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Review

Instantaneous effects of prefrontal transcranial magnetic stimulation on brain oxygenation: A systematic review

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ABSTRACT

This systematic review investigates how prefrontal transcranial magnetic stimulation (TMS) immediately influences neuronal excitability based on oxygenation changes measured by functional magnetic resonance imaging (fMRI) or functional near-infrared spectroscopy (fNIRS). A thorough understanding of TMS-induced excitability changes may enable clinicians to adjust TMS parameters and optimize treatment plans proactively. Five databases were searched for human studies evaluating brain excitability using concurrent TMS/fMRI or TMS/fNIRS. Thirty-seven studies (13 concurrent TMS/fNIRS studies, 24 concurrent TMS/fMRI studies) were included in a qualitative synthesis. Despite methodological inconsistencies, a distinct pattern of activated nodes in the frontoparietal central executive network, the cingulo-opercular salience network, and the default-mode network emerged. The activated nodes included the prefrontal cortex (particularly dorsolateral prefrontal cortex), insula cortex, striatal regions (especially caudate, putamen), anterior cingulate cortex, and thalamus. High-frequency repetitive TMS most consistently induced expected facilitatory effects in these brain regions. However, varied stimulation parameters (e.g., intensity, coil orientation, target sites) and the inter- and intra-individual variability of brain state contribute to the observed heterogeneity of target excitability and co-activated regions. Given the considerable methodological and individual variability across the limited evidence, conclusions should be drawn with caution.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation (NIBS) technique that modulates neuronal activity by applying electromagnetic pulses to the scalp. TMS enables neuroscientists and clinicians to investigate and modulate neural function in healthy populations and those with neuropsychiatric conditions. The variants of TMS protocols have evolved from single-pulse to repetitive TMS (rTMS). Single-pulse TMS is commonly used to probe the functional role of a specific brain region by interfering with or otherwise modulating specific cortical activities (Mizutani-Tiebel et al., 2022). rTMS at high and low frequencies is associated with corresponding increases and decreases cortical excitability, thereby considered a tool for inducing cortical plasticity (Hoogendam et al., 2010). The U.S. Food and Drug Administration (FDA) has approved several forms of rTMS of the dorsolateral prefrontal cortex (DLPFC) as a treatment for patients with major depressive disorder (MDD) (Blumberger et al., 2018; O'Reardon et al., 2007). Meanwhile, researchers are also devoting efforts to maximize the efficacy of prefrontal rTMS for other psychiatric disorders, such as schizophrenia (Mehta et al., 2019) and substance dependence (Zhang et al., 2019). In principle, rTMS is a therapeutic technique with tremendous prospects to normalize brain activity and alleviate symptoms of some psychiatric disorders. However, the responses of individuals to psychiatric rTMS treatment highly fluctuates (Cocchi and Zalesky, 2018; Dunlop et al., 2016); a deeper understanding of such variability is needed.

In contrast to applying TMS to the motor cortex in neurology, of which the effects can be measured directly by using motor-evoked potentials, one of the challenges for prefrontal TMS in psychiatry is the absence of a direct measure of its effects. The integrated use of TMS and

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neuroimaging technology, such as functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), and electroencephalography (EEG), provides the opportunity to estimate indicators of functional changes following prefrontal cortex (PFC) stimulation. Concurrently using TMS with neuroimaging allows researchers to assess its instantaneous ("online") effects. The instantaneous brain response to TMS can illuminate the functional recruitment of cortices directly stimulated by the induced electromagnetic field and the connected regions that are activated as a result. Such concurrent setup may enable researchers and clinicians to prospectively adjust TMS parameters and optimize treatment protocols during treatments. fMRI and fNIRS, in combination with TMS, can detect brain excitability by means of stimulation-induced hemodynamic (i.e., oxygenated/deoxygenated blood) responses with a relatively higher spatial resolution (Blockley et al., 2013; Leon-Carrion and Leon-Dominguez, 2012). Nevertheless, there are technical and practical differences between the two techniques. For example, although they both measure hemodynamic responses, fMRI measures the changes in blood oxygenation level-dependent (BOLD) signals that are related to the magnetic properties of hemoglobin, while fNIRS measures changes in the concentration of oxygenated and deoxygenated hemoglobin (HbO and HbR) using near-infrared light. Despite these and other differences, including temporal/spatial resolution, portability, and accessibility, both techniques detect blood oxygenation changes and are thus indirect measures of brain excitability. Besides, fMRI and fNIRS are compatible with various rTMS protocols (including spaced TMS) (Bergmann et al., 2021; Curtin et al., 2019; Mizutani-Tiebel et al., 2022). In contrast to classical before-after designs (i.e., "offline" TMS), concurrent TMS/fMRI or TMS/fNIRS requires dedicated hardware to ensure optimal timing and minimization of artifacts (for details, see (Bergmann et al., 2021; Parks, 2013)). Specifically for concurrent TMS/fMRI techniques, an adequate experimental design is needed to successfully interleave TMS pulses with MR slice acquisition (for details, see (Bergmann et al., 2021)).

To date, several concurrent TMS/fMRI and TMS/fNIRS studies have been conducted to elucidate the local and remote effects of various prefrontal TMS protocols. Nonetheless, these studies are heterogeneous in their experimental setup (i.e., TMS protocols, conditions, and populations) and their results. Several previous reviews aimed to summarize this literature with various degrees of scope and depth. Curtin et al. (2019) set up broad inclusion criteria, summarizing integrated TMS and fNIRS studies by an omnibus analysis; thus, the prefrontal TMS-induced immediate brain activity change was unclear. Bergmann et al. (2021) and Mizutani-Tiebel et al. (2022) summarized concurrent TMS/fMRI studies, broadly introducing the technique and its related experimental and clinical applications. Most recently, Rafiei and Rahnev (2022) conducted a concurrent TMS/fMRI studies review investigating the immediate effect of TMS on blood-oxygen-level-dependent (BOLD) activity. While highly informative, only the local effects of TMS were examined and reported, as studies that did not report TMS local effects were excluded. However, these studies may contain meaningful information on the immediate BOLD response of remote brain regions. Therefore, a thorough understanding of the local and remote brain oxygenation changes during and immediately after prefrontal TMS stimulation remains unclear. In this systematic review, we conduct a comprehensive review of concurrent TMS/fMRI and TMS/fNIRS studies to investigate their effects on the engagement of local and remote brain regions and their hemodynamic responses during and immediately after prefrontal TMS.

2. Methods

2.1. Data source and literature search

The protocol of this review was registered in the International Prospective Register of Systematic Reviews, PROSPERO (CRD42023411713, March 2023). This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The literature search was conducted in five databases/search engines (PubMed, Embase, PsycINFO via ProQuest, Web of Science, and the Cochrane Library Database) and additionally from references of the searched articles. Search terms included variations of "TMS", "PFC", "fNIRS", and "fMRI"; details of the full search strategy are presented in the Supplementary Materials. The initial search was conducted on February 10th, 2023, followed by an update search on June 8th, 2023. Two researchers (AX and MJ) independently screened potentially relevant records based on their titles and abstracts, with conflicts resolved by a third author (PQ). The full text of each candidate article was accessed and reviewed to determine its eligibility.

2.2. Inclusion and exclusion criteria

We included studies that utilized fMRI/fNIRS to monitor functional brain activity during and immediately after applying prefrontal TMS. All experimental studies involving controlled and exploratory studies published in English were considered for inclusion. No restrictions were placed on the population group. Studies that conducted TMS over a motor region in addition to PFC when fMRI/fNIRS recording, or combined TMS with other interventions, including pharmacological, psychotherapeutic approaches, and other NIBS, were not considered eligible. As the prefrontal TMS-induced plasticity could be influenced by the priming effects of NIBS to other brain regions and by pharmacological/psychotherapeutic factors (Ridding and Ziemann, 2010). Non-experimental studies were further excluded, including reviews, book chapters and studies published as conference abstracts. In this review, our primary interested outcomes were: (1) brain regions and networks engaged, and; (2) the direction (the increase or decrease) of brain hemodynamic response to prefrontal TMS stimulation.

2.3. Data extraction and quality assessment

Data were extracted independently from eligible studies by two researchers (AX and MJ) and put into customized tables. Information was extracted on the following parameters: (1) general information on the publication (author, year of publication); (2) characteristics of participants (population, sample size, gender, age, handedness); (3) TMS parameters (target site, the method for determining target site, coil position, TMS protocol, intensity, frequency, comparisons/controls/sham conditions); (4) fMRI/fNIRS parameters (design, measure sites, time of repetition (TR)/echo time (TE) for fMRI studies or data segments for fNIRS studies), and; (5) the main findings of the engaged brain regions and networks, and their corresponding responses. Due to the heterogeneity in methodology of the eligible studies, it was not possible to conduct a meta-analysis; thus, a qualitative synthesis of the findings is presented here instead. Findings for brain regions responses to various TMS protocols (single-/paired-pulse TMS, low-/high-frequency rTMS, and theta-burst stimulation(TBS)) in healthy and patientscohorts are presented in the figures and tables below. We categorized the reported gyrus and sulcus to cortex level (e.g., superior frontal gyrus to PFC) in the results and discussion section for consistency, while the regions presented in the original articles are retained in Supplementary Table S3. Replicated results (same engaged brain regions in either hemisphere with an increase or decrease brain oxygenation) reported in at least two independent studies are summarized in the main text as our primary outcomes. In the current study, we will refer to BOLD/HbO increasing as "activation" and BOLD/HbO decreasing as "deactivation". Furthermore, we summarized the results based on whether they were local effects (i.e., the stimulation-induced brain oxygenation changes located within the same Brodmann Area, BA, of stimulation) or remote effects (i.e., the stimulation-induced brain oxygenation changes located outside the BA of stimulation). As findings of activated brain networks are of focus in a limited number of studies, we reported them in detail.

