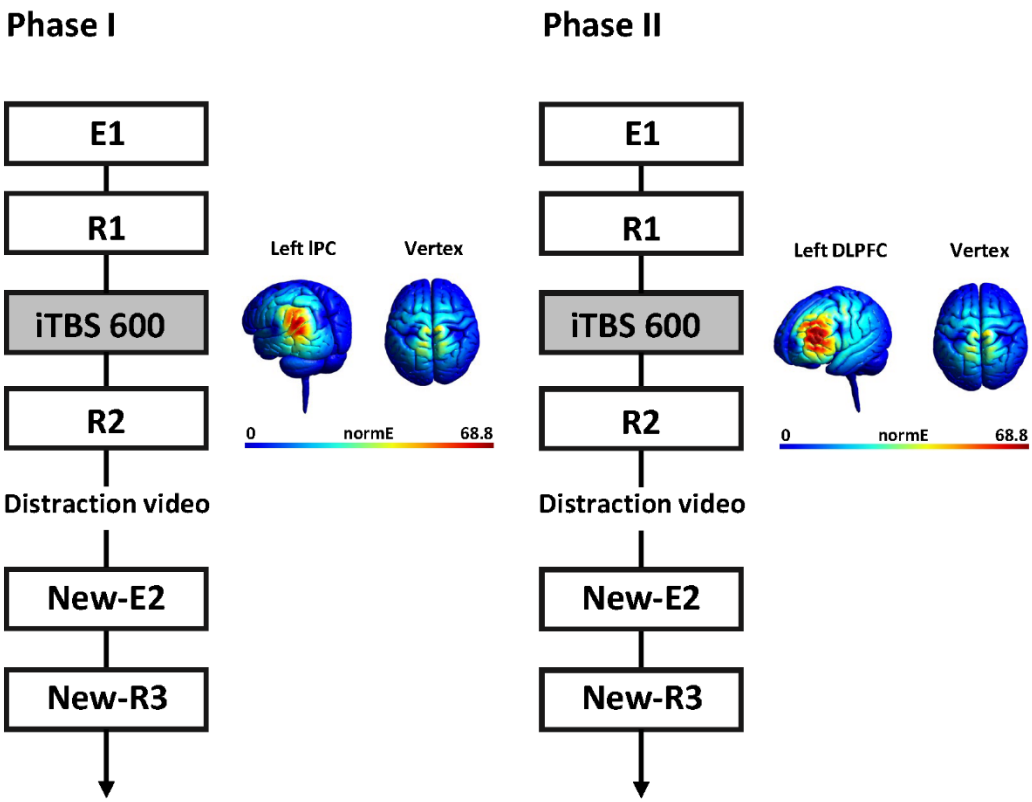

Figure 2. 2 Sequence of consecutive phases of the experiment. E1, first encoding period; R1, first recall period; iTBS 600, intermittent theta-burst stimulation; R2, second recall period; New-E2, new encoding period; New-R3, new recall period. Electrical field (e-fields) for active and control stimulation locations were also shown, with red indicating peak intensity. lPC, lateral parietal cortex; DLPFC, dorsolateral prefrontal cortex.

2.3.3 Associative memory test

We used an in-house designed face-word associative memory test, which was adapted from [11]. During encoding periods, participants were required to try their best to memorize as many face-word associations as possible depicted on a computer screen. Each encoding period consisted of 20 face-word pairs (10 female faces), and each pair was presented for 8 seconds at the center of a white screen and with a 5-second inter-stimulus-interval between pairs. Pairs consisted of a monochrome frontal human face (360x480 pixels) and an English word written in black below (see Figure 2.3). Besides, words were read aloud once by the computer at the appearance of each pair. To ensure internal validity, all face images were taken from the subtest "facial recognition" from the Chinese version of the Rivermead Behavioural Memory Test [18, 19]. Furthermore, all words were selected from the MRC Psycholinguistic Database (www.psych.rl.ac.uk), were nouns between four and six letters in length, had familiarity ratings of between 500 to 700, concreteness ratings of between 400 to 700 and Kucera-Francis written frequencies of between 200-2000. Pairs were presented according to a pre-randomized computer-generated sequence.

During recall periods, participants viewed the same set of faces as in the encoding period but in a different randomized order. Each face was presented for 8 seconds, followed by a 5-second inter-stimulus-interval. During each face presentation, participants had to type the remembered word matching the face, followed by pressing 'enter' using a standard computer keyboard. Word recall for each face was scored as

correct or incorrect, ignoring plurality. Reaction time was recorded. Participants failing to type a word within 8 seconds received a reminder ('too slow') on the screen. Prior to the experiment, participants received a training trial consisting of five face-word pairs not included in the main trial. The PsychToolbox-3 (PTB-3) software was used for task presentation.

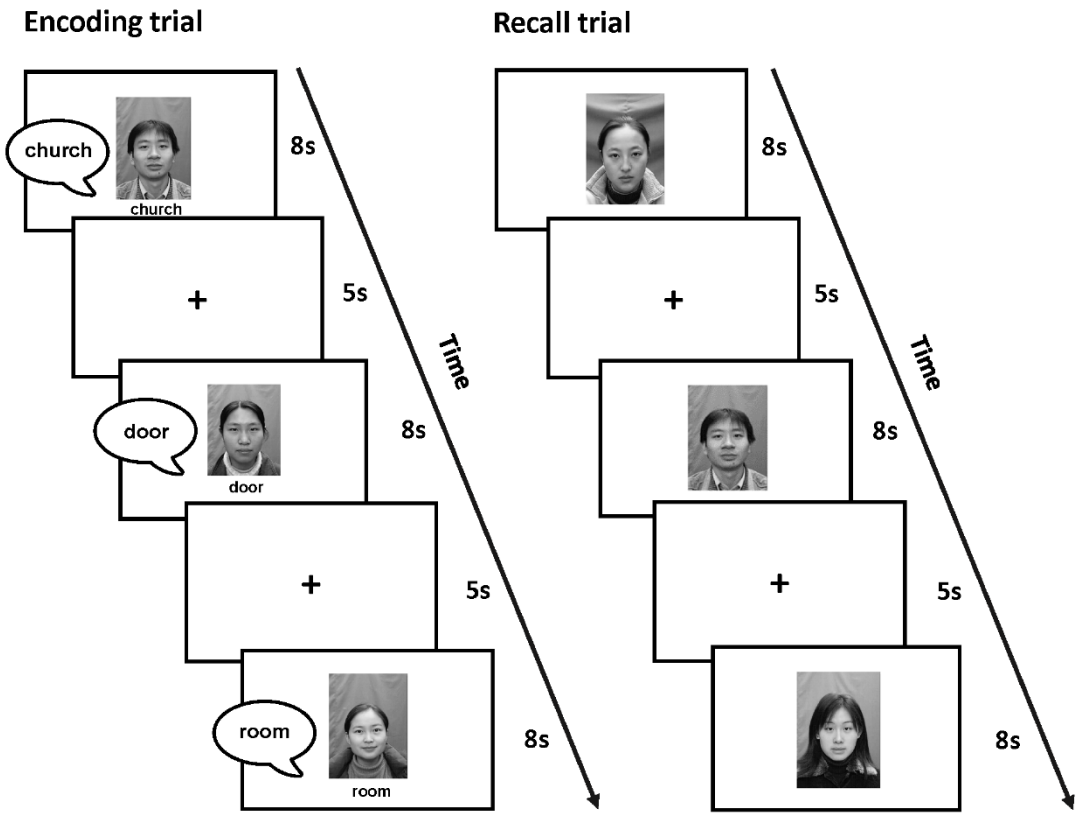

Figure 2. 3 Overview of the associative memory test.

2.3.4 Stimulation protocol

iTBS was delivered using a MagPro magnetic stimulator (MagVenture, Denmark K) and a figure-of-eight shaped cool coil (Cool-B65). We followed the original iTBS protocol described by Huang et al., comprising 3-pulse 50-Hz bursts, applied at 5 Hz with a 2-second train and an inter-train-interval of 8 seconds [3]. The individual resting motor threshold (RMT) was determined during the first visit before the experiment and was defined as the minimum stimulation intensity over the left primary motor cortex (M1) that could elicit a motor evoked potential (MEP) of no less than 50 μV in 5 out of 10 trials over the contralateral first dorsal interosseous muscle [20, 21].

Stimulation targets were identified and monitored during the stimulation using neuro-navigation (LOCALITE® TMS Navigator Germany). The target within the left lPC was defined at Montreal Neurological Institute (MNI) coordinate [-47, -68, +36], a target identified as having the highest functional connectivity with the hippocampus [11]. The left DLPFC was targeted at MNI coordinate [-38, +44, +26] as done previously [9]. Vertex stimulation at MNI coordinate [0, -42, +73] served as control condition so that participants could experience the somatic sensation and the clicking sound that iTBS produces [10]. Control stimulation of the vertex was based on the assumption that this brain region is not part of the prefrontal temporo-parietal memory network [22]. All participants, as well as research personnel handling participants during the entire experiment, were blinded to the group allocation (except for the TMS operator applying iTBS). Possible side effects, including headache, nausea or dizziness

were assessed after each stimulation.

2.3.5 Statistical analysis

Six participants were excluded from the statistical analysis due to technical problems during the experiment, language bias, or other (personal) factors. Hence, data from 26 participants in Phase I, 28 participants in Phase II, and 15 participants in Phase III were subjected to statistical analysis. Linear mixed model analysis was conducted to test the effects of iTBS on memory recall using stimulation location (real, control) and recall (R1, R2, New-R3) as within-subjects factors, and number of correctly recalled associations normalized to baseline values (R1) as dependent variable. Separate models were calculated for the three study phases. Post hoc models and pairwise comparisons were conducted in case of main or interaction effects in the global models. Statistical significance was set at $P<0.05$, corrected for multiple comparisons using the Bonferroni procedure, unless specified otherwise. SPSS version 24 for Windows (SPSS Inc., Chicago, Illinois; www.spss.com) was used for statistical analyses.

2.4 Results

Demographic information of participants is depicted in Table 2.1. First, we analyzed data from Phase I, that is, we investigated the effects of lPC stimulation on recall performance in comparison to vertex stimulation. Mixed models analysis did not reveal a main effect of location ($F_{(1,110)}=1.8$, $P=0.177$) but a main effect of recall ($F_{(2,141)}=28.0$, $P<0.001$) and an interaction of location*recall ($F_{(2,158)}=4.5$, $P=0.012$). Post-hoc

comparisons indicated a significant performance increase for New-R3 compared to R1 and R2 for lPC stimulation, as well as vertex stimulation (all $P<0.05$, corrected). However, performance increase at New-R3 was significantly lower for lPC compared to vertex stimulation ($P=0.045$) (see Figure 2.4).

Next, we analyzed data collected in Phase II, i.e., we investigated the effects of DLPFC stimulation on recall performance in comparison to vertex stimulation. Mixed models analysis revealed a main effect of recall ($F_{(2,106)}=43.8$, $P<0.001$) but no main effect of location ($F_{(1,94)}=0.3$, $P=0.601$) and no interaction of recall*location ($F_{(2,119)}=0.4$, $P=0.679$). Post-hoc comparisons indicated a significant performance increase for New-R3 compared to R1 and R2 for DLPFC stimulation, as well as vertex stimulation (all $P<0.05$, corrected). However, exploratory comparison for DLPFC stimulation revealed a decrease in performance at R2 compared to R1 ($P=0.002$, uncorrected). Moreover, performance after DLPFC stimulation at R2 was significantly lower than performance after lPC stimulation at R2 ($P=0.036$, uncorrected) (see Figure 2.4).

Finally, we investigated recall performance for participants in Phase III receiving no stimulation. This was done in order to determine unspecific stimulation effects by quantifying the effect of repeated encoding and recall of associations alone. Here, mixed models analysis revealed a main effect of recall ($F_{(2,81)}=7.1$, $P=0.001$) but no main effect of visit ($F_{(1,81)}=0.01$, $P=0.910$) and no interaction of recall*visit ($F_{(2,81)}=0.1$, $P=0.863$). Post-hoc comparisons indicated a significant performance increase for New-

R3 compared to R1 and R2 (all $P<0.05$, corrected). See Figure 2.4 for mean performances from all three study phases. For non-standardized values, see Table 2.2.

Table 2. 1 Demographics of study participants.

	Phase I (N=26)	Phase II (N=28)	Phase III (N=15)
Age (years)	25.73±3.26	23.57±3.81	25.87±2.33
Sex (F/M)	14/12	14/14	7/8
Education (years)	19.23±2.70	19.68±2.50	21.6±2.02

Values represent means±SD for age and education, and sums for sex. F, female; M, male.

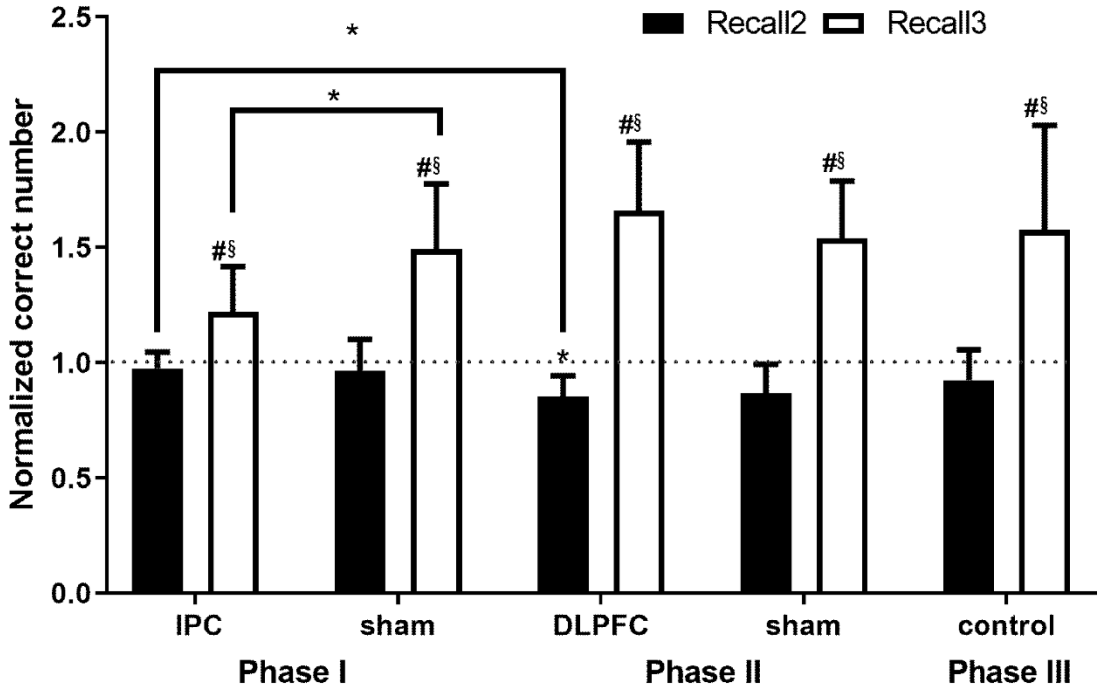

Figure 2. 4 Overall memory performance for the three study phases. Depicted are means and standard deviations for R2 and New-R3, normalized to baseline values (Recall 1, dashed line). # and § indicate a significant increase in R2 and New-R3, respectively, compared to baseline. The large asterisk indicates a significant difference for the comparison of lPC versus vertex stimulation in Phase I (corrected for multiple comparisons). Small asterisks indicate a significant reduction for R2 after DLPFC stimulation and difference to R2 after lPC stimulation (uncorrected). lPC, lateral parietal cortex; DLPFC, dorsolateral prefrontal cortex.

Table 2. 2 Memory performance.

	Phase I		Phase II		Phase III
	LPC (N=26)	Vertex (N=26)	DLPFC (N=28)	Vertex (N=28)	No stimulation (N=15)
R1#	9.58±3.56	8.04±3.83	8±4.23	6.71±3.05	6.83±3.95
R2	9.31±3.81	7.73±3.87	7.07±4.66	6.07±3.43	6.4±4.15
New-R3	10.77±3.87	10.46±4	11.07±4.13	9.57±4.27	8.37±3.71

Depicted are means±SD for non-standardized recall performance of participants in the three study phases. R1, recall 1 before stimulation; R2, recall 2 directly after stimulation; New-R3, recall of newly encoded associations after stimulation. lPC, lateral parietal cortex; Sham, vertex stimulation; DLPFC, dorsolateral prefrontal cortex. # Pairwise comparisons indicated no significant differences between study phases at baseline (R1) (phase I *vs*. phase II, p= 0.14; Phase I *vs*. Phase III p=0.07; phase II *vs.* phase III, p=1.00). However, pairwise comparisons between stimulation conditions (LPC, DLPFC, Vertex, No stimulation) indicated significantly higher values for the LPC stimulation compared to the no stimulation condition, but no significant differences between other conditions.

2.5 Discussion

Recent animal research indicates that excitatory brain stimulation opens a time window of increased permissiveness to change and remodeling of neural representations [6]. In the current study, we set out to translate this finding into the realm of human cognition by investigating the effects of iTBS on associative memory. Contrary to our hypothesis, we found no evidence for an increased recall capacity of newly encoded face-word associations after active, compared to sham stimulation. iTBS of the left DLPFC, as well as the left lPC did not increase recall capacity compared to sham stimulation. Instead, recall capacity of newly encoded associations was lower after lPC stimulation in comparison to sham stimulation. Moreover, DLPFC stimulation tended to reduce recall of previously learned associations immediately after the stimulation.

Hence, our study does not support the notion that stimulation-induced loosening of neural associations and permissiveness for change, as observed in animals, translates to human association learning. Our study differs in various aspects to Kozyrev et al. (2018) including the applied stimulation protocol, the stimulated brain region, and the species investigated, which may explain the diverging results. Moreover, Kozyrev et al. measured orientation selectivity in the cat visual cortex, whereas we studied human association learning retrieval, two functions associated with very different neurophysiological processes [23, 24]. Hence, stimulation effects on these processes may likely differ as well.

We observed an impediment of newly acquired association memory following lPC stimulation. This indicates that lPC stimulation modulates recall performance contrary to our expectations. Our results show that lPC stimulation hinders, rather than facilitates reorganization and permissiveness to new encoding. This can be explained by an increased proactive interference from previously encoded associations. That is, the repeated recall of the previously learned associations strengthens the combination patterns learned in E1, which interferes with the memory formation of new learning (New-E2).

Regarding DLPFC stimulation, we observed a lower recall capacity directly after stimulation compared to before stimulation and compared to lPC stimulation. Although this effect was observed only on an exploratory basis and with an uncorrected level of significance, this finding is in line with the results from Kozyrev et al. indicating that excitatory stimulation increases response variability directly after stimulation. Despite being involved in episodic memory, the DLPFC is not part of the cortical networks interacting with the hippocampus [25]. Studies postulate a specific role of the DLPFC for controlling memory retrieval by suppressing irrelevant information [26]. Hence, our result indicates that neural reorganization after rTMS observed by Kosyrev et al. [6] is transferable only to the DLPFC due to its specific function to suppress irrelevant information during memory retrieval. However, our findings are only limited to the short-term memory performance, further studies are needed to investigate the effects of iTBS on long-term memory performance and memory consolidation."

2.6 Conclusion

In conclusion, our results indicate that lPC stimulation strengthens previously encoded associations, thereby hindering neural reorganization and permissiveness to new encoding. Conversely, DLPFC stimulation lowers the recall capacity of previously encoded associations, possibly due to an increase in response variability directly after stimulation.

2.7 Author's contribution

For the work presented in this chapter, the author contributed to the following aspects of the study: Methodology; Software; Investigation; Data Curation; Formal Analysis; Writing-Original Draft; Writing-Review & Editing; Visualization.

2.8 References

1. Terao, Y. and Y. Ugawa, Basic mechanisms of TMS. Journal of clinical neurophysiology, 2002. 19(4): p. 322-343.
2. Fatemi-Ardekani, A., Transcranial magnetic stimulation: physics, electrophysiology, and applications. Crit Rev Biomed Eng, 2008. 36(5-6): p. 375-412.
3. Huang, Y.-Z., et al., Theta Burst Stimulation of the Human Motor Cortex. Neuron, 2005. 45(2): p. 201-206.
4. Benali, A., et al., Theta-burst transcranial magnetic stimulation alters cortical inhibition. J Neurosci, 2011. 31(4): p. 1193-203.
5. Larson, J. and E. Munkácsy, Theta-burst LTP. Brain Research, 2015. 1621: p. 38-50.
6. Kozyrev, V., et al., TMS-induced neuronal plasticity enables targeted remodeling of visual cortical maps. Proc Natl Acad Sci U S A, 2018. 115(25): p. 6476-6481.
7. Eichenbaum, H. and N.J. Cohen, From conditioning to conscious recollection: Memory systems of the brain. From conditioning to conscious recollection: Memory systems of the brain. 2001, New York, NY, US: Oxford University Press. x, 583-x, 583.
8. Hammer, A., C. Tempelmann, and T.F. Münte, Recognition of face-name associations after errorless and errorful learning: an fMRI study. BMC Neurosci, 2013. 14: p. 30.

9. Hawco, C., et al., Differing Time of Onset of Concurrent TMS-fMRI during Associative Memory Encoding: A Measure of Dynamic Connectivity. Front Hum Neurosci, 2017. 11: p. 404.

10. Nilakantan, A.S., et al., Stimulation of the Posterior Cortical-Hippocampal Network Enhances Precision of Memory Recollection. Curr Biol, 2017. 27(3): p. 465-470.

11. Wang, J.X., et al., Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science, 2014. 345(6200): p. 1054-7.

12. Hendrikse, J., et al., Multi-day rTMS exerts site-specific effects on functional connectivity but does not influence associative memory performance. Cortex, 2020. 132: p. 423-440.

13. Tambini, A., D.E. Nee, and M. D'Esposito, Hippocampal-targeted Theta-burst Stimulation Enhances Associative Memory Formation. J Cogn Neurosci, 2018. 30(10): p. 1452-1472.

14. Eschmann, K.C.J., R. Bader, and A. Mecklinger, Improving episodic memory: Frontal-midline theta neurofeedback training increases source memory performance. Neuroimage, 2020. 222: p. 117219.

15. Oldfield, R.C., The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia, 1971. 9(1): p. 97-113.

16. Yang, N., et al., Translation, cultural adaption, and test-retest reliability of Chinese versions of the Edinburgh Handedness Inventory and Waterloo Footedness Questionnaire. Laterality, 2018. 23(3): p. 255-273.

17. Rossi, S., et al., Screening questionnaire before TMS: an update. Clin Neurophysiol, 2011. 122(8): p. 1686.

18. Man, D.W.-k. and R. Li, Assessing Chinese Adults' Memory Abilities. Clinical Gerontologist, 2002. 24(3-4): p. 27-36.

19. Fong, K.N.K., et al., The clinical utility, reliability and validity of the Rivermead Behavioural Memory Test—Third Edition (RBMT–3) in Hong Kong older adults with or without cognitive impairments. Neuropsychological Rehabilitation, 2019. 29(1): p. 144-159.

20. Rothwell, J.C., et al., Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl, 1999. 52: p. 97-103.

21. Rossini, P.M., et al., Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalography and clinical neurophysiology, 1994. 91(2): p. 79-92.

22. Nettekoven, C., et al., Dose-dependent effects of theta burst rTMS on cortical excitability and resting-state connectivity of the human motor system. J Neurosci, 2014. 34(20): p. 6849-59.

23. Wagner, A.D., et al., Parietal lobe contributions to episodic memory retrieval. Trends Cogn Sci, 2005. 9(9): p. 445-53.

24. Shapley, R., M. Hawken, and D.L. Ringach, Dynamics of orientation selectivity in the primary visual cortex and the importance of cortical inhibition. Neuron,

2003. 38(5): p. 689-99.

25. Kim, S., et al., Selective and coherent activity increases due to stimulation indicate functional distinctions between episodic memory networks. Sci Adv, 2018. 4(8): p. eaar2768.

26. Eichenbaum, H., Prefrontal-hippocampal interactions in episodic memory. Nat Rev Neurosci, 2017. 18(9): p. 547-558.

Chapter 3 Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study

This work has been published by the author of this thesis as an article in the journal "*Frontiers in Psychiatry*" in 2022

Part of this research was presented orally online at *The 33rd Hybrid World Congress of Neuropsychopharmacology,* held from June 9–13, 2022, in Taiwan, China.

This work was presented orally online at the *Annual meeting of the Society for Functional Near-infrared Spectroscopy*, held from October 9–12, 2022, in Boston, USA.

3.1 Abstract

Introduction: Intermittent theta-burst stimulation (iTBS) is a noninvasive brain stimulation paradigm that has demonstrated promising therapeutic benefits for a variety of neuropsychiatric disorders. It has recently garnered widespread favor among researchers and clinicians, owing to its comparable potentiation effects as conventional high-frequency repetitive transcranial magnetic stimulation (rTMS), but administered in a much shorter time frame. However, there is still a lack of agreement over the optimal stimulation intensity, particularly when targeting the prefrontal regions. The objective of this study was to systematically investigate the influence of different stimulation intensities of iTBS, applied over the left dorsolateral prefrontal cortex (DLPFC), on brain activity and executive function in healthy adults.

Methods: Twenty young healthy adults were enrolled in this randomized cross-over experiment. All participants received a single session iTBS over the left DLPFC at intensities of 50%, 70% or 100% of their individual resting motor threshold (RMT), each on separate visits. Functional near-infrared spectroscopy (fNIRS) was used to measure changes of hemoglobin concentrations in prefrontal areas during the verbal fluency task (VFT) before and after stimulation.

Results: After stimulation, iTBS to the left DLPFC with 70% RMT maintained the concentration change of oxyhemoglobin (HbO) in the target area during the VFT. In contrast, 50% ($t_{(17)}$=2.203, P=0.042, d=0.523) and 100% iTBS ($t_{(17)}$=2.947, P=0.009, d=0.547) significantly decreased change of HbO concentration, indicating an inverse U-shape relationship between stimulation intensity and prefrontal hemodynamic

response in healthy young adults. Notably, improved VFT performance was only observed after 70% RMT stimulation ($t_{(17)}$=2.511, *P*=0.022, *d*=0.592). Moreover, a significant positive correlation was observed between task performance and the difference in HbO concentration change in the targeted area after 70% RMT stimulation (r=0.496, *P*=0.036) but not after 50% or 100% RMT stimulation.

