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Investigating the hemodynamic response to iTBS of the left DLPFC: A concurrent iTBS/fNIRS study

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ABSTRACT

Background: Intermittent theta burst stimulation (iTBS) targeting the left dorsolateral prefrontal cortex (DLPFC) is an established treatment regimen for major depressive disorder, but its instantaneous effects on neural excitability during and immediately after the stimulation remain unclear. This study aimed to investigate the hemodynamic response in the bilateral DLPFC during and immediately after iTBS and explored factors that may modulate iTBS-induced excitability.

Methods: We measured the prefrontal hemodynamic response before, during, and after iTBS using concurrent iTBS/functional near-infrared spectroscopy (fNIRS) in healthy participants across multiple sessions (3–11 visits, ≥48 hours apart). We investigated the moderating effect of several inter- and intra-individual variables. To this end, we analyzed the average change of oxygenated (HbO) and deoxygenated hemoglobin (HbR) in the stimulated and contralateral DLPFC and used generalized linear mixed models (GLMMs) to test for potential moderators.

Results: Twenty participants completed 157 concurrent iTBS/fNIRS sessions in total. HbR increased significantly during iTBS (0.247 ± 0.032, $p < 0.001$) in the stimulated DLPFC, while the contralateral DLPFC showed significant decreases in HbR during (-0.046 ± 0.017, $p = 0.024$) and after the stimulation (-0.05 ± 0.018, $p = 0.015$). No significant change in HbO was observed. GLMM revealed that age ($\beta = 0.033$, $p = 0.004$), sex ($\beta = -0.248$, $p = 0.004$), education years ($\beta = -0.094$, $p < 0.001$), the personality trait agreeableness ($\beta = -0.013$, $p = 0.005$), and positive affect ($\beta = -0.032$, $p = 0.012$) significantly influenced local HbR response during iTBS, and sex ($\beta = 0.305$, $p = 0.012$) significantly influenced local HbO response during iTBS.

Conclusion: This study revealed a pronounced increase in HbR during iTBS in the stimulated DLPFC, alongside decreased HbR contralaterally both during and post-stimulation. Furthermore, our study highlights the importance of individual factors in understanding iTBS effects on cortical excitability.

1. Introduction

Intermittent theta burst stimulation (iTBS), a variant of repetitive transcranial magnetic stimulation (rTMS) targeted to the left dorsolateral prefrontal cortex (lDLPFC), is approved by the U.S. Food and Drug Administration (FDA) for pharmaco-treatment-resistant major depressive disorder (MDD). In the past decades, the application of iTBS on the DLPFC has developed rapidly as a treatment for various psychiatric disorders [1–3]. However, one of the challenges for prefrontal TMS applications is the absence of a direct readout of its instantaneous effects during and immediately after the stimulation, which hinders the understanding of the neural mechanisms underlying its clinical effects. The concurrent use of iTBS with neuroimaging techniques provides an opportunity to estimate the magnitude of the resultant cortical excitability evoked by rTMS directly in regions beneath the coil (local excitability) as well as inter-regionally in remote regions not stimulated (remote

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excitability) [4–6]. Such a setup helps to understand the modulatory effect of iTBS on neuroplasticity and to optimize iTBS treatment.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive brain imaging technique that applies optical signals to measure cortical hemoglobin concentration changes (oxygenated, HbO, and deoxygenated hemoglobin, HbR), yielding indexes of neuronal activity [7]. fNIRS has the advantage of being less susceptible to TMS-induced electromagnetic interference, which makes it an ideal neuroimaging method for real-time monitoring of the neural response during and immediately after iTBS [8]. In addition, fNIRS stands out for its simplicity in setup, cost-effectiveness and efficiency, making it a robust and replicable option. Recently, numerous studies have applied concurrent TMS/fNIRS in the motor system [4] and prefrontal cortex [6] to investigate the TMS-induced brain hemodynamic response. Notably, single-pulse TMS or separated blocks of trains of high-\low-frequency rTMS were mostly applied in these studies; in contrast, iTBS of the lDLPFC was rarely investigated.

In a previous longitudinal concurrent iTBS/fNIRS single case study, we found that caffeine intake, time-of-day of receiving stimulation, and daily emotions moderate the instantaneous hemodynamic response to iTBS of the lDLPFC [9]. In a subsequent cross-sectional study of a dataset of n = 56, we observed that the participants' gender significantly moderates the hemodynamic response to iTBS [10]. Although both studies were inconsistent with regards to the nature (HbO vs. HbR) and the direction (increase vs. decrease) of the response to iTBS, they suggest a moderating role of several inter- and intra-individual factors on iTBS-induced hemodynamic changes [9,10]. However, a major limitation of these two studies was the use of a single-channel fNIRS device directly below the TMS coil, limiting the investigation of the iTBS-induced hemoglobin changes to a small cortical region within the lDLPFC. Thus, replicating this work in a larger sample and using a multichannel fNIRS device is necessary. In addition, several intra- and inter-individual factors that were not investigated in the above studies potentially influence iTBS-induced hemodynamic changes. These factors include physical activity, sleep, personality or brain state [11–13]. Uncovering the effects of these factors on iTBS-induced neural response would facilitate the development of therapeutic iTBS for precision psychiatry [14]. Indeed, previous studies indicated that personality traits can predict the antidepressant response to treatment with rTMS [15–18] and modulate motor cortex excitability [13], although the latter finding could not be replicated [19].

Therefore, the current study aimed to shed light on the hemodynamic response in bilateral DLPFC during and immediately after iTBS using a multichannel fNIRS setup. We also aimed to replicate the influence of sex, time-of-day, daily emotions, and coffee intake found in our previous studies [9,10], and further investigate the effects of age, education years, personality traits, physical activity, sleep efficiency and brain state on iTBS-induced hemodynamics [11–13]. We hypothesized that iTBS induces significant hemodynamic changes during the stimulation in both targeted DLPFC and contralateral DLPFC. Furthermore, we hypothesized that such iTBS-induced hemodynamic changes are modulated by inter- and intra-individual variables.