The quality of eligible studies was assessed by AX and MJ independently using the "National Institutes of Health (NIH) Study Quality Assessment Tool for Observational Cohort and Cross-sectional Studies" and "NIH Quality Assessment Tool for Controlled Intervention Studies" according to the study design (National Institutes of Health, 2014; Lim et al., 2021) A consensus reached through discussion.

3. Results

3.1. Literature search

Fig. 1 displays the flow chart summarizing the study selection process. A further breakdown of the searches performed in each database is presented in Supplementary Table S1. 3482 articles were identified from the electronic databases and reference searches. After removing duplicates, 1889 articles underwent title and abstract screening, with 97 articles full-text screened. 37 studies (24 concurrent TMS/fMRI studies and 13 concurrent TMS/fNIRS studies) met the inclusion criteria for this review.

3.2. Study quality assessment

Fig. 2 summarizes our study quality assessment, while a full breakdown for each studycan be found in Supplementary Table S2. Studies scored favorably on items related to reporting research objectives, exposures (i.e., TMS stimulation) and outcome measures (i.e., fMRI or fNIRS), but poorly on recruiting representative participants of the target population and justifying the sample size or presenting a statistical power. Participants in controlled intervention studies (studies no.7, 8, 35, and 36) showed good adherence to the experiment and low dropout rates. Cross-sectional studies (studies no.1–6, 9–34, and 37) conducted TMS stimulation and fMRI/fNIRS measurements concurrently, therefore, scored poorly on items 6 ("For the analyses in this paper, was the exposure of interest measured prior to the outcome being measured?") and 7 ("Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?"). Randomized allocation was not adequate in some controlled intervention studies.

3.3. Study characteristics

From the 24 concurrent TMS/fMRI studies and 13 concurrent TMS/fNIRS studies met the eligibility criteria, the studies' sample size ranged from 5 to 49 and involved healthy individuals or clinical participants, including patients with depression, schizophrenia, or cocaine/alcohol dependence. Participants' characteristics that may influence the effects of TMS stimulation, were reported in most included studies (34 out of 37), such as age, gender and handedness of participants (see Tables 1 and 2).

3.3.1. Concurrent TMS/fMRI and TMS/fMRI protocols

The included studies utilized various TMS protocols, including single-/paired-pulse TMS, low-frequency rTMS (≤1 Hz), high-frequency rTMS (>1 Hz) and theta burst stimulation (TBS). DLPFC was the most frequently stimulated site (25/37, 68 %). Navigation methods included reference to the MNI coordinates from previous studies, the 5 cm rule, the Beam-F3 method, the 10/20 EEG system, or coordinates from resting-state fMRI functional connectivity analysis. However, less than one-third of studies reported the TMS coil orientations during stimulation, with TMS coil handles placed at a 45° angle from the midline and pointed towards posterior direction most heavily utilized. The experimental TMS intensities varied from 28 % to 130 % of the resting motor threshold (rMT). The details of the above information can be found in Tables 1 and 2. fNIRS is optical thus free from electromagnetic interference, this enables it to be compatible with "online" TMS stimulation. Therefore, all concurrent TMS/fNIRS studies in the current review collected fNIRS signals throughout the TMS session. However, for concurrent TMS/fMRI design, continuous fMRI scanning is only possible with careful and precise interleaving of TMS pulses with MR signal acquisition. Bergmann and colleagues summarized five variations of the interleaving method (Bergmann et al., 2021); three were used in the included studies. Seventeen TMS/fMRI studies delivered TMS pulses during the delay between image acquisition volumes (see Fig. 3A), while other studies delivered TMS pulses between volumes and within volumes (n = 3, see Fig. 3C) or by alternating with echo planar imaging (EPI) slices (n = 4, see Fig. 3B).

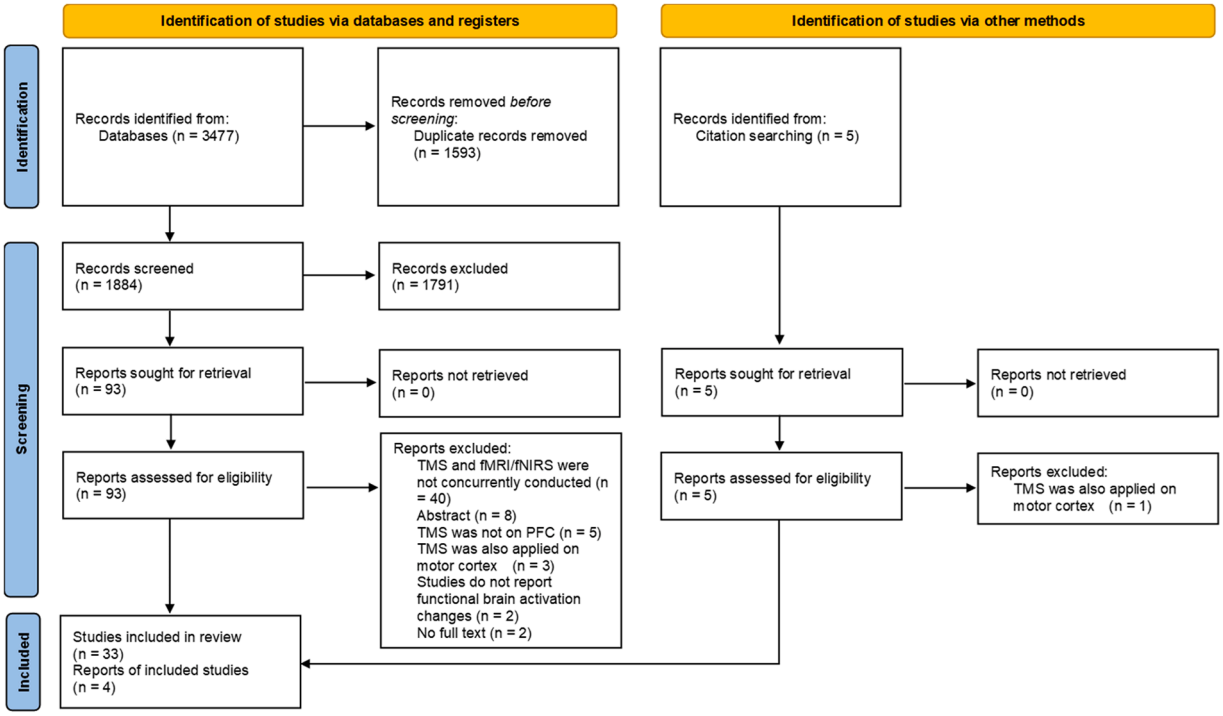

Fig. 1. PRISMA flow diagram.