Conclusion: The linear relationship between stimulation intensity and behavioral outcomes reported in previous conventional rTMS studies may not be translated to iTBS. Instead, iTBS at 70% RMT may be more efficacious than 100% RMT.

3.2 Introduction

Transcranial magnetic stimulation (TMS) is a well-established non-invasive brain stimulation technique that elicits action potentials through application of a magnetic field on the scalp [1]. Repetitive transcranial magnetic stimulation (rTMS) has been shown to modify cortical excitability beyond the stimulation session. The underlying mechanism of these effects may be related to modulated long-term potentiation (LTP) and long-term depression (LTD), as observed in animal studies [2]. Recently, theta-burst stimulation (TBS), a potent form of rTMS, has gained increased attention, due to its comparable potentiation effects as conventional rTMS, but administered in a much shorter time frame [3]. TBS consists of a series of 3-pulse bursts at 50 Hz (theta rhythm), designed to mimic the firing patterns of hippocampal neurons in rats [4] and has been demonstrated to optimally induce LTP in animal studies [5]. In humans, TBS protocols were first tested on the primary motor cortex at an intensity of 80% active motor threshold (AMT) by Huang et al. [3] who showed that the intermittent form of TBS (iTBS) induces excitatory effects while the continuous form of TBS (cTBS) induces inhibitory effects on brain activity. Since its first description, TBS has been applied to other non-motor areas. The past decade has seen the rapid development of application of TBS on the dorsolateral prefrontal cortex (DLPFC) for the treatment of various neurological and psychiatric disorders [6-9]. However, questions have been raised about the optimal parameters for maximizing the response to TBS. For instance, one of the current discussions pertains to the TBS intensity used for the DLPFC neuromodulation. Huang & Rothwell (2004) reported an increased MEP with

increasing intensity (50%, 70% and 80% AMT) of 50Hz burst stimulations of the motor cortex. [10]. In more recent treatment studies, TBS is used at wide ranging intensities, from 80% AMT to 120% resting motor threshold (RMT) [11, 12]. In conventional rTMS studies, an almost linear relationship between stimulation intensity and neuromodulation is assumed in conventional rTMS studies [13, 14]. However, caution should be taken when directly transferring this relationship from conventional rTMS to TBS, as the mechanism by which they alter brain excitability appears to differ [2, 15, 16]. Furthermore, it is still unknown whether the linear relationship reported by Huang & Pothwell using low (50%-80% AMT) TBS intensity in motor cortex also exists in high (≧80% AMT) intensity prefrontal stimulation.

Functional near infrared spectroscopy (fNIRS) allows to assess the concentration change of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in biological tissue [17]. This is achieved by transmitting near infrared light (~700-1000 nm) into the brain and taking advantage of the transparency difference of tissue within this near infrared optical window [18]. fNIRS has been demonstrated to be a very promising tool to monitor functional brain activity in a wide range of applications and populations, especially for the frontal lobe [17, 19]. Previous studies reported a robust correlation between the NIRS signal, and the blood oxygenation level dependent (BOLD) signal as measured by functional magnetic resonance imaging (fMRI) [20-22]. In the past three decades, fNIRS has become increasingly popular due to its low cost, safety, portability, and tolerability [19, 23, 24]. The verbal fluency task (VFT) is a

widely used neuropsychological test to evaluate executive functions in which subjects are instructed to generate as many unique words as possible from a category (phonemic or semantic) within a given time limit [25, 26]. Previous and recent research demonstrate VFT-induced activation in frontal cortices, including the left DLPFC [27, 28].

Our study sets out to systematically investigate the influence of different stimulation intensities of iTBS, applied at the left DLPFC, on brain activity and executive function in healthy adults. We probed (1) a hypothesized linear relationship between iTBS intensity and activation of the DLPFC; and (2) a linear relationship between task performance and stimulation intensity.

3.3 Materials and Methods

3.3.1 Participants

Convenience sampling was used for recruitment at the Hong Kong Polytechnic University from May 2021 to July 2021. We included twenty right-handed, healthy adults in this study (age: 22.3±3.54 years, 10 female). Participants had to be native Chinese speakers between the age of 18 and 35 years and completed at least six years of formal education. They had to have normal or corrected to normal eyesight and be able to understand the verbal instructions. Subjects with any of the following conditions were excluded from this study: (1) a history of seizure; (2) current or past psychiatric disorders; (3) current or past severe internal or neurological illness; (4) any TMS

contraindications; (5) history of substance dependence or abuse within the last 3 months; (6) intake of any medication (i.e., benzodiazepines, anticonvulsants) known to affect the excitation threshold. The study was conducted according to the Declaration of Helsinki and received the ethical approval from the Human Subjects Ethics Subcommittee (HSESC20181212008) of the Hong Kong Polytechnic University. Written informed consent was obtained from all participants before enrollment.

3.3.2 Study design and setting

This study was a prospective, randomized cross-over clinical trial with repeated measures. Subjects were instructed to visit our lab three times with seven to nine days between each visit. After enrollment, they were randomly assigned to receive iTBS at an intensity of 50%, 70% or 100% RMT in each session. The sequence of stimulation intensities was determined by a simple, computer-generated, random number list and counterbalanced among subjects. fNIRS measurements were performed immediately before and around 15 minutes (i.e., the time required to place the fNIRS probe on a subject's head) after stimulation. During both fNIRS measurements, before and after stimulation, subjects performed the VFT. The summary of the procedure is illustrated in the flowchart shown in Figure 3.1. This study is a part of a research program which has been registered at clinicaltrials.gov (NCT04031105).

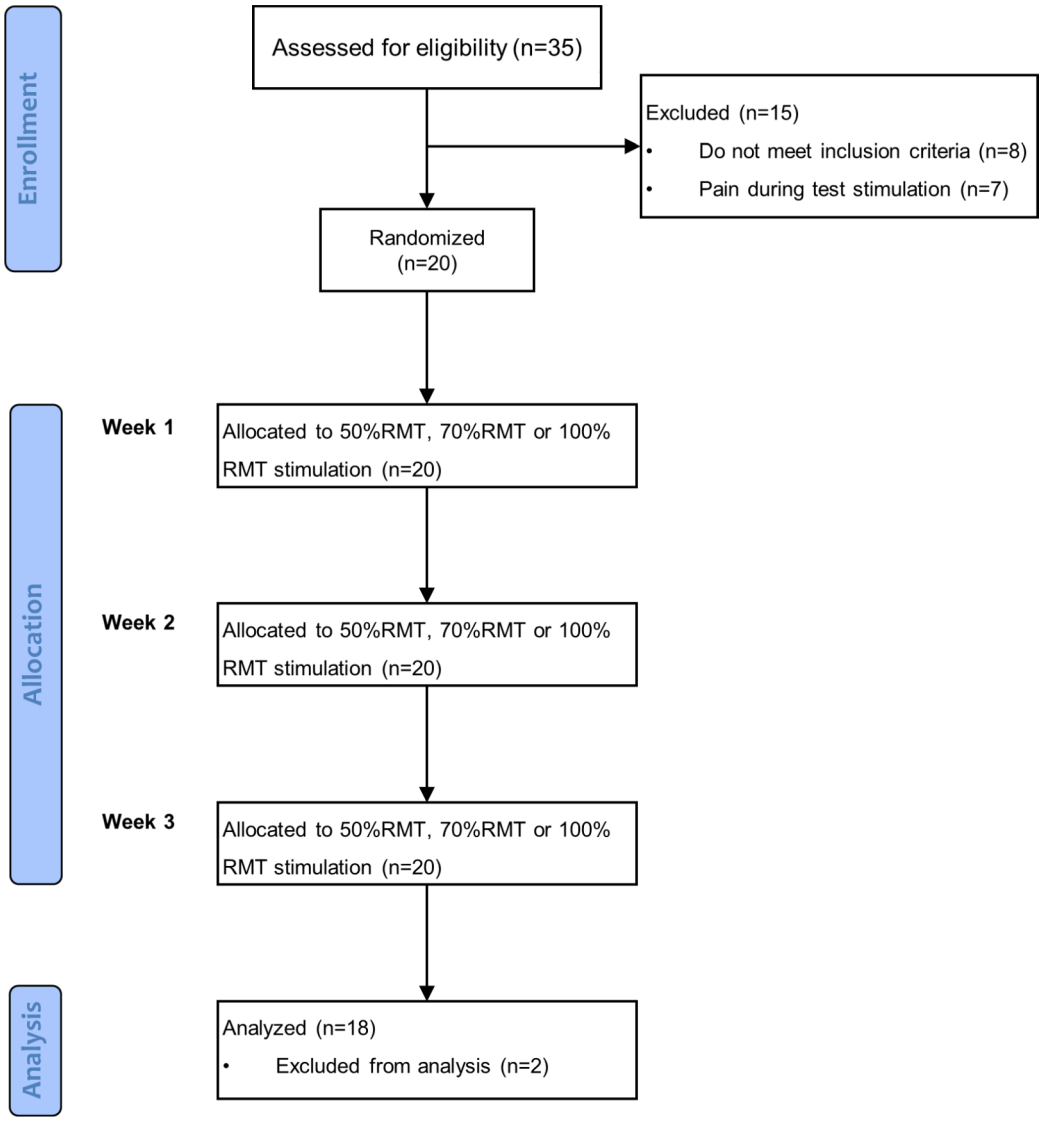

Figure 3. 1 Flowchart of the experiment procedure.

3.3.3 Intermittent theta burst stimulation

iTBS was delivered using a figure-of-eight shaped cooling coil (Cool-B65), connected to a MagPro magnetic stimulator (MagVenture, Denmark). We adhered to the initial 3-minute iTBS protocol (3 pulses×10 bursts×20 trains=600 pulses) developed by Huang et al. [3], which consists of 20 trains of 3-pulse bursts with 50 Hz intra-burst frequency. Each train contains 10 bursts delivered at 5 Hz and separated by 8 seconds of rest. The RMT for each subject was determined using a single pulse at the left primary motor cortex, defined as the minimum intensity capable of eliciting motor evoked potentials (MEPs) with at least 50 μV peak-to-peak amplitude in at least five out of ten consecutive measurements of the relaxed right first dorsal interosseous muscle (FDI). iTBS was delivered at intensities of 50%, 70% or 100% RMT for each subject on a given session. 70% RMT was chosen because it corresponds to 80% active motor threshold used in study that first reported the application of TBS in human [3]. We utilized 100% RMT due to the higher neural activity response to increased stimulation intensity observed in conventional rTMS studies [14, 29]. In addition, stimulation at 50% RMT was regarded as an active control condition as a previous study reported that TBS at a low intensity did not affect brain excitability [30]. We targeted the left DLPFC at the MNI coordinate of (x-38, y+44, z+26), as done previously [31, 32]. The stimulation target was identified and monitored by a navigation system (LOCALITE® TMS Navigator Germany) during iTBS. Self-reported side effects were documented after each stimulation, using the self-rate Numeric Pain Rating Scale (from 0 [No Pain] to 10 [Worst Imaginable Pain]) [33]. All subjects were naïve to TMS.

3.3.4 fNIRS measurement

Hemodynamic activity was measured using a continuous wave near-infrared (695 and 830 nm) spectroscopy device (ETG-4000, Hitachi Medical Co., Tokyo, Japan) with a sampling rate of 10 Hz. We used a 3×11 probe design with 52 channels for data collection (Figure 3.2). The probe was placed on the forehead with the lower edge aligned with the T4-Fpz-T3 line of International 10-20 system and the sixth column aligned with the brain's middle line. The area between two nearby sources and detectors is defined as a channel (Ch). The distance between a pair of emitter and detector was 3 cm, which allowed to measure the concentration change of HbO and HbR at 2-3cm below the skin and scalp surface. The probe was registered to the surface of the standard brain embedded in the AtlasViewer toolbox [34] and projected to the cortex to estimate the MNI coordinate of each channel (the midpoint between each pairs of source and detector) (Table 3.1). The estimation of probabilistic anatomical locations of channels based on the Brodmann area (BA) atlas shows that our probe arrangement enabled to detect the hemoglobin changes in bilateral DLPFC (BA 9, 46), frontopolar area (BA 10), anterior superior temporal gyrus (BA 22) and middle temporal gyrus (BA 21) (Table 3.1). Participants were told to sit still and avoid head movements during the measurement. Measurements started once the fNIRS signal was stable.

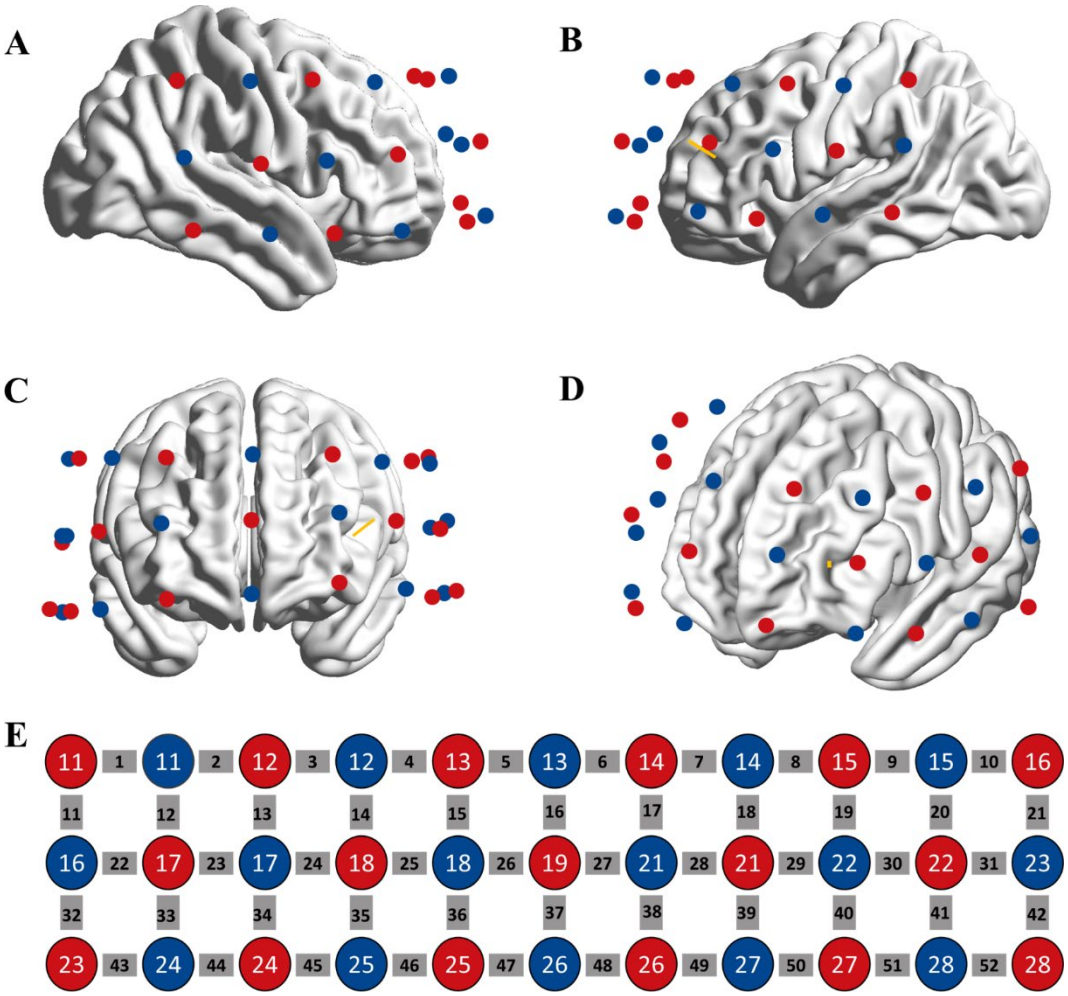

Figure 3. 2 Location of fNIRS sources (red circle) and detectors (blue circle) on the head as seen from the right (a), left (b), anterior (c), and left frontal (d) perspectives. (d) The sources and detectors were laid out in a 3*11 configuration. The grey squares represent measuring channels. The yellow bar denotes the projection of stimulation target.

Table 3. 1 MNI coordinates of each channel's midpoint and the estimated corresponding BA area for each channel.

CHANNEL NUMBER	MNI COORDINATE			BRODMANN AREA	ESTIMATED PROBABILITY
	X	Y	Z		
CH01	62.333	-42.333	49.667	40 - Supramarginal gyrus part of Wernicke's area	1
CH02	60.333	-13.667	50.667	4 - Primary Motor Cortex	0.394
				3 - Primary Somatosensory Cortex	0.344
				6 - Pre-Motor and Supplementary Motor Cortex	0.151
				1 - Primary Somatosensory Cortex	0.112
CH03	50	13.333	51.333	9 - Dorsolateral prefrontal cortex	0.612
				6 - Pre-Motor and Supplementary Motor Cortex	0.376
				44 - pars opercularis, part of Broca's area	0.012
CH04	31.333	34.333	52.333	9 - Dorsolateral prefrontal cortex	0.642
				8 - Includes Frontal eye fields	0.358
CH05	9	47	53	9 - Dorsolateral prefrontal cortex	0.687
				8 - Includes Frontal eye fields	0.313
CH06	-15.667	45.667	50.333	9 - Dorsolateral prefrontal cortex	0.893
				8 - Includes Frontal eye fields	0.107
CH07	-37.667	31.667	48	9 - Dorsolateral prefrontal cortex	0.919
				8 - Includes Frontal eye fields	0.045
				46 - Dorsolateral prefrontal cortex	0.022
				45 - pars triangularis Broca's area	0.009
				44 - pars opercularis, part of Broca's area	0.004
CH08	-51	11.667	46.667	6 - Pre-Motor and Supplementary Motor Cortex	0.457
				9 - Dorsolateral prefrontal cortex	0.358
				44 - pars opercularis, part of Broca's area	0.185
CH09	-60.333	-13.667	46.667	3 - Primary Somatosensory Cortex	0.357
				4 - Primary Motor Cortex	0.307
				1 - Primary Somatosensory Cortex	0.213

				6 - Pre-Motor and Supplementary Motor Cortex	0.087
				43 - Subcentral area	0.036
CH10	-62.667	-35.667	48.333	40 - Supramarginal gyrus part of Wernicke's area	0.806
				2 - Primary Somatosensory Cortex	0.162
				1 - Primary Somatosensory Cortex	0.032
CH11	64.333	-53.333	33	40 - Supramarginal gyrus part of Wernicke's area	0.413
				22 - Superior Temporal Gyrus	0.302
				39 - Angular gyrus, part of Wernicke's area	0.252
				48 - Retrosubicular area	0.034
CH12	69.667	-23	34.333	2 - Primary Somatosensory Cortex	0.731
				1 - Primary Somatosensory Cortex	0.215
				40 - Supramarginal gyrus part of Wernicke's area	0.035
				43 - Subcentral area	0.019
CH13	63	4.667	36.667	6 - Pre-Motor and Supplementary Motor Cortex	0.674
				4 - Primary Motor Cortex	0.165
				43 - Subcentral area	0.106
				44 - pars opercularis, part of Broca's area	0.051
				3 - Primary Somatosensory Cortex	0.004
CH14	48.667	32.667	38.667	45 - pars triangularis Broca's area	0.421
				44 - pars opercularis, part of Broca's area	0.237
				9 - Dorsolateral prefrontal cortex	0.204
				46 - Dorsolateral prefrontal cortex	0.138
CH15	24	52	42.667	9 - Dorsolateral prefrontal cortex	0.955
				46 - Dorsolateral prefrontal cortex	0.045
CH16	-5	58.667	41	9 - Dorsolateral prefrontal cortex	0.85
				10 - Frontopolar area	0.15
CH17	-30.333	48.333	38.333	9 - Dorsolateral prefrontal cortex	0.583
				46 - Dorsolateral prefrontal cortex	0.417
CH18	-48.667	29.667	37.333	45 - pars triangularis Broca's area	0.474

				44 - pars opercularis, part of Broca's area	0.386
				9 - Dorsolateral prefrontal cortex	0.096
				46 - Dorsolateral prefrontal cortex	0.044
CH19	-61	5	34.667	6 - Pre-Motor and Supplementary Motor Cortex	0.646
				43 - Subcentral area	0.139
				4 - Primary Motor Cortex	0.131
				44 - pars opercularis, part of Broca's area	0.077
				3 - Primary Somatosensory Cortex	0.007
CH20	-66	-19.333	36.667	2 - Primary Somatosensory Cortex	0.492
				1 - Primary Somatosensory Cortex	0.354
				43 - Subcentral area	0.131
				3 - Primary Somatosensory Cortex	0.023
CH21	-65.333	-45	36.333	40 - Supramarginal gyrus part of Wernicke's area	0.817
				48 - Retrosubicular area	0.157
				22 - Superior Temporal Gyrus	0.023
				39 - Angular gyrus, part of Wernicke's area	0.003
CH22	71	-35.667	17.667	22 - Superior Temporal Gyrus	0.779
				48 - Retrosubicular area	0.118
				40 - Supramarginal gyrus part of Wernicke's area	0.078
				2 - Primary Somatosensory Cortex	0.025
CH23	69	-4	20	43 - Subcentral area	0.777
				22 - Superior Temporal Gyrus	0.125
				6 - Pre-Motor and Supplementary Motor Cortex	0.05
				48 - Retrosubicular area	0.047
CH24	60	24.667	22.667	45 - pars triangularis Broca's area	0.617
				44 - pars opercularis, part of Broca's area	0.383
CH25	41.667	50.667	28.667	46 - Dorsolateral prefrontal cortex	0.756
				45 - pars triangularis Broca's area	0.244
CH26	12.667	66	30.667	10 - Frontopolar area	0.795
				9 - Dorsolateral prefrontal cortex	0.205

CH27	-19.333	62.667	29.667	10 - Frontopolar area	0.563
				9 - Dorsolateral prefrontal cortex	0.219
				46 - Dorsolateral prefrontal cortex	0.219
CH28	-42.667	46.667	27.667	46 - Dorsolateral prefrontal cortex	0.523
				45 - pars triangularis Broca's area	0.477
CH29	-56	25	25.667	45 - pars triangularis Broca's area	0.592
				44 - pars opercularis, part of Broca's area	0.408
CH30	-65	-1.333	25.667	43 - Subcentral area	0.746
				6 - Pre-Motor and Supplementary Motor Cortex	0.228
				4 - Primary Motor Cortex	0.026
CH31	-69	-29.333	23.667	2 - Primary Somatosensory Cortex	0.419
				22 - Superior Temporal Gyrus	0.309
				48 - Retrosubicular area	0.165
				42 - Primary and Auditory Association Cortex	0.061
				40 - Supramarginal gyrus part of Wernicke's area	0.046
CH32	71	-46.333	2.667	21 - Middle Temporal gyrus	0.459
				22 - Superior Temporal Gyrus	0.355
				37 - Fusiform gyrus	0.147
				20 - Inferior Temporal gyrus	0.039
CH33	72	-15.333	1.667	22 - Superior Temporal Gyrus	0.556
				21 - Middle Temporal gyrus	0.444
CH34	62.667	14.333	8.333	48 - Retrosubicular area	0.414
				6 - Pre-Motor and Supplementary Motor Cortex	0.303
				44 - pars opercularis, part of Broca's area	0.228
				45 - pars triangularis Broca's area	0.052
				38 - Temporopolar area	0.003
CH35	54	43	10	45 - pars triangularis Broca's area	0.709
				46 - Dorsolateral prefrontal cortex	0.291
CH36	28.667	67	16.667	10 - Frontopolar area	0.927
				46 - Dorsolateral prefrontal cortex	0.073

CH37	-4.333	70	16	10 - Frontopolar area	1
CH38	-34	61.333	17.333	46 - Dorsolateral prefrontal cortex	0.522
				10 - Frontopolar area	0.478
CH39	-51.667	40.667	14.333	45 - pars triangularis Broca's area	0.909
				46 - Dorsolateral prefrontal cortex	0.091
CH40	-60	17.333	14.333	44 - pars opercularis, part of Broca's area	0.419
				6 - Pre-Motor and Supplementary Motor Cortex	0.268
				45 - pars triangularis Broca's area	0.217
				48 - Retrosubicular area	0.096
CH41	-67.667	-10	11.667	22 - Superior Temporal Gyrus	0.648
				43 - Subcentral area	0.217
				48 - Retrosubicular area	0.135
CH42	-70	-41.333	8.667	22 - Superior Temporal Gyrus	0.787
				21 - Middle Temporal gyrus	0.212
CH43	73	-26.667	-11.667	21 - Middle Temporal gyrus	0.853
				20 - Inferior Temporal gyrus	0.147
CH44	66.333	1.667	-11.333	21 - Middle Temporal gyrus	0.849
				38 - Temporopolar area	0.123
				48 - Retrosubicular area	0.027
CH45	57	34.333	-4.667	45 - pars triangularis Broca's area	0.554
				38 - Temporopolar area	0.208
				47 - Inferior prefrontal gyrus	0.147
				46 - Dorsolateral prefrontal cortex	0.091
CH46	43.667	60.333	-1.667	10 - Frontopolar area	0.486
				46 - Dorsolateral prefrontal cortex	0.478
				47 - Inferior prefrontal gyrus	0.02
				11 - Orbitofrontal area	0.016
CH47	12.333	74	2.667	10 - Frontopolar area	0.848
				11 - Orbitofrontal area	0.152
CH48	-19.333	72	4.667	10 - Frontopolar area	0.766

				11 - Orbitofrontal area	0.234
CH49	-44.333	55.667	3.333	46 - Dorsolateral prefrontal cortex	0.759
				10 - Frontopolar area	0.241
CH50	-56	34.667	2.333	45 - pars triangularis Broca's area	0.925
				38 - Temporopolar area	0.058
				46 - Dorsolateral prefrontal cortex	0.016
CH51	-62	3.667	-1.333	48 - Retrosubicular area	0.527
				21 - Middle Temporal gyrus	0.289
				38 - Temporopolar area	0.174
				6 - Pre-Motor and Supplementary Motor Cortex	0.01
CH52	-71	-22.333	-5.333	21 - Middle Temporal gyrus	0.915
				22 - Superior Temporal Gyrus	0.085

3.3.5 Verbal fluency task

The design of the VFT was adapted from previous fNIRS studies, which utilized a counterbalanced block design [25, 35, 36] (see Figure 3.3). The task consisted of two experimental blocks and two control blocks. Animals and means of transportation were used as semantic categories for the VFT before stimulation (VFT version 1) while clothes and fruits/vegetables were used as categories for the VFT after stimulation (VFT version 2). Both versions started with a 60-second block of the control condition, followed by a 60-second block of the experimental condition. During the experiment, subjects sat comfortably and 50 cm in front of a computer screen. During the experimental condition, participants were told to generate as many words as possible that belonged to the semantic category shown on the centre of the screen without repetition. During the control block, they needed to repeat the numbers "1,2,3,4,1,2,3,4…" at a steady pace, as done previously [25]. The purpose of these control blocks was to account for changes in hemodynamic response caused by talking. Prior to the start of the task, subjects were given a practice trial (i.e., semantic category of flowers) to ensure that they understood how to complete the task correctly. The overall duration of the VFT task was 240 s. All stimuli were presented using E-Prime 2 (Psychology Software Tool, Pittsburgh, PA, USA).