2. Methods

2.1. Study design and participants

This study was a prospective, cross-sectional clinical trial with repeated measures. We included 20 right-handed (assessed by the Edinburgh Handedness Questionnaire [20]), healthy adults (age 25.65 ± 4.85 years, 10 male). Subjects were excluded if they met any of the following criteria: (1) a current or past diagnosis of psychiatric, neurological disorders, or severe internal illness; (2) any contraindication to iTBS or fNIRS; (3) substance dependence/abuse within the last 3 months; (4) psychiatric disorders in their first-degree relatives; (5) pregnancy. All included participants underwent continuous measurement of prefrontal hemodynamic response before (3 min), during (3 min), and after (3 min) lDLPFC-iTBS using concurrent iTBS/fNIRS (see section 2.2.) across multiple sessions. To investigate the impact of intra-individual factors, while considering the time expenditure for participants and researchers, each participant underwent a minimum of three sessions [21] and a maximum of 15. All sessions were separated by at least 48 hours to minimize carry-over effects from the iTBS [21,22]. Potential moderators were assessed using corresponding measurements at the first visit (for inter-individual factors) or on each visit day (for intra-individual factors, see section 2.3.). The procedure of the study is summarized in Fig. 1. This study was prospectively registered at clinicaltrials.gov (NCT06104462) and was conducted according to the Declaration of Helsinki with ethical approval from the Institutional Review Board of the Hong Kong Polytechnic University (HSEARS20220812002-02). Written informed consent was obtained from every enrolled participant.

2.2. Concurrent iTBS/fNIRS

2.2.1. Intermittent theta burst stimulation

We utilized the standard iTBS protocol developed by Huang et al. [23], comprising 20 trains of stimulation. Each train consists of ten 3-pulse bursts at an intra-burst frequency of 50 Hz, delivered at 5 Hz, followed by an 8-s rest period. A total of 600 pulses were administered during this 3-min iTBS protocol. Stimulation was delivered with a MagProX100 magnetic stimulator (MagVenture, Denmark) and a figure-of-eight shaped cooling coil (Cool-B65) targeting the lDLPFC at an intensity of 90 % of the individual resting motor threshold (RMT). This intensity level was chosen to ensure compliance and robust DLPFC activation [9,10]. RMT was determined at the first experimental visit as the lowest intensity to elicit motor evoked potentials with at least 50 μV peak-to-peak amplitude in the relaxed right first dorsal interosseous muscle five out of ten times when consecutively stimulating the left primary motor cortex (M1) with a single pulse. The left M1-Hand was identified using electrode position C3 of the international 10–20 EEG system [24]. Then, the hotspot was manually searched based on the methods described by Ortega-Robles et al. and Rossini et al. [25,26]. To account for the increased distance between the TMS coil and the skull due to the fNIRS optode beneath the coil (10 mm), we adjusted the intensity using the equation:

$$\text{AdjMT\%} = \text{MT} + 2.8 * (\text{Dsitex-Dm1}) \text{ [27]} \quad \text{[Equation 1]}$$

The specific target site of the lDLPFC was determined via the TMS neuronavigation system (LOCALITE, Bonn, Germany) at the Montreal Neurological Institute (MNI) coordinates (x = −38, y = +44, z = +26; Brodmann area, BA, 46) [28]. The TMS coil was positioned above the fNIRS probe at the target site under neuronavigation guidance, minimizing pressure to reduce coil vibrational movement artifacts. Any self-reported side effects were documented immediately post-stimulation to mitigate potential dropouts.

2.2.2. Functional near-infrared spectroscopy

A multichannel continuous wave (785 and 830 nm) near-infrared spectroscopy system, NIRxBorealis (NIRx Medical System), was utilized to measure the cortical hemodynamic activity before, during, and after iTBS, with a sampling rate of 6.26 Hz. The system features specially designed optodes (10 mm in height) for compatibility with TMS. Twenty-one standard optodes (13 sources and 8 detectors) and eight short-distance detectors were placed over the bilateral frontal lobes according to the international 10–20 EEG system, resulting in 28 standard channels (CH) and eight short-distance channels (SSC) (Fig. 2a). Plastic spacers maintained approximately 3 cm in each standard CH to measure hemodynamic changes in the cerebral cortex. The SSC, set at an 8 mm distance, effectively identifies and eliminates TMS-related artifacts, including movement artifacts (coil and muscle-twitch movement)

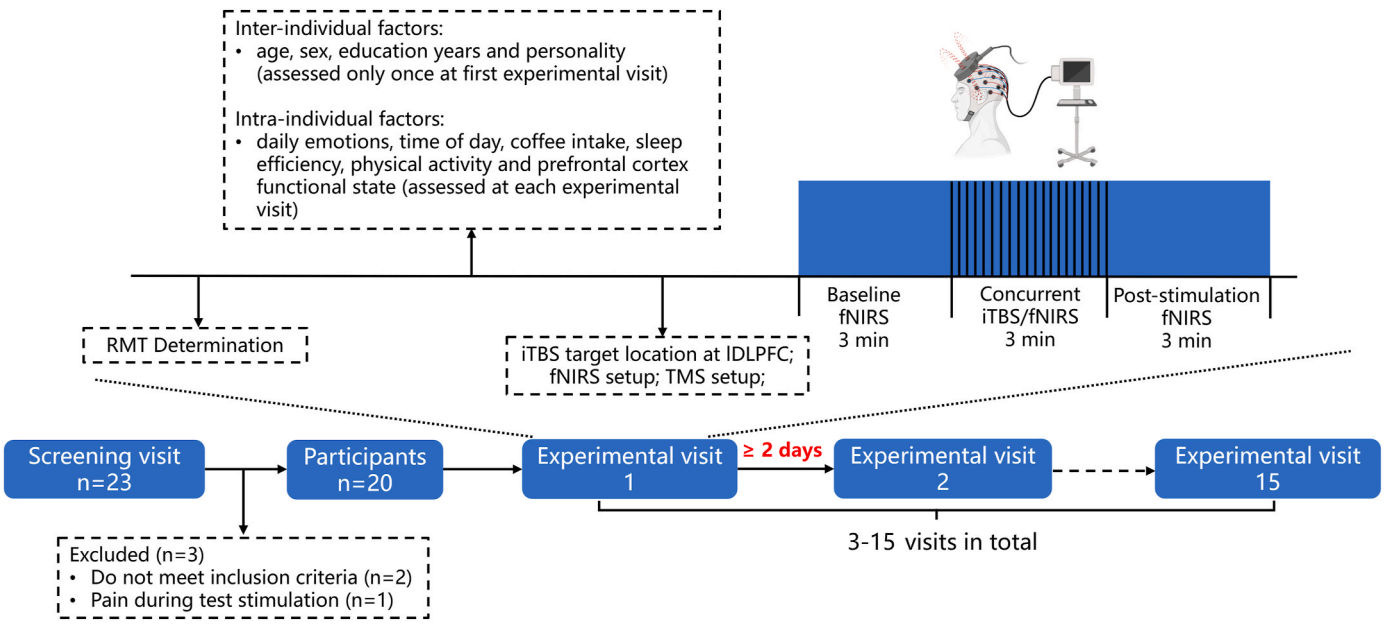

Fig. 1. Diagram of the experimental design.