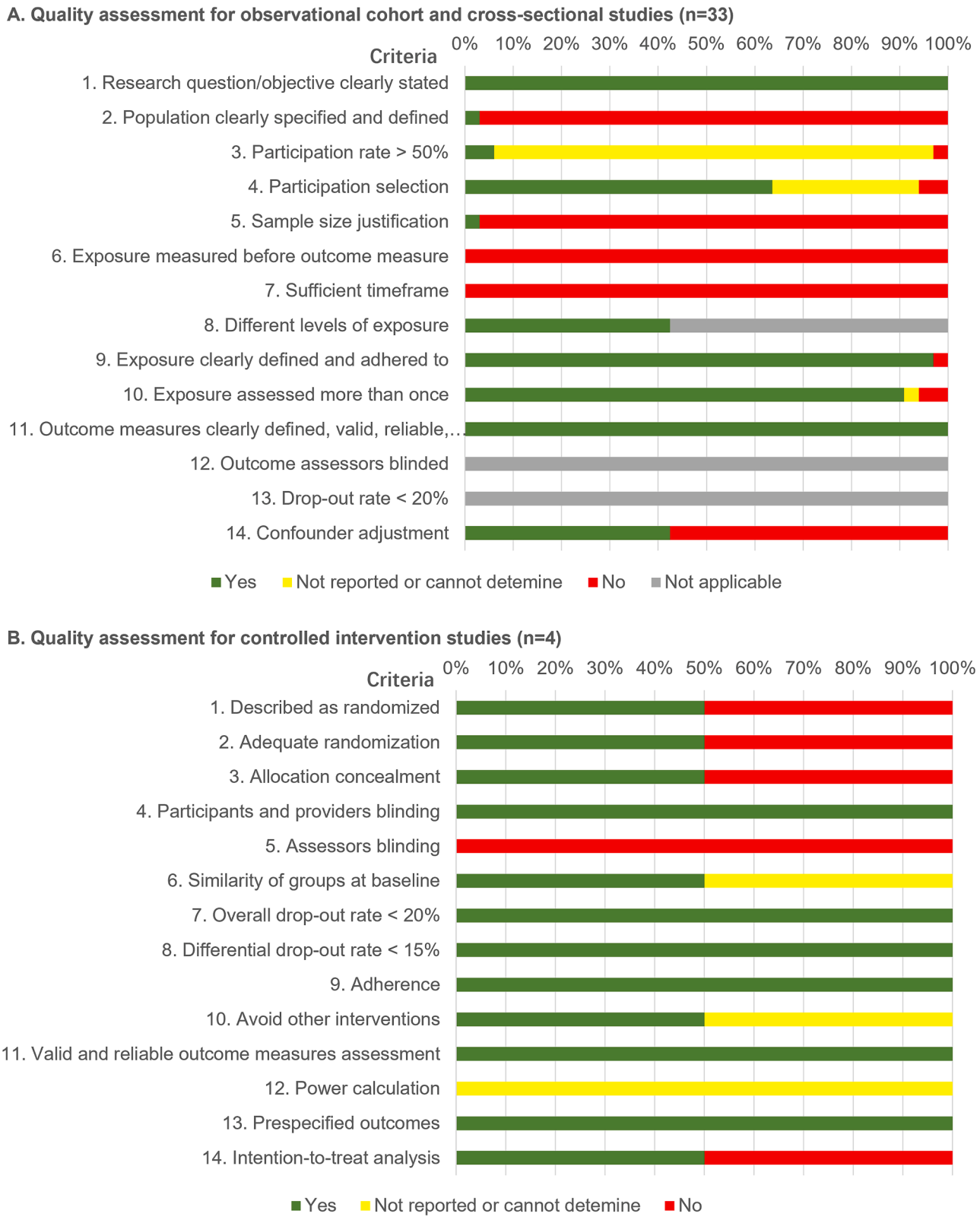

Fig. 2. Summary of study quality assessment presented as a percentage of all eligible studies.

3.4. Effects of single- or paired-pulse TMS at rest

3.4.1. Healthy population

Eleven studies targeted the PFC with single- or paired-pulse TMS (studies no.1–5, 9–10, and 25–28). In these 11 studies, ten studies stimulated the left DLPFC (studies no.2–5, 9–10, and 25–28) with studies no. 5 and 10 also stimulating the left medial prefrontal cortex(MPFC). The remaining study stimulated the left ventrolateral PFC (study no.1).

Out of the 11 studies, seven studies (63.6 % of the studies) reported local stimulation-induced activations/deactivations. When targeting the

Table 1
Studies investigating instantaneous effects of prefrontal TMS on brain oxygenation with fMRI.

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
Single/paired-pulse TMS															
1	Sydnor et al. (2022)	45 healthy participants (18 males, age 28 ± 8.6 years)	/	L VLPFC (left amygdala	rsfMRI (prefrontal-amygdala functional connectivity peak location)	not report	single pulse, 5–7 single pulses/ block, total 12 blocks	120 % rMT	2.4/4.8/ 7.2 s	/	whole brain	event-related	2000/30	at rest	RA↑
2	Oathes et al. (2021)	14 healthy participants (8 males, age 28.71 ± 4.95 years)	/	L DLPFC	peak location rsfMRI FC of frontal-sgACC/ amygdala	coil handle facing backward	single pulse, 5–7 single pulses/ block, total 12 blocks	120 % rMT	2.38/4.76/ 7.14 s	multiple stimulation sites for each participant	whole brain	block	2400/30	at rest	RA
3	Hawco et al. (2018)	22 healthy participants (6 males, age 25.5 ± 3.9 years)	/	L DLPFC	mid-point between F3 and F5 (10/ 20 EEG system)	45° posterior relative to the midline.	single pulse, 25 single pulsed/ condition, 2 conditions/ scan, total 4 scans	100 % rMT	8.5~14.5 s	control condition: 40 % rMT stimulation	whole brain	event-related	2100/30	at rest	LA↑, RA↑
4	Dowdle et al. (2018)	20 healthy participants (6 males, age 26.8 ± 4.9 years)	/	L DLPFC	Beam-F3 method	not report	single pulse, 20 pulses/ condition, 1 condition/ session, total 4 sessions	90, 100, 110, 120 % rMT	10/13/15 s	TMS coil was placed on a 3 cm of open-cell reticulated foam padding, which was firmly compressed on the head	whole brain	event-related	1000/23	at rest	RA↑
5	Hanlon et al. (2013)	17 healthy participants (age 21–45 years)	/	L DLPFC; L MPFC	location of F3, location of FP1 (10/20 EEG system)	not report	single pulse, 6 pulses/ trial, 1 trail/ condition, total 2 conditions	100 % rMT	10.18 s	TMS of primary visual cortex	whole brain	event-related	2520/23	at rest	LA, RA
6	Kearney-Ramos et al. (2018)	49 cocaine-dependent participants (26 males, age	/	L VMPFC	location of FP1 (10/20 EEG system)	not report	single pulse, ?	100 % rMT	10~12 s	/	whole brain	event-related	2500/23	at rest	RA↑

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Table 1 (*continued*)

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
		38.5 ± 8.9 years)													
7	Hanlon et al. (2017)	25 chronic cocaine users and 24 alcohol-dependent individuals (?,?)	/	L MPFC	location of FP1 (10/20 EEG system)	not report	single pulse, 20 pulses before and after active/ sham cTBS	110 % rMT	10.18 s	sham cTBS between TMS/fMRI sessions	whole brain	event-related	2500/23	at rest	RA↑ (before cTBS > after cTBS)
8	Hanlon et al. (2015)	11 chronic cocaine users (?,?)	/	L MPFC	location of FP1 (10/20 EEG system)	not report	single pulse, 20 pulses before and after active/ sham cTBS	110 % rMT	10.18 s	sham cTBS between TMS/fMRI sessions	whole brain	event-related	2500/23	at rest	RA↑ (before cTBS > after cTBS)
9	Pantazatos et al. (2023)	11 healthy participants (5 males, age 30.5 ± 8.8 years)	/	L DLPFC	Beam-F3 method	not report	single pulse, 46 pulses/ session, total 6 sessions	100~120 % rMT	triggered depending on EEG alpha phase	TMS triggered at four alpha phase bins	whole brain	event-related	1600/11, 32.16, 53.32	at rest	Prefrontal alpha phase dependent NE (FC and effective connectivity).
		17 MDD patients (5 males, age 48.2 ± 13.5 years)	/	L DLPFC	Beam-F3 method	not report	single pulse, 46 pulses/ session, total 6 sessions	100~120 % rMT	triggered depending on EEG alpha phase	TMS triggered at four alpha phase bins	whole brain	event-related	1750/ 11.2, 32.36, 53.52	at rest	Prefrontal alpha phase dependent NE (FC) and RA
10	Hanlon et al. (2016)	18 cocaine users (age 35.1 ± 7.8 years)	18 non-drug-using controls (age 36.2 ± 8.6 years)	L DLPFC L MPFC	location of F3 location of FP1	not report	single pulse, 12 pulses/ trail, 1 trail/ condition, total 2 conditions	110 % rMT	12 s	drug-using controls	whole brain	event-related	6700/87	at rest	Cocaine uses: LA and RA when target L MPFC; RA when target L DLPFC. Controls: RA when target L MPFC; LA and RA when target L DLPFC.
Low-frequency rTMS															
11	Caparelli et al. (2022b)	17 healthy participants (9 males, age 37.1 ± 11.2 years)	/	L DLPFC site 1; L DLPFC site 2; R DLPFC;	L DLPFC site 1: −50, 30, 36 (MNI); L DLPFC site 2: "5 cm rule" −41, 16, 54 (MNI);	not report	train, 30 pulses/ train, 1 train/ block, total 3 blocks	100 % rMT	0.4 Hz	/	whole brain	block	2500/27	at rest	RA↑, NE when stimulating all target sites. NE when stimulating R

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Table 1 (*continued*)

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
					R DLPFC: the contralateral side of site 1, 50, 30, 36 (MNI)										DLPFC compared with L DLPFC sites
12	Webler et al. (2022)	20 healthy right-handed participants (13 males, age 27.3 ± 3.3 years)	/	L DLPFC	location of F3 (10–20 EEG system)	not report	train, 7 pulses/ train/ block, total 6 blocks	100 % rMT	0.42 Hz	n-back task without TMS	whole brain	event-related	2400/35	during n-back task	RA↑
13	Rafiei et al. (2021)	5 healthy participants (3 males, age 24–33 years)	/	R DLPFC	not report	not report	condition 1 and 2: train, 10 pulses/ train, 3 trains/ block, total 10 blocks; condition 3: burst, 4 pulses/ burst, 5 bursts/ trail, 3 trails/ block, total 10 blocks	condition 1: 50 % rMT; condition 2 and 3: 100 % rMT;	condition 1 and 2: 1 Hz; condition 3: 12.5 Hz	/	partial brain coverage near the top of the head	block	1000/30	at rest	No difference between conditions in RA
		6 healthy participants (3 males, age 24–37 years)	/	L DLPFC	coordinates from functional connectivity based on a previous fMRI scan	not report	train, each condition contains 30 pulses/ train, 1 train/ block, 15 blocks/ session, total 2 session	100 % rMT	condition 1: 5 Hz; condition 2: 8.33 Hz; condition 3: 12.5 Hz; condition 4: 25 Hz.	/	whole brain	event-related	1240/ 30	at rest	No difference between conditions in LA
14	Chen et al. (2013)	24 healthy participants (14 males, age 26.5 ± 0.9 years)	/	R pMFG (CEN node) R aMFG (SN node)	rsfMRI ICA-identified networks from a separate participant	not report	train, 7 pulses/ train/ block, 10 blocks/ condition, total 2 conditions	120 % rMT	0.4 Hz	/	whole brain	block	2000/ 30	at rest	NE