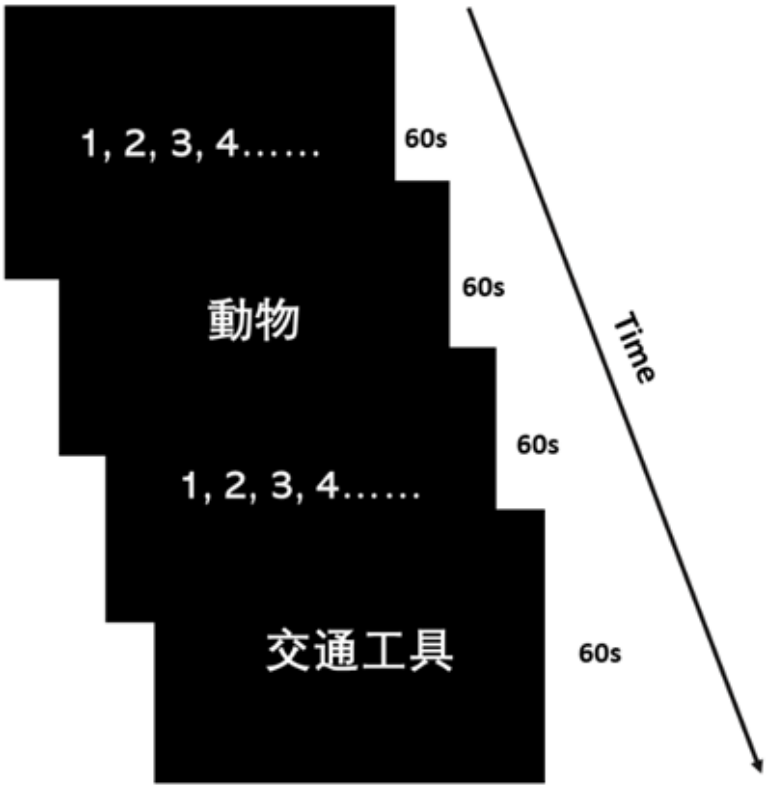

Figure 3. 3 The experimental design of verbal fluency task.

3.3.6 Data analysis

3.3.6.1 fNIRS data analysis

fNIRS data analysis was performed using the HOMER 2 toolbox and custom scripts developed in MATLAB 2013b (The MathWorks, Inc., Natick, MA) [37]. For preprocessing, channels with an optical density higher than 140 dB were excluded for further analysis to omit saturated channels [38]. The raw fNIRS data was then converted to optical density (OD) [39]. Motion artifacts were detected and corrected by a mixed approach based on the spline interpolation method and Slvitzky-Golay filtering of each channel [40]. A bandpass filter (0.002-0.08Hz) was then employed to remove physiological noise caused by heartbeat, respiration and drifts [41]. These preprocessed signals were converted to the concentration change of HbO (ΔHbO) based on the modified Beer-Lambert Law with a differential pathlength factor of six [42, 43] The time course HbO concentration change (0-60 seconds) for the experimental conditions was calculated using the *hmrR_BlockAvg* function [37]. Lastly, the data of experimental blocks were averaged. Baseline correction was performed per experimental block using the mean of the last five seconds signal of control block [44]. We also investigated the hemodynamic response during the early VFT task period (0-30s) because a previous study reported that the early semantic VFT phase (0-30s) was supported by executive functions while the late phase (31-60s) was mainly dependent on the semantic network activation [45]. The region of interest was defined as the stimulated area that corresponds most closely to the location of Ch28. In this study, we used HbO signals as an indicator of hemodynamic response since HbO is more sensitive to regional

cerebral blood flow than Hb [46]. The mean of HbO concentration change for different groups were used for further analysis. To visualize the difference of the left DLPFC activation during VFT task before and after stimulation, we contrasted the mean of ΔHbO (0-60s) before and after stimulation for each intensity using paired t-test results. This analysis yielded three t-maps which show the t-value for ch28 at each intensity. The t-values and MNI coordinates were first converted to *.img files using nirs2im function (https://www.alivelearn.net/?p=2230) in the xjview toolbox (https://www.alivelearn.net/xjview/). Next, the transformed image files were visualized on a 3D brain model (ICBM512 template) using a BrainNet Viewer toolbox [47].

3.3.6.2 Statistical analysis

One-way repeated measures analysis of variance (ANOVA) was used to compare the baseline difference of VFT performance and brain activity. In order to investigate the stimulation effects, behavioral as well as imaging data were analyzed by two-way repeated measures ANOVA using time (pre, post) and intensity (50%, 70%, 100%) as within-subjects factors. In case of significant main effects, post hoc pairwise comparisons were corrected using Fisher least significant difference (LSD) procedure in accordance with the closed test principle: post hoc comparisons were declared nonsignificant if the global p value of the main effect (testing equality of both time points or of all 3 intensities simultaneously) was nonsignificant but carried out without further correction in case of a significant global main effect. Statistical significance was set at $P<0.05$. Pearson correlation was used to analyze the relationship between VFT

performance and difference of ΔHbO. SPSS version 24 for Windows (SPSS Inc., Chicago, Illinois; www.spss.com) was used for statistical analyses.

3.4 Results

Two subjects were excluded from the data analysis due to poor quality of fNIRS signals and interruption of the program during measurement. Finally, 18 subjects (9 female, mean age: 22.30±3.54 years) were included for the data analysis. One-way repeated measures ANOVA did not reveal a significant difference in the time interval between the second fNIRS measurement and iTBS between groups (50%RMT group: 20.780± 2.533 min; 70%RMT group: 19.889±2.720 min; 100%RMT group: 20.778±2.942 min; $F_{2,34}$=0.727, *P*=0.491). Prior to stimulation, the subjects generated 41.39±10.05, 40.11±7.75, 42.33±9.00 accurate words for 50%, 70% and 100% RMT stimulation condition, respectively. After stimulation these values increased to 43.67±9.42 ($t_{(17)}$=1.06, *P*=0.305, *d*=0.249), 44.61±8.24 ($t_{(17)}$=2.511, *P*=0.022, *d*=0.592) and 44.28±9.04 ($t_{(17)}$=1.421, *P*=0.173, *d*=0.335), respectively. The averaged fNIRS signal during the VFT task in the left DLPFC (Ch28) among different conditions is shown in Figure 3.4 A. There were no baseline differences regarding VFT behavioral performance ($F_{2,34}$=0.500, *P*=0.611, η_p^2=0.029) and brain activity ($F_{2,34}$=0.267, *P*=0.767, η_p^2=0.015) between groups. Two-way repeated measures ANOVA on VFT accuracy showed a significant main effect of time ($F_{1,17}$=4.455, *P*=0.05, η_p^2=0.208) but not of intensity ($F_{2,34}$=0.165, *P*=0.849, η_p^2=0.010) nor an interaction of time×intensity ($F_{2,34}$=0.958, *P*=0.394, η_p^2=0.053). Exploratory post-hoc comparisons indicated a

significant performance increase after stimulation compared to baseline at the intensity of 70%RMT ($t_{(17)}$=2.511, *P*=0.022, *d*=0.592) but not at the other two intensities (*P*>0.05) (Figure 3.4 B). Brain activation analysis for the early task period showed a significant main effect of time ($F_{1,17}$=4.873, *P*=0.041, η_p^2=0.223), and an interaction effect of time and intensity ($F_{2,34}$=4.442, *P*=0.019, η_p^2=0.207) but no main effect of intensity ($F_{2,34}$=2.130, *P*=0.134, η_p^2=0.111). Post-hoc analyses using change scores to resolve the interaction effect indicated significantly higher HbO values post stimulation at 70% RMT, compared to 50% ($t_{(17)}$=2.203, *P*=0.042, *d*=0.523) and 100% RMT ($t_{(17)}$=2.947, *P*=0.009, *d*=0.547) (Figure 3.4 C). Analysis for early phase behavioral performance also showed the same inverse U-shape curve despite not reaching significance (time: $F_{1,17}$=0.349, *P*=0.563, η_p^2=0.020; intensity: $F_{2,34}$=0.015, *P*=0.985, η_p^2=0.001; time×intensity: $F_{2,34}$=1.528, *P*=0.232, η_p^2=0.082) (Figure. 3.4 D). No significant results were observed when looking at the HbO change averaged across the whole task period (Figure 3.5). However, the correlation analysis revealed a significant positive correlation between behavioral accuracy and the difference in HbO concentration change in left DLPFC after 70% RMT stimulation (Pearson's r= 0.496, *P*=0.036) but not after the other two intensities (Figure 3.6).

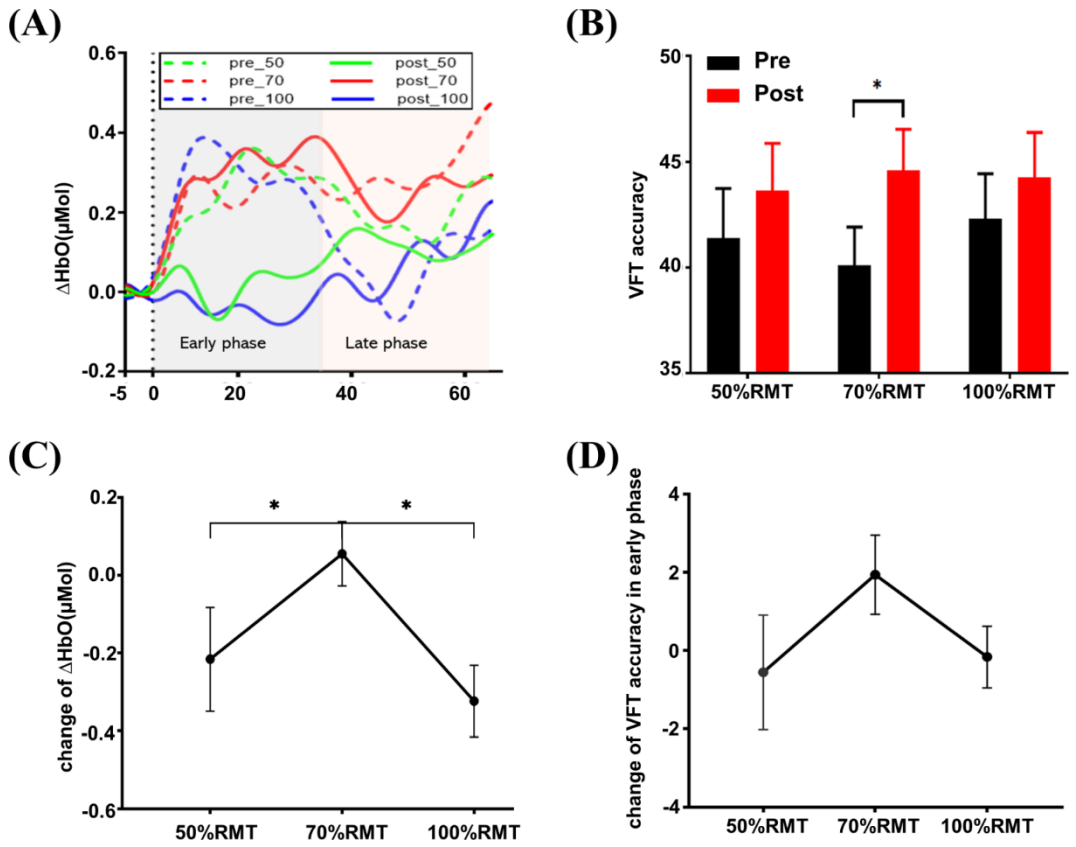

Figure 3. 4 (A) Group averaged time course HbO concentration change during the experimental condition in the left DLPFC (Ch28) before and after stimulation at each intensity. The Y-axis represents the mean of ΔHbO. (B) VFT behavior performance (mean±SEM) for the whole task period (0-60s). (C) Change of ΔHbO in the early task phase (0-30s) for each stimulation intensity. Data were calculated by subtracting the mean of ΔHbO before stimulation from the mean of ΔHbO after stimulation. (D) VFT behavior performance change (mean±SEM) in early task phase for each stimulation intensity. *P<0.05

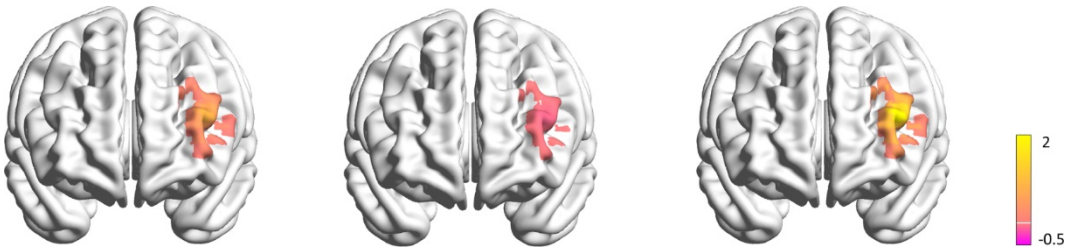

Figure 3. 5 Maps of the left DLPFC activation difference before and after stimulation during VFT task in 50% RMT condition (left), 70%RMT condition (middle), 100% RMT condition (right). The color bar indicates the t-values render over on a 3D head model. The yellow color represents less ΔHbO after stimulation, while the purple color represents more ΔHbO after stimulation.

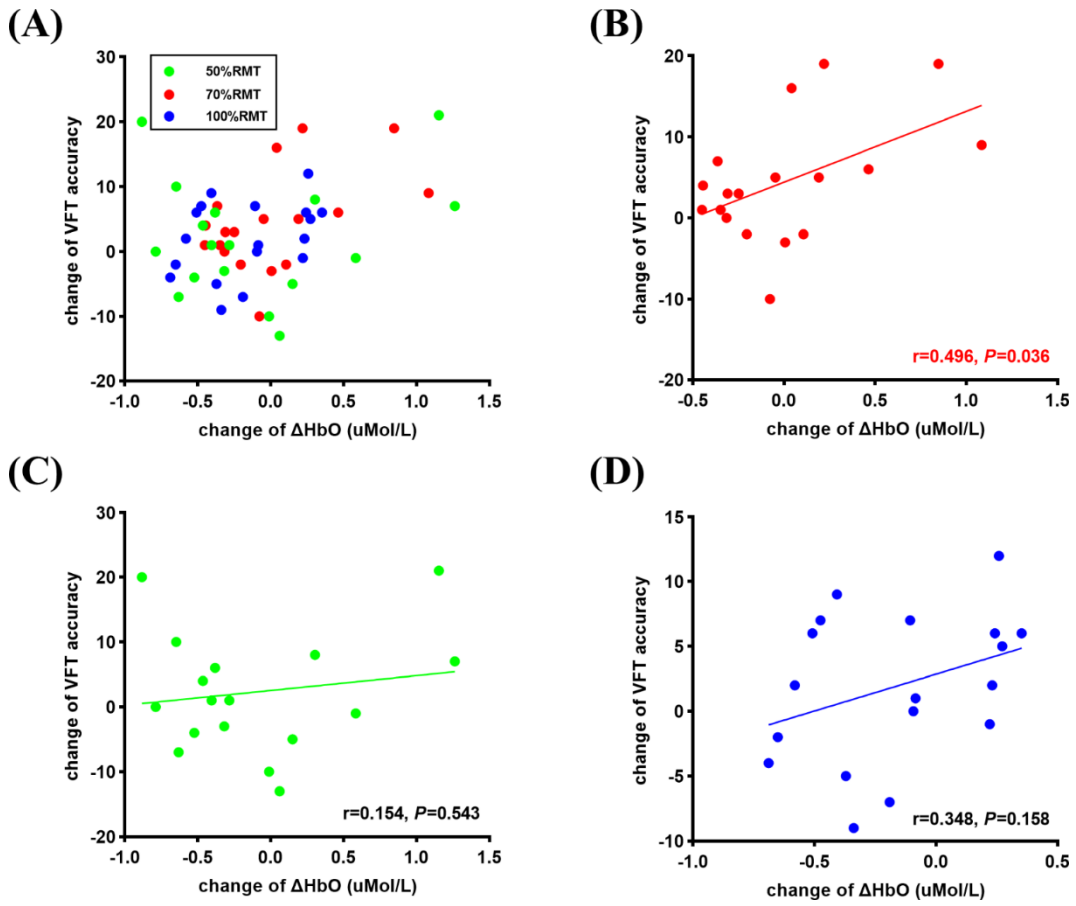

Figure 3. 6 (A) Correlation between change of corrected words generated during VFT task and change of ΔHbO at all stimulation intensities Correlation between change of corrected words generated during VFT task and change of ΔHbO in 70% RMT stimulation (B), 50% RMT stimulation condition (C) and 100% RMT stimulation (D).

3.5 Discussion

In this study, we investigated the effects of varying stimulation intensities of iTBS of the left DLPFC on executive function and underlying cortical activity using fNIRS. While several previous studies have investigated iTBS effects on the brain using electroencephalogram (EEG) [9, 48, 49], we investigated such effects using fNIRS, as it is more tolerant to lip and jaw movements during VFT task performance [50]. In all stimulation intensity, descriptively, the number of words generated by subjects after stimulation increased than before stimulation. However, the improvement in executive performance was only significant after 70% RMT stimulation. Besides, iTBS to the left DLPFC with 70% RMT maintained the concentration change of HbO in the target area, whereas 50% iTBS and 100% iTBS decreased change of HbO concentration, indicating an inverse U-shape relationship between stimulation intensity and prefrontal hemodynamic response. Moreover, a significant positive correlation was observed between behavioral accuracy and the difference in HbO concentration change in the targeted area after 70% RMT stimulation.

The modest enhancements of VFT performance in all intensity conditions supports the beneficial effects of excitatory stimulation of iTBS stimulation on executive functioning [51, 52]. However, contrary to our hypothesis, our results did not demonstrate a linear relationship between stimulation intensity and brain activity, as observed in conventional rTMS studies [14, 53] and a study examining low TBS intensity [10]. Specifically, we found significant improvement of executive function

only after 70% RMT iTBS; the corresponding hemodynamic response revealed that iTBS to the left DLPFC with 70% RMT maintained the concentration change of HbO in the target area, whereas 50% iTBS and 100% iTBS decreased ΔHbO. A possible explanation for these observations is related to mechanisms of theta-frequency-dependent LTP induction [54, 55]. Normally, a single burst activates a glutamatergic (excitatory) synapse and a gamma-aminobutyric acid (GABA)-ergic (inhibitory) synapse on a pyramidal neuron, producing both an excitatory postsynaptic potential (EPSP) and inhibitory postsynaptic potential (IPSP) on this neuron. This IPSP undercuts the EPSP triggered by this burst and the next burst for a short period of time, preventing the hyperexcitability of the downstream pyramidal neuron. However, this IPSP can be suppressed for a short period of time if a second burst is delivered at theta frequency [55]. The underlying mechanism is the further GABA release from the GABAergic presynaptic terminal that follows this second burst, inhibits future GABA release through activation of $GABA_B$ autoreceptors [56]. Consequently, this GABA-mediated disinhibitaion induces LTP effects via activation of N-methyl-D-aspartate (NMDA) receptors [57]. A previous study reported that a second burst delivered at 200 milliseconds after the initial burst produces maximal excitatory effects by using this mechanism of disinhibition – i.e., by inducing more GABA release to activate $GABA_B$ autoreceptors [54, 56]. Bursts given outside of this window (above or below 200 ms) may not result in such optimal effects in human brains, possibly because burst effects encounter an already-present IPSP from previous activations or recovered IPSP [55, 58]. An important caveat is that the onset of this disinhibition may be modulated by stimulus

intensity [58]. Therefore, TBS at high intensities (such as 100% RMT) may off-set this temporal window and fail to elicit the maximal excitatory effects of theta frequency on brain activity. Consistent with this view, Chung et al. found that iTBS at 75% RMT intensity showed maximal neuromodulatory effects on brain activity in humans [59].

We observed a relative lower ΔHbO following 50% and 100% RMT stimulation compared to before stimulation despite increased VFT performance. This appears to be contradictory to the general understanding of the neurovascular coupling phenomenon. According to this principle, a cognitively demanding task such as the VFT should lead to a rise in HbO needs, indicating an increase in cortical activation, as a result of increased neuronal mobilization [28, 60, 61]. It is theorized that higher cortical activation should be accompanied with better behavioral performance, since higher cortical activation suggests more cognitive resources are being mobilized to complete a task [62]. However, previous studies also reported that increased DLPFC activation may be a compensatory strategy for reduced available neural resources, or alternatively, an inefficient employment of neural resources [63, 64]. Recent evidence suggests that excitatory rTMS to the left DLPFC increases neural efficiency, observed as reduced concentration change of total hemoglobin after stimulation during Speed of Processing task [65]. This finding corroborates cognitive efficiency theories which propose that people with more efficient cortical processing require less cognitive resources to achieve better performance [63, 66, 67]. Therefore, TBS benefits to behavioral performance may be due to improved efficiency of neurons, such that the same levels

of cortical activation (captured by fNIRS) provide increased processing power, improving performance.

Imaging results revealed a significantly higher HbO concentration change following 70% RMT stimulation than 50% RMT and 100% RMT only in the early task phase but not the whole task period. This can be explained by the dynamic model of retrieval process involved in the semantic fluency tasks. A previous study indicated that early phases of the semantic VFT task is mediated more by executive processes while the late phase is mainly dependent on semantic network activation [45]. It has been well established that the DLPFC plays an important role in supporting executive control [68-71]. Therefore, it is not surprising that the potentially optimal iTBS intensity enhanced the excitability of the left DLPFC and further boosted the behavioral performance.

Certainly, our study is not free of limitations. First, we did not have a real sham condition in this experiment. Nonetheless, our study included a low intensity (50% RMT) condition, comparable to a number of TMS studies that have adopted the strategy of lowering stimulation intensity as a sham condition [48, 72, 73]. Second, due to the inherent limitation of the fNIRS equipment used, such as the height profile of our fNIRS probes we were unable to measure the hemodynamic response to iTBS during and immediately after the stimulation. To demonstrate this, further studies using a concurrent TMS-fNIRS set up are needed. Thirdly, Fisher LSD method does not offer full control of the type I error. However, it is known to preserve the experiment-wise

type I error at the nominal significance level if there are three groups [74]. Fourth, the choice of intensities used in our study is not representative of all often-used stimulation intensities in clinical settings (e.g., 90%RMT, 110%RMT and 120%RMT). We adopted relatively lower TBS intensities, as an endorsed advantage of TBS protocols in clinical applications is the lower necessary intensity for treatment, allowing for more comfortable sessions [75, 76]. Additionally, on methodological grounds, our results are comparable to Huang et al. (2005), who used low intensities (80% AMT) to study the patterned effects of TBS on MEPs. Even so, our findings have limited generalizability to suprathreshold TBS intensities. Further studies comparing these effects are needed.

3.6 Conclusion

The linear association between stimulation intensity and behavioral improvement observed in healthy people receiving conventional rTMS may not extend to iTBS. Our investigation revealed an inverted U-shaped association between iTBS intensity and the excitatory effects on brain activity, suggesting that iTBS at 70% RMT may be more efficacious than 100% RMT.

3.7 Author's Contribution

For the work presented in this chapter, the author contributed to the following aspects of the study: Conceptualization; Methodology; Software; Investigation; Data Curation; Formal Analysis; Writing-Original draft; Writing-Review & Editing; Visualization.

3.8 References

1. Terao, Y. and Y. Ugawa, Basic mechanisms of TMS. Journal of clinical neurophysiology, 2002. 19(4): p. 322-343.
2. Klomjai, W., R. Katz, and A. Lackmy-Vallée, Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med, 2015. 58(4): p. 208-213.
3. Huang, Y.-Z., et al., Theta Burst Stimulation of the Human Motor Cortex. Neuron, 2005. 45(2): p. 201-206.
4. Diamond, D.M., T.V. Dunwiddie, and G.M. Rose, Characteristics of hippocampal primed burst potentiation in vitro and in the awake rat. J Neurosci, 1988. 8(11): p. 4079-88.
5. Capocchi, G., M. Zampolini, and J. Larson, Theta burst stimulation is optimal for induction of LTP at both apical and basal dendritic synapses on hippocampal CA1 neurons. Brain Res, 1992. 591(2): p. 332-6.
6. Blumberger, D.M., et al., Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet, 2018. 391(10131): p. 1683-1692.
7. He, W., J.-C. Wang, and P.-Y. Tsai, Theta Burst Magnetic Stimulation Improves Parkinson's-Related Cognitive Impairment: A Randomised Controlled Study. Neurorehabilitation and Neural Repair, 2021. 35(11): p. 986-995.
8. Bation, R., et al., Intermittent theta burst stimulation for negative symptoms of

schizophrenia—A double-blind, sham-controlled pilot study. npj Schizophrenia, 2021. 7(1): p. 10.