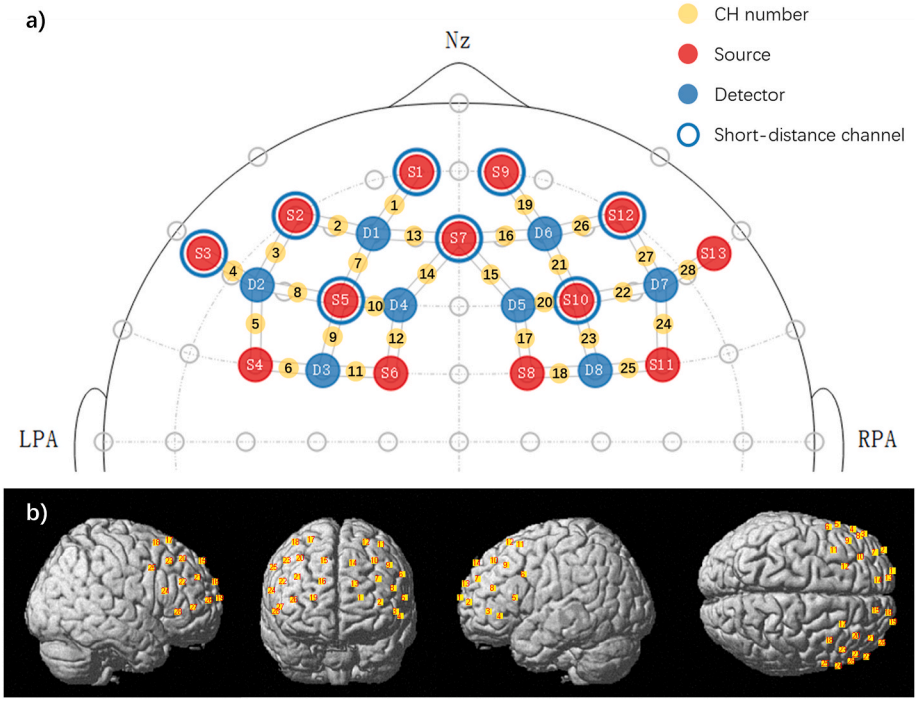

Fig. 2. Arrangement of the fNIRS optodes and channels. a) The optode design. b) The location of standard channels. Channels 14 and 25 were excluded from all datasets due to bad signal quality observed in more than 50 % of the datasets.

and superficial tissue artifacts [8].

We used three cap sizes (54, 56 and 58 cm), each equipped with the same fNIRS probes, to accommodate varying head sizes among participants. To localize the coordinates of individual CHs within each cap size on the MNI standard brain template, we utilized a 3D digitizer (PATRIOT, Polhemus) for coordinate estimation and the NIRS_SPM toolbox [29] for spatial registration (Fig. 2b). According to the estimated spatial registration on MNI, we defined two regions of interest (ROIs): stimulated DLPFC and contralateral DLPFC (both in BA 46), with the greatest percentage (>80 %) of overlapping channels, for subsequent analysis. For the 56 cm cap, CH-7 and CH-21 served as anatomical markers for the two ROIs, while CH-2 and CH-26 were used for the 54 cm and 58 cm caps.

fNIRS signals were acquired in a quiet room with dim lighting. During acquisition, participants lay comfortably in a chair, closed their eyes, and were instructed to remain awake without talking or moving.

2.2.3. *fNIRS data processing*

To comprehensively depict the hemodynamic response to iTBS, we utilized both HbO and HbR as indicators. Offline data preprocessing was conducted using the *HomER2* toolbox [30] and customized scripts in Matlab 2017a (The MathWorks Inc.). Each channel's raw signal in every

dataset was visually inspected to exclude channels with poor signal quality, determined by predefined criteria for acceptable dRange (with a lower threshold of 500 μV and an upper threshold of 1 V), specific to the NIRxBorealis system, as well as cardiac power using spectral analysis [31], thus omitting them from further analysis. The raw signals were converted into optical density and then into concentration change of HbO (ΔHbO) and HbR (ΔHbR) based on the modified Beer-Lambert Law [32]. Individual analyses were conducted on ΔHbO and ΔHbR. For each