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Table 1 (*continued*)

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
15	Nahas et al. (2001)	5 healthy right-handed participants (3 males, age 34 ± 6 years)	/	L DLPFC	5 cm forward to M1	not report	train, 21 pulses/ train, 1 train/ condition, 3 conditions/ block, total 7 blocks	80 %, 100 %, 120 % rMT	1 Hz	rest	whole brain	block	3000/ 40	at rest	LA↑, RA↑
16	Ge et al. (2022)	38 outpatients with treatment-resistant depression (12 males, age 41.84 ± 16.12 years)	/	R DLPFC	Beam-F3 method	not report	train, 300 pulses/ train/ block, total one block	100 % rMT	1 Hz	/	whole brain	event-related	1000/ 30	at rest	NE
17	Li et al. (2004)	14 patients with depression (5 males, age 18–58 years)	/	L DLPFC	5 cm forward to M1	not report	train, 21 pulses/ train, 1 train/ block, total 7 blocks	100 % rMT	1 Hz	rest	whole brain	block	3000/ ?	at rest	LA↑, RA
18	Eshel et al. (2020)	20 depressed patients (?,?)	21 matched healthy cohort	L DLPFC	rsfMRI ICA-identified networks from a separate participant	not report	train, 7 pulses/ train, 1 train/ block, total 10 blocks	120 % rMT	0.42 Hz	/	whole brain	block	2000/ 30	at rest	RA↑ in both depressed patients and healthy controls (healthy controls > patients)
High-frequency rTMS															
19	Caparelli et al. (2022a)	15 healthy adults (7 males, age 36.94 ± 11.89 years)	/	L DLPFC site 1; L DLPFC site 2; R DLPFC;	L DLPFC site 1: −50, 30, 36 (MNI); L DLPFC site 2: "5 cm rule" −41, 16, 54 (MNI); R DLPFC: the contralateral side of site 1, 50, 30, 36 (MNI)	not report	burst, 5 pulses/ burst, 30 bursts/ block, total 3 blocks	100 % rMT	10 Hz	/	whole brain	block	2500/ 27	at rest	RA↑, NE when stimulating all target sites, but no difference between all targets in RA.
13	Rafiei et al. (2021)	5 healthy participants (3 males, age 24–33 years)	/	R DLPFC	not report	not report	condition 1 and 2: train, 10 pulses/ train, 3	condition 1: 50 % rMT; condition	condition 1 and 2: 1 Hz;	/	partial brain coverage near the	block	1000/ 30	at rest	No difference between conditions in RA

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Table 1 (*continued*)

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
							trains/ block, total 10 blocks; condition 3: burst, 4 pulses/ burst, 5 bursts/ trail, 3 trails/ block, total 10 blocks	2 and 3: 100 % rMT;	condition 3: 12.5 Hz		top of the head				
		6 healthy participants (3 males, age 24–37 years)	/	L DLPFC	coordinates from functional connectivity based on a previous fMRI scan	not report	train, each condition contains 30 pulses/ train, 1 train/ block, 15 blocks/ session, total 2 session	100 % rMT	condition 1: 5 Hz; condition 2: 8.33 Hz; condition 3: 12.5 Hz; condition 4: 25 Hz.	/	whole brain	event-related	1240/ 30	at rest	No difference between conditions in LA
20	Jackson et al. (2021)	20 healthy right-handed participants (5 males, age 21.6 ± 3.36 years)	/	R DLPFC	central coordinates of peak activation from event-related fMRI/ MNI coordinates (44,31,28) from literature	not report	burst, 3 pulses/ burst, 32 burst/ block, 2 block/run, total 8 runs	110 % rMT	13 Hz	control condition: 40 % rMT stimulation during shape/ color task	whole brain	event-related	2450/ 30	during shape/color task	RA↑
21	Hawco et al. (2017)	17 right-handed (4 males, mean age 22.6)	/	L DLPFC	Beam-F3 method	handle pointing 45° away from the midline toward the back of the head.	burst, 3 pulses/ burst, 1 burst/trail, 30 trails/ condition, total 4 conditions (i.e., three TMS conditions start at either 0.2, 0.6, 1 s	100 % rMT	10 Hz	no TMS condition	whole brain	event-related	3000/30	during memory encoding task	RA↑ (stimulation onset at 0.2 *s* > 0.6 *s* > 1s

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Table 1 (*continued*)

No.	Authors	Experimental group	Control/ sham group	TMS parameters							fMRI parameters			During task/at rest	Reported local/ remote/ network effects*
				TMS target site	TMS target navigation	TMS coil position	protocol	intensity	frequency of train/ burst or interval of single pulse	comparisons, controls or sham conditions	fMRI measured site	Design	TR/TE in ms		
							after onset and one no TMS condition)								
22	Feredoes et al. (2011)	16 healthy right-handed participants (9 males, age 25 ± 0.9 years)		R DLPFC	MNI coordinates from previous literature	45°from the midline with the handle pointing in a posterior direction	burst, 3 pulses/ burst, 1 burst/trail, 30 trails/ condition, total 8 conditions	40 %, 110 % rMT	11 Hz	/	whole brain	event-related	3000/50	during visual working memory task	RA↑
23	Tik et al. (2023)	14 healthy right-handed participants (6 males, age 28 ±3.9 years)	13 participants (4 male, age 30±8 years)	L DLPFC	−42,28,21 (MNI coordinates from literature)	45° angle in relation to the surface of the skull	burst, 3 pulses/ burst, 5 bursts/ intensity, total 20 bursts, each burst was applied every 30s	randomly 80 %, 90 %, 100 %, 110 % rMT	10 Hz	Sham TMS: empty coil housing was placed between RF and TMS coil.	whole brain	event-related	1000/38	at rest	LA↑, RA↑
24	Webler et al. (2020)	8 unmedicated participants with schizophrenia (7 male, age 43 ± 6.0 years)	11 matched healthy controls (10 male, age 36.9 ± 7.9 years)	L BA9	coordinates from literature	not report	burst, 3 pulses/ burst, 7 burst/ block, total 5 blocks	randomly 0 %, 80 %, 100 %, 120 % rMT	10 Hz	healthy controls	whole brain	event-related	2000/35	at rest	LA↑, RA↑, NE (patients > healthy controls)

Abbreviations: aMFG = anterior middle frontal gyrus, BA = Brodmann area, CEN = central executive network, cTBS = continuous theta burst stimulation, DLPFC = dorsolateral prefrontal cortex, EEG = electroencephalography, FC=functional connectivity, *L* = left, LA = local activation, M1 = primary motor cortex, MPFC = medial prefrontal cortex, NE = network effects, PFC = prefrontal cortex, pMFG = posterior middle frontal gyrus, RA = remote activation, rMT = resting motor threshold, *R* = right, rsfMRI = resting-state fMRI, SN = cingulo-opercular salience network, VLPFC = ventrolateral prefrontal cortex, VMPFC = ventromedial prefrontal cortex, ? = information could not be extracted from the publication, ↑ = increase, .↑ = decrease.

* Studies may not look into local/ remote/ network effects explicitly, therefore only reported effects were listed, which does not implicate that there were no unreported effects. LA/RA without ↑ or ↑ means both increased or decreased activation is observed in local/remote areas.

Table 2
Studies investigating instantaneous effects of prefrontal TMS on brain oxygenation with fNIRS.