9. Philip, N.S., et al., Theta-Burst Transcranial Magnetic Stimulation for Posttraumatic Stress Disorder. Am J Psychiatry, 2019. 176(11): p. 939-948.

10. Huang, Y.-Z. and J.C. Rothwell, The effect of short-duration bursts of high-frequency, low-intensity transcranial magnetic stimulation on the human motor cortex. Clinical Neurophysiology, 2004. 115(5): p. 1069-1075.

11. Chu, H.-T., et al., Efficacy and tolerability of theta-burst stimulation for major depression: A systematic review and meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2021. 106: p. 110168.

12. Lowe, C.J., et al., The effects of theta burst stimulation (TBS) targeting the prefrontal cortex on executive functioning: A systematic review and meta-analysis. Neuropsychologia, 2018. 111: p. 344-359.

13. Speer, A.M., et al., Intensity-dependent regional cerebral blood flow during 1-Hz repetitive transcranial magnetic stimulation (rTMS) in healthy volunteers studied with H215O positron emission tomography: i. effects of primary motor cortex rTMS. Biological Psychiatry, 2003. 54(8): p. 818-825.

14. Kähkönen, S., et al., Prefrontal transcranial magnetic stimulation produces intensity-dependent EEG responses in humans. NeuroImage, 2005. 24(4): p. 955-960.

15. Luo, J., et al., High-Frequency Repetitive Transcranial Magnetic Stimulation (rTMS) Improves Functional Recovery by Enhancing Neurogenesis and

Activating BDNF/TrkB Signaling in Ischemic Rats. International journal of molecular sciences, 2017. 18(2): p. 455.

16. Rounis, E. and Y.Z. Huang, Theta burst stimulation in humans: a need for better understanding effects of brain stimulation in health and disease. Exp Brain Res, 2020. 238(7-8): p. 1707-1714.

17. Kim, H.Y., et al., Application of Functional Near-Infrared Spectroscopy to the Study of Brain Function in Humans and Animal Models. Mol Cells, 2017. 40(8): p. 523-532.

18. Jöbsis, F.F., Noninvasive, infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters. Science, 1977. 198(4323): p. 1264-7.

19. Pinti, P., et al., The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Ann N Y Acad Sci, 2020. 1464(1): p. 5-29.

20. Heinzel, S., et al., Variability of (functional) hemodynamics as measured with simultaneous fNIRS and fMRI during intertemporal choice. NeuroImage, 2013. 71: p. 125-134.

21. Funane, T., et al., Concurrent fNIRS-fMRI measurement to validate a method for separating deep and shallow fNIRS signals by using multidistance optodes. Neurophotonics, 2015. 2(1): p. 015003.

22. Sato, H., et al., A NIRS–fMRI investigation of prefrontal cortex activity during a working memory task. Neuroimage, 2013. 83: p. 158-173.

23. Ferrari, M. and V. Quaresima, A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. NeuroImage, 2012. 63(2): p. 921-935.

24. Yeung, M.K. and J. Lin, Probing depression, schizophrenia, and other psychiatric disorders using fNIRS and the verbal fluency test: A systematic review and meta-analysis. Journal of Psychiatric Research, 2021. 140: p. 416-435.

25. Yeung, M.K., et al., Altered Frontal Lateralization Underlies the Category Fluency Deficits in Older Adults with Mild Cognitive Impairment: A Near-Infrared Spectroscopy Study. Front Aging Neurosci, 2016. 8: p. 59.

26. Shao, Z., et al., What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Frontiers in Psychology, 2014. 5.

27. Wagner, S., et al., A coordinate-based ALE functional MRI meta-analysis of brain activation during verbal fluency tasks in healthy control subjects. BMC neuroscience, 2014. 15(1): p. 1-13.

28. Yeung, M.K., Frontal cortical activation during emotional and non-emotional verbal fluency tests. Scientific Reports, 2022. 12(1): p. 8497.

29. Nahas, Z., et al., Unilateral left prefrontal transcranial magnetic stimulation (TMS) produces intensity-dependent bilateral effects as measured by interleaved BOLD fMRI. Biol Psychiatry, 2001. 50(9): p. 712-20.

30. Doeltgen, S.H. and M.C. Ridding, Low-intensity, short-interval theta burst stimulation modulates excitatory but not inhibitory motor networks. Clinical

Neurophysiology, 2011. 122(7): p. 1411-1416.

31. Zhang, B.B.B., et al., Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 2021. 14(4): p. 924-926.

32. Fox, M.D., et al., Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry, 2012. 72(7): p. 595-603.

33. Childs, J.D., S.R. Piva, and J.M. Fritz, Responsiveness of the Numeric Pain Rating Scale in Patients with Low Back Pain. Spine, 2005. 30(11): p. 1331-1334.

34. Aasted, C., et al., Anatomical guidance for functional near-infrared spectroscopy: AtlasViewer tutorial. Neurophotonics, 2015. 2(2): p. 020801.

35. Patra, A., A. Bose, and T. Marinis, Performance difference in verbal fluency in bilingual and monolingual speakers. Bilingualism: Language and Cognition, 2020. 23(1): p. 204-218.

36. Tupak, S.V., et al., Differential prefrontal and frontotemporal oxygenation patterns during phonemic and semantic verbal fluency. Neuropsychologia, 2012. 50(7): p. 1565-1569.

37. Huppert, T.J., et al., HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt, 2009. 48(10): p. D280-98.

38. Li, X., et al., Brain correlates of motor complexity during observed and executed actions. Scientific Reports, 2020. 10(1): p. 10965.

39. Yücel, M.A., et al., Best practices for fNIRS publications. Neurophotonics, 2021. 8(1): p. 012101.

40. Jahani, S., et al., Motion artifact detection and correction in functional near-infrared spectroscopy: a new hybrid method based on spline interpolation method and Savitzky-Golay filtering. Neurophotonics, 2018. 5(1): p. 015003.

41. Kirilina, E., et al., Identifying and quantifying main components of physiological noise in functional near infrared spectroscopy on the prefrontal cortex. Front Hum Neurosci, 2013. 7: p. 864.

42. Kocsis, L., P. Herman, and A. Eke, The modified Beer-Lambert law revisited. Phys Med Biol, 2006. 51(5): p. N91-8.

43. Delpy, D.T., et al., Estimation of optical pathlength through tissue from direct time of flight measurement. Phys Med Biol, 1988. 33(12): p. 1433-42.

44. Bai, Z., et al., Cortical mapping of mirror visual feedback training for unilateral upper extremity: A functional near-infrared spectroscopy study. Brain and Behavior, 2020. 10(1): p. e01489.

45. Raboutet, C., et al., Performance on a semantic verbal fluency task across time: dissociation between clustering, switching, and categorical exploitation processes. J Clin Exp Neuropsychol, 2010. 32(3): p. 268-80.

46. Strangman, G., et al., A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage, 2002. 17(2): p. 719-731.

47. Xia, M., J. Wang, and Y. He, BrainNet Viewer: a network visualization tool for

human brain connectomics. PLoS One, 2013. 8(7): p. e68910.

48. Zhang, J.J., Z. Bai, and K.N.K. Fong, Priming Intermittent Theta Burst Stimulation for Hemiparetic Upper Limb After Stroke: A Randomized Controlled Trial. Stroke (1970), 2022. 53(7): p. 2171-2181.

49. Chung, S.W., et al., The effects of individualised intermittent theta burst stimulation in the prefrontal cortex: A TMS-EEG study. Hum Brain Mapp, 2019. 40(2): p. 608-627.

50. Pinti, P., et al., The present and future use of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. Annals of the New York Academy of Sciences, 2020. 1464(1): p. 5-29.

51. Wu, X., et al., Improved Cognitive Promotion through Accelerated Magnetic Stimulation. eNeuro, 2021. 8(1).

52. Cheng, C.M., et al., Different forms of prefrontal theta burst stimulation for executive function of medication- resistant depression: Evidence from a randomized sham-controlled study. Prog Neuropsychopharmacol Biol Psychiatry, 2016. 66: p. 35-40.

53. Padberg, F., et al., Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology, 2002. 27(4): p. 638-45.

54. Larson, J., D. Wong, and G. Lynch, Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. Brain Res, 1986. 368(2): p. 347-50.

55. Larson, J. and E. Munkácsy, Theta-burst LTP. Brain research, 2015. 1621: p. 38-50.

56. Davies, C., S. Davies, and G. Collingridge, Paired-pulse depression of monosynaptic GABA-mediated inhibitory postsynaptic responses in rat hippocampus. The Journal of physiology, 1990. 424(1): p. 513-531.

57. Davies, C.H., et al., GABA autoreceptors regulate the induction of LTP. Nature, 1991. 349(6310): p. 609-11.

58. Cash, R.F., et al., Late cortical disinhibition in human motor cortex: a triple-pulse transcranial magnetic stimulation study. J Neurophysiol, 2010. 103(1): p. 511-8.

59. Chung, S.W., et al., Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum Brain Mapp, 2018. 39(2): p. 783-802.

60. Husain, S.F., et al., Functional near-infrared spectroscopy during the verbal fluency task of English-Speaking adults with mood disorders: A preliminary study. J Clin Neurosci, 2021. 94: p. 94-101.

61. Phillips, A.A., et al., Neurovascular coupling in humans: Physiology, methodological advances and clinical implications. J Cereb Blood Flow Metab, 2016. 36(4): p. 647-64.

62. Biswal, B.B., et al., Task-Dependent Individual Differences in Prefrontal Connectivity. Cerebral Cortex, 2010. 20(9): p. 2188-2197.

63. Rypma, B., et al., Neural correlates of cognitive efficiency. NeuroImage, 2006.

33(3): p. 969-979.

64. Stuss, D.T. and R.T. Knight, Principles of frontal lobe function. 2002, Oxford ;: Oxford University Press.

65. Curtin, A., et al., Enhancing neural efficiency of cognitive processing speed via training and neurostimulation: An fNIRS and TMS study. NeuroImage, 2019. 198: p. 73-82.

66. Gimenez, P., et al., Neuroimaging correlates of handwriting quality as children learn to read and write. Frontiers in human neuroscience, 2014. 8: p. 155.

67. Gold, B.T., et al., Lifelong bilingualism maintains neural efficiency for cognitive control in aging. Journal of Neuroscience, 2013. 33(2): p. 387-396.

68. Smith, E.E. and J. Jonides, Storage and executive processes in the frontal lobes. Science, 1999. 283(5408): p. 1657-1661.

69. Kane, M.J. and R.W. Engle, The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. Psychonomic bulletin & review, 2002. 9(4): p. 637-671.

70. MacDonald, A.W., et al., Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science, 2000. 288(5472): p. 1835-1838.

71. Miller, E.K. and J.D. Cohen, An integrative theory of prefrontal cortex function. Annual review of neuroscience, 2001. 24(1): p. 167-202.

72. Dieler, A.C., et al., Can intermittent theta burst stimulation as add-on to psychotherapy improve nicotine abstinence? Results from a pilot study.

European addiction research, 2014. 20(5): p. 248-253.

73. Zhang, J.J. and K.N.K. Fong, The Effects of Priming Intermittent Theta Burst Stimulation on Movement-Related and Mirror Visual Feedback-Induced Sensorimotor Desynchronization. Frontiers in Human Neuroscience, 2021. 15.

74. Meier, U., A note on the power of Fisher's least significant difference procedure. Pharm Stat, 2006. 5(4): p. 253-63.

75. Cárdenas-Morales, L., et al., Mechanisms and applications of theta-burst rTMS on the human motor cortex. Brain Topogr, 2010. 22(4): p. 294-306.

76. Suppa, A., et al., Ten Years of Theta Burst Stimulation in Humans: Established Knowledge, Unknowns and Prospects. Brain Stimul, 2016. 9(3): p. 323-335.

Chapter 4 Priming theta-burst stimulation: the importance of the right timing

Part of this work was presented orally at *The 6th Neurotechnology Innovation Forum & Founding Conference of the Basic and Translational Neuromodulation Branch of Chinese Neuroscience Society.* held from April 26–28, 2024, in Shanghai, China.

Part of this work was presented as a poster at the *The 35th CINP World Congress of Neuropsychopharmacology*, held from May 23-26, 2024, in Tokyo, Japan.

Part of this work was presented as a poster at the *1st Meeting of Neuromodulation Society in China Great Bay Area,* held from June 7-8, in Zhuhai, China.

Part of this work has been accepted as a poster presentation at the *6th Brain Stimulation Conference*, will hold from 23-26 February 2025, in Kobe, Japan.

The manuscript for the work presented in this chapter is currently in preparation.

4.1 Abstract

Background: Intermittent theta burst stimulation (iTBS) is a noninvasive brain stimulation tool capable of increasing cortical excitability beyond the stimulation period. Its ability to quickly produce modulatory effects has made prefrontal iTBS an increasingly popular therapeutic approach for treating psychiatric conditions like depression. However, the large inter-individual response variability necessitates strategies for optimizing iTBS efficacy. The priming stimulation protocol comprises a priming stimulation before a test stimulation, with the priming stimulation being able to enhance the effects of the test stimulation by utilizing the principle of therapeutically beneficial metaplasticicy. However, the optimal time interval between priming and test stimulation is still unknown.

Objective: This study sought to systematically examine the neuromodulatory effects of priming TBS stimulation in the left DLPFC among individuals with depressive symptoms.

Methods: One hundred and sixty subjects were involved in this study. The priming TBS protocol comprised a priming continuous TBS (cTBS) followed by a subsequent iTBS. The experimental conditions included real or sham cTBS immediately followed by iTBS, real cTBS followed by iTBS after a 10-minute and 20-minute delay. TBS was administered to the left DLPFC at the intensity of 70% of their individual resting motor threshold. Brain activity of the left DLPFC was assessed using functional near-infrared spectroscopy before and after stimulation. Behavioral effects were evaluated using verbal fluency task (VFT) and emotion recognition accuracy (ERA) task.

Results: Our results revealed a significant decrease of ΔHbO after all priming stimulation conditions. Notably, this effect was significantly more pronounced and robust in the 10-min interval priming TBS condition compared to other conditions. However, there were no differences in VFT performance across the different priming TBS groups, as all groups showed improved performance. No significant differences were found regarding the ERA performance.

Conclusion: Our findings indicate that a 10-minute interval between cTBS and iTBS appears to be the optimal timing to alter the hemodynamic effects of iTBS by leveraging metaplasticity mechanisms. However, these differences do not translate into measurable behavioral differences, at least not for the tasks under investigation. These results underscore the potential of priming TBS protocols to enhance the efficacy of rTMS treatments for psychiatric disorders by optimizing stimulation timing and leveraging therapeutically beneficial metaplasticity.

4.2 Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a widely used non-invasive brain stimulation technique to modulate brain excitability in targeted brain regions [1]. This capability has made rTMS a valuable tool in the treatment of various neurological and psychiatric conditions, including depression [2]. Theta burst stimulation (TBS), an advanced form of rTMS, has become widely recognized for achieving comparable effects to traditional rTMS while significantly reducing the required administration time [3]. TBS is typically categorized into two types: intermittent TBS (iTBS) and continuous TBS (cTBS). iTBS shows excitatory effects on brain activity operating through mechanisms resembling long-term potentiation (LTP), whereas cTBS shows inhibitory effects through mechanisms similar to long-term depression (LTD) [3]. Currently, iTBS targeting the left dorsolateral prefrontal cortex (DLPFC) is a well-established protocol for treating depression, as this region is typically underactive in individuals with the disorder [4].

Despite its effectiveness, the overall treatment efficacy of iTBS for depression remains suboptimal [5]. One possible reason is the brain's inherent self-protective system, known as homeostatic metaplasticity, which may constrain the benefits of external brain stimulation [6]. The Bienenstock-Cooper-Munro theory explains this phenomenon by proposing a “sliding threshold” for synaptic plasticity. According to this theory, a recent history of low neuronal activity lowers the threshold for future LTP induction, making further excitation more likely. Conversely, high levels of recent neuronal activity raise

the threshold, decreasing the likelihood of further excitation [7].

To enhance the efficacy of rTMS effects, researchers have proposed priming stimulation protocols that take advantage of homeostatic metaplasticity [8]. These protocols involve administering a priming stimulation, followed by a variable break, and then a test stimulation [8-10]. Supporting this approach, studies have shown that the excitatory effects of iTBS on the motor cortex are amplified when preceded by inhibitory cTBS [11, 12]. Additionally, research investigating the antidepressant effects of priming rTMS found significantly higher antidepressant efficacy for a 1-Hz priming protocol compared to a protocol without priming stimulation [9].

The timing of priming stimulation is one of the kay factor in shaping the nature of metaplasticity—whether it will be homeostatic or non-homeostatic [13, 14]. Research indicates that shorter intervals between stimulations are more likely to promote non-homeostatic metaplasticity due to the lingering effects of the initial stimulation, while longer intervals are associated with homeostatic responses [15]. For instance, studies have demonstrated that a 10-minute interval between cTBS and iTBS sessions elicits homeostatic effects in young adults [16], whereas no interval fails to produce such effects as reported by transcranial direct current stimulation study [17]. To date, no study has systematically investigated the timing effects of priming TBS stimulation on the left DLPFC.

Functional near-infrared spectroscopy (fNIRS) is an optical diffusion technique that allows noninvasive imaging of cortical activity [18]. This is achieved by shining near-infrared light through the skull and measuring the concentration change of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HbR) in the brain cortex [19]. Its portability, affordability, and suitability for natural settings have made it an increasingly popular tool in neurophysiological and neuropsychiatric research [20]. fNIRS has been particularly valuable in investigating frontal lobe activity. Studies employing fNIRS have demonstrated significantly lower frontal activation in individuals with depression compared to healthy controls during verbal fluency task (VFT) [21]. Moreover, research by Curtin et al. further suggests that rTMS is able to enhance the frontal activation as measured by fNIRS. This improvement in frontal lobe activity is associated with enhanced executive function [22]. Furthermore, even individuals with subclinical depressive symptoms can experience impairment in executive function and facial emotion recognition [23-25]. These individuals also often exhibit imbalances in their behavioral activation and inhibition systems (BAS/BIS) [26], as well as altered positive and negative affect [27].

Our study aimed to systematically investigate the neuromodulatory effects of priming TBS stimulation in the left DLPFC among individuals with depressive symptoms. We hypothesized that the stimulation interval between priming stimulation and test stimulation will affect the effects of the priming TBS protocol. Specifically, we hypothesized that a 10-minute interval will potentiate the effect of the test iTBS,

whereas 0-minute will eliminate it, and a 20-minute interval will have no effect (i.e., result in no difference, relative to sham priming TBS). Furthermore, the second objective of our research was to examine the effects of priming TBS stimulation in the context of executive function and emotion regulation in people with depressive symptoms. We hypothesized that optimal priming stimulation would improve performance of VFT and facial emotion recognition tasks in people with depressive symptoms.

4.3 Materials and Methods

4.3.1 Study design and participants

This study was a randomized controlled trial with parallel groups. Randomization was stratified by the factors age, gender and education years. Participants were recruited through convenience sampling at The Hong Kong Polytechnic University between December 2022 and January 2024. The study protocol was pre-registered on ClinicalTrials.gov (NCT04031105) and received ethical approval from the Human Subjects Ethics Subcommittee of The Hong Kong Polytechnic University (HSESC20181212008).

Eligibility criteria included right-handedness (Edinburgh Handedness Questionnaire score $\geqslant$ +60) [28], age between 18 and 35 years, Patient Health Questionnaire-9 (PHQ-9) $\leqslant$14, native Chinese speaker, normal or corrected-to-normal vision, at least six years of formal education, comprehension of verbal instructions, and the ability to provide

informed consent. Exclusion criteria encompassed current or past psychiatric or neurological disorders, unstable medical conditions requiring further investigation or treatment, any contraindications to transcranial magnetic stimulation (TMS) as per established safety checklists [29, 30], use of medications affecting neural activity (e.g., benzodiazepines, anticonvulsants), or inability to tolerate the experimental procedure.

Potential participants were first screened by phone. Those who met initial eligibility criteria were invited for an in-person baseline assessment. This assessment included the Patient Health Questionnaire (PHQ-9) for depressive symptoms [31], the International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) for positive and negative affectivity [32, 33], and the Behavioral inhibition /Behavioral Activation System (BIS/BAS) scale for dispositional sensitivity to BIS/BAS [34]. Eligible participants were then allocated to one of four stimulation conditions:

- Condition 1: cTBS administered before iTBS with a 10-minute gap (10-min interval priming TBS);
- Condition 2: cTBS administered before iTBS with a 20-minute gap (20-min interval priming TBS);
- Condition 3: cTBS administered immediately before iTBS (0-min interval priming TBS);
- Condition 4: sham cTBS administered immediately before iTBS (sham priming TBS).

To minimize potential interference during the intervals between stimulations, all participants were required to complete a simple, low-demand color-filling activity. Figure 4.1 illustrates an overview of the experiment procedure.

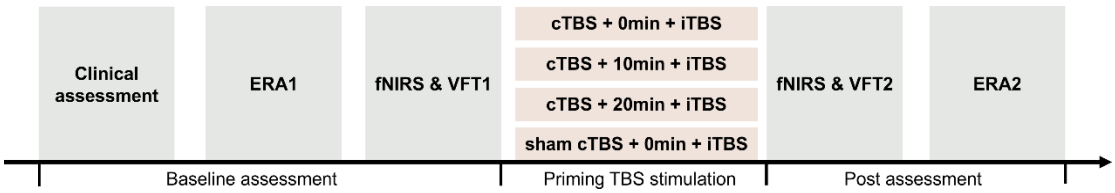

Figure 4. 1 Schematic diagram of the experimental design.

4.3.2 Sample size calculation

The sample size calculation was based on previous studies demonstrating the effects of priming TBS [16] and demonstrating group differences in prefrontal activation after TMS using fNIRS [35, 36]. Hence, for detecting significant differences between conditions, a sample size of N=128 was determined using an effect size of F=0.15, a power of 0.8 and an alpha level of 0.05 using G*Power 3.0.10 (ANOVA: Repeated measures, within-between interaction). Given an expected drop-out rate of 20%, a conservative sample size was set for 160 participants (i.e., 40 participants for each of the 4 conditions).

4.3.3 Behavioral inhibition /Behavioral Activation System (BIS/BAS) scales

The Chinese version of BIS/BAS scale was used to investigate the individual differences in dispositional sensitivity to BIS/BAS [34]. The scale consists of 18 items covering four factors: BAS-Fun, BAS-Drive, BAS-Reward responsiveness, and BIS. Responses to each item were provided on a four-point Likert scale, from "strongly disagree" to "strongly agree". The BIS/BAS scale has demonstrated good reliability and validity for measuring personality constructs [37].

4.3.4 The International Positive and Negative Affect Schedule Short Form (I-PANAS-SF)

The Chinese version of the I-PANAS-SF was used to evaluate participants' positive

affectivity and negative affectivity [33]. This nine-item scale measures the affective dimension of subjective well-being including four affective states (active, attentive, determined, and inspired) and five negative affective states (afraid, ashamed, nervous, hostile, and upset). Participants were asked to indicate the degree to which each adjective reflected their emotional state over the previous two weeks. The Cronbach's alpha values were above 0.7, demonstrating acceptable internal consistency [33].

4.3.5 Theta burst stimulation

The protocols established by Huang et al. [3] were implemented, including a 3-minute iTBS protocol (600 pulses delivered as 3 pulses per burst × 10 bursts per train × 20 trains) and a 40-second cTBS protocol (600 pulses). [3]. A figure-of-eight cooling coil (MagVenture Cool-B65) connected to a MagPro X100 magnetic stimulator (MagVenture, Denmark) was employed for TBS administration. Coil placement was guided by a neuronavigation system (LOCALITE® TMS Navigator, Germany) to ensure accurate targeting of the left DLPFC, identified using MNI coordinates x = -38, y = +44, z = +26 [38, 39]. The coil handle was positioned at a 45° angle from the midline, pointing backwards and laterally. Stimulation intensity was set at 70% of each participant's resting motor threshold (RMT) [36]. The RMT was assessed by delivering single magnetic pulses to the left primary motor cortex. The objective was to identify the minimum stimulation intensity required to evoke motor-evoked potentials (MEPs) in the right first dorsal interosseous muscle. An MEP was considered valid if it displayed a peak-to-peak amplitude of at least 50 μV. The threshold criterion was met

if this response occurred in at least five out of ten consecutive trials. [40]. For sham cTBS, the coil was positioned at a 90° angle to the scalp, with one wing of the figure-of-eight coil touching the scalp [41]. After each stimulation session, self-reported side effects as well as the pain during stimulation assessed by self-rate Numeric Pain Rating Scale (from 0 [No Pain] to 10 [Worst Imaginable Pain]) [42] were documented.

4.3.6 fNIRS measurement

Neural activity was monitored using fNIRS during a VFT session. The ETG-4000 system (Hitachi Medical Co., Tokyo, Japan), a continuous-wave fNIRS device operating at wavelengths of 695 nm and 830 nm with a sampling frequency of 10 Hz, was utilized to estimate brain activation by detecting changes in oxygenated and deoxygenated hemoglobin levels. A probe setup consisting of a 3×11 configuration with 17 sources and 16 detectors resulted in 52 channels (Figure 4.2.). Each channel represented the area between a source-detector pair separated by 3 cm, enabling the measurement of hemoglobin concentration changes roughly 2-3 cm beneath the scalp, corresponding to the cerebral cortex surface [43]. Sources and detectors were stabilized in a customized plastic plate to ensure stable optode-scalp coupling. The probe was positioned to cover the frontal and temporal regions, ensuring its lower edge corresponded to the T3-Fpz-T4 line specified by the International 10-10 EEG system. The central column of the array was carefully aligned with the midline of the head for accurate placement [44].