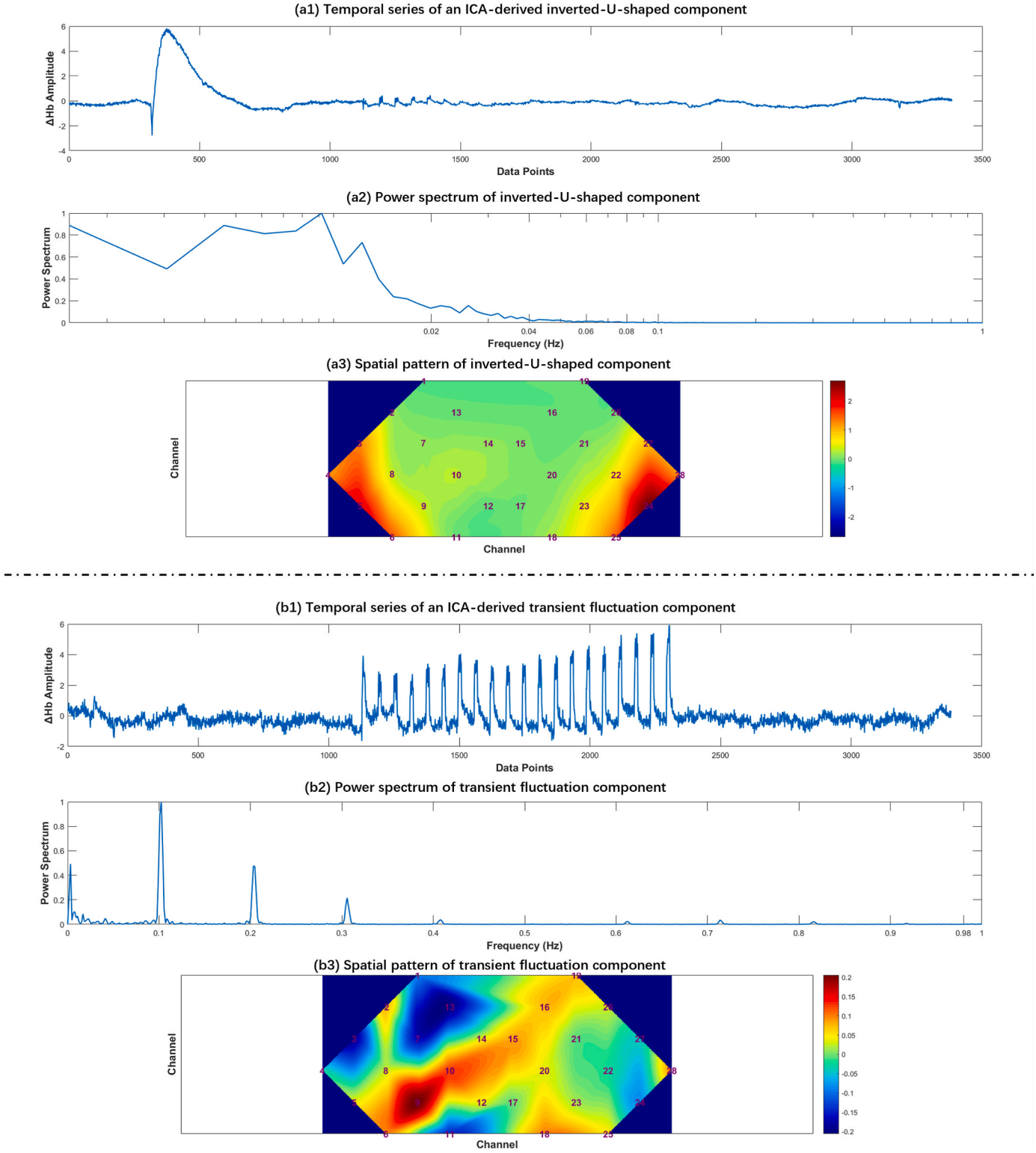

Fig. 3. Temporal series (a1, b1), power spectrum (a2, b2), and spatial pattern (a3, b3) of a representative ICA-derived inverted-U-shaped component at resting state and transient fluctuation component during stimulation from a randomly selected participant. (a) Temporal series of an ICA-derived inverted-U-shaped component has a spike spanning about 40–60 s and is observed in bilateral marginal channels that cover lateral inferior frontal gyrus; (b) The transient fluctuation component occurs simultaneously with each 2-s stimulation period, especially on the stimulated side.

standard channel, the most correlated SSC was selected as a regressor for short-separation regression across the entire measurement sequence [33]. This process involved employing a least-squares approach [34–37] to eliminate superficial tissue artifacts and mitigate movement artifacts. Independent component analysis (ICA) was performed for each participant to remove U-shaped or inverted-U-shaped components potentially induced by deep breathing or unknown slow movements during the resting state (3 min before/after iTBS) [38], as well as to address transient fluctuations that coincided with each burst of TMS pulses, since both components are challenging to detect and correct through conventional methods. Before applying ICA, we performed principal component analysis (PCA) to reduce signal dimensionality to the number of principal components (PCs) that retain at least 99 % of data variance [38,39]. For ICA decomposition, we adopted *FastICA v2.5* (www.cis.hut.fi/projects/ica/fastica/) with the following parameter settings: the number of independent components (ICs) = number of PCs, the maximum number of iterations = 10000, epsilon = 0.00001, approach = "deflation", initial value = "random", nonlinearity = "skew", finetune = "on", and stabilization = "on" [39]. A U-shaped or inverted-U-shaped IC component was identified based on the following criteria: (a) the IC's time series exhibits a long temporal range (e.g., 40–60 s) of a U-shaped or inverted-U-shaped spike during the resting period; (b) the IC occurs in bilateral marginal channels that cover lateral inferior frontal gyrus [38]. In the case of transient fluctuations, the IC was selected using the following criteria: (a) the IC's time series displays multiple peaks and shifts within a short temporal range, aligning within each 2 s of iTBS stimulation; (b) the IC occurs in channels located on the stimulated hemisphere. Fig. 3 presents the temporal series, power spectrum, and spatial pattern of a representative inverted-U-shaped component and transient fluctuation. ICs exhibiting these characteristics were targeted for removal. After performing ICA, residual motion artifacts may persist, potentially resulting in the overestimation or underestimation of the true hemodynamic response. This could lead to false negatives or false positives at the level of statistical inference [40]. Therefore, following ICA, we conducted wavelet-based motion artifact removal (with $\alpha = 0.1$) [41] and applied a low-pass filter, setting the high-frequency cut-off at 0.09 Hz to eliminate residual motion artifacts and high-frequency physiological components (e.g., heartbeats, breathing, Mayer wave). To capture the cumulative effects of iTBS, low-frequency signals were preserved for a complete trend of the hemodynamic response over the entire session. Finally, baseline correction was performed using the mean of the 3-min signal collected during the resting state before iTBS. We then calculated the mean of the hemoglobin concentration change during (3 min) and after (3 min) iTBS. These calculated mean values, representing the hemoglobin concentration change for each stimulation phase, were subsequently included in the statistical analysis.

Outliers for all the measurements were screened using box plots. The decision to retain or exclude outliers in the subsequent analysis was made by considering the data collection process and comparing them with neighboring channels and other personal data of the individual.

2.3. Inter- and intra-individual moderators

Potential inter-individual variables were assessed at the first experimental visit. These variables included demographic variables (age, sex, education years) and personality assessed with the self-report version of the NEO-Five-Factor Inventory (NEO-FFI) [42]. The NEO-FFI assessed five personality traits: neuroticism, extraversion, openness, agreeableness, and consciousness. The raw score of each trait was converted into a sex-specific standardized T-score according to the norm table provided by the manual [42,43].

Potential intra-individual variables, including time-of-day, daily emotions, coffee intake, sleep efficiency, physical activity levels, and prefrontal cortex functional state, were collected at each experimental visit. Differing from our previous study, in this current study, participants received iTBS in the morning or afternoon without fixed timings, following a randomized and counterbalanced manner. Additionally, the intake timing and amount of coffee were not controlled; instead, coffee was consumed according to an individual's usual routine. Daily emotions (positive affect, PA, and negative affect, NA) were assessed using the International Positive and Negative Affect Schedule Short Form (I-PANAS-SF) [44]. Other variables included sleep efficiency, assessed using wrist-wearable devices based on the sleep-staging Fitbit model (Fitbit Inspire) [45], physical activity levels using the International Physical Activity Questionnaire – short form (IPAQ-SF) [46], as well as prefrontal cortex functional state, assessed by the accuracy rate of Three-Back Task and Sustained Attention to Response Task.