No.	Study	Experimental group	Control/ shame group	TMS parameters							fNIRS parameters			During task/at rest	Reported local/ remote/ network effects
				TMS target site	TMS target navigation	TMS coil position degree	protocol	intensity	frequency of train/burst or interval of single pulse	comparisons, controls or sham conditions	fNIRS measured site	Design	Data segments		
Single/paired-pulse TMS															
25	Curtin et al. (2017)	17 healthy right-handed participants (9 males, age 26.6 ± 2.6 years)	/	L DLPFC	location of F3 (10/20 EEG system)	not report	condition 1: single pulse, 1 pulse/trial, total 10 trials; condition 2: train, 30 pulses/ train, 1 train/ trial, total 10 trials; condition 3: TBS burst, 3 pulses/burst, 10 bursts/trial, total 10 trials	condition 1 and 2: 110 % rMT; condition 3: 90 % rMT;	condition 1: 42 s interpulse interval; condtition2: 15 Hz; condition 3: 50 Hz pulses spaced at 5 Hz	Sham TMS: reversing the coil with same sounds and vibrations of stimulation at high frequency without the corresponding flux	Frontopolar region of the DLPFC (BA11)	block	During stimulation and 15 s after the onset of stimulation	at rest	Greater LA↑ in condition 2 and 3 than condition 1
26	Thomson et al. (2013)	single pulse TMS group: 12 healthy participants (7 males, age 25–47 years); rTMS group: 8 healthy participants 4 males, age 22–42 years);	/	L DLPFC	location between F3 and AF3 (10/ 20 EEG system	condition 1:45°, 135°, 225° angle from the midline in an anticlockwise direction; condition 2: 45°, 225° angle from the midline in an anticlockwise direction;	condition 1: single pulse, 30 single pulses/ coil orientation, total 3 coil orientations; condition 2: train, 20 pulses/ train, 1 train/ block, 30 blocks/coil orientations, total 2 coil orientations.	single pulse: 130 % rMT; rTMS: 120 % rMT;	condition 1: 25 s interpulse interval; condition 2:1 Hz	/	bilateral DLPFC	block	5 s before stimulation to 10 s after the onset of stimulation	at rest	Greater LA↑ in condition 1; and RA in condition 2 when coil at 45°
27	Thomson et al. (2011b)	12 right-hand participants (5 males, age 29 ± 6 years)	10 right-hand participants (6 males, age 27 ± 3 years)	L DLPFC	location between F3 and F5 (10/ 20 EEG system)	45° angle from the midline	single pulse, 15 pulses/ condition, total 3 conditions	90 %, 110 %, 130 % rMT	25 s interpulse interval	sham TMS to L PFC by putting the coil 10 cm away from the head;	L DLPFC	block	5 s before stimulation to 10 s after the onset of stimulation	at rest	LA↑
28	Thomson et al. (2011a)	8 right-hand participants (6 males, age 30 ± 6 years)	10 right-hand participants (6 males, age 27 ± 3 years)	L DLPFC	location between F3 and F5 (10/ 20 EEG system)	45° angle from the midline	condition 1: single pulse, 20 pulses/trial; condition 2: paired-pulse (SICI), 20 paired pulse/ trial; condition 3: paired-pulse	condition 1: 120 % rMT; condition 2 &3: test stimulation 120 % rMT, conditioning 70 % rMT;	2 ms, 15 ms, 25 s inter-stimulus interval	sham TMS to L DLPFC by putting the coil 11 cm away from the head;	L DLPFC	block	5 s before stimulation to 25 s after the onset of stimulation	at rest	LA↑ in all conditions but faster return to baseline in condition 1.

(*continued on next page*)

Table 2 (*continued*)

No.	Study	Experimental group	Control/ shame group	TMS parameters							fNIRS parameters			During task/at rest	Reported local/ remote/ network effects
				TMS target site	TMS target navigation	TMS coil position degree	protocol	intensity	frequency of train/burst or interval of single pulse	comparisons, controls or sham conditions	fNIRS measured site	Design	Data segments		
							(IFC), 20 paired pulse/trial;								
Low-frequency rTMS															
26	Thomson et al. (2013)	single pulse TMS group: 12 healthy participants (7 males, age 25–47 years); rTMS group: 8 healthy participants 4 males, age 22–42 years);	/	L DLPFC	location between F3 and AF3 (10/ 20 EEG system)	condition 1:45°, 135°, 225° angle from the midline in an anticlockwise direction; condition 2: 45°, 225° angle from the midline in an anticlockwise direction;	condition 1: single pulse, 30 single pulses/ coil orientation, total 3 coil orientations; condition 2: train, 20 pulses/ train, 1 train/ block, 30 blocks/coil orientations, total 2 coil orientations.	single pulse: 130 % rMT; rTMS: 120 % rMT;	condition 1: 25 s interpulse interval; condition 2:1 Hz	/	bilateral DLPFC	block	5 s before stimulation to 10 s after the onset of stimulation	at rest	Greater LA↑ in condition 1; and RA in condition 2 when coil at 45°
29	Cao et al. (2013)	12 healthy participants (9 males, age 22.17 ± 2.62 years)	/	L DLPFC	location between F3 and AF3 (10/ 20 EEG system)	not report	train, 5, 10 or 25 pulses/train, 20 trains/ condition, total 3 conditions	110 % rMT	1, 2, 5 Hz	/	bilateral DLPFC	block	onset of stimulation to 25 s after the onset of stimulation	at rest	2 and 5 Hz induced greater LA and RA changes than 1 Hz
30	Thomson et al. (2012a)	13 right-hand participants (4 males, age 30 ± 6 years)	10 right-hand participants (6 males, age 27 ± 3 years)	L DLPFC	location between F3 and AF3 (10/ 20 EEG system)	not report	train, 2 or 4 pulses/train, 1 train/block, 20 blocks/ condition, total 2 conditions	130 % rMT;	0.2 Hz	4 pulses protocol over motor cortex; sham TMS to L PFC by putting the coil 10 cm away from the head;	L DLPFC	block	5 s before stimulation to 40 s after the onset of stimulation	at rest	LA↑ (experiment group > sham group)
31	Thomson et al. (2012b)	6 right-hand participants (3 males, age 26 ± 4 years)	/	L DLPFC	location between F3 and AF3 (10/ 20 EEG system)	45° angle from the midline	train, 600 pluses/train, 1 train/block, 2 blocks/session, 1 session/ condition, total 2 conditions	80 %, 120 % rMT	1 Hz	/	L DLPFC	block	during the 10mins stimulation to 1 min after stimulation	at rest	LA↑
32	Aoyama et al. (2009)	10 healthy right-handed participants (7 males, age 37.5 ± 10.9 years)	/	R DLPFC	a position 5 cm anterior to M1	the long axis of the figure-of-eight coil was parallel to the Fz–Cz line	train, 60 pulses/ train, 1 train/ condition, total 3 condition	28 %, 41 %, 58 %, rMT	1 Hz	disconnected coil placed and the stimulus was delivered by another coil (50 cm behind the participants)	left PFC (one of three channels on the left DLPFC)	block	30 s before the onset of stimulation to 120 s after stimulation	at rest	RA↑
33	Hanaoka et al. (2007)	11 healthy right-handed participants (10 males, age 26–45 years)	/	R DLPFC	a position 5 cm anterior to M1	not report	train, 60 pulses/ train, 1 train/ block, total 3 blocks	50 % rMT	1 Hz	coil placed 50 cm behind the participants with only click sounds but no stimulation	left PFC (one of three channels on the left DLPFC)	block	20 s before the onset of stimulation to 120 s after stimulation	at rest	RA↑
High-frequency rTMS, including TBS															

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Table 2 (*continued*)

No.	Study	Experimental group	Control/ shame group	TMS parameters							fNIRS parameters			During task/at rest	Reported local/ remote/ network effects
				TMS target site	TMS target navigation	TMS coil position degree	protocol	intensity	frequency of train/burst or interval of single pulse	comparisons, controls or sham conditions	fNIRS measured site	Design	Data segments		
25	Curtin et al. (2017)	17 healthy right-handed participants (9 males, age 26.6 ± 2.6 years)	/	L DLPFC	location of F3 (10/20 EEG system)	not report	condition 1: single pulse, 1 pulse/trial, total 10 trials; condition 2: train, 30 pulses/ train, 1 train/ trial, total 10 trials; condition 3: TBS burst, 3 pulses/burst, 10 bursts/trial, total 10 trials	condition 1 and 2: 110 % rMT; condition 3: 90 % rMT;	condition 1: 42 s interpulse interval; condtition2: 15 Hz; condition 3: 50 Hz pulses spaced at 5 Hz	Sham TMS: reversing the coil with same sounds and vibrations of stimulation at high frequency without the corresponding flux	Frontopolar region of the DLPFC (BA11)	block	During stimulation and 15 s after the onset of stimulation	at rest	Greater LA↑ in condition 2 and 3 than condition 1
29	Cao et al. (2013)	12 healthy participants (9 males, age 22.17 ± 2.62 years)	/	L DLPFC	location between F3 and AF3 (10/ 20 EEG system)	not report	train, 5, 10 or 25 pulses/train, 20 trains/ condition, total 3 conditions	110 % rMT	1, 2, 5 Hz	/	bilateral DLPFC	block	onset of stimulation to 25 s after the onset of stimulation	at rest	2 and 5 Hz induced greater LA and RA changes than 1 Hz
34	Shinba et al. (2018)	15 right-handed drug-resistant MDD patients (11 males, age 45.4 ± 10.8 years)	/	L DLPFC	5.5 cm anterior to the MT location	not report	train, 40 pulses/ train, 1 train/ block, 75 blocks/session, 1 session/day, 5 days/week, total 6 weeks	120 % rMT	10 Hz	/	Forehead (Fpz)	block	60 s before stimulation to 26 s after the onset of stimulation	at rest	RA↑
35	Struckmann et al. (2021)	18 treatment-resistant MDD patients (8 males, age 30 ± 11 years)	21 treatment-resistant MDD patients (10 males, age 29 ± 9 years)	DMPFC	MNI coordinates from previous literature	not report	burst, 3 pulses/ burst, 10 bursts/train, 40 trains/session, total 2 session	90 % rMT	pulse at 50 Hz, bust at 5 Hz	TENS stimulation mimics active TMS pulses	bilateral PFC	event-related	8 s 'off' within each train	at rest	RA↑
36	Struckmann et al. (2022)	17 patients with treatment-resistant depression (8 males, age 30.9 ± 10.3 years)	17 patients with treatment-resistant depression (8 males, age 27.1 ± 7.2 years)	DMPFC	MNI coordinates from previous literature	not report	burst, 3 pulses/ burst, 10 bursts/train, 40 trains/session, total 2 session	90 % rMT	pulse at 50 Hz, bust at 5 Hz	TENS stimulation mimics active TMS pulses	bilateral DLPFC	event-related	8 s 'off' within each train	at rest	RA↑
37	Curcic-Blake et al. (2022)	13 schizophrenia patients (10 males, age 39.2 ± 11.4 years)	14 healthy controls (8 males, age 36.3 ± 13.7 years)	R DLPFC	location of F4 (10/20 EEG system)	not report	train, 30 pulses/ train, 1 train/ block, total 10 blocks	60 % rMT	10 Hz	healthy controls	bilateral IPL	block	5 s before stimulation to 60 s after the onset of stimulation	at rest	RA↑ in both patients and healthy controls (healthy controls > patients)

Abbreviations: BA = Brodmann area, DLPFC = dorsolateral prefrontal cortex, DMPFC = dorsomedial prefrontal cortex, EEG = electroencephalography, IFC = intracortical facilitation, IPL = inferior parietal lobe, *L* = left, LA = local activation, NE = network effects, M1 = primary motor cortex, MDD = major depressive disorder, PFC = prefrontal cortex, pMFG = posterior middle frontal gyrus, RA = remote activation, rMT = resting motor threshold, *R* = right, SICI = short interval intracortical inhibition, TBS = theta burst stimulation, TENS = transcutaneous electrical nerve stimulation, ↑ = increase, .↑ = decrease.