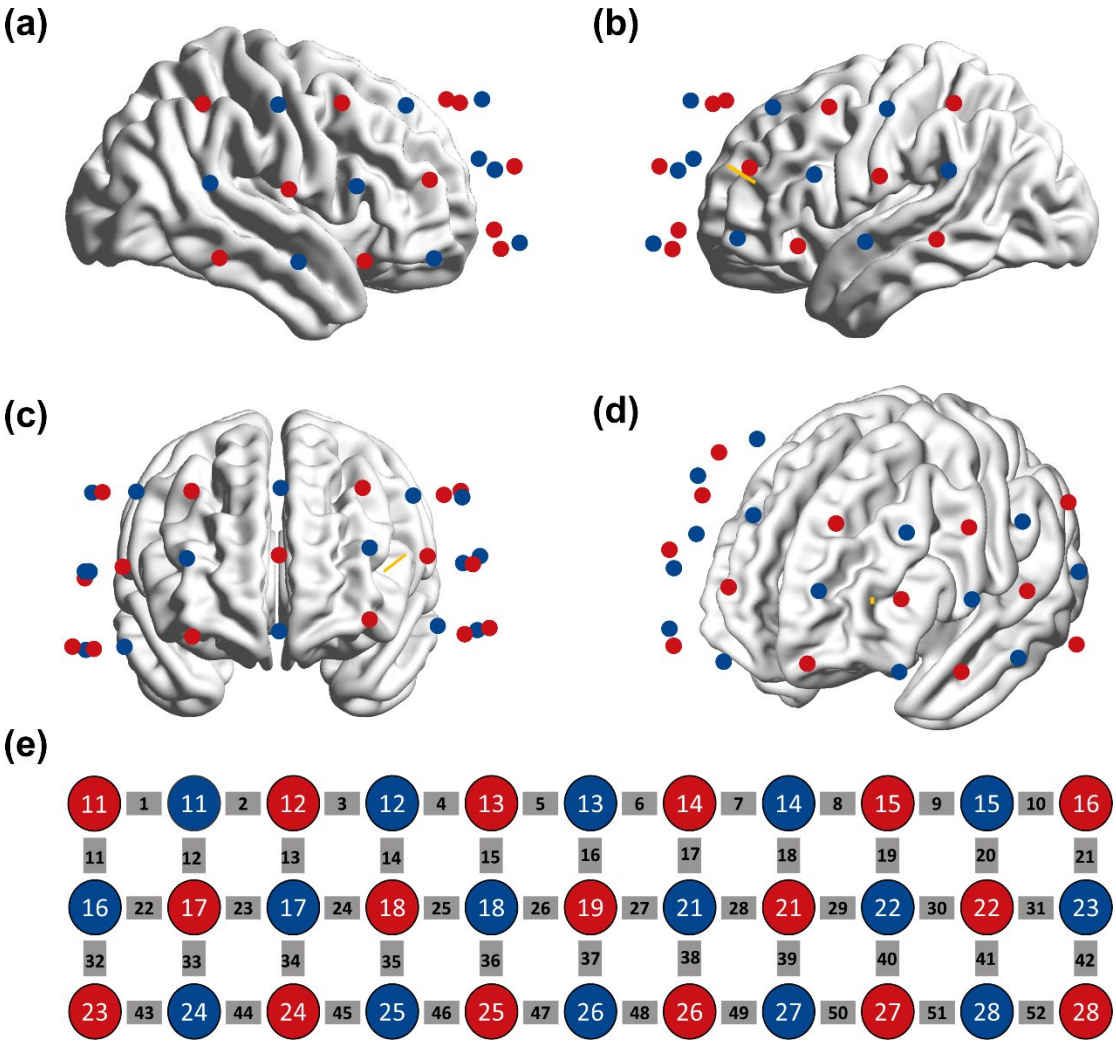

Figure 4. 2 Placement of fNIRS optodes and measurement channels. Panels show the positions of sources (red markers) and detectors (blue markers) from various perspectives: (a) right, (b) left, (c) front, and (d) left-frontal views. (e) Diagram of the 3×11 source-detector layout, where gray blocks indicate individual measurement channels. The yellow bar highlights the estimated location of the stimulation target.

Following each fNIRS measurement, a Polhemus 3D digitizer (Patriot^{TM} USA, Polhemus) was used to record the 3D positions of the sources and detectors for every participant. The AtlasViewer toolbox [45] was employed to estimate channel locations by aligning the probe to a scaled Colin brain atlas based on individual head dimensions. This process enabled the determination of MNI coordinates for each channel's midpoint. NIRS_SPM was utilized to perform probabilistic anatomical localization of each channel based on Brodmann areas (BA) [46]. The findings revealed that the probe covered the regions of bilateral DLPFC (BA 9, 46), frontopolar area (BA 10), anterior superior temporal gyrus (BA 22), and middle temporal gyrus (BA 21). During the measurement, participants were placed in a quiet room and instructed to remain motionless. Measurements commenced once the fNIRS signal had stabilized. To mitigate chronobiological effects on brain excitability and fNIRS signals, experiments were preferentially scheduled in the afternoon, resulting in 147 out of 163 datasets being collected between 13:00 and 18:00.

4.3.7 Verbal fluency task (VFT)

The VFT was performed directly before and after stimulation. A counterbalanced block design was used for the VFT [47-49]. The task consisted of three 60-second experimental blocks interspersed with four 60-second control blocks, commencing and concluding with control blocks (Figure 4.3 a). Two variants of the VFT were employed. The pre-stimulation version (Version 1) used semantic categories of animals, occupations, and means of transportation, while the post-stimulation version (Version

2) used countries, clothes, and fruits/vegetables. The order of category presentation was randomized within each version. During the experimental blocks, participants were asked to verbally produce as many unique words as they can that correspond to the category displayed on the computer screen. In control blocks, participants were asked to repeatedly count from one to four at a consistent pace to account for speech-related hemodynamic changes [47]. Task comprehension was confirmed through a practice trial using the category "flowers" and a control block. The entire task lasted 420 seconds and was administered using E-Prime 2 (Psychology Software Tool, Pittsburgh, PA, USA). Participants were positioned in a quiet room and directed to remain motionless and minimize movement throughout the task.

4.3.8 Emotion recognition accuracy task (ERA task)

The ERA task was performed before and after VFT. Participants were presented with 64 digitized color images of Chinese facial expressions depicting emotions, sourced from the Tsinghua facial expression database [50]. The stimuli comprised 16 images each of sad, happy, fearful and neutral expressions on young Chinese faces. Equal numbers of male and female faces were included for each emotion. In each trial, a single image was displayed for up to 6 seconds in random order. Participants were instructed to identify the emotion using specific keyboard keys ('A' for sad, 'S' for happy, 'K' for fearful, and 'L' for neutral) within the presentation time [51] (Figure 4.3 b). Trials progressed upon response or after the 6-second limit, followed by a 500-millisecond pause between trials. Two distinct but comparable sets of stimuli, balanced for

emotional intensity, were used before and after stimulation.

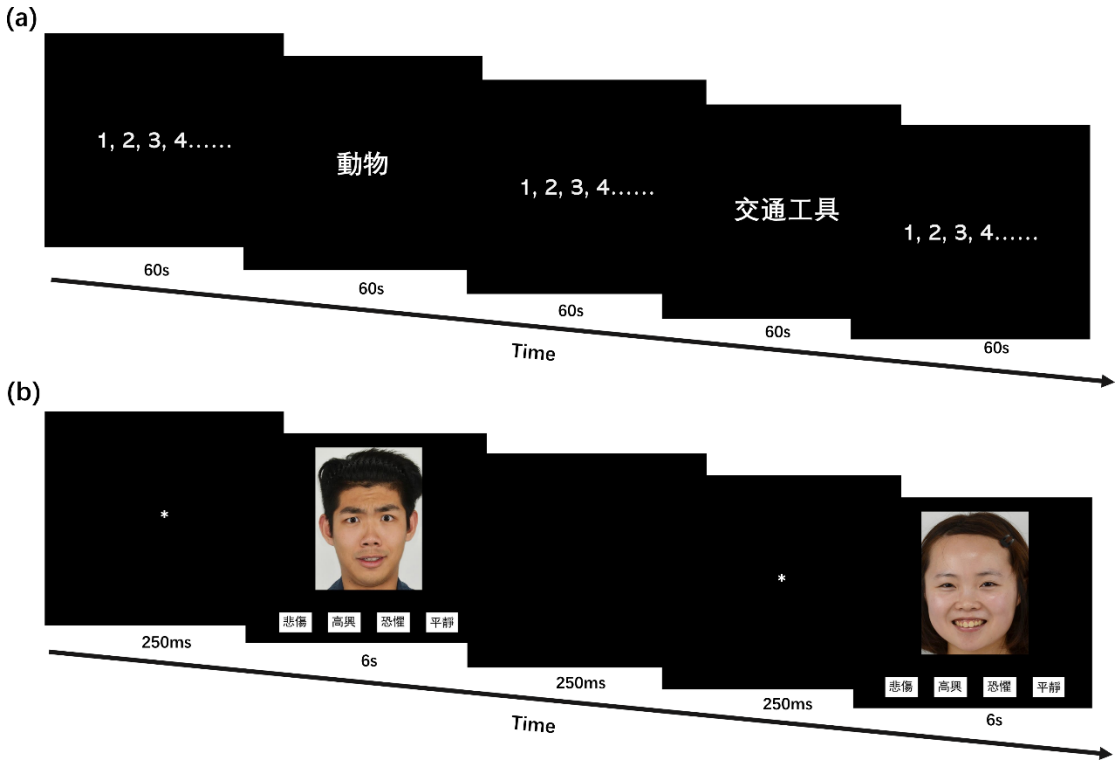

Figure 4. 3 Schematic diagram of behavioral tasks. (a)VFT. (b) ERA.

4.4 Data analysis

4.4.1 fNIRS data analysis

The analysis of fNIRS data was conducted using the HOMER 2 toolbox [52] along with custom MATLAB 2013b scripts (The MathWorks, Inc., Natick, MA). During preprocessing, channels with optical density readings exceeding 140 dB were excluded to eliminate saturated channels [53]. The raw fNIRS signals were then converted into optical density (OD) [19]. To address motion artifacts, a hybrid approach combining spline interpolation [54] and wavelet filtering [55] was applied to each channel, as recommended by Novi et al. for fNIRS speech studies [56]. A bandpass filter with a range of 0.008-0.05 Hz was used to remove low-frequency drifts and high-frequency noise [57]. After preprocessing, the signals were converted to changes in hemoglobin concentration (ΔHbO and ΔHbR) according to the modified Beer-Lambert Law, applying a differential path length factor of six [58, 59]. The hmrR_BlockAvg function [52] was used to calculate the HbO concentration changes over time (0-60 seconds) for the experimental conditions. Baseline correction was performed for each block by subtracting the mean signal from the five seconds preceding the task [60]. Signals from experimental blocks were then averaged for each run. The left DLPFC (Brodmann 46 area) was identified as the region of interest (ROI). Channel location estimation revealed that ch 28, ch38, ch39, and ch49 measured signals from the left Brodmann 46 area. The hemodynamic response from channels within the ROI was averaged. Since HbO signals typically exhibit a better signal-to-noise ratio [61-63], they were used as the primary indicator of the hemodynamic response, although HbR changes were also

included in the results [64]. The mean ΔHbO values during experimental blocks (0-60 seconds) were calculated to quantify the hemodynamic response. To visualize activation differences in the DLPFC during the verbal fluency task (VFT) before and after stimulation, paired t-tests were conducted to contrast the ΔHbO means for each group. This produced t-maps illustrating t-values within the ROI for each condition. The t-values and corresponding MNI coordinates were converted into *.img files using the nirs2img function (https://www.alivelearn.net/?p=2230). The resulting image files were then visualized on a 3D brain model (ICBM512 template) using the BrainNet Viewer toolbox [65], facilitated by the xjView toolbox (https://www.alivelearn.net/xjview/).

4.4.2 Statistical analysis

We used IBM SPSS Statistics version 29 (IBM Corp., Chicago, IL; https://www.ibm.com/products/spss-statistics) for statistical analyses. Baseline demographic information and clinical parameters were compared between conditions using one-way analysis of variance (ANOVA) for continuous variables and Chi-square tests for categorical variables. To evaluate stimulation effects, we used a mixed-design ANOVA (within-subject factor: time, between-subject factor: condition, interaction effect: time by condition) to compare behavioral and imaging data. The score of BAS reward responsiveness (BAS-RR) was put as a covariate, as previous study reported that reward sensitivity modulates brain activity in the prefrontal cortex [66] and serves as a strong indicator of depression vulnerability [67]. Dependent variables comprised

the change in VFT performance (post-pre, pre-pre) and mean change of ΔHbO of LDLPFC (post-pre, pre-pre), as well as change in ERA performance (reaction time and accuracy). In case of any significant time *condition interaction effect was revealed, post hoc pairwise comparisons were conducted to compare dependent variables between conditions with Bonferroni correction. Exploratory subgroup analyses were performed to investigate the potentially differential effects of depressive symptoms severity. The cutoff score of PHQ-9 was used to divide our sample into low depressive symptom group (PHQ-9≤4) and high depressive symptom group (PHQ-9≥5). The statistical significance level was set at P=0.05. Pearson correlation was conducted to assess the association between changes in VFT performance and changes in ΔHbO levels.

4.5 Results

Five subjects were excluded from data analysis due to low-quality fNIRS signals or technical issues. Finally, 155 subjects (mean age: 23.01±3.487 years, 108 female) were included in the final analysis. At baseline assessment, no significant differences were observed between groups in terms of demographic characteristics or clinical scores (Table 4.1.).

Table 4. 1 Characteristics of participants.

	Group 1 (N=39)	Group 2 (N=39)	Group 3 (N=39)	Group 4 (N=38)	*P* value
Age, y, mean±SD	23.870±4.124	22.590±2.962	22.740±3522	22.820±3.212	0.351
Gender (F/M)	23/16	30/9	27/12	28/10	0.337
Education years, mean±SD	18.900±2.113	18.330±2.043	18.690±2.515	18.710±1.985	0.712
Baseline assessment					
PHQ-9	5.330±3.963	5.210±3.563	5.950±3.927	5.030±3.635	0.728
BIS/BAS Scales					
BAS_D	7.769±2.265	8.282±2.102	7.872±1.922	8.132±1.818	0.670
BAS_FS	9.256±2.731	10.359±2.570	9.718±2.417	10.553±2.310	0.094
BAS_RR	6.359±1.857	6.205±1.866	6.000±1.451	6.290±1.859	0.524
BIS	9.205±2.922	8.949±2.762	8.923±2.475	9.342±3.165	0.898
I-PANAS-SF					
PA	12.410±3.424	11.590±3.508	11.667±3.198	12.105±3.245	0.671
NA	9.846±3.521	9.615±3.711	10.282±3.387	9.553±3.326	0.791
Handedness	90.000±12.350	87.700±13.660	84.600±16.200	89.200±13.630	0.344
RMT	46.050±11.152	47.030±8.904	47.690±10.554	48.660±8.553	0.698

F, female; M, male. PHQ-9: Patient Health Questionnaire-9; BIA/BAS: The Behavioral Inhibition and Activation Systems Scales; BAS_D: BAS_Drive; BAS_FS: BAS Fun Seeking; BAS_RR: BAS Reward Responsiveness; I-PANAS-SF: International Positive and Negative Affect

Schedule Short Form; PA: positive affect; NA: Negative affect; RMT: resting motor threshold

4.5.1 Stimulation effects on brain activity

Analysis of left DLPFC activity revealed a significant main effect of condition (F=3.408, P=0.019, Partial η^2=0.064) and time (F=12.442, P<0.001, Partial η^2=0.077) as well as time by condition interaction effect (F=3.408, P=0.019, Partial η^2=0.064). Post hoc pairwise analysis demonstrated that after stimulation, all conditions exhibited a significant decrease in ΔHbO during the VFT task (all P<0.05, Bonferroni corrected). Notably, the decrease of ΔHbO in the 10-min interval priming TBS condition was significantly greater than in the 0-min interval priming TBS condition (P=0.017, Bonferroni corrected) (Figure 4.4). Figure 4.5 illustrates the differences in left DLPFC activation (pre- vs. post-stimulation) during the VFT across all conditions. Group-averaged time courses of HbO and HbR concentration changes in the left DLPFC during the VFT for all priming conditions are shown in Figure 4.6.

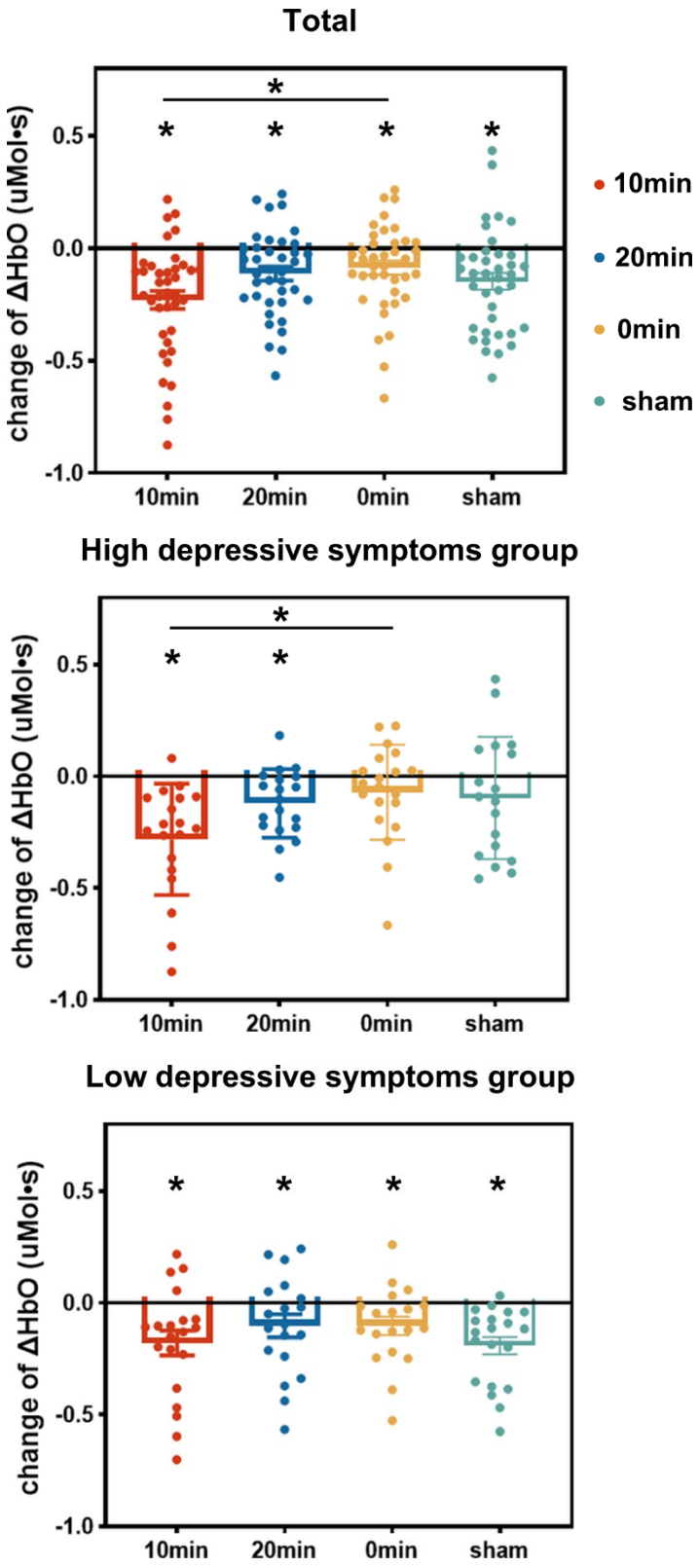

Figure 4. 4 Effects of priming TBS on brain activity. Change of ΔHbO across priming TBS conditions: (top) full sample; (middle): subgroup with high depressive symptoms; (bottom): subgroup with low depressive symptoms. * P<0.05

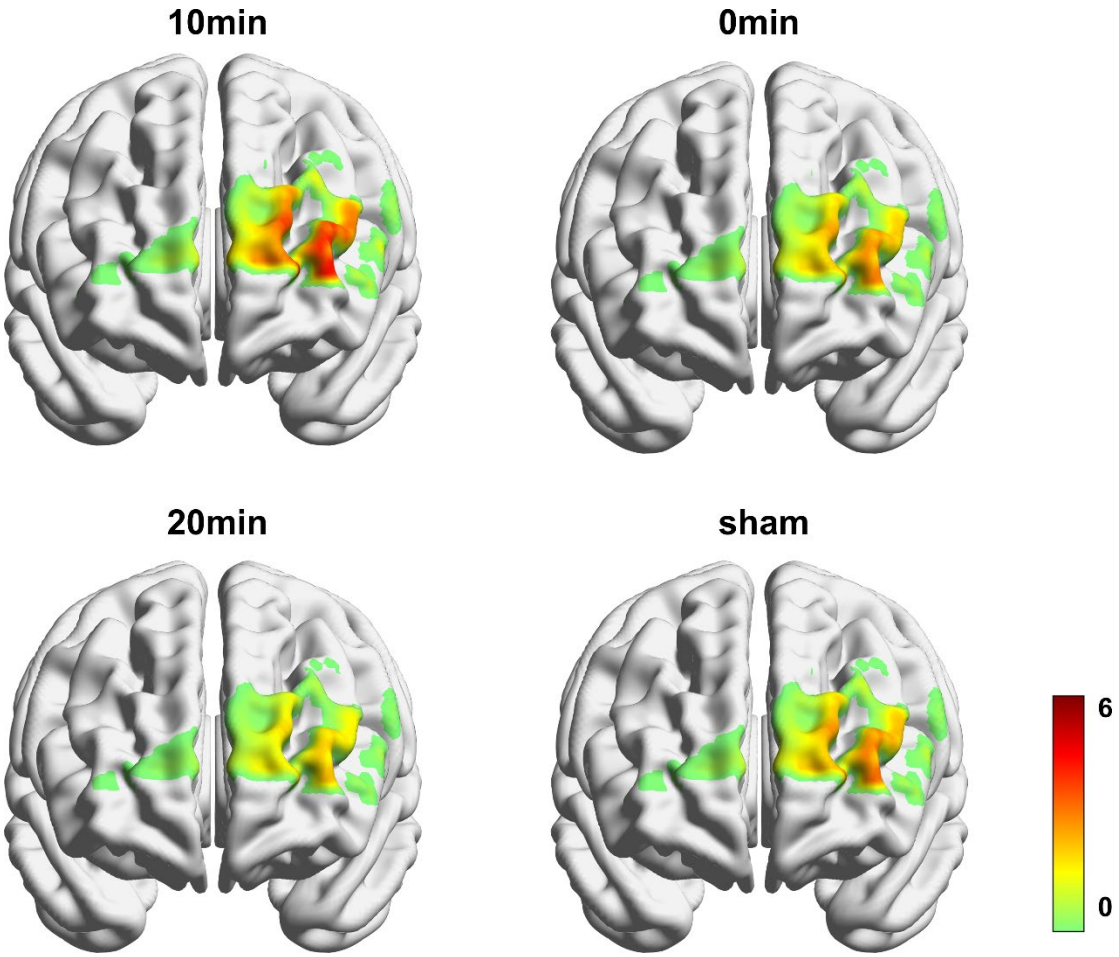

Figure 4. 5 Visualization of activation differences in the left DLPFC before and after stimulation during the VFT across all stimulation conditions. The color bar represents t-values mapped onto a 3D head model. Red indicates a decrease in ΔHbO following stimulation, while green represents an increase in ΔHbO.

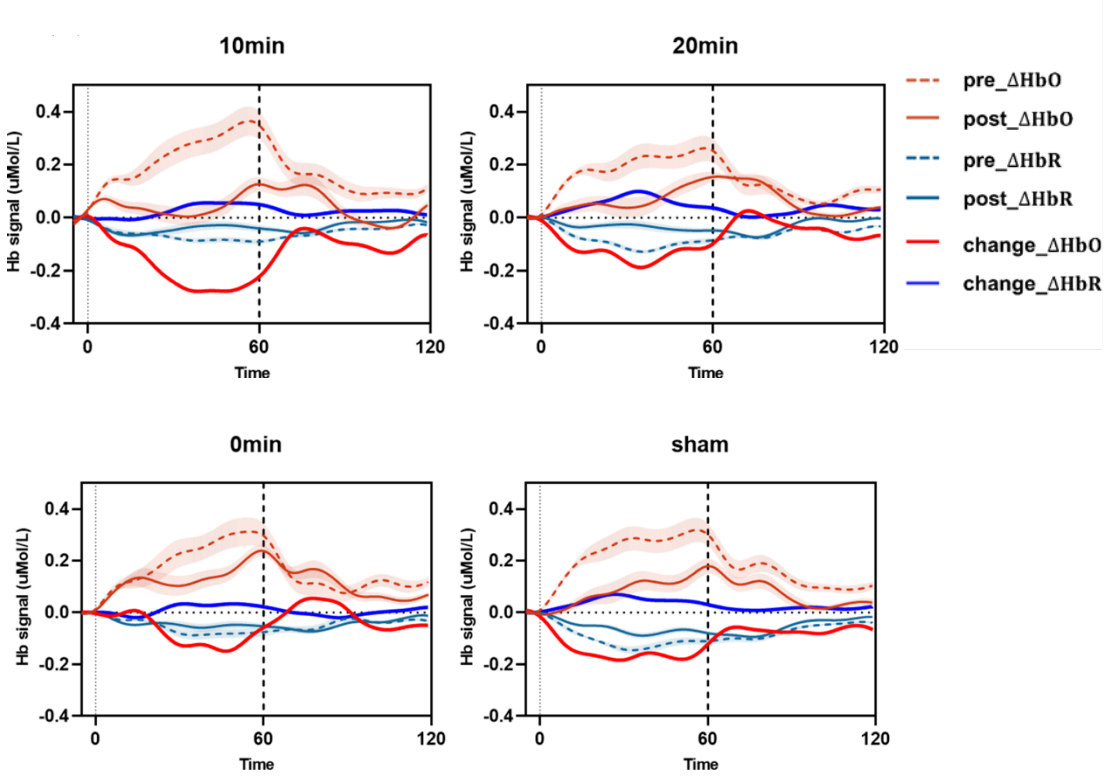

Figure 4. 6 Group-averaged time courses of ΔHbO and ΔHbR concentration changes in the left DLPFC during the VFT task under all priming stimulation conditions. Dashed lines depict pre-stimulation data, while solid lines show post-stimulation data. The Y-axis represents the mean ΔHbO concentration change. Bold red lines indicate the difference in ΔHbO concentrations (post-stimulation minus pre-stimulation), while bold blue lines represent the corresponding difference for ΔHbR.