2.4. Statistical analysis

One-way repeated measures analysis of variance (ANOVA) was used to compare HbO and HbR before, during, and after iTBS. To test the effects of potential moderators on iTBS-induced hemodynamic response in bilateral DLPFC, we used a general linear mixed model (GLMM) with the participant as a random effect of intercept and slope. We started off with a model comparison following the statistical flow described by Koike et al. [47]. Repeated measures along with basic demographic variables (age, sex, education years, and age × sex) were assessed under the first-order autoregressive (AR1) covariance structure in the model [48–50]. We evaluated the collinearity of potential variables using variance inflation factors with a cut-off value set at 5. No collinearity was identified. All possible regression models ($16 = 2^4$) were compared to identify the best-fitted model where all the coefficients were significant ($p < 0.05$) and that had the smallest Akaike information criterion (Supplementary Tables S1–S5). After obtaining the best-fitted model, the significance threshold for interpreting the effects of demographic variables and subsequent tests for the effects of remaining variables on iTBS-induced hemodynamic response in the two ROIs (i.e., the stimulated lDLPFC and the contralateral DLPFC) was adjusted to $p < 0.025$ (i.e., 0.05/2, based on Bonferroni adjustments). The remaining variables were tested by individually adding them to the best-fitted model as independent variables, and all possible combinations were compared. All statistical analyses were performed using SPSS version 22.0 (SPSS Inc. IL, USA, Chicago). Cohen's f^2 and the simulation of selected GLMM (see section 4.3.) were analyzed using R version 4.4.2 (The R Foundation for Statistical Computing, Vienna, Austria), 'nlme', and 'MuMIn' packages.

3. Results

All included participants completed 157 iTBS/fNIRS sessions (3–11 sessions per participant). Two sessions from two participants were excluded from the analysis due to poor signal quality. Additionally, the HbO signal during and after iTBS and the HbR signal after iTBS from one session of a third participant were also omitted from the analysis due to poor signal quality from the selected channel. Therefore, 154 sessions' HbO signal during and after iTBS, and HbR signal after iTBS; and 155 sessions' HbR signal during iTBS were further analyzed. The demographic information and assessment results from each session are listed in Table 1.

3.1. iTBS-induced hemodynamic changes during and after the stimulation

One-way repeated measures ANOVA revealed that there were significant overall differences in HbR before, during, and after iTBS in the stimulated DLPFC ($F_{2,152} = 40.252$, $p < 0.001$, partial $\eta^2 = 0.208$) and contralateral DLPFC ($F_{2,154} = 5.394$, $p = 0.005$, partial $\eta^2 = 0.034$). HbR significantly increased during iTBS (mean ± standard error: 0.247 ± 0.032, $p < 0.001$, corrected) and returned to baseline after stimulation in the stimulated DLPFC. In contrast, the contralateral DLPFC exhibited significant HbR decreases both during (−0.046 ± 0.017, $p = 0.024$, corrected) and after stimulation (−0.05 ± 0.018, $p = 0.015$, corrected).

Table 1
Demographic information and assessment results.

	Participants (N = 20, sessions = 157)
Age, years, mean (SD)	25.65 (4.85)
Sex, male: female	10:10
Education years, mean (SD)	17.82 (1.82)
NEO-FFI personality traits, mean (SD)	
Neuroticism	45.65 (11.08)
Extraversion	51.98 (11.48)
Openness	56.69 (11.77)
Agreeableness	56.78 (7.73)
Conscientiousness	51.90 (12.07)
Number of measurements, mean (Range)	7.85 (3–11)
Time of day, sessions	
Morning	79
Afternoon	78
Coffee intake, N (sessions)	10 (25)
I-PANAS-SF, mean (SD)	
Positive affect	11.25 (3.05)
Negative affect	7.92 (3.52)
Sleep efficiency, mean (SD)	0.87 (0.03)
SART, total errors, mean (SD)	5.83 (6.49)
3-back task, total accuracy rate, mean (SD)	0.94 (0.07)
IPAQ-level, sessions	
Low level	15
Moderate level	78
High level	64

Abbreviations: SD = standard deviation, NEO-FFI = the NEO-Five-Factor Inventory, I-PANAS-SF = the International Positive and Negative Affect Schedule Short Form, SART = Sustained Attention to Response Task, IPAQ = the International Physical Activity Questionnaire (short form).

Furthermore, a significant overall difference was observed among measurement phases in HbO in the stimulated DLPFC ($F_{2,154} = 3.309$, $p = 0.042$, partial $\eta^2 = 0.021$). However, this difference between each phase was no longer significant after the Bonferroni adjustment for multiple comparisons (Fig. 4).

3.2. Effects of potential moderators on iTBS-induced hemodynamic changes

GLMMs were conducted on Hb components that showed significant changes in their temporal patterns (Fig. 4a). These components included the ΔHbR during and after iTBS in the bilateral DLPFCs and the ΔHbO during iTBS in the stimulated DLPFC. The GLMM analysis revealed that age, sex, and education years significantly moderated iTBS-induced hemodynamic changes in the stimulated DLPFC, indexed by ΔHbR during stimulation. Specifically, a positive effect of age ($\beta = 0.033$, $p = 0.004$) and a negative effect of education year ($\beta = -0.094$, $p < 0.001$) was observed on HbR increases. That is, observed HbR increases during iTBS rose with age but shrunk with education years. Moreover, male participants exhibited greater HbR increases compared to female participants ($\beta = 0.248$, $p = 0.004$, see Table 2 and Fig. 5). The effect size (Cohen's f^2) of the above demographic variables in GLMM is 0.25. Finally, HbR increases were negatively associated with the personality trait agreeableness ($\beta = -0.013$, $p = 0.005$, Cohen's $f^2 = 0.33$) and with PA ($\beta = -0.032$, $p = 0.012$, Cohen's $f^2 = 0.31$, see Table 3 and Fig. 5). Sex was the only significant moderator of the iTBS-induced HbO change in the stimulated DLPFC, showing greater HbO decreases in male participants compared to female participants ($\beta = 0.305$, $p = 0.012$, Cohen's $f^2 = 0.07$, see Table 2 and Fig. 5). No other significant moderators of hemodynamic changes during or after iTBS were identified (Supplementary Table S6).

4. Discussion

4.1. Local and remote hemodynamic response to iTBS

The present study investigated the hemodynamic response patterns in the bilateral DLPFC during and after iTBS of the lDLPFC. We also explored the relationship between the iTBS-induced hemodynamic response and various inter- and intra-individual variables in a group of healthy participants, utilizing multiple repeated measures across days. Our results indicated an increase in HbR during iTBS in the stimulated DLPFC. This finding is consistent with our previous work using a frequency-domain NIRS device [10]. fNIRS measures the hemodynamic response, which is linked to neuronal activity through neurovascular coupling (NVC) [51,52]. NVC is the mechanism by which neuronal activity regulates cerebral blood flow (CBF), ensuring an appropriate balance between the brain's blood supply and the local cellular metabolism demands. Typically, an increase in HbO alongside a decrease in HbR reflects cortical activation [53]. Interestingly, the real-time hemodynamic response observed in the stimulated lDLPFC in our study exhibited a reversed pattern, despite the expected excitatory effects of iTBS, which are generally associated with long-term potentiation (LTP)-like effects [54]. While LTP-like effects are typically observed after stimulation [23,54], the specific neural processes occurring during iTBS require further elucidation. Three aspects may be considered.