*Studies may not look into local/ remote/ network effects explicitly, therefore only reported effects were listed, which does not implicate that there were no unreported effects. LA/RA without ↑ or ↑ means both increased or decreased activation is observed in local/remote areas.

left DLPFC, the local area was activated in studies no.3 and 5; and deactivated in studies no.10 and 26–28. When targeting other PFC subregions (i.e., the left MPFC in studies no.5 and 10), the local area was deactivated.

Theremote brain regions affected included the contralateral PFC, caudate, anterior cingulate cortex (ACC), insula cortex, amygdala, and auditory cortex. The contralateral PFC was activated in studies no. 4, 5, and 10, and deactivated in study no.5 when targeting the left MPFC (27.3 % of the studies). The caudate exhibited ipsilateral activations in study no.10 and bilateral activations in studies no.3 and 4 (27.3 % of the studies). The ACC showed stimulation-induced activations/de-activations in 54.5 % of the studies, with studies no.2 and 3 reporting ipsilateral activations and deactivations, respectively, studies no.4 and 9 reported contralateral activations or prefrontal alpha phase-dependent activations/deactivations, and finally, studies no.5 and 10 reported bilateral activations. Meanwhile, the ipsilateral insula cortex (in studies no.3 and 10), amygdala (in studies no.2 and 10) and auditory cortex (in studies no.3 and 5) were activated in 18.2 % of the studies. Other affected brain regions reported by single studies are presented in Supplementary Table S3.

Single-pulse TMS over left DLPFC moreover showed network effects on DLPFC-subgenual ACC (sgACC) network instudy no.9. Using generalized Psychophysiological Interactions analysis (PPI), the study found that single-pulse TMS-evoked DLPFC-sgACC functional connectivity and effective connectivity depended on the prefrontal EEG alpha phase.

3.4.2. Clinical population

Single-pulse TMS stimulation was delivered to people with substance use disorders (i.e., cocaine and alcohol in studies no.6–8 and 10) or MDD (study no.9). Three studies stimulated the left MPFC (studies no.7–8 and 10), two studies stimulated the left DLPFC (studies no.9–10), and one study stimulated the left ventromedial prefrontal cortex (VMPFC, study no.6). All the four studies conducted on cocaine or alcohol users exhibited stimulation-induced remote activations in bilateral striatum (i.e., caudate, putamen and nucleus accumbens), ACC, and insula. Continuous TBS (cTBS) at ventromedial PFC was observed to decrease the single-pulse TMS-induced hemodynamic activations (studies no.7–8). Other affected brain regions (e.g., local DLPFC in study no.10) reported by single studies are presented in Supplementary Table S3.

At network level, study no.9 also showed the same prefrontal EEG alpha-hase-dependent DLPFC-sgACC functional connectivity responses in MDD patients as found in the healthy population (reported in section 3.4.1).

3.5. Effects of low-frequency rTMS at rest

3.5.1. Healthy population

Nine studies applied prefrontal low-frequency rTMS in healthy populations (studies no.11, 14–15, 18, 26, and 30–33). Specifically, six studies and three stimulated the left and right DLPFC, respectively (studies no.11, 15, 18, 26, and 30–31 and studies no.11, and 32–33). One study stimulated both right anterior middle frontal gyrus (MFG) and posterior MFG (study no.14).

Out of the nine studies, four studies (44.4 % of the studies) reported local stimulation-induced activations/deactivations in left DLPFC. In study no.15 and 26, the local area was activated. In studies no.30–31, the local area was deactivated.

When the DLPFC was targeted, the remote brain regions affected included the PFC, insula cortex, auditory, and motor cortex. The PFC exhibited contralateral activations in studies no.15 and 26, and de-activations in studies no.32–33, as well as ipsilateral deactivations in study no.11 (55.6 % of the studies). The insula cortex exhibited activations in 22.2 % of the studies, with contralateral activations only in study no.11 and bilateral activations in study no.15. The bilateral auditory and motor cortices showed activations in studies no.11 and 15 (22.2 % of the studies). Other influenced brain regions reported by

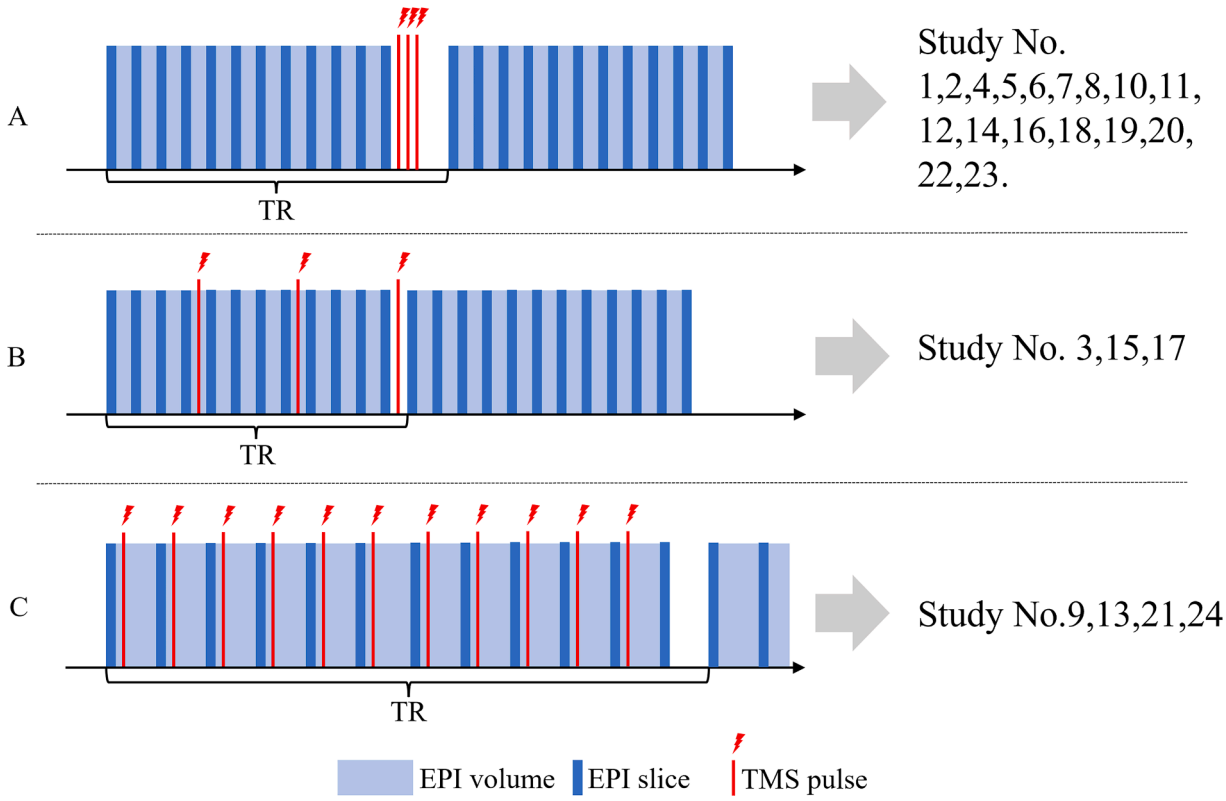

Fig. 3. Concurrent TMS/fMRI designs utilized in the included studies. (A) Single-pulse TMS or burst of rTMS delivered during the delay between image acquisition volumes. (B) single-pulse TMS or trains of rTMS delivered at between volumes and within volumes. (C) train of rTMS is interleaved alternatingly with EPI slices. Abbreviations: TR = time of repetition.

single studies are presented in Supplementary Table S3.

Two studies reported the effects of low-frequency rTMS on networks (studies no.11 and 14). In study no.11, connectivity within multiple network components from an Independent Component Analysis (ICA) was found to be affected by TMS of both sides of DLPFC. However, facilitated functional connectivity was observed only at the striatum and thalamus component and the default-mode network (DMN) component when TMS was applied to the right DLPFC, but not to the left. In study no.14, when only applying TMS to posterior MFG (i.e., central executive network (CEN) node), negative DMN PPI connectivity with the CEN and cingulo-opercular salience network (SN) was observed.

