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Short communication

Sex differences in brain excitability revealed by concurrent iTBS/fNIRS

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ABSTRACT

Sex differences have been claimed an imperative factor in the optimization of psychiatric treatments. Intermittent theta-burst stimulation (iTBS), a patterned form of repetitive transcranial magnetic stimulation, is a promising non-invasive treatment option. Here, we investigated whether the real-time neural response to iTBS differs between men and women, and which mechanisms may mediate these differences. To this end, we capitalized on a concurrent iTBS/functional near-infrared spectroscopy setup over the left dorsolateral prefrontal cortex, a common clinical target, to test our assumptions. In a series of experiments, we show (1) a biological sex difference in absolute hemoglobin concentrations in the left dorsolateral prefrontal cortex in healthy participants; (2) that this sex difference is amplified by iTBS but not by cognitive tasks; and (3) that the sex difference amplified by iTBS is modulated by stimulation intensity. These results inform future stimulation treatment optimizations towards precision psychiatry.

1. Introduction

Sex differences are highly common in the prevalence and manifestation of psychiatric disorders such as depression and substance abuse (Kessler et al., 2005). For presenting symptoms of these disorders, repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (lDLPFC) is a demonstrably efficacious therapy, as recently summarized by us (Kan et al., 2023b). Recent evidence indicates sex differences in brain-based predictors of pharmacotherapeutic anti-depressive treatment response (Wilson et al., 2023). However, while these results have the potential to improve clinical decision making for pharmacotherapy, sex differences in rTMS treatment response and the underlying neural mechanisms remain unclear. Uncovering the underlying biological mechanisms of presumed sex-specific treatment effects can optimize treatment response and facilitate precision medicine (Hanlon and McCalley, 2022; Mauvais-Jarvis et al., 2020). In a series of experiments, we investigated whether the real-time neural response to intermittent theta-burst stimulation (iTBS) in the lDLPFC differs between women and men, and which neural mechanisms may mediate these differences.

2. Methods

A total of 142 healthy, right-handed participants, including 84 females and 58 males were recruited and subjected to four experiments. Participants were screened by an experienced clinical team member and consent forms were obtained after explaining all study related procedures to participants. Inclusion criteria for all experiments were an age between 18 and 35, right handedness assessed using the Edinburgh Inventory (Oldfield, 1971), and physical and mental health. Exclusion criteria were any psychiatric disorder according to DSM 5 criteria, as well as common TMS and fNIRS exclusion criteria. All experiments conformed with the Declaration of Helsinki and were approved by the Institutional Review Board of The Hong Kong Polytechnic University (HSEARS20200120005, HSEARS20200120005, HSEARS20181212008, HSEARS2021032300).

Prefrontal excitability was assessed using functional near-infrared spectroscopy (fNIRS), a cost efficient and user-friendly neuroimaging

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modality that allows to capture hemoglobin concentration changes. fNIRS is ideal to measure the neural effects of rTMS in real time, given that fNIRS measurements are not subject to electromagnetic interference produced by rTMS. For experiment 1–3, we used frequency-domain NIRS (OxiTs; ISS Inc, Champaign, Illinois USA) and the fNIRS probe consisting of eight emitters at two wavelengths (687 and 830 nm) and one detector. The absolute concentrations of oxy-hemoglobin (HbO) and deoxy-hemoglobin (HbR) were detected by measuring the change in the intensity modulation and phase shift (Fantini and Sassaroli, 2020). Here, we capitalized on a concurrent iTBS/fNIRS setup that allows measuring the instantaneous effect of iTBS on absolute HbO and HbR concentrations (Kan et al., 2023a). The fNIRS probe was placed directly below the TMS coil on the lDLPFC, separated by a 3D-printed polyethylene bridge (Fig. 1a, see details in supplementary). For stimulation, a figure-of-eight cooling coil (Cool-B65) and the MagPro magnetic stimulator (MagVenture, Denmark) were used with a standard 3-minute iTBS protocol (Huang et al., 2005). The stimulation target, lDLPFC, was located using a neuronavigation system (Localite, Bonn, Germany) with MNI coordinates (x=-38, y=+44, z=+26).

For experiment 4, we used the frequency-domain fNIRS system as detailed above, as well as a continuous wave functional near-infrared (695 and 830 nm) spectroscopy (CW-fNIRS) device (ETG-4000, Hitachi Medical Co., Tokyo, Japan) with a sampling rate of 10 Hz to collect hemoglobin concentration changes during two cognitive tasks, the n-back task and verbal fluency task (VFT). These tasks operationalize working memory and language processing ability, respectively, and are commonly used when probing DLFPC function in healthy and depressed participants (Akiyama et al., 2018; Rodriguez-Jimenez et al., 2009). Detailed materials and methods are provided in SI Appendix.