(i) iTBS reduces metabolic activity and oxygen consumption in the stimulated region. This explanation follows the classical interpretation of increased HbR. It is possible that iTBS leads to an immediate reduction in metabolic activity within the stimulated region, as outlined in a recent review article [55]. This notion is supported by a study involving high-frequency rTMS in animal models, which showed decreases in glucose metabolism in the stimulated parietal cortex during stimulation [56]. Given the coupling between glucose and oxygen metabolism in neuronal activity, along with their strong association with CBF—responsible for supplying oxygen and glucose to brain regions [57,58]—decreased metabolic activity in the stimulated DLPFC may associate with lower oxygen consumption, leading to an accumulation of HbR as indicated by our fNIRS findings.

(ii) iTBS increases metabolic activity and oxygen consumption in local regions, but this is accompanied by an increase in HbR levels. The iTBS-induced neural activity occurs in the order of milliseconds, leading to rapid consumption of oxygen before functional hyperaemia occurs, which results in an initial increase in HbR [59]. Over time, this effect becomes cumulative, with sustained high oxygen consumption and the accumulation of metabolic byproducts (HbR), even once functional hyperaemia begins. This explanation is consistent with the temporal dynamics of HbO and HbR changes we observed (see Fig. 4a). Furthermore, this hypothesis is supported by previous concurrent TMS/fNIRS studies on the prefrontal cortex, where decreased HbO levels were observed during single-pulse TMS [60,61], and increased HbO levels were seen during low-frequency rTMS [60].

(iii) iTBS activates both cortical regions and vasculature: We also consider the possibility that iTBS not only activates cortical neurons but also directly stimulates the vasculature. Non-invasive brain stimulation (NIBS), such as TMS, has been shown to directly activate the vasculature, potentially disrupting the typical recruitment order in NVC [62,63]. As a result, the hemodynamic response captured by fNIRS might reflect a direct vascular response (e.g., at the capillary level) rather than the NVC-mediated changes typically seen with neuronal activation. However, whether such vascular activation leads to an increase in HbR as observed in our study requires further investigation.

Future research will be needed to determine which interpretation is correct. Regardless, our findings demonstrate that iTBS-induced hemodynamic changes differ fundamentally from those elicited by physiological brain activation, such as through motor or cognitive tasks.

Contrary to our findings, a recent concurrent iTBS/functional magnetic resonance imaging (fMRI) study by Chang et al. [64] reported an

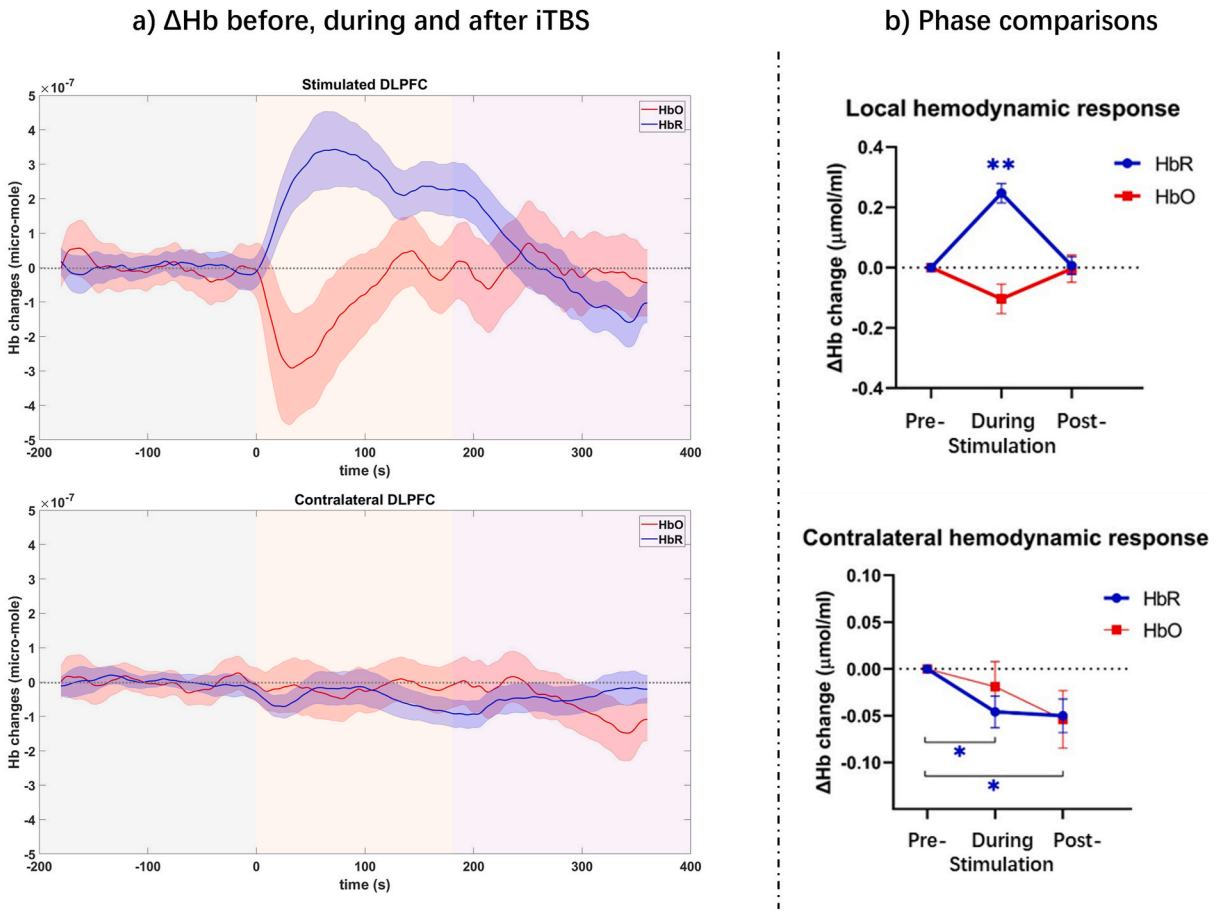

Fig. 4. Hemodynamic response before, during, and after iTBS in stimulated DLPFC and contralateral DLPFC. (a) Hb concentration changes before, during, and after iTBS. Lines and shading indicate the mean ± 95 % confidence interval. (b) Comparisons between the mean Hb changes of each measurement phase (pre-/during-/post-stimulation phase). Dots and bar indicate the mean ± 1 standard error. Bold lines indicate overall significant differences among the three phases. * with color: $p_{\text{Bonferroni-corrected}} < 0.05$; ** with color: $p_{\text{Bonferroni-corrected}} < 0.001$.