Subgroup analysis showed a significant main effect of condition (F=3.685, P=0.016, Partial η^2=0.135) and time (F=9.383, P=0.003, Partial η^2=0.117), as well as an interaction effect of time by condition (F=3.685, P=0.016, Partial η^2=0.135) for the high depressive symptom group but not for the low depressive symptom group (all $P>0.5$). Further post hoc pairwise comparisons for the high depressive symptom group revealed that 10-min and 20-min interval priming stimulation significantly decreased the change of ΔHbO after stimulation but not for other stimulation protocols. Moreover, the decrease following 10-min interval priming stimulation was significantly larger than for the 0-min interval condition (P=0.047, Bonferroni corrected) and marginally significant for the sham condition (P=0.059, Bonferroni corrected). In the low depressive group, exploratory analysis indicated that all stimulation conditions significantly decreased the change of ΔHbO (all $p<0.05$, Bonferroni corrected) (Figure 4.4).

4.5.2 Stimulation effects on behavioral performance

4.5.2.1 VFT performance

The analysis of VFT performance yielded a significant main effect of time (F=26.206, $P<0.001$, Partial η^2=0.150) but not interaction effect of time by condition (F=1.360, P=0.250, Partial η^2=0.027). Post hoc pairwise comparison demonstrated an improvement of VFT performance after stimulation across all conditions (all $P<0.001$, Bonferroni corrected). Subgroup analysis yielded significant main effects of time in both the high depressive symptom group (F=9.788, P=0.003, Partial η^2=0.124) and low

depressive symptom group (F=14.469, P<0.001, Partial η^2=0.164). Post hoc pairwise comparison indicated significant improvements in VFT performance in both groups for all conditions (all P<0.05, Bonferroni corrected) (Figure 4.7).

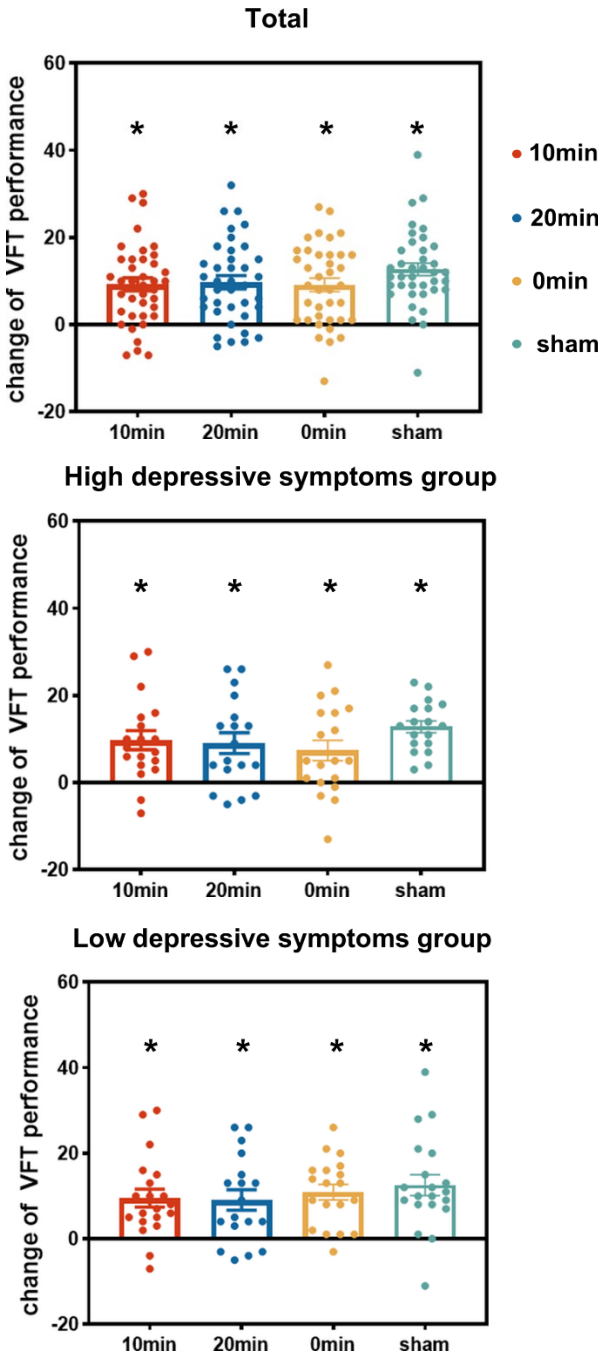

Figure 4. 7 Effects of priming TBS on VFT performance. Change of VFT performance across priming TBS conditions: (left) full sample; (center): subgroup with high depressive symptoms; (right): subgroup with low depressive symptoms. * P<0.05

4.5.2.2 ERA performance

An analysis of ERA reaction time revealed a significant main effect of time across the entire sample (F=11.857, P<0.001, partial η^2=0.074). Further subgroup analysis demonstrated a significant main effect of time in the high depressive symptom group (F=9.249, P=0.003, partial η^2=0.115) but not for the low depressive symptom group (F=2.111, P=0.151, partial η^2=0.028). Post-hoc tests revealed faster responses after stimulation in both the overall sample and the high depressive symptom group (all P<0.050) (Figure 8a). No significant differences were observed in ERA accuracy for any group (all P>0.050) (Figure 4.8).

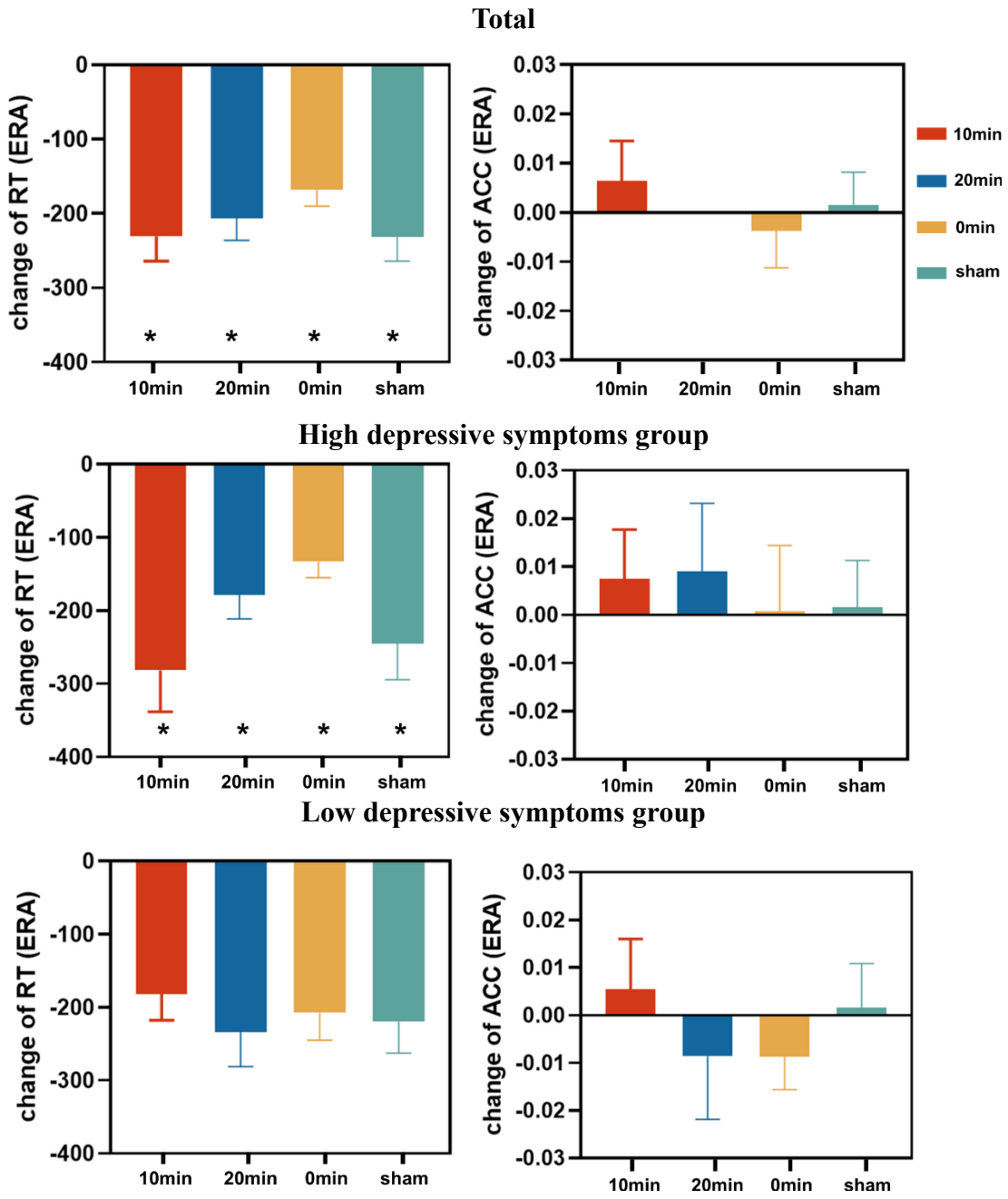

Figure 4. 8 Effects of priming TBS on ERA performance. Reaction time change of ERA task across priming TBS conditions: (top left) full sample; (middle left): subgroup with high depressive symptoms; (bottom left): subgroup with low depressive symptoms. Accuracy changes of ERA task across priming TBS conditions: (top right) full sample; (middle right): subgroup with high depressive symptoms; (bottom right): subgroup with low depressive symptoms. * P<0.05

4.5.3 Correlation between VFT performance and brain activity

The correlation analysis did not reveal any significant relationship between change of ΔHbO and change of VFT performance (P>0.05). (Figure 4.9)

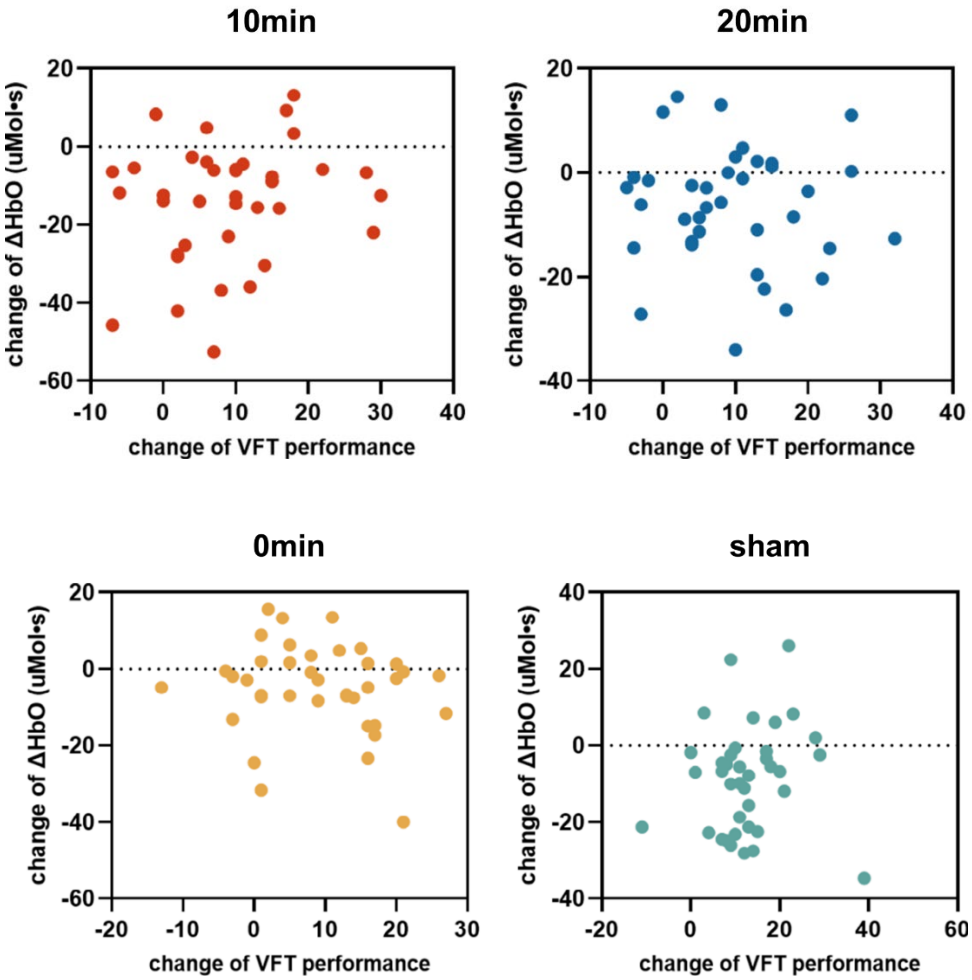

Figure 4. 9 Correlation between changes of VFT performance and changes of ΔHbO across priming TBS conditions.

4.6 Discussion

To our knowledge, this study is the first to systematically investigate the timing effects of priming TBS on left DLPFC. Our results indicate that all priming groups exhibited a decrease in ΔHbO during the VFT task post-stimulation compared to pre-stimulation. Notably, this effect was significantly more pronounced in the group that received 10-min interval priming TBS protocol. However, there were no differences in VFT performance across the different priming TBS groups, as all groups showed improved performance. These results suggest that a 10-minute interval between cTBS and iTBS may be the optimal timing to enhance the hemodynamic effects of iTBS by leveraging metaplasticity mechanisms, although these differences do not translate into measurable behavioral differences.

Unexpectedly, we observed a decrease in ΔHbO following stimulation, which appears contradictory to the typical neurovascular coupling phenomenon where increased ΔHbO signifies heightened brain activity. However, this finding is not unique to our study. Li et al. reported a significant reduction in ΔHbO in most ROIs during sub-threshold 10Hz rTMS stimulation [68]. Similarly, Thomson et al. found that single-pulse TMS at 130% RMT significantly decreased HbO in the left prefrontal cortex (PFC) [69]. Mochizuki et al. also reported decreased HbO during single-pulse TMS at 140% active motor threshold (AMT) [70], an intensity equivalent to approximately 100% RMT. The author suggested that suprathreshold single-pulse TMS leads to increased oxygen consumption that exceeds the arterial oxygen supply, causing a net decrease in

HbO levels [71]. These findings, along with our own, suggest that both high-intensity single-pulse TMS and low-intensity high-frequency rTMS can induce decreased HbO during neuronal activity. Two potential explanations exist for this phenomenon. First, intense or frequent stimulation may dramatically increase oxygen consumption, exceeding the rate of arterial supply and leading to a net decrease in HbO (Mochizuki et al., 2006a). Second, TBS may enhance neuronal efficiency, allowing for equivalent or improved performance with lower levels of cortical activation, as reflected by the decreased ΔHbO measured by fNIRS. This hypothesis aligns with findings from MEP studies, where lower intensity single-pulse TMS can evoke MEP amplitudes comparable to those elicited by higher intensities after excitatory stimulation, suggesting increased neural efficiency [3]. Our observation of decreased ΔHbO may therefore reflect this improved neuronal efficiency, with lower cortical activation levels still supporting the observed performance improvements.

Our study also revealed differential priming effects based on depressive symptom severity. The 10-minute interval priming TBS condition consistently showed a decrease in ΔHbO after stimulation in both low and high depressive symptom groups. In contrast, the sham priming TBS group only demonstrated a similar decrease in the low depressive symptom group. This differentiation may stem from our use of a PHQ-9 score cutoff of 4 to classify depression severity. The low depressive symptom group in our study is comparable to healthy subjects in other research, while the high depressive symptom group aligns with individuals experiencing mild to moderate depression.

Although previous studies have reported lower prefrontal activation levels in individuals with subclinical depression [72], we did not observe significant baseline differences between our low and high depressive symptom groups. This may be because our participants were not formally diagnosed with depressive disorders and exhibited less severe symptoms than those in other studies [72]. Nonetheless, the distinct responses to the priming TBS protocol support the notion that changes in prefrontal activation can occur before a formal diagnosis is made. The robust effects observed with the 10-minute interval priming TBS suggest that this protocol has stronger excitatory effects compared to single iTBS alone, indicating that a 10-minute interval is optimal for enhancing stimulation efficacy.

Despite these neurophysiological changes, we did not observe differences in VFT performance among the different priming TBS groups, nor did we find a correlation between changes in ΔHbO and behavioral outcomes. This lack of correlation was unexpected, as we anticipated that the neurophysiological effects would translate into observable behavioral changes. However, we are not alone in observing this disconnect; previous studies have also reported a lack of strong behavioral changes despite significant neurophysiological effects following a single session of TMS [73, 74]. One possible explanation is that neurophysiological measures, such as ΔHbO, may be more sensitive to subtle changes induced by neuromodulatory interventions than behavioral performance. Another explanation could be that a single session of TBS is insufficient to elicit measurable behavioral effects, highlighting the need for repeated sessions to

observe significant behavioral changes.

4.7 Limitations

Our study has several limitations. Due to the study design and equipment constraints, we were unable to measure brain activation changes immediately after cTBS. However, prior research indicates that the inhibitory effects of cTBS can last up to 60 minutes post-stimulation. Additionally, we applied equivalent intensities for both priming and test stimulations, leaving the optimization of priming protocol parameters other than the time interval for future research. Further investigation is needed to determine the most effective stimulation parameters for enhancing treatment outcomes.

4.8 Conclusion

A 10-minute interval between cTBS and iTBS appears to be the optimal timing for priming TBS protocols targeting the left DLPFC. This interval effectively decreases ΔHbO while improved VFT performance persists, suggesting increased neural efficiency in the targeted area. Moreover, our findings imply that deficiencies in left frontal activity may manifest at subclinical depression stage. These results highlight the potential of priming TBS protocols to enhance the efficacy of rTMS treatments for depression and other neurological disorders by optimizing stimulation timing and leveraging metaplasticity.

4.9 Author's contribution

For the work presented in this chapter, the author contributed to the following aspects of the study: Conceptualization; Methodology; Software; Investigation; Data Curation; Formal Analysis; Writing-Original draft; Writing-Review & Editing; Visualization.

4.10 References

1. Terao, Y. and Y. Ugawa, Basic mechanisms of TMS. Journal of clinical neurophysiology, 2002. 19(4): p. 322-343.
2. Klomjai, W., R. Katz, and A. Lackmy-Vallée, Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med, 2015. 58(4): p. 208-213.
3. Huang, Y.-Z., et al., Theta Burst Stimulation of the Human Motor Cortex. Neuron, 2005. 45(2): p. 201-206.
4. Cohen, S.L., et al., A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. Brain Stimul, 2022. 15(1): p. 73-75.
5. Hsu, J.H., et al., Impact of prior treatment on remission with intermittent theta burst versus high-frequency repetitive transcranial magnetic stimulation in treatment resistant depression. Brain Stimul, 2019. 12(6): p. 1553-1555.
6. Müller-Dahlhaus, F. and U. Ziemann, Metaplasticity in human cortex. Neuroscientist, 2015. 21(2): p. 185-202.
7. Cooper, L.N. and M.F. Bear, The BCM theory of synapse modification at 30: interaction of theory with experiment. Nat Rev Neurosci, 2012. 13(11): p. 798-

810.

8. Iyer, M.B., N. Schleper, and E.M. Wassermann, Priming stimulation enhances the depressant effect of low-frequency repetitive transcranial magnetic stimulation. J Neurosci, 2003. 23(34): p. 10867-72.

9. Fitzgerald, P.B., et al., Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. J Clin Psychopharmacol, 2008. 28(1): p. 52-8.

10. Zhang, J.J., Z. Bai, and K.N.K. Fong, Priming Intermittent Theta Burst Stimulation for Hemiparetic Upper Limb After Stroke: A Randomized Controlled Trial. Stroke (1970), 2022. 53(7): p. 2171-2181.

11. Murakami, T., et al., Homeostatic metaplasticity of corticospinal excitatory and intracortical inhibitory neural circuits in human motor cortex. J Physiol, 2012. 590(22): p. 5765-81.

12. Mastroeni, C., et al., Brain-Derived Neurotrophic Factor – A Major Player in Stimulation-Induced Homeostatic Metaplasticity of Human Motor Cortex? PLOS ONE, 2013. 8(2): p. e57957.

13. Goldsworthy, M.R., J.B. Pitcher, and M.C. Ridding, Spaced Noninvasive Brain Stimulation: Prospects for Inducing Long-Lasting Human Cortical Plasticity. Neurorehabil Neural Repair, 2015. 29(8): p. 714-21.

14. Karabanov, A., et al., Consensus Paper: Probing Homeostatic Plasticity of Human Cortex With Non-invasive Transcranial Brain Stimulation. Brain Stimulation, 2015. 8(3): p. 442-454.

15. Monte-Silva, K., et al., Shaping the optimal repetition interval for cathodal transcranial direct current stimulation (tDCS). J Neurophysiol, 2010. 103(4): p. 1735-40.

16. Opie, G.M., et al., Priming theta burst stimulation enhances motor cortex plasticity in young but not old adults. Brain Stimulation, 2017. 10(2): p. 298-304.

17. Fricke, K., et al., Time course of the induction of homeostatic plasticity generated by repeated transcranial direct current stimulation of the human motor cortex. J Neurophysiol, 2011. 105(3): p. 1141-9.

18. Kim, H.Y., et al., Application of Functional Near-Infrared Spectroscopy to the Study of Brain Function in Humans and Animal Models. Mol Cells, 2017. 40(8): p. 523-532.

19. Yücel, M.A., et al., Best practices for fNIRS publications. Neurophotonics, 2021. 8(1): p. 012101.

20. Ferrari, M. and V. Quaresima, A brief review on the history of human functional near-infrared spectroscopy (fNIRS) development and fields of application. NeuroImage, 2012. 63(2): p. 921-935.

21. Yeung, M.K. and J. Lin, Probing depression, schizophrenia, and other psychiatric disorders using fNIRS and the verbal fluency test: A systematic review and meta-analysis. J Psychiatr Res, 2021. 140: p. 416-435.

22. Curtin, A., et al., A Systematic Review of Integrated Functional Near-Infrared Spectroscopy (fNIRS) and Transcranial Magnetic Stimulation (TMS) Studies.

Front Neurosci, 2019. 13: p. 84.

23. Yang, T. and L. Xiang, Executive control dysfunction in subclinical depressive undergraduates: Evidence from the Attention Network Test. J Affect Disord, 2019. 245: p. 130-139.

24. Malekizadeh, H., et al., Deficits in specific executive functions manifest by severity in major depressive disorder: a comparison of antidepressant naïve inpatient, outpatient, subclinical, and healthy control groups. Front Psychiatry, 2023. 14: p. 1225062.

25. Maniglio, R., et al., Biased processing of neutral facial expressions is associated with depressive symptoms and suicide ideation in individuals at risk for major depression due to affective temperaments. Compr Psychiatry, 2014. 55(3): p. 518-25.

26. Kasch, K.L., et al., Behavioral activation and inhibition systems and the severity and course of depression. J Abnorm Psychol, 2002. 111(4): p. 589-97.

27. Rude, S.S., et al., Self-report and Cognitive Processing Measures of Depressive Thinking Predict Subsequent Major Depressive Disorder. Cognitive Therapy and Research, 2010. 34(2): p. 107-115.

28. Yang, N., et al., Translation, cultural adaption, and test-retest reliability of Chinese versions of the Edinburgh Handedness Inventory and Waterloo Footedness Questionnaire. Laterality, 2018. 23(3): p. 255-273.

29. Rossi, S., et al., Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues:

Expert Guidelines. Clin Neurophysiol, 2021. 132(1): p. 269-306.

30. McClintock, S.M., et al., Consensus Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. J Clin Psychiatry, 2018. 79(1).

31. Kroenke, K., R.L. Spitzer, and J.B. Williams, The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med, 2001. 16(9): p. 606-13.

32. Thompson, E.R., Development and Validation of an Internationally Reliable Short-Form of the Positive and Negative Affect Schedule (PANAS). Journal of Cross-Cultural Psychology, 2007. 38(2): p. 227-242.

33. Liu, J.-D., et al., Chinese version of the international positive and negative affect schedule short form: factor structure and measurement invariance. Health and Quality of Life Outcomes, 2020. 18(1): p. 285.

34. Yan-zhang, L., et al., The Chinese Version of the BIS/BAS Scale:Reliability and Validity. Chinese mental health journal, 2008. 22: p. 613-616.

35. Zwanzger, P., et al., Inhibitory repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex modulates early affective processing. Neuroimage, 2014. 101: p. 193-203.

36. Zhang, B.B.B., et al., Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study. Frontiers in Psychiatry, 2022. 13.

37. Li, Y., Y. Xu, and Z. Chen, Effects of the behavioral inhibition system (BIS), behavioral activation system (BAS), and emotion regulation on depression: A

one-year follow-up study in Chinese adolescents. Psychiatry Research, 2015. 230(2): p. 287-293.

38. Fox, M.D., et al., Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry, 2012. 72(7): p. 595-603.

39. Zhang, B.B.B., et al., Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 2021. 14(4): p. 924-926.

40. Rossini, P.M., et al., Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clinical Neurophysiology, 2015. 126(6): p. 1071-1107.

41. Lisanby, S.H., et al., Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. Biol Psychiatry, 2001. 49(5): p. 460-3.

42. Childs, J.D., S.R. Piva, and J.M. Fritz, Responsiveness of the numeric pain rating scale in patients with low back pain. Spine (Phila Pa 1976), 2005. 30(11): p. 1331-4.

43. Okada, E. and D.T. Delpy, Near-infrared light propagation in an adult head model. II. Effect of superficial tissue thickness on the sensitivity of the near-infrared spectroscopy signal. Appl Opt, 2003. 42(16): p. 2915-22.