3.5.2. Clinical population

Three studies (studies no.16–18) applied low-frequency TMS to the PFC, specifically the right DLPFC (study no.16) and left DLPFC (studies no.17–18), in participants with depression. When targeting to the left DLPFC, one of the three studies (study no.17, 33.3 % of the studies) reported local stimulation-induced activations, with the other two studies (study no.17–18, 66.7 % of the studies) reporting remote activations in contralateral PFC. The activations in contralateral DLPFC in study no.17 were higher in depressed patients than in healthy participants. Other influenced brain regions reported by single studies are presented in Supplementary Table S3.

Only one study (study no.16) reported that low-frequency rTMS induced widespread (43 edges between 50 nodes), acute and transient decreases in functional connectivity.

3.6. Effects of high-frequency rTMS at rest

3.6.1. Healthy population

Five studies applied prefrontal high-frequency rTMS, including intermediate TBS (iTBS), in healthy populations (studies no.19, 23–25, and 37). Three from the 5 studies stimulated the left DLPFC (studies no.19, 23 and 25), two studies stimulated the right DLPFC (study no.19 and 37), and one study stimulated the left BA 9 (study no.24).

Out of the five studies, two studies (studies no.23 and 25, 40 % of the studies) reported local stimulation-induced activations in the stimulated left DLPFC. Other affected remote brain regions reported by single studies are presented in Supplementary Table S3.

Two studies (studies no.19 and 24) reported the effects of high-frequency rTMS on networks. Study no.24 showed that stimulation facilitated functional connectivity between bilateral DLPFC. In study no.19, ICA showed that stimulation facilitated many networks that were either common or specific to the stimulation sites (both left and right DLPFC). However, laterality differences were only observed at the left executive control network and dorsal ACC-DLPFC/dorsomedial PFC components.

3.6.2. Clinical population

High-frequency rTMS (including iTBS) was delivered to patients with depression (studies no.34–36) or schizophrenia (studies no.24 and 37). In patients with depression, therapeutic high-frequency rTMS protocols were applied over the dorsomedial PFC ($X = 0$, $Y = 30$, $Z = 30$ in study no.35–36) or the left DLPFC (study no.34).

All three studies (100 % of the studies) conducted on depressed patients reported only remote PFC hemodynamic increases. Specifically, study no.35 showed bilateral activations, study no.34 showed midline PFC activations, and study no.36 showed unilateral PFC activations (i.e., TMS at dorsomedial PFC ($X = 0$, $Y = 30$, $Z = 30$) activated left DLPFC). In study no.34, 80 % of depressed patients in the first session of treatment showed activations at the midline of PFC, but the rate reduced to 60 % in the last session. In studies no.35–36, the activated PFC was observed during the fifth and last treatment session. The two studies conducted on patients with schizophrenia reported inconsistent regional

effects when stimulation was delivered to left BA 9 and right DLPFC, respectively (study no.24 and 37). Study no.24 reported local activation, see Supplementary Table S3.

3.7. Effects of TMS during tasks

Four studies applied prefrontal TMS stimulation during working memory and related information coding tasks (studies no.12, and 20–22). The stimulation was specifically delivered to the right DLPFC (studies no.12 and 20) or left DLPFC (study no.21–22). High-frequency rTMS stimulation-induced activation in regions where task stimuli were represented when a distractor was present (study no.22). In study no.21, time-specific differences in high-frequency rTMS stimulation-induced activations (200 > 600 > 1000 ms) were observed in both local (ipsilateral medial frontal cortex) and remote brain regions (lateral frontal and anterior cingulate, ipsilateral middle temporal cortex, and visual areas) during a memory encoding task. High-frequency rTMS stimulation also activated the ipsilateral ACC and contralateral DLPFC when coding task-relevant information (study no.20). Only one study (study no.12) applied low-frequency rTMS during an n-back task and reported TMS-induced greater deactivations in remote areas (the middle and superior temporal gyrus and DMN nodes) during high cognitive load (two-back task) than low cognitive load (one-back task). Detailed information on the influenced brain regions can be found in Supplementary Table S3.

3.8. TMS parameters and the effect of TMS

Eight studies investigated the relationship between intensity and TMS-induced neuronal changes (studies no.4, 13, 15, 22, 24, 27, and 31–32). Three studies respectively applied low and high frequencies rTMS and single-pulse TMS, and did not observe any differences between intensities in stimulation-induced brain hemodynamic response (studies no.4, 13, and 24). However, two studies reported that low-frequency rTMS at higher intensity induced greater activations (studies no.15 and 22). In contrast, three other studies showed that low-frequency rTMS at higher intensity induced greater deactivation in ipsilateral PFC (studies no.27, and 31–32).

Three studies adopted different TMS protocols at the same intensity to compare the effects on cortical hemodynamic response (studies no.25, and 28–29). Study no.28 observed differences in the temporal characteristics of the hemodynamic induced by single-pulse and paired-pulse TMS, with the ipsilateral DLPFC activation induced by paired-pulse TMS returning to baseline faster. Study no.25 found that high-frequency rTMS activated the cortical region beneath the coil to a greater extent compared to single-pulse TMS. Contrarily, study no.29 reported that high-frequency rTMS induced greater activations in both local and contralateral DLPFC compared to low-frequency rTMS.

One study investigated the impact of coil orientation on TMS-induced changes in prefrontal blood oxygenation and found that holding the coil at 45° induced greater bilateral DLPFC activations compared to the coil orientations at 135° and 225° (study no.26). Another study applied rTMS with different high frequencies (5 to 25 Hz) over the left DLPFC and did not observe any difference in the induced local brain hemodynamic response (study no.13).

4. Discussion

4.1. Local and remote effects of prefrontal TMS

In this review, we summarized the results of research studying the instantaneous effects of prefrontal TMS on brain oxygenation by concurrently using fMRI or fNIRS. Inconsistent results were observed, may due to differences in stimulation parameters (e.g., intensity, frequency, duration, no. of pulses), participant variability, and other methodological variability. About 38 % of the included studies reported local effects of prefrontal TMS (14 out of 37 studies). Among them, single-/paired-pulse TMS studies in healthy populations at rest most consistently reported stimulation-induced deactivations in local brain regions in five out of 11 studies (refer to section 3.4.1 for details). High-frequency rTMS, on the other hand, most consistently induced expected facilitatory effects in local brain regions in four out of 13 studies, (see Fig. 4).

When looking at the engagement of remote brain regions during prefrontal TMS, various cortical and subcortical regions were reported to be involved (see Supplementary Table S3 and Fig. 4). Although some inconsistent factors existed, after excluding areas that might be impacted by peripheral co-stimulation (i.e., auditory cortex activated by TMS click sound, sensorimotor cortex activated by cranial nerve stimulation, afferent feedback from muscle twitches in face, jaw or neck, and TMS coil vibration caused tactile sensations) (Bergmann et al., 2021), specific affected regions involving the PFC, particularly the DLPFC in single-/paired-pulse TMS and low-/high-frequency rTMS studies, the insula cortex in single-/paired-pulse TMS and low-frequency rTMS studies, striatal regions (especially caudate and putamen) in single-/paired-pulse TMS studies, the ACC in single-/paired-pulse TMS studies, and the thalamus in single-/paired-pulse TMS studies emerged most frequently (each was reported by at least three studies with the same protocols, showing consistent response directions, see Fig. 4).

Most of these engaged brain regions are also known as the key nodes of certain brain networks, such as DMN (i.e., a network composed of dorsal MPFC, posterior cingulate cortex, precuneus, and angular gyrus), SN (i.e., a network composed of the anterior insula and dorsal ACC) and CEN (i.e., a network composed of DLPFC and posterior parietal cortex). Several included studies also demonstrated the involvement of these networks during prefrontal TMS stimulation (Caparelli et al., 2022b, 2022a; Chen et al., 2013). Therefore, our findings in this systematic review lend further credence to the neural excitability effects of prefrontal TMS on the stimulated and remote brain regions through cortico-cortical or cortico-subcortical pathways.

4.2. Variability of local and remote effects

However, whether TMS could robustly induce hemodynamic changes in these brain regions remains unknown. The rate of the reviewed studies explicitly reported significant blood oxygenation changes is less than 40 %, even for the stimulated PFC. Furthermore, when reported, the response direction varies, particularly in single- or paired-pulse TMS and low-frequency rTMS studies (see Fig. 4 and section 3.5.1). From a simplistic perspective, low-frequency rTMS would be expected to induce inhibitory effects (decreasing brain oxygenation), while high-frequency rTMS (including iTBS) would be expected to induce facilitatory effects (increasing brain oxygenation) (Hoogendam et al., 2010; Speer et al., 2000). However, this review found a large proportion of excitatory remote effects compared to inhibitory effects, regardless of the stimulation protocol employed (see Fig. 4). The potential variability of local and remote effects of prefrontal TMS at present may limit the development of standardized procedures and treatment in psychiatric disorders. Thus, the causes of variability need to be discussed critically.