Table 2
Effect of age, sex and education years on iTBS-induced hemodynamic changes.

		Regions	Main effect				Interaction
			(Intercept)	Age	Sex	Edu_years	Age × Sex
HbR-during iTBS							
	Left	DLPFC	**1.219**	**0.033**	**−0.248**	**−0.094**	
	Right	DLPFC	−0.05				
HbR-after iTBS							
	Right	DLPFC	**−0.05**				
HbO-during iTBS							
	Left	DLPFC	**−0.221**		**0.305**		

Coefficients of the significant independent variables for each dependent variable (iTBS-induced hemodynamic changes [μM.mm]) are listed. Bold shows $p < 0.05/2$.
Abbreviation: DLPFC = dorsal lateral prefrontal cortex, HbO = oxygenated-hemoglobin; HbR = deoxygenated-hemoglobin, Edu_years = educational years.

increase in the blood-oxygen-level-dependent (BOLD) signal during iTBS in the stimulated DLPFC. fMRI assesses neuronal activation by detecting local concentrations of paramagnetic HbR and produces the BOLD signal, which increases as HbR levels decrease [59]. Several factors may account for the discrepancies between this study and our findings. First, this study used an iTBS intensity of 80 % of the RMT, while we used 90 %. The current study applied iTBS at 90 % RMT, rather than lower intensities, because 90 % RMT has been commonly used in previous concurrent iTBS/fNIRS studies [9,10,65]. One of these studies demonstrated that iTBS at 90 % RMT induced significant differences in hemodynamic changes between male and female participants, whereas lower intensities (50 % or 70 % RMT) did not [10]. Additionally, iTBS at 90 % RMT over left DLPFC is part of the most recently FDA-approved protocol for treatment-resistant major depression (Stanford Accelerated Intelligent Neuromodulation Therapy, SAINT) [3]. Second, differences exist in the concurrent iTBS/fMRI study's interleaved design and analysis method, which involved generalized linear model analysis at theta burst block level, while we analyzed data at the session level. These methodological differences likely captured distinct aspects of the hemodynamic response. Future research could benefit from a simultaneous iTBS/fNIRS/fMRI study, which is technically feasible with advanced equipment. Such studies could validate findings from each technique and clarify existing inconsistencies. Cross-validating results between these methods would further enhance the reliability of our findings and improve our interpretation of brain activity patterns.

Moreover, our current study provided additional insights into the

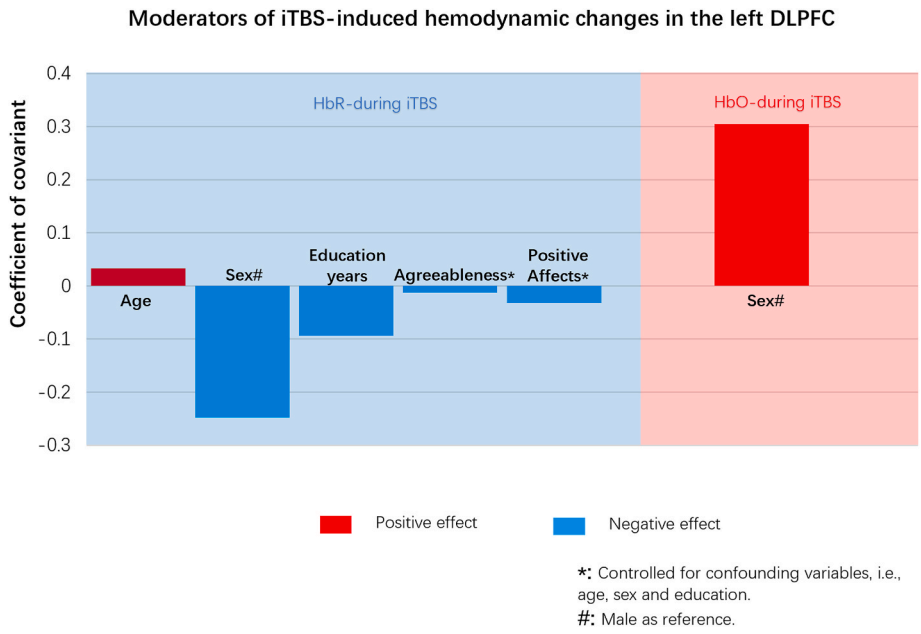

Fig. 5. Moderators of iTBS-induced hemodynamic changes.

Table 3
Effect of personality traits and positive affects on iTBS-induced hemodynamic changes.

Variables		Regions	Main effect	Confounders			
				(Intercept)	Age	Sex	Edu-years
HbR-during iTBS							
NEO-FFI: Agreeableness	Left	DLPFC	**−0.013**	**2.209**	**0.032**	**−0.241**	**−0.106**
I-PANAS-SF: PA	Left	DLPFC	**−0.032**	**1.751**	**0.044**	**−0.244**	**−0.118**
NEO-FFI: Conscientiousness	Right	DLPFC	0.004	**−0.230**			

Coefficients of the significant independent variables for each dependent variable (iTBS-induced hemodynamic changes [μM.mm]) are listed. Bold shows $p < 0.05/2$.
Abbreviation: DLPFC = dorsal lateral prefrontal cortex, HbR = deoxygenated-hemoglobin, Edu_years = educational years, NEO-FFI = the NEO-Five-Factor Inventory, I-PANAS-SF = the International Positive and Negative Affect Schedule Short Form, PA = positive affect.

hemodynamic response to iTBS in the contralateral DLPFC, revealing decreases in HbR both during and after iTBS. This finding aligns with Chang et al. [64] and confirms the functional engagement of remote brain regions indirectly activated by iTBS through cortico-cortical or cortico-subcortical pathways [5]. However, information regarding deep subcortical regions may remain obscured in our study, as fNIRS can only penetrate about 2 cm beneath the cortical surface.