44. Nuwer, M.R., et al., IFCN standards for digital recording of clinical EEG. Electroencephalography and Clinical Neurophysiology, 1998. 106(3): p. 259-261.

45. Aasted, C., et al., Anatomical guidance for functional near-infrared spectroscopy: AtlasViewer tutorial. Neurophotonics, 2015. 2(2): p. 020801.

46. Tak, S., et al., Sensor space group analysis for fNIRS data. Journal of Neuroscience Methods, 2016. 264: p. 103-112.

47. Yeung, M.K., et al., Altered Frontal Lateralization Underlies the Category Fluency Deficits in Older Adults with Mild Cognitive Impairment: A Near-Infrared Spectroscopy Study. Front Aging Neurosci, 2016. 8: p. 59.

48. Patra, A., A. Bose, and T. Marinis, Performance difference in verbal fluency in bilingual and monolingual speakers. Bilingualism: Language and Cognition, 2020. 23(1): p. 204-218.

49. Tupak, S.V., et al., Differential prefrontal and frontotemporal oxygenation patterns during phonemic and semantic verbal fluency. Neuropsychologia, 2012. 50(7): p. 1565-1569.

50. Yang, T., et al., Tsinghua facial expression database – A database of facial expressions in Chinese young and older women and men: Development and validation. PLOS ONE, 2020. 15(4): p. e0231304.

51. Maniglio, R., et al., Biased processing of neutral facial expressions is associated with depressive symptoms and suicide ideation in individuals at risk for major depression due to affective temperaments. Comprehensive Psychiatry, 2014.

55(3): p. 518-525.

52. Huppert, T.J., et al., HomER: a review of time-series analysis methods for near-infrared spectroscopy of the brain. Appl Opt, 2009. 48(10): p. D280-98.

53. Li, X., et al., Brain correlates of motor complexity during observed and executed actions. Scientific Reports, 2020. 10(1): p. 10965.

54. Scholkmann, F., et al., How to detect and reduce movement artifacts in near-infrared imaging using moving standard deviation and spline interpolation. Physiol Meas, 2010. 31(5): p. 649-62.

55. Molavi, B. and G.A. Dumont. Wavelet based motion artifact removal for Functional Near Infrared Spectroscopy. in 2010 Annual International Conference of the IEEE Engineering in Medicine and Biology. 2010.

56. Novi, S.L., et al., Functional near-infrared spectroscopy for speech protocols: characterization of motion artifacts and guidelines for improving data analysis. Neurophotonics, 2020. 7(1): p. 015001.

57. Kirilina, E., et al., Identifying and quantifying main components of physiological noise in functional near infrared spectroscopy on the prefrontal cortex. Front Hum Neurosci, 2013. 7: p. 864.

58. Kocsis, L., P. Herman, and A. Eke, The modified Beer-Lambert law revisited. Phys Med Biol, 2006. 51(5): p. N91-8.

59. Delpy, D.T., et al., Estimation of optical pathlength through tissue from direct time of flight measurement. Phys Med Biol, 1988. 33(12): p. 1433-42.

60. Bai, Z., et al., Cortical mapping of mirror visual feedback training for unilateral

upper extremity: A functional near-infrared spectroscopy study. Brain and Behavior, 2020. 10(1): p. e01489.

61. Tung, H., et al., Left Frontotemporal Region Plays a Key Role in Letter Fluency Task-Evoked Activation and Functional Connectivity in Normal Subjects: A Functional Near-Infrared Spectroscopy Study. Front Psychiatry, 2022. 13: p. 810685.

62. Nguyen, T., et al., Investigation of brain functional connectivity in patients with mild cognitive impairment: A functional near-infrared spectroscopy (fNIRS) study. J Biophotonics, 2019. 12(9): p. e201800298.

63. Zhang, H., et al., Is resting-state functional connectivity revealed by functional near-infrared spectroscopy test-retest reliable? J Biomed Opt, 2011. 16(6): p. 067008.

64. Strangman, G., et al., A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. Neuroimage, 2002. 17(2): p. 719-731.

65. Xia, M., J. Wang, and Y. He, BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One, 2013. 8(7): p. e68910.

66. Fuentes-Claramonte, P., et al., Reward Sensitivity Modulates Brain Activity in the Prefrontal Cortex, ACC and Striatum during Task Switching. PLOS ONE, 2015. 10(4): p. e0123073.

67. Kujawa, A., Reduced reward responsiveness and depression vulnerability: Consideration of social contexts and implications for intervention.

Psychophysiology, 2024. 61(6): p. e14528.

68. Li, R., et al., Cortical Hemodynamic Response and Connectivity Modulated by Sub-threshold High-Frequency Repetitive Transcranial Magnetic Stimulation. Front Hum Neurosci, 2019. 13: p. 90.

69. Thomson, R.H., et al., Blood oxygenation changes resulting from suprathreshold transcranial magnetic stimulation. Brain Stimulation, 2011. 4(3): p. 165-168.

70. Mochizuki, H., et al., Cortical hemoglobin-concentration changes under the coil induced by single-pulse TMS in humans: a simultaneous recording with near-infrared spectroscopy. Exp Brain Res, 2006. 169(3): p. 302-10.

71. Mochizuki, H., et al., Cortical hemoglobin-concentration changes under the coil induced by single-pulse TMS in humans: A simultaneous recording with near-infrared spectroscopy. Experimental Brain Research, 2006. 169(3): p. 302-310.

72. Herrmann, M.J., A.-C. Ehlis, and A.J. Fallgatter, Bilaterally Reduced Frontal Activation During a Verbal Fluency Task in Depressed Patients as Measured by Near-Infrared Spectroscopy. The Journal of Neuropsychiatry and Clinical Neurosciences, 2004. 16(2): p. 170-175.

73. Chung, S.W., et al., Impact of different intensities of intermittent theta burst stimulation on the cortical properties during TMS-EEG and working memory performance. Hum Brain Mapp, 2018. 39(2): p. 783-802.

74. Hill, A.T., et al., Effects of prefrontal bipolar and high-definition transcranial direct current stimulation on cortical reactivity and working memory in healthy

adults. Neuroimage, 2017. 152: p. 142-157.

Chapter 5 Rethinking intensity: Repetitive transcranial magnetic stimulation across ethnic populations

The manuscript for the work presented in this chapter is currently in preparation.

5.1 Abstract

Repetitive transcranial magnetic stimulation (rTMS) targeting the left dorsolateral prefrontal cortex is a widely used adjunctive therapy for various neurological and psychiatric disorders. Traditionally, the standard practice for dosing rTMS has involved adjusting the intensity to a defined percentage of the motor threshold. However, we perceive anatomical differences among '*White',* '*Han Chinese*' and '*Black or African American'* ethnic groups that result in unequal doses of stimulation at the left dorsolateral prefrontal cortex, a prime target for therapeutic rTMS. Therefore, we hypothesize that diverse ethnic populations experience different therapeutic effects with FDA-approved rTMS protocols that have been adopted globally. This also raises concerns about varying therapeutic effects and potential biases in existing research comparing efficacy across ethnicities. More importantly, our hypothesis emphasizes the need to tailor rTMS safety guideline for diverse ethnic populations. We call for well-powered clinical trials to systematically examine the effects of rTMS intensity in diverse ethnic groups.

5.2 Introduction and hypothesis

Repetitive transcranial magnetic stimulation (rTMS) is a widely used adjunctive therapy for various neurological and psychiatric disorders including depression, fibromyalgia, Parkinson's disease, addiction, and schizophrenia, among others [1]. rTMS involves applying magnetic pulses to a specific brain region, with the left dorsolateral prefrontal cortex (DLPFC) being a clinical prime target [2, 3]. For over three decades, the standard practice for dosing rTMS has involved adjusting the stimulation intensity at the target region to a defined percentage of the motor threshold, the minimum intensity needed to elicit a motor response at the motor cortex [4, 5]. Notably, US FDA-approved rTMS protocols generally use 120% of the motor threshold, which has been adopted globally [6]. However, underlying this strategy is the assumption of a uniform relationship between the stimulation intensity and its therapeutic effects. That means we may have assumed that the ratio of scalp-to-cortex distance at the left dorsolateral prefrontal cortex to the motor cortex is identical across individuals. Considering anatomical differences such as head morphologies among diverse world populations [7], the authors see a need to re-examine this generic strategy for determining rTMS intensity and hypothesize that the optimal intensity differs among ethnic groups.

5.3 Contributing observation 1: ethnic differences in the scalp-to-cortex distance

We examined the scalp-to-cortex distances at the left DLPFC and the left motor cortex

among three ethnic groups (aged 22-35 years): 821 '*White*', 165 '*Black or African American*', and 159 '*Han Chinese*' individuals. We obtained unprocessed T1-weighted and T2-weighted structural MRI images from of the Human Connectome Project (https://db.humanconnectome.org) and the Chinese Human Connectome Project (https://doi.org/10.11922/sciencedb.01374). We defined the locations of the left DLPFC and the motor cortex as the 10-10 EEG positions F3 and C3, respectively [8]. We used the SimNIBS package to segment the MRI images and created a head volume conductor model for each individual [9]. The results were visually inspected for errors in tissue boundary establishment. We calculated the scalp-to-cortex distance as the Euclidean distance between the EEG position and the nearest site on the gray matter.

We found that the '*White'* individuals had a larger mean scalp-to-cortex distance at the left DLPFC compared to the motor cortex (mean F3/C3 distance ratio=1.077). The relationship was reversed for the '*Han Chinese*' individuals (mean F3/C3 distance ratio=0.939). The '*Black or African American*' individuals had similar mean distances at the two cortices (mean F3/C3 distance ratio=0.992). An analysis of covariance, controlling for age and gender as covariates, revealed that the scalp-to-cortex distance ratio significantly differed among the three ethnic groups ($F_{2,1141}$=75.580, $p<0.001$, η^2=0.112). Post hoc pairwise comparisons showed that the '*White*' individuals had a significantly larger ratio than both the '*Han Chinese*' and the '*Black or African American*' individuals (p's < 0.001, Bonferroni corrected) (Figure. 5.1 a).

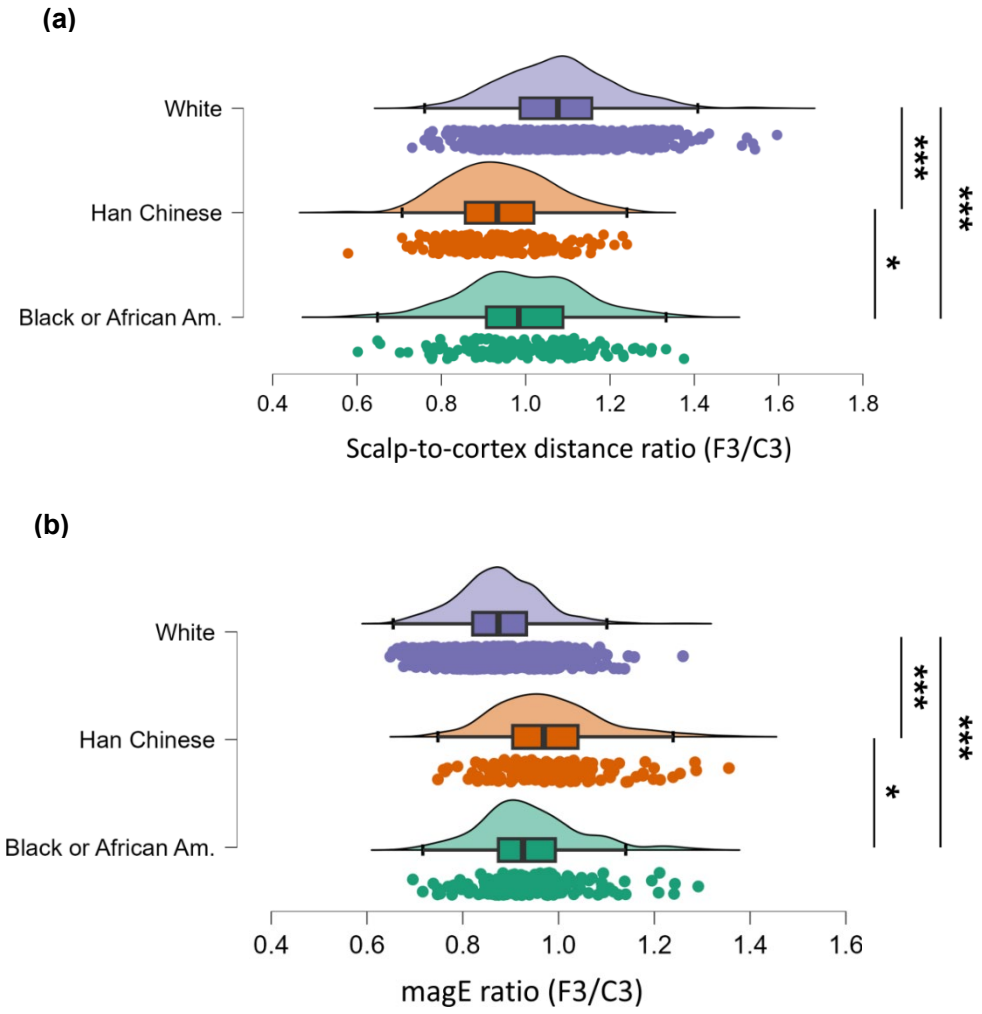

Figure 5. 1 Scalp-to-cortex distance ratio and electric field strength ratio across ethnicities. (a) scalp-to-cortex distance ratio (F3/C3) for the left DLPFC relative to the motor cortex in 'White', 'Han Chinese', and 'Black or African American' individuals. A ratio greater than 1 indicates a larger scalp-to-cortex distance at the left dorsolateral prefrontal cortex compared to the motor cortex. (b) electric field strength ratio (F3/C3) for the left DLPFC relative to the motor cortex in the three ethnic groups. A ratio below 1 indicates lower electric field strength in the left DLPFC compared to the motor cortex. *: $p<0.05$, ***: $p<0.001$.

5.4 Contributing observation 2: simulated optimal intensities for different ethnic groups

The marked differences in scalp-to-cortex distances led us to investigate the electric field strength induced by rTMS in the two cortices. We simulated the electric field strength for the three ethnic groups using SimNIBS 4.1.0 [10]. We assumed a standard rTMS treatment coil (MagVenture Cool-B65) [11] was positioned on the scalp at the EEG position F3 (left dorsolateral prefrontal cortex) and C3 (motor cortex) at a 45-degree angle to the midline, with the handle pointing posteriorly [8]. We set the stimulation intensity to 1e6 A/s and calculated the induced electric field strength as the average value [12] for every gray matter voxel within a 10-mm-radius sphere centered at the cortical projections from the EEG position F3 or C3 [13]. The F3 projection was at (x=-35.5, y=49.4, z=32.4 mm) and C3 at (x=-52.2, y=-16.4, z=57.8 mm) in Montreal Neurological Institute coordinates. An analysis of covariance, controlling for age and gender, indicated a significant effect of ethnicity on the electric field strength ratio of the left dorsolateral prefrontal cortex to the motor cortex ($F_{2,1141}$=86.333, $p<0.001$, η^2=0.128). While all groups exhibited an F3/C3 electric field strength ratio below 1, suggesting weaker stimulation received by the left DLPFC compared to the motor cortex, the ratio differed significantly between the groups (p's<0.001, Bonferroni corrected). On average, '*White*' individuals received lower electric field strength in the left DLPFC compared to the left motor cortex (F3/C3=0.875) when compared with '*Han Chinese*' individuals (F3/C3=0.977) and '*Black or African American*' individuals (F3/C3=0.940) (Figure. 5.1 b). Specifically, if stimulation intensities at the left DLPFC

were set to the FDA-approved 120% of the motor threshold, then on average, '*Han Chinese*' individuals would receive an equivalent intensity of 134% to stimulate '*White'* individuals, and '*Black or African American'* individuals would receive an equivalent intensity of 129% to stimulate '*White'* individuals.

5.5 Implications of the hypothesis

Our analyses revealed significant differences in the scalp-to-cortex distances among the '*White',* '*Han Chinese*' and '*Black or African American'* ethnic groups. We further showed that the three ethnic groups would receive unequal doses of stimulation at the left dorsolateral prefrontal cortex, a prime target for therapeutic rTMS, even when the stimulation was applied at the same percentage of the motor threshold. Our findings align with previous empirical research and modeling studies [14, 15]. Therefore, we hypothesize that the three ethnic groups experience varying clinical effects with standard FDA-approved rTMS protocols. Specifically, we presume that '*Han Chinese*' and '*Black or African American*' individuals have been suboptimally stimulated with standard rTMS stimulation protocols, considering that early rTMS clinical trials were predominantly conducted in North America and recruited disproportionately more '*White*' individuals (thus, these protocols were presumably better optimized for the '*White*' ethnic group) [16-19]. Our hypothesis further suggests that systematic biases may exist in previously published meta-analyses in terms of comparing therapeutic effects across ethnicities and summarizing effect size estimates. More importantly, our hypothesis highlights the need to tailor rTMS safety guidelines for different ethnic

groups. Indeed, our simulation revealed that the FDA-approved stimulation intensity of 120% of the motor threshold, when applied to an average '*Han Chinese*' individual, may generate an electric field strength equivalent to that produced by an intensity of 134% applied to an average '*White'* individual. Yet, rTMS at an intensity of 130% or above remains largely uncharted in research and is subject to a sharply reduced maximum safe train duration to prevent seizures [20].

5.6 Testing the hypothesis

We propose a series of rTMS clinical trials across the globe to test our hypothesis. We propose to start with trials on major depressive disorder, the disorder with the strongest evidence for the efficacy of rTMS on the DLPFC. These trials will require coordinated planning and implementation across study sites to ensure a comparable treatment process. The first trial will focus on '*Han Chinese'* and '*White*' patients, since this pair of ethnic groups demonstrated the largest difference in the scalp-to-cortex distance ratio. The standard, FDA-approved stimulation intensity of 120% of the motor threshold and the intensity of 108% adjusted for '*Han Chinese'* will be applied to patients from both ethnic groups. We expect that the more effective treatment intensity, in terms of response or remission rates, will vary between the two ethnic groups. We estimate that a few hundred patients per ethnic group will allow the detection of such clinically meaningful differences. If the results turn out to be positive, we may proceed with comparisons involving *'Black or African American'* and '*White'* patients in a similar manner, though that would be a study on a much larger scale. Findings from this series

of trials may give birth to a readily implementable strategy that benefits patients who cannot have magnetic resonance imaging scans for more precise structural measurements due to cost, availability, or safety considerations.

5.7 Author's contribution

For the work presented in this chapter, the author contributed to the following aspects of the study: Conceptualization; Methodology; Software; Data Curation; Formal Analysis; Writing-Original Draft; Writing-Review & Editing; Visualization.

5.8 References

1. Fatemi-Ardekani, A., Transcranial magnetic stimulation: physics, electrophysiology, and applications. Crit Rev Biomed Eng, 2008. 36(5-6): p. 375-412.
2. Kan, R.L.D., et al., 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, 2023. 10(4): p. 252-259.
3. Hallett, M., Transcranial magnetic stimulation and the human brain. Nature, 2000. 406(6792): p. 147-150.
4. Rothwell, J.C., et al., Magnetic stimulation: motor evoked potentials. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl, 1999. 52: p. 97-103.

5. Turi, Z., et al., Selecting stimulation intensity in repetitive transcranial magnetic stimulation studies: A systematic review between 1991 and 2020. Eur J Neurosci, 2021. 53(10): p. 3404-3415.
6. Cohen, S.L., et al., A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 2022. 15(1): p. 73-75.
7. Ge, J., et al., Increasing diversity in connectomics with the Chinese Human Connectome Project. Nat Neurosci, 2023. 26(1): p. 163-172.
8. Jurcak, V., D. Tsuzuki, and I. Dan, 10/20, 10/10, and 10/5 systems revisited: Their validity as relative head-surface-based positioning systems. NeuroImage, 2007. 34(4): p. 1600-1611.
9. Puonti, O., et al., Accurate and robust whole-head segmentation from magnetic resonance images for individualized head modeling. NeuroImage, 2020. 219: p. 117044.
10. Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.
11. Drakaki, M., et al., Database of 25 validated coil models for electric field simulations for TMS. Brain Stimul, 2022. 15(3): p. 697-706.
12. Saturnino, G.B., et al., SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation, in

Brain and Human Body Modeling: Computational Human Modeling at EMBC 2018, S. Makarov, M. Horner, and G. Noetscher, Editors. 2019, Springer Copyright 2019, The Author(s). Cham (CH). p. 3-25.

13. Okamoto, M., et al., Three-dimensional probabilistic anatomical cranio-cerebral correlation via the international 10-20 system oriented for transcranial functional brain mapping. Neuroimage, 2004. 21(1): p. 99-111.

14. Thomas, C., et al., Influence of the effect of race on cortical current flow due to ECT. Brain Stimulation, 2019. 12(2): p. 526.

15. Datta, A., et al. Exploration of the Effect of Race on Cortical Current Flow Due to Transcranial Direct Current Stimulation: Comparison across Caucasian, Chinese, and Indian Standard Brains. in 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2018.

16. Lisanby, S.H., et al., Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. Neuropsychopharmacology, 2009. 34(2): p. 522-34.

17. George, M.S., et al., A two-site pilot randomized 3 day trial of high dose left prefrontal repetitive transcranial magnetic stimulation (rTMS) for suicidal inpatients. Brain Stimul, 2014. 7(3): p. 421-31.

18. Levkovitz, Y., et al., Efficacy and safety of deep transcranial magnetic stimulation for major depression: a prospective multicenter randomized

controlled trial. World Psychiatry, 2015. 14(1): p. 64-73.

19. O'Reardon, J.P., et al., Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry, 2007. 62(11): p. 1208-16.

20. Rossi, S., et al., Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol, 2009. 120(12): p. 2008-2039.

Chapter 6 Normal component of TMS-induced electric field is correlated with depressive symptom relief in treatment-resistant depression

This work has been published by the author of this thesis in the journal "*Brain stimulation*" in 2022.

Access to the publication: https://doi.org/10.1016/j.brs.2022.09.006

This work has been presented as a poster in the *5th International Brain Stimulation Conference*, held from February 18-22, 2023, in Lisbon, Portugal, and published as a conference abstract in the journal "*Brain stimulation*".

Access to the conference abstract: https://doi.org/10.1016/j.brs.2023.01.780

6.1 Abstract

Background: Recent research suggests that the diversity of the transcranial magnetic stimulation (TMS) induced electric fields (EF) in the brain due to individual differences in head morphology may partly explain the response variation to TMS.

Objective: We aimed to investigate the relationship between TMS-induced EF characteristics and antidepressant effects in patients with treatment resistant depression (TRD).

Methods: Data from twelve TRD patients who received 3 weeks of daily sequential bilateral theta burst stimulation (TBS) were included for analysis. TMS-induced EF were computed in the finite element models created based on each subject's head. Left and right stimulation regions in the DLPFC were chosen as regions of interest (ROIs). The strength ($||E||$), tangential ($E_{||}$), and normal ($E_{\perp}$) component of EF were calculated as the sum of the respective average values within the left and right ROI to simulate the real stimulation "dose" that patients received. The magnitude of $E_{\perp}$ component ($|E_{\perp}|$) was defined as the sum of the average absolute value of both left and right $E_{\perp}$ inside an ROI.

Results: Generalized linear mixed model showed a significant interaction effect between time and $|E_{\perp}|_{sum}$ on The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) scores (F=8.911, P=0.01), but not for other EF characteristics. Pearson correlation analyses confirmed that the change in IDS-C scores was only significantly correlated with $|E_{\perp}|_{sum}$ component (r=-0.752, P=0.005).

Conclusions: Our results indicate that the magnitude of $E_{\perp}$ component of the TMS-

induced EF is associated with the antidepressant response to bilateral sequential TBS treatment in patients with TRD. Future studies using a tailored TMS treatment approach may consider maximizing the $|E_{\perp}|$ component in order to enhance clinical effects.

6.2 Introduction

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that modulates brain activity by producing an electric field (EF) in the targeted brain region [1, 2]. Theta burst stimulation (TBS), a patterned form of rTMS, is an FDA approved therapy for treatment resistant depression (TRD) [3]. However, reported effect sizes and response rates are heterogeneous [4-6]. Recent research suggests that the diversity of the induced EF in the brain due to individual differences in head morphology may partly explain the response variation to TMS [7, 8]. Yet, predicting the clinical response based on EF calculations continues to be a challenge, as we still lack a clear understanding of the key EF component responsible for the observed treatment response. To inform this research gap, Fox et al. used positron emission tomography (PET) to examine TMS-induced cortical activation and found that "TMS active regions" had a higher EF normal component ($E_{\perp}$) in the inward direction (i.e., entering the cortex perpendicular to its surface) [9]. Conversely, recent computational simulation modeling research reported that the tangential component ($E_{\parallel}$) and the overall magnitude of the EF ($||E||$) were most relevant to TMS-induced effects [10].

The current study aimed to systematically investigate the relationship between TMS-induced EF characteristics and antidepressant effects in patients with TRD. We hypothesized that the reduction of depressive symptoms after three weeks of stimulation treatment would be proportional to the magnitude of one or more of the

proposed EF components in the stimulated brain region.