3. Results and discussion

In a first step (Experiment 1), we examined sex differences in absolute hemoglobin concentrations in the lDLPFC, given that sex differences are known to exist in cerebrovasculature, scalp thickness and brain size (Eliot et al., 2021). Frequency-domain fNIRS was applied in a group of 66 healthy right-handed participants including 38 females and 28 age- and education-matched males for a 3-minute measurement at rest. We observed higher absolute concentrations of HbO and HbR in males compared to females (average sex difference: HbO 11.98 μM, $p<0.001$, hedges' g = 1.48; HbR 2.70 μM, $p=0.003$, hedges' g = 0.77, see Fig. 1b). These results corroborate previous findings of sex differences in cerebral hemoglobin concentrations (Auger et al., 2016).

Next (Experiment 2), we examined a potential sex difference in iTBS-induced instantaneous excitability of the lDLPFC by using the concurrent iTBS/fNIRS setup. Fifty-six participants including 32 females and 24 age- and education-matched males were included and hemoglobin concentrations were measured 3-minutes before, during, and 3-minutes after standard iTBS (600 pulses at 80–90% resting motor threshold, rMT). Compared to baseline, there was an increase in HbR concentration during (0.24±0.49 μM, $p=0.001$, hedges' g = 0.68) but not after stimulation (0.02±0.52 μM, $p=0.869$) across participants. Moreover, males exhibited higher iTBS-induced HbR concentration changes compared to females (males: 0.41±0.48 ΔμM; females: 0.10±0.46 ΔμM, $p=0.018$, hedges' g = 0.66), see Fig. 1c. Regarding HbO, there were no iTBS-induced changes during stimulation and no gender differences in these changes (see supplementary for details). These results indicate that baseline sex differences in oxygen consumption (absolute HbR concentrations) are further amplified by neural tissue-excitation through iTBS (increases in absolute HbR concentrations). However, probing the relationship between baseline levels and iTBS-induced changes in HbR indicated no significant correlation (males: $r=0.05$; females: $r=0.15$;