4.2. Potential moderators of iTBS-induced hemodynamic response

We replicated the effects of sex and daily emotional state—specifically, PA—on iTBS-induced hemodynamics, with both factors influencing HbR rather than HbO [9,10]. Our findings also highlight the effect of age, education years, and agreeableness as a personality trait on local HbR changes during iTBS. Age, sex, education years, and personality are stable determinants that contribute to inter-individual variability in response to iTBS. In contrast, PA fluctuates daily, affecting participants' responses from session to session and leading to both inter- and intra-individual variability. This variability is often overlooked in clinical settings, where understanding inter-individual variations could assist in identifying biological subtypes beforehand, and modifying intra-individual variations could increase clinical effectiveness and minimize variability.

The influence of age, sex, education years, and personality traits on cortical plasticity induced by NIBS has been observed in various studies targeting the motor cortex [11–13,66,67]. Our study confirms these findings and extends them to the DLPFC. Age and sex have been extensively studied in NIBS research, with several potential biological explanations proposed for their moderating effects. These explanations include sex-specific differences in prefrontal scalp-to-cortex distance and varying levels of sex hormones including estradiol and progesterone [68], as well as age- and sex-related structural variations, such as differences in cerebral volumes, cortical thicknesses, and differences in gray matter density [68,69]. Education year is often used as a proxy of cognitive reserve. Young adults with higher cognitive reserve may exhibit enhanced glutamatergic and GABAergic tone, which help regulate the balance between excitatory and inhibitory processes, thereby maintaining neuronal homeostasis and potentially enhancing neural efficiency [67]. Our results are potentially consistent with this explanation. Regarding personality traits, previous studies have suggested a link between these traits and different patterns of hypothalamic-pituitary-adrenal (HPA) axis regulation [70], which plays an important role in the response to rTMS [71]. For instance, Pulopulos et al. [18] observed that iTBS of the DLPFC induced a decrease in cortisol secretion in stressed healthy participants with higher cooperativeness scores—a personality trait overlapping with agreeableness and extraversion dimensions of the NEO-FFI model. Both agreeableness and extraversion have been shown to predict TMS antidepressant response [17,72]. Given that agreeableness remains relatively stable during antidepressant treatment [73], our findings suggest that it could serve as a robust predictor, enabling us to anticipate individual cortical responses to iTBS.

Finally, we found that daily PA moderates iTBS-induced neuronal activity. PA reflects positive and pleasant moods associated with enthusiasm and activeness. Increasing evidence suggests that an individual's brain state (e.g., cognitive-emotional state) at the moment of stimulation influences TMS effects on neural and behavioral outcomes [74,75]. For example, Isserles et al. [76] reported that negative emotional reactivation, but not positive, contributed to successful TMS treatment in depressed patients. These findings indicate a potential difference between healthy and depressed populations or between neuronal and behavioral outcomes compared to our findings. Future studies focusing on depressed patients are needed to explore the clinical or excitability-based foundations of this potential difference.

Although other individual-specific variables, such as coffee intake and time of day, did not significantly influence iTBS-induced neuronal activity in the current study, they may still have an effect under certain conditions. For example, our previous study demonstrated that caffeine intake of exactly 200 mg, 1 h prior to iTBS, and receiving iTBS at specific times (e.g., 10:00 a.m. or 5:00 p.m.) could significantly influence iTBS-induced neural excitability [9]. However, feasibility constraints in the current study prohibited us from controlling these variables.

4.3. Limitations

Our study is subject to several limitations. First, the sample size is relatively small. Despite only including an arbitrary number of 20 participants given resource constraints, our study encompassed 157 concurrent iTBS/fNIRS datasets, averaging 7.85 datasets per participant. This is sufficient for exploring intra-individual variables and meets the minimum outcome event criteria for statistical analysis which requires approximately ten outcome events per variable in the GLMM regression model [77]. This was also confirmed by a post-hoc power analysis, indicating >90 % statistical power for each of the tested moderators. Thus, we are confident that our study was adequately powered. Given our sample size and study design, AR1 provided an optimal balance between flexibility and computational feasibility. Future work could explore subject-specific covariance structures to better accommodate heterogeneity. Additionally, the model selection strategy we used introduces a potential risk of circular inference [78]. To address this, we adopted an approach suggested for non-circular analysis [78]. Specifically, we simulated each selected GLMM 2000 times by subjecting randomized data as noise to model the effect of selection under the null hypothesis. The results indicated that all selected models retained significance for all included factors in at least 92.4 % of the simulations, supporting the robustness of our results. Fourth, the specific fNIRS probe positioned directly beneath the TMS coil introduced systematic TMS-related artifacts during data collection. To address this, we applied SSR regression and ICA to remove these artifacts channel by channel, which significantly increased the time and complexity of our analysis. A more ideal solution would involve using a sham coil that mimics auditory and scalp stimulation sensations during measurements. The signal collected in the sham stimulation condition could then serve as regressors, enabling researchers to effectively remove those confounding factors. Hence, the lack of a sham iTBS condition in our study constitutes another significant limitation, as we cannot rule out that factors such as scalp sensation or auditory stimulation influenced hemodynamic changes. Although the current study focused on healthy participants, it employed iTBS, a TMS protocol for major depression with proven therapeutic efficacy. Therefore, the observed instantaneous effects of iTBS on brain excitability contribute to a better understanding of its mechanism of action in treating depression. Additionally, our findings imply that observed moderators of the hemodynamic response may also affect treatment outcomes. However, whether age, sex, years of education, the personality trait agreeableness and PA have treatment-moderating effects remains to be investigated in future clinical iTBS trials.

5. Conclusion

Our study provides insights into the neural mechanisms of clinical iTBS treatment at the single session level, demonstrating a pronounced increase in HbR during iTBS in the stimulated DLPFC, alongside decreased HbR contralaterally during and after stimulation. Furthermore, our study highlights the importance of considering individual factors, including age, sex, education years, personality trait agreeableness and PA, when investigating the effects of iTBS on cortical excitability.

CRediT authorship contribution statement

Adam W.L. Xia: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Minxia Jin:** Writing – review & editing, Methodology, Investigation. **Bella B.B. Zhang:** Writing – review & editing, Methodology, Investigation. **Rebecca L.D. Kan:** Writing – review & editing, Methodology. **Tim T.Z. Lin:** Methodology, Investigation. **Penny P. Qin:** Writing – review & editing. **Xiao Wang:** Investigation. **Wanda M.W. Chau:** Writing – review & editing. **Nancy M.X.Y. Shi:** Investigation. **Priya Kannan:** Writing – review & editing. **Erin Y. Lu:** Resources. **Tifei Yuan:** Writing – review & editing. **Jack Jiaqi Zhang:** Writing – review & editing. **Georg S. Kranz:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Data curation, Conceptualization.

Data availability

The data is available from the corresponding author upon reasonable request.

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Declaration of competing interest

The authors have no conflict of interest related to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.02.008.

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