6.3 Materials and methods

The analysis was based on a subsample of patients from a longitudinal, clinical trial published previously [11]. Data of twelve TRD patients were included. Patients underwent 3 weeks of daily sequential bilateral TBS. Standard intermittent TBS (iTBS; 20 trains, 600 pulses) was utilized to stimulate the left dorsolateral prefrontal cortex (DLPFC) at Montreal Neurological Institute (MNI) coordinates x=-38, y=44, z=26, whereas continuous TBS (cTBS; 600 continuous pulses) was used to stimulate the right DLPFC at MNI coordinates x=38, y=44, z=26 in individual subject space, and at an intensity of 120% resting motor threshold (RMT). Targets were based on a previous study that indicated largest antidepressant effects and strongest negative functional connectivity with the subgenual cingulate cortex compared with other DLPFC locations [12]. MRI scans and clinical assessments were performed at baseline and after the last TBS session (for details, see [13]). TBS induced EF were simulated in anatomically realistic, volume conductor head models by the finite element method (FEM) using SimNIBS v3.2 [14-16]. Individual T1- and T2- weighted structural MRI data were used for head model reconstruction. Segmentation was inspected to prevent tissue boundary establishment errors [17]. A coil model of MagVenture MC-B70 was used for computations, which displays similar penetration depth and focality to the coil used for stimulation (MagVenture Cool-B70) [18]. The TMS coil was positioned over the patient's head according to the location extracted from the neuro-navigation system

(LOCALITE® TMS Navigator Germany) with the handle pointing towards the vertex. The stimulation intensity was determined using the relative dI/dt (current rate-of-change) value obtained directly from the TMS stimulator (MagPro X100, Magventure, Tonica Elektronik A/S, Denmark). Left and right stimulation regions in the DLPFC at MNI coordinates (±38, 44, 26) were chosen as regions of interest (ROIs) and defined as spheres (r=5mm) in head models (Figure 6.2 a). EF characteristics were analyzed on the ROI level. ||E||, $E_{\parallel}$ and $E_{\perp}$ were calculated as the sum of the respective average values within the left and right ROI to simulate the real stimulation "dose" that patients received. The magnitude of $E_{\perp}$ component ($|E_{\perp}|$) was defined as the sum of the average absolute value of both left and right $E_{\perp}$ inside an ROI. In an exploratory post-hoc analysis, EF characteristics were also investigated separately for the left and right ROI. Generalized liner mixed model (GLMM, repeated measure: time; main effect: time, ||E||, $E_{\parallel}$, $E_{\perp}$and $|E_{\perp}|$; interaction effect: time by each characteristics of EF; dependent variable: IDS-C score) and post-hoc pairwise comparisons were used to analyze the relationship between EF characteristics and clinical improvement. Following the GLMM, we performed Pearson's correlations to confirm associations between antidepressant treatment effects and EF characteristics. Post-hoc analyses were corrected for multiple comparisons using the Bonferroni procedure. The level of statistical significance was set at $P<0.05$.

6.4 Results

GLMM indicated a significant interaction effect between time and $|E_{\perp}|_{sum}$ on IDS-C

scores (F=8.911, P=0.01) (Figure 6.1), but not for other EF characteristics. Post-hoc pairwise comparison showed significantly lower estimated IDS-C scores after treatment compared to baseline scores (mean±SD=-15.5±2.327; t_{14}=-6.662, P<0.001, corrected). Pearson correlation analyses confirmed a negative correlation between change in IDS-C scores after treatment and the $|E_{\perp}|_{sum}$ component (r=-0.752, P=0.005, corrected P=0.0125, Figure 6.2 b). No other EF characteristics showed significant associations with IDS-C scores (Figure 6.2 c-e) (see Table 6.1 and Table 6.2 for further details). When investigating each ROI separately, we observed a negative correlation between $|E_{\perp}|_{right}$ and change of IDS-C scores (r=-0.781, P=0.003, Figure 6.3 a) but not for the left ROI (r=-0.458, P=0.135 Figure 6.3 b).

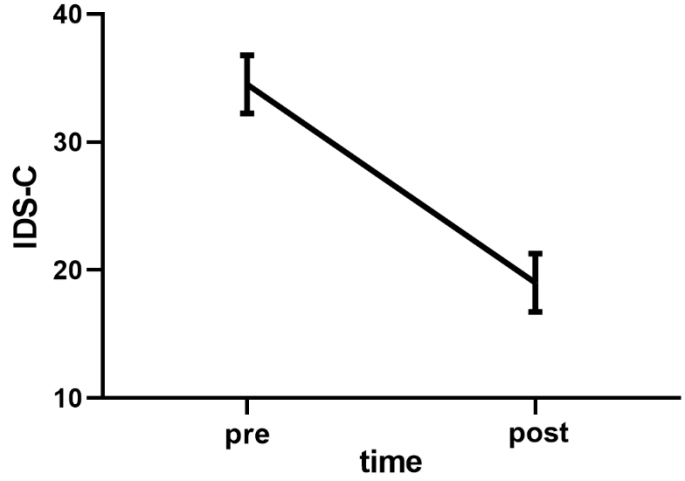

Figure 6. 1 The generalized linear mixed models (GLMM) model estimated IDS-C value affected by sum of magnitude of E⊥ component at different time.

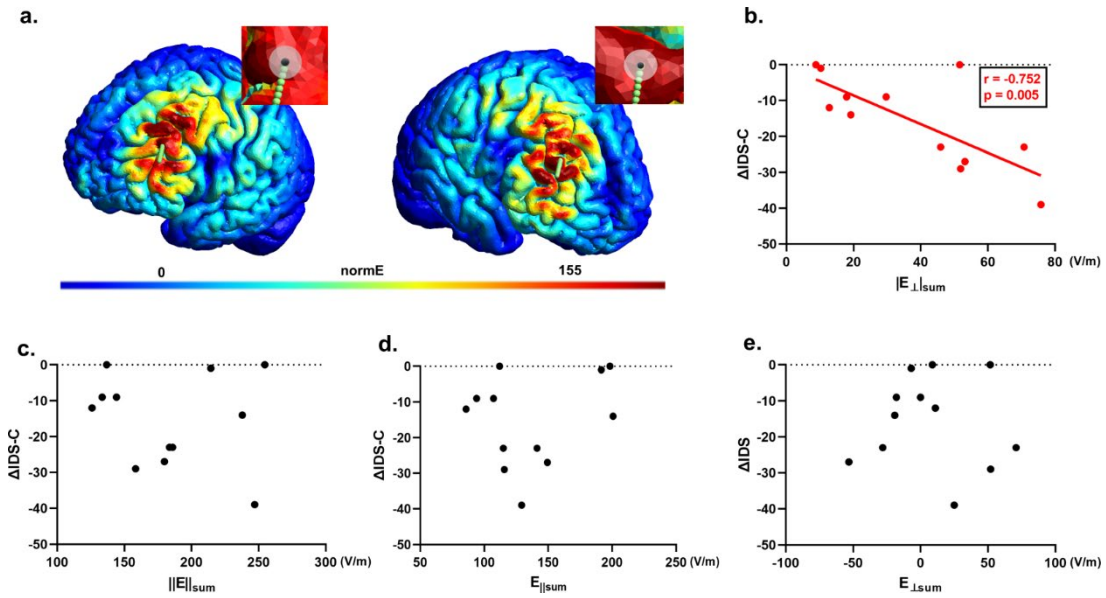

Figure 6. 2 (a) Simulation results of the EF distribution in the left (left side of image) and right (right side) hemispheres demonstrated using data from one subject. Close-up shows the ROI in the left (left side) and right (right side) hemispheres. The gray circle indicates the ROI used for calculating EF characteristics. The black dot indicates both the stimulation target and the TMS coil's center. The green line indicates the current direction in the coil. (b) Correlation between change in IDS-C scores and |E⊥|, with the latter calculated as the sum of both left and right ROI. (c) Correlation between change in IDS-C scores and |E|, with the latter calculated as the sum of both left and right ROI. (d) Correlation between change in IDS-C scores and E||, with the latter calculated as the sum of both left and right ROI. (e) Correlation between change in IDS-C scores and E⊥,with the latter calculated as the sum of both left and right ROI.

Table 6. 1 Tests of Fixed Effects for depressive severity.

Fixed effects	F	Df1	Df2	P value
Time	0.670	1	14	.427
$\|E\|_{sum}$	.194	1	14	.667
$E//_{sum}$	.760	1	14	.398
$E_{\perp sum}$	.802	1	14	.386
$\| E_{\perp}\|_{sum}$	.305	1	14	.589
Time*$\|E\|_{sum}$	.295	1	14	.596
Time*$E//_{sum}$	1.384	1	14	.259
Time*$E_{\perp sum}$	2.214	1	14	.159
Time*$\| E_{\perp}\|_{sum}$	8.911	1	14	.010

Table 6. 2 Estimates of Fixed Effects for depressive severity.

Fixed effects	**Coefficient**	**SD**	**t**	**P value**	**95% Confidence Interval**	
					Lower	Upper
Intercept	28.619	9.818	2.915	.011	7.561	49.677
Time=1	-8.214	10.036	-.818	.427	-29.740	13.311
Time=0	ref	ref	ref	ref	ref	ref
$\|E\|_{sum}$	-.012	.121	-.101	.921	-.271	.247
$E//_{sum}$	.018	.124	.148	.885	-.248	.285
$E_{\perp sum}$	.001	.072	.009	.993	-.154	.155
$\| E_{\perp}\|_{sum}$	.150	1.427	1.051	0.311	-.156	.456
[Time=1] * $\|E\|_{sum}$	-.067	.123	-.543	.596	-.332	.198
[Time=0] * $\|E\|_{sum}$	ref	ref	ref	ref	ref	ref
[Time=1] * $E//_{sum}$	.149	.127	1.176	.259	-.123	.422
[Time=0] * $E//_{sum}$	ref	ref	ref	ref	ref	ref
[Time=1] * $E_{\perp sum}$	.109	.074	1.489	0.159	-.048	.267
[Time=0] * $E_{\perp sum}$	ref	ref	ref	ref	ref	ref
[Time=1] * $\| E_{\perp}\|_{sum}$	-.435	.146	-2.985	**0.01**	-.748	-.123
[Time=0]*$\|E_{\perp}\|_{sum}$	ref	ref	ref	ref	ref	ref

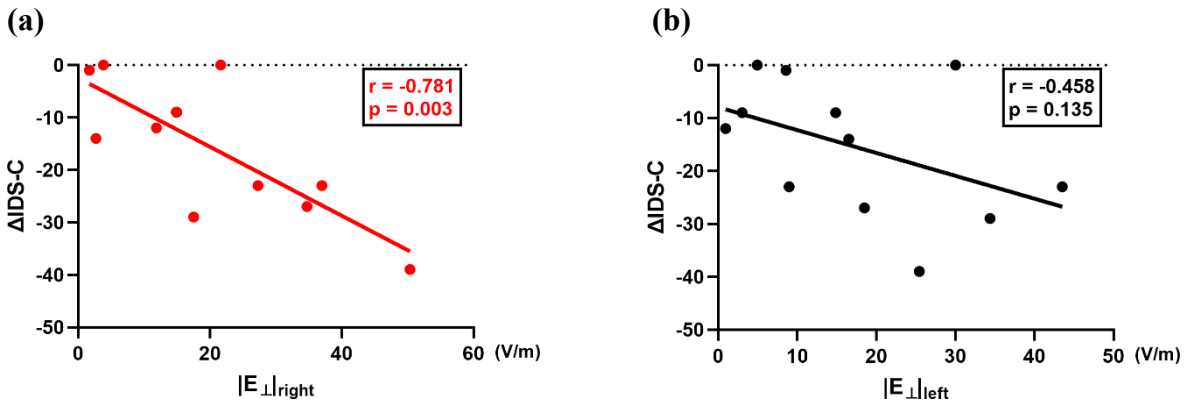

Figure 6. 3 (a) Correlation between change in IDS-C scores and |E⊥|, with the later calculated in the right ROI; (b) Correlation between change in IDS-C scores and |E⊥|, with the later calculated in the left ROI.

6.5 Discussion

To our knowledge, this is the first study using a computational simulation modeling approach to investigate the association between TMS-induced EF characteristics and clinical improvement in TRD patients. Our findings indicate that the $|E_{\perp}|$ component rather than $||E||$ or $E_{\parallel}$ in the DLPFC is related to symptom improvement. This is in line with a previous study indicating a correlation between the $E_{\perp}$component and TMS induced effects [19]. However, the exact mechanism of how TMS stimulates the brain is still a matter of debate. On the one hand, research suggests that not only $E_{\perp}$ but also the $||E||$ and $E_{\parallel}$ substantially contribute to the neuronal depolarization [7, 10] On the other hand, the cortical column cosine model claims that the stimulation effect is proportional to the cosine of the angle between the EF and the normal of the cortical surface [9]. The latter explanation seems to be the most parsimonious explanation for our data, with recent findings bolstering the rationale for this theoretical model. Aberra et al. [7] reported that TMS initiates action potentials at the axon terminal, with layer 5 pyramidal cells (the main integration unit of the cortical column) demonstrating the lowest depolarization thresholds and preferentially activated by the $E_{\perp}$ component. More studies are needed to resolve these controversial results, and to clarify the clinical significance of EF characteristics for left and right DLPFC in bilateral stimulation protocols. Lastly, we observed a significant correlation only for the right but not for left DLPFC when examining each hemisphere separately, an observation that requires replication.

6.6 Conclusion

In conclusion, our results suggest that the magnitude of $E_{\perp}$ component of the TMS-induced EF is associated with the antidepressant response to bilateral sequential TBS in patients with TRD. Future studies using a tailored TMS treatment approach may consider maximizing the $|E_{\perp}|$ component in order to enhance clinical effects. However, our results are exploratory and must be interpreted with caution due to the limited sample size.

6.7 Author's contribution

For the work presented in this chapter, the author contributed to the following aspects of the study: Conceptualization; Methodology; Software; Data Curation; Formal Analysis; Writing-Original Draft; Writing-Review & Editing; Visualization.

6.8 References

1. Klomjai, W., R. Katz, and A. Lackmy-Vallée, Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med, 2015. 58(4): p. 208-213.
2. Terao, Y. and Y. Ugawa, Basic mechanisms of TMS. Journal of clinical neurophysiology, 2002. 19(4): p. 322-343.
3. Cohen, S.L., et al., A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation, 2022. 15(1): p. 73-75.

4. Blumberger, D.M., et al., Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet, 2018. 391(10131): p. 1683-1692.

5. Desmyter, S., et al., Accelerated Intermittent Theta Burst Stimulation for Suicide Risk in Therapy-Resistant Depressed Patients: A Randomized, Sham-Controlled Trial. Front Hum Neurosci, 2016. 10: p. 480.

6. Corp, D.T., et al., Large-scale analysis of interindividual variability in theta-burst stimulation data: Results from the 'Big TMS Data Collaboration'. Brain Stimul, 2020. 13(5): p. 1476-1488.

7. Aberra, A.S., et al., Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain Stimul, 2020. 13(1): p. 175-189.

8. Stenroos, M. and L.M. Koponen, Real-time computation of the TMS-induced electric field in a realistic head model. Neuroimage, 2019. 203: p. 116159.

9. Fox, P.T., et al., Column-based model of electric field excitation of cerebral cortex. Hum Brain Mapp, 2004. 22(1): p. 1-14.

10. Weise, K., et al., A novel approach to localize cortical TMS effects. Neuroimage, 2020. 209: p. 116486.

11. Stöhrmann, P., et al., Effects of bilateral sequential theta-burst stimulation on functional connectivity in treatment-resistant depression: First results. J Affect Disord, 2023. 324: p. 660-669.

12. Fox, M.D., et al., Efficacy of transcranial magnetic stimulation targets for depression is related to intrinsic functional connectivity with the subgenual cingulate. Biol Psychiatry, 2012. 72(7): p. 595-603.

13. Stöhrmann, P., et al., Effects of bilateral sequential theta-burst stimulation on functional connectivity in treatment-resistant depression: first results. medRxiv, 2022: p. 2022.02.16.22271078.

14. Saturnino, G.B., K.H. Madsen, and A. Thielscher, Electric field simulations for transcranial brain stimulation using FEM: an efficient implementation and error analysis. J Neural Eng, 2019. 16(6): p. 066032.

15. Saturnino, G.B., et al., SimNIBS 2.1: A Comprehensive Pipeline for Individualized Electric Field Modelling for Transcranial Brain Stimulation, in Brain and Human Body Modeling: Computational Human Modeling at EMBC 2018, S. Makarov, M. Horner, and G. Noetscher, Editors. 2019, Springer Copyright 2019, The Author(s). Cham (CH). p. 3-25.

16. Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.

17. Nielsen, J.D., et al., Automatic skull segmentation from MR images for realistic volume conductor models of the head: Assessment of the state-of-the-art. NeuroImage, 2018. 174: p. 587-598.

18. Drakaki, M., et al., Database of 25 validated coil models for electric field

simulations for TMS. Brain Stimul, 2022. 15(3): p. 697-706.

19. Opitz, A., et al., Physiological observations validate finite element models for estimating subject-specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex. NeuroImage, 2013. 81: p. 253-264.

Chapter 7 Conclusions

7.1 Conclusions

This thesis addressed several key challenges in the application of iTBS, including variable individual responses, optimal stimulation intensity, timing in priming protocols, and the influence of anatomical differences. By investigating the mechanisms of iTBS and identifying parameters affecting its efficacy, this work contributes to the optimization of iTBS protocols for future clinical use. The use of fNIRS provided valuable insights into iTBS-induced brain activity changes, furthering our understanding of this promising therapeutic intervention. This research lays the groundwork for more effective and personalized iTBS for future use.

Study I: Pilot Study I

This study demonstrated that stimulating the DLPFC and LPC with iTBS produced distinct effects on brain activity patterns and associative learning, highlighting the specific roles these regions play in memory.

Study II: Pilot Study II

This pilot study investigated the impact of varying iTBS intensity on the left DLPFC in healthy adults. The results indicated that 70% RMT might to the most effective stimulation intensity.

Study III: main study

This study examined how timing influences the neuromodulatory effects of priming TBS in individuals with depressive symptoms. These findings highlight the potential of priming TBS protocols to enhance the efficacy of iTBS by optimizing stimulation timing and utilizing metaplasticity mechanisms.

Study IV: computational study I

This study explored how neurobiological sources of variability, specifically the scalp-to-cortex distance, influence TMS dose reaching the brain. The results indicated significant ethnic differences in scalp-to-cortex distance and associated electric field strengths. The findings highlight the need to account for individual anatomical variability when designing stimulation protocols.

Study V: computational study II

In this study, the relationship between TMS-induced electric field characteristics and antidepressant effects was investigated in patients with TRD. The results showed that the normal component of the electric field was significantly associated with symptom relief, providing insights into the neurobiological mechanisms underlying TMS efficacy in depression.

7.2 Clinical applications of the studies

The collective findings of my studies have significant implications for clinical practice, particularly in optimizing TMS protocols and developing personalized approaches for TMS delivery targeting the left DLPFC.

The study in Chapter 2 highlights the importance of specific training following TMS, suggesting that pairing TMS with cognitive training could enhance the overall effectiveness of the intervention. This finding supports the integration of TMS with task-specific cognitive exercises to amplify neuroplastic effects and improve clinical outcomes, particularly in cognitive rehabilitation and enhancement.

The study in Chapter 3 demonstrates that iTBS at subthreshold intensity is also efficacious. This finding has the potential to revolutionize clinical practice by improving patient comfort during iTBS treatment. Current FDA-approved iTBS protocols require stimulation at 120% of the RMT, which can cause significant pain or discomfort for many patients. Reducing the intensity to subthreshold levels could make TMS treatments more tolerable and accessible, particularly for patients with high sensitivity to discomfort, without compromising treatment efficacy.

The study in Chapter 4 explores the time interval between priming stimulation and test stimulation, providing insights into the temporal dynamics of neuroplasticity induced by iTBS. By identifying the optimal time interval (e.g., 10 minutes) for priming TBS protocol, clinicians can leverage the benefits of metaplasticity to design more effective

stimulation protocols. Optimizing the timing of stimulation may also reduce variability in patient responses to TMS, leading to more predictable and reliable clinical outcomes. The studies in Chapters 5 and 6 highlight the importance of individual differences, such as head morphology, in determining the distribution of TMS-induced EF. These findings underscore the need for personalized TMS protocols tailored to the unique anatomical characteristics of each individual. For patients with TRD, clinicians can refine rTMS protocols by maximizing the normal component of the electric field, thereby enhancing treatment efficacy and improving therapeutic outcomes.

Overall, the findings from my studies collectively contribute to advancing the clinical application of TMS, particularly by paving the way for more personalized interventions and reducing variability in TMS responses. However, it is important to note that most participants included in my studies were from a healthy population. Therefore, the translation of these findings to clinical populations should be approached with caution. Further research is necessary to validate these results in clinical settings.

7.3 Limitations of the studies

This thesis research included several limitations. First, the absence of brain activity measures in the study presented in Chapter 2 hindered a full understanding of how iTBS leads to behavioral changes. Second, the stimulation intensity used in pilot study II (Chapter 3) restricts the generalizability of findings regarding suprathreshold iTBS effects. Third, the setup and design of the main study (Chapter 4) prevented

measurement of brain activity immediately following the initial preconditioning stimulation. Fourth, in Chapter 5, the lack of behavioral and clinical outcome measures limited the ability to connect variations in TMS dose to differences in treatment effects. Finally, the small sample size of the final study (Chapter 6) necessitates larger-scale future research to replicate and validate the findings.

7.4 Future research directions

Building upon the findings of this thesis, future research should focus on two key areas: personalized, state-dependent TMS protocols and individualized electric field modeling for optimized stimulation. The priming TBS study in this thesis attempted to modulate brain activity to a lower state before leveraging metaplasticity to enhance the effects of subsequent stimulation. However, recent research indicates that the effects of TMS on brain networks depend not only on recent brain state history but also on ongoing oscillatory and cognitive brain states [1]. These states are crucial for determining the immediate effects of TMS and are directly related to "target engagement" in TMS therapy. Future studies could incorporate cognitive tasks during TMS to investigate state-dependent effects. Separately, utilizing EEG-informed or EEG-triggered closed-loop TMS protocols, which stimulate at specific amplitudes or phases of simultaneously recorded EEG oscillations, may also improve treatment response.

Furthermore, the traditional practice of dosing rTMS in non-motor areas by adjusting intensity to a percentage of motor threshold overlooks individual anatomical

differences, leading to variations in the actual dose reaching the target brain area, even at the same stimulation intensity [2, 3]. This dose variability likely contributes to the observed variability in treatment response [4]. Therefore, future research should explore electric field-optimized TMS to address this limitation and improve the precision and efficacy of TMS treatments.

7.5 References

1. Sack, A.T., et al., Target Engagement and Brain State Dependence of Transcranial Magnetic Stimulation: Implications for Clinical Practice. Biol Psychiatry, 2024. 95(6): p. 536-544.
2. Datta, A., et al. Exploration of the Effect of Race on Cortical Current Flow Due to Transcranial Direct Current Stimulation: Comparison across Caucasian, Chinese, and Indian Standard Brains. in 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2018.
3. Ge, J., et al., Increasing diversity in connectomics with the Chinese Human Connectome Project. Nature Neuroscience, 2023. 26(1): p. 163-172.
4. Thielscher, A., A. Antunes, and G.B. Saturnino. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? in 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015.

APPENDICES

APPENDIX 1. Journal's approval for using chapter 2 in the thesis.

Outlook

Re: reuse published article in my phd thesis [241204-010209]

发件人 Permissions Helpdesk <permissionshelpdesk@elsevier.com>
日期 周四 2024/12/5 14:45
收件人 ZHANG, bcllabingbing [Studcnt] <bcllabingbing.zhang@ >

Dear Prof. Bingbing ZHANG,

Thank you for contacting us.

As an Elsevier journal author, you retain the right to Include the article in a thesis or dissertation (provided that this is not to be published commercially) whether in full or in part, subject to proper acknowledgment; see https://www.elsevier.com/about/policies/copyright for more information. As this is a retained right, no written permission from Elsevier is necessary.

As outlined in our permissions licenses, this extends to the posting to your university's digital repository of the thesis provided that if you include the published journal article (PJA) version, it is embedded in your thesis only and not separately downloadable.

Thank you.

Kind regards,

Thomas Rexson Yesudoss
Copyrights Specialist
ELSEVIER | HCM - Health Content Management

Visit Elsevier Permissions

APPENDIX 2. Journal's approval for using chapter 3 in the thesis.

Outlook

RE: apply for reusing published article in my thesis

发件人 Frontiers in Psychiatry - Production <psychiatry.production.office@frontiersin.org>
日期 周四 2024/12/5 18:41
收件人 ZHANG, Bella Bingbing [RS] <bella-bingbing.zhang@ >

CAUTION: External email. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear Bingbing,

Thank you for your email. Frontiers authors retain full copyright in their own articles, so you are free to reuse your work in whatever way you would like. Additionally, as your work is published under a CC-BY 4.0 license, it is free for anyone to use.

We would simply ask that you cite your article as follows in your thesis:

Zhang BBB, Kan RLD, Giron CG, Lin TTZ, Yau S-Y and Kranz GS (2022) Dose-response relationship between iTBS and prefrontal activation during executive functioning: A fNIRS study. Front. Psychiatry 13:1049130. doi: 10.3389/fpsyt.2022.1049130

Best wishes,

Tim

Tim West (he/him)
Production Specialist

Production Team

Production Manager: Marcin Tomaszkow

Frontiers | Production Office

Frontiers

35 New Broad St

London

EC2M 1NH

Office T +41 21 510 17 06

Do you need help? Visit our Production Help Center page for more information.

APPENDIX 3. Journal's approval for using chapter 6 in the thesis.

Outlook

Re: reuse published article in my thesis [241204-010374]

发件人 Permissions Helpdesk <permissionshelpdesk@elsevier.com>
日期 周四 2024/12/5 14:44
收件人 ZHANG, bellabingbing [Student] <bellabingbing.zhang@ >

CAUTION: This email is not originated from PolyU. Do not click links or open attachments unless you recognize the sender and know the content is safe.

How was our service today?
Thumbs up *Thumbs down*

Dear Prof. Bingbing ZHANG,

Thank you for contacting us.

As an Elsevier journal author, you retain the right to Include the article in a thesis or dissertation whether in full or in part, subject to proper acknowledgment; see https://www.elsevier.com/about/policies/copyright for more information. As this is a retained right, no written permission from Elsevier is necessary.

As outlined in our permissions licenses, this extends to the posting to your university's digital repository of the thesis provided that if you include the published journal article (PJA) version, it is embedded in your thesis only and not separately downloadable.

Thank you.

Kind regards,

Thomas Rexson Yesudoss
Copyrights Specialist
ELSEVIER | HCM - Health Content Management

Visit Elsevier Permissions