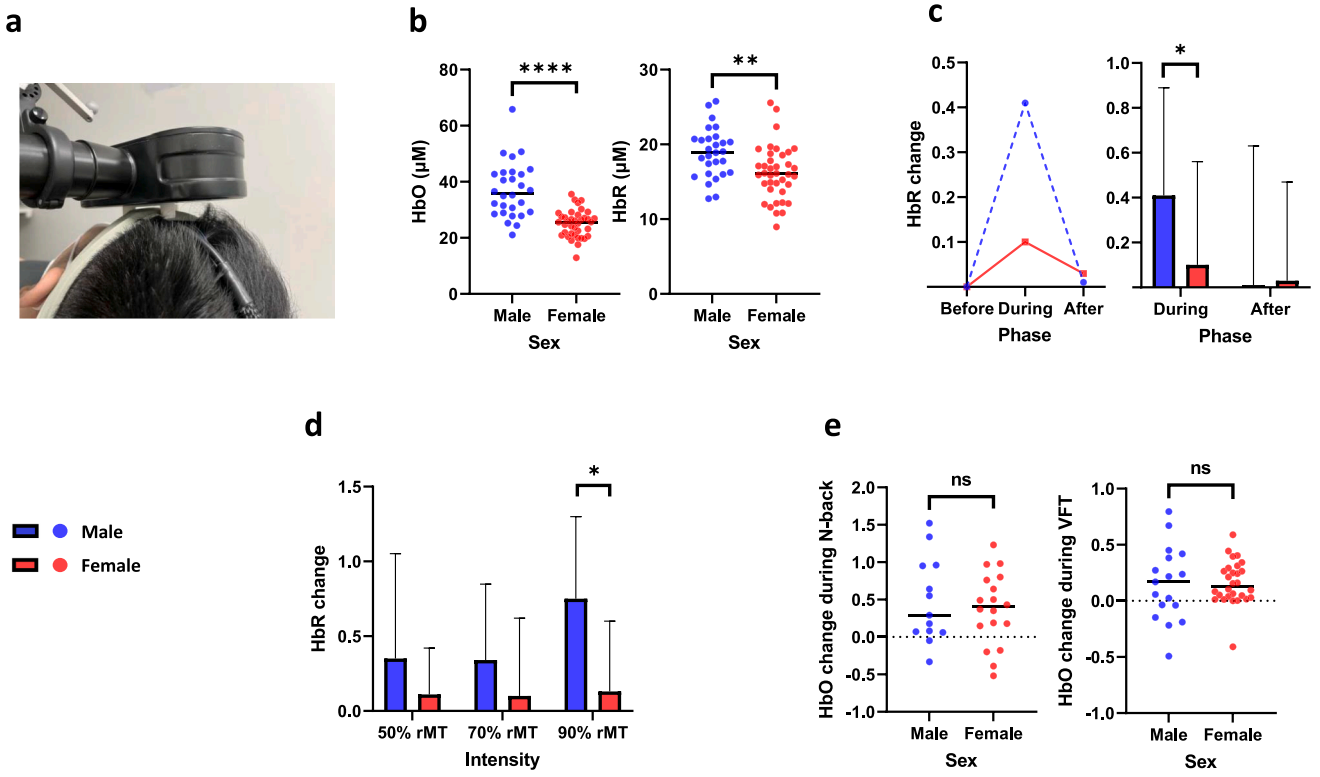

Fig. 1. (a) Coil-bridge-optode setup for concurrent iTBS/fNIRS; (b) Sex difference in absolute hemoglobin concentration at rest; (c) Sex difference in iTBS induced HbR concentration changes; (d) Intensity-dependent sex differences in iTBS induced HbR concentration changes; (e) Task-induced relative hemoglobin concentration changes. One asterisk (*) indicates a p-value of less than 0.05. Two asterisks (**) indicate a p-value of less than 0.01 and three asterisks (***) indicate a p-value less than 0.001. "ns" indicates a p-value larger than 0.05.

combined: r=0.16, all p>0.1). Nevertheless, these results further elucidate the neural mechanisms underlying sex differences in the antidepressant efficacy of rTMS in depression (Adamson et al., 2022).

In a third experiment (Experiment 3), we examined whether sex differences in iTBS-induced HbR concentration changes are modulated by stimulation intensity. To this end, we tested a subsample of the above sample with n=24 (12 females) participants on three separate visits in order to systematically probe the effects of three subthreshold intensities of iTBS at 50%, 70%, and 90% rMT. Despite a significant main effect of sex in HbR concentration changes (F=8.918, p=0.004), post-hoc pairwise contrasts only revealed a significant sex difference with a stimulation intensity of 90% rMT, with increased iTBS-induced absolute HbR concentration changes in males (0.75±0.51 ΔμM) compared to females (0.125±0.51 ΔμM), p=0.004, hedges' g = 1.22, see Fig. 1d. This result suggests that the optimal stimulation intensity for therapeutic iTBS may differ between the sexes and provides insights for treatment optimization towards precision psychiatry (Lee et al., 2021; Padberg et al., 2002).

Finally (Experiment 4), we investigated whether observed sex differences are stimulation-specific, or whether they are also observed when the lDLPFC is probed by two cognitive challenges. To this end, we administered two frequently used cognitive tasks, the n-back task and the VFT to a group of 71 participants (n-back task: 31 participants, 18 females; VFT: 45 participants, 28 females). Given that sex differences in cognition are small and generally overestimated (Hyde, 2005), we expected small sex effects in our sample. Indeed, we found no evidence for significant sex differences in task-induced hemoglobin concentration changes for either task (n-back: ΔHbO, p=0.575; ΔHbR p=0.906; VFT: ΔHbO p=0.276; ΔHbR p=0.816). Moreover, there was no significant sex difference in task performance in either task (n-back task: p=0.831; VFT: p=0.158), see Fig. 1e. These results concur with reported small to close-to-zero effects in 80% of studied psychological sex differences (Hyde, 2005) and indicate that sex differences in the lDLPFC are stimulation specific.

We repeated analyses for experiments 1–4 using age, years of education or rMT as covariates of no interest to test their potential of confounding our main findings. These analyses revealed that our main findings remained robust even after accounting for these factors. For details, see the Supplementary 2.2.

Taken together, our experiments provide evidence for a biological sex difference in absolute hemoglobin concentrations at rest in the lDLPFC. This sex difference is amplified not by cognitive tasks that activate the prefrontal regions, but by iTBS, a supraphysiological challenge, as evidenced by higher stimulation-induced hemoglobin concentration changes in males. Moreover, stimulation-induced sex differences are modulated by stimulation intensity, indicating that the optimal stimulation intensity for therapeutic iTBS may differ between the sexes. In conclusion, our results provide evidence that sex-specific effects of stimulation-induced prefrontal excitability are an important aspect to consider in the advancement of brain stimulation protocols towards precision psychiatry (Mauvais-Jarvis et al., 2020).

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CRediT authorship contribution statement

Kenneth N.K. Fong: Supervision. **Minxia Jin:** Data curation, Validation. **Penny P.I. Qin:** Data curation, Validation. **Adam W.L. Xia:** Validation, Data curation. **Alvin H.P Tang:** Validation, Data curation. **Tim T.Z. Lin:** Methodology, Formal analysis, Data curation. **Bella B.B. Zhang:** Writing – original draft, Formal analysis, Data curation. **Rebecca L.D. Kan:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Georg S. Kranz:** Writing – review & editing, Supervision, Resources, Funding acquisition, Formal analysis, Conceptualization. **Suk-Yu Yau:** Supervision. **Benjamin Becker:** Supervision, Writing – review & editing.

Declaration of Competing Interest

None.

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Data, Materials, and Software Availability

All study data are available at Mendeley Data: https://data.mendeley.com/datasets/bmbvrjtsnw/1.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ajp.2024.104043.

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