4.2.1. TMS parameters affecting both local and remote effects

Different stimulation intensities or coil positions/orientations may cause varying hemodynamic changes in local and remote regions. An almost linear correlation between stimulation intensity and neuromodulation in PFC is assumed in conventional rTMS studies (Kähkönen et al., 2005; Speer et al., 2003). However, the present review demonstrates the non-linear effect of stimulation intensities for rTMS. Two out of seven studies reported increased activations with higher intensity low-frequency rTMS, three studies reported increased deactivation with higher intensity low-frequency rTMS.Meanwhile two studies found no significant differences in hemodynamic responses between intensities

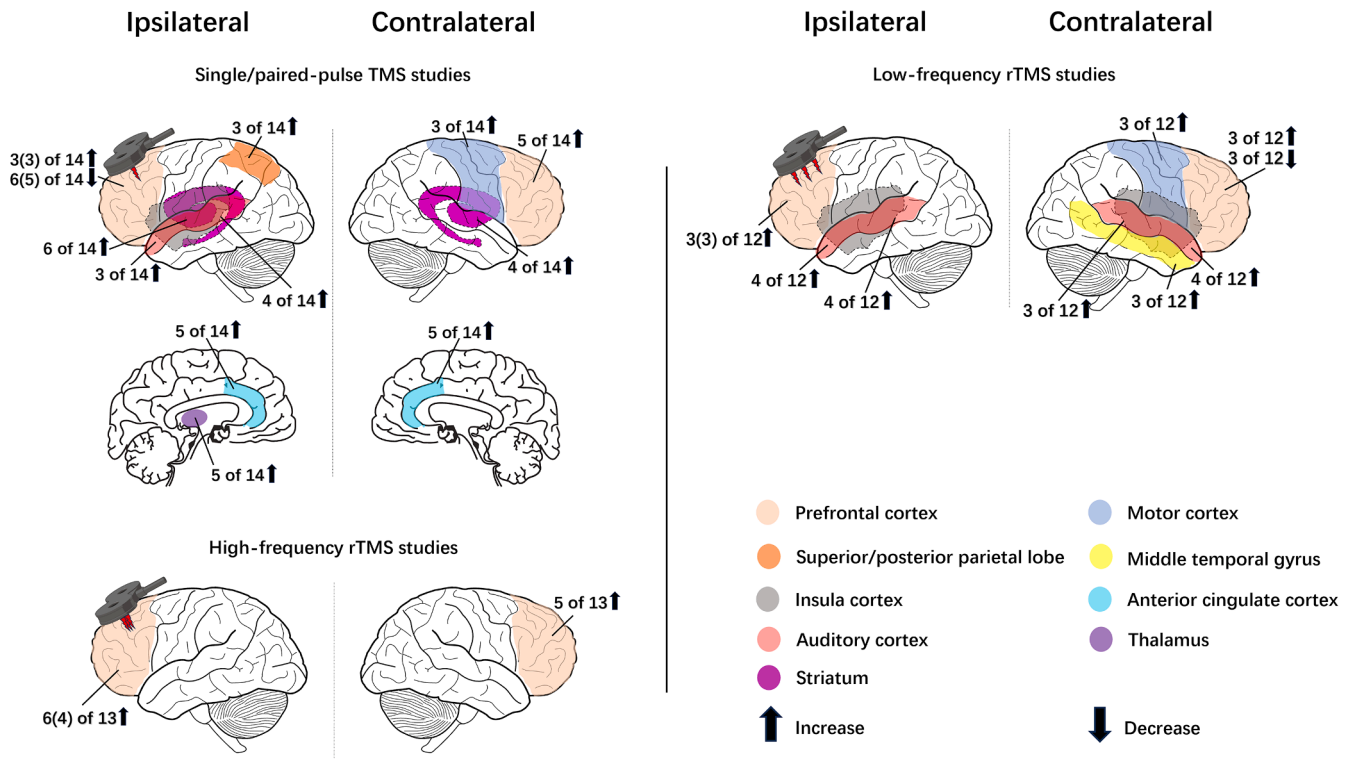

Fig. 4. Summary of regional hemodynamic changes during prefrontal TMS.
Note: Upper left: Single and paired-pulse TMS; upper right: low-frequency rTMS studies; lower left: high-frequency rTMS studies. 1) The fractions indicate the proportions of studies that reported blood oxygenation changes in the corresponding regions in all single/paired-pulse TMS/ low-frequency rTMS/ high-frequency rTMS studies that reported local or remote activation. 2) The number in parentheses indicates the number of articles reporting local effects. 3)The two brain hemispheres and the TMS coil icon are only used to represent the "ipsilateral" and "contralateral" and do not represent the actual stimulation target. 4) Only brain regions that were reported by at least three studies are shown in this figure. 5) The high-frequency rTMS studies included iTBS studies. Two of the iTBS studies (studies no.33 and 35) targeted at dorsomedial prefrontal cortex ($X = 0$, $Y = 30$, $Z = 30$) and reported activation in left and bilateral DLPFC, respectively.

(see section 3.8). The relationship between intensity and TMS-induced hemodynamic changes in PFC therefore needs stronger evidence to establish well-powered dose-response curves. Future studies with an extensive range of intensities are needed to draw the dose-response curves.

For TMS orientation, coil orientation at 45° was consistently used by most studies that reported their position strategies. Nonetheless, only Thomson et al. (2013) systematically investigated the effects of TMS coil orientations on TMS-induced hemodynamic changes and observed that coil orientation at 45° could induce significant prefrontal hemodynamic increases (see section *3.8*). However, the optimal coil orientation maps developed by Gomez-Tames et al. (2018) showed that the optimal coil position for inducing high electric field strength is inconsistent in regions out of sensorimotor areas. Orienting the coil at 45° over PFC may not always be optimal. An individualized optimal coil orientation may be preferable for obtaining the most effective stimulation.

4.2.2. Highly localized and divergent effects potentially hiding local effects

Apart from different stimulated intensities or coil positions/orientations, TMS-evoked neuronal activation beneath the coil without inducing hemodynamic changes may also account for inconsistent engagement of local regions. Bergmann et al. (2021) speculated that the TMS-induced local neural effects can exhibit high localization, potentially leading to divergent effects on the BOLD signal in multiple spots within a voxel. These effects may balance each other out at the voxel level. Likewise, Rafiei and Rahnev (2022) proposed that TMS-induced periods of increased and decreased neuronal firing underneath the coil could cancel each other out and lead to a lack of hemodynamic response. A previous electrical stimulation study observed a similar increase and decrease in neuronal activity in animal model. Critically, the authors explained that the decrease might result from the long-lasting release of γ-aminobutyric acid, which does not affect hemodynamic changes, instead of continuous inhibitory neuronal activity that could cause hemodynamic increases (Krnjevic et al., 1964). In addition, Logothetis (2008) argued that changes in excitation-inhibition balance (including balanced increases in the excitatory and inhibitory conductance), no matter whether they lead to net excitation/inhibition, require regional metabolic energy accompanied by hemodynamic changes. The explanation by Bergmann et al. (2021) thus seems to be more reasonable.

4.2.3. Target sites affecting remote effects

Stimulation of remote subregions corresponding to different regions of the PFC target may account for the variability in engaging remote regions. Hanlon et al. (2013) showed that applying TMS to two unique prefrontal targets (DLPFC vs. VMPFC) activated different remote subcortical circuits. Moreover, using different methods to determine the exact target may cause variations in location. A variety of approaches (i.e. MNI coordinates from the literature, the 5 cm rule, the Beam-F3 method, locations of the 10/20 EEG system, and coordinates from resting-state fMRI functional connectivity analysis) were utilized by reviewed studies to determine the DLPFC target. More recently, emerging evidence reveals that the neuro-navigational methods, depending on structural/functional MRI data, consistently ensure the placement of the TMS coil to DLPFC; however, the Beam-F3 method locates the stimulated target anterior to the DLPFC, whereas the 5 cm rule method locates posteriorly (Fitzgerald, 2021). Consequently, minor deviations in target localization can result in engaging disparate remote brain regions during stimulation. However, Caparelli and colleagues did not find significant differences in stimulation-induced activation between two targeting methods (MNI coordinates from the literature vs. the 5 cm rule) (Caparelli et al., 2022a, 2022b).

4.2.4. Other possible factors affecting the response in local and remote brain regions

The varying directions of response over the local and remote brain regions may be due to the changes in brain excitability in response to TMS stimulation being state-dependent (Sack et al., 2024; Giron et al., 2023). State dependence refers to the initial activation state of the stimulated brain regions can influence the effect of an external stimulation such as TMS (Bradley et al., 2022; Silvanto et al., 2008). Previous research on perception and behavior also indicated that TMS tended to selectively stimulate the less active neurons in a given population (Silvanto et al., 2007). In recent years, significant advances have been made in combining TMS stimulation with EEG and fMRI, enabling researchers to deliver stimulation adaptively and provide evidence in our review that concurs with this view. A recent study utilized the simultaneous fMRI-EEG-TMS technique to investigate how prefrontal EEG alpha phase moderates the impact of prefrontal TMS on brain oxygenation (Pantazatos et al., 2023). Their results demonstrate the instantaneous effects of prefrontal TMS vary as a function of the prefrontal alpha rhythm. However, the current state of the stimulated region at the moment of stimulation was not typically controlled in our included studies. The neural states of brain regions and networks (e.g., cognitive brain state, oscillatory brain state and recent brain state history) can vary on a short timescale, from day to day and across conditions (e.g., contextual, behavioral, mental, and cognitive conditions) (Clow et al., 2014; Padberg et al., 2021; Poldrack et al., 2015; Reichert et al., 2021; Sack et al., 2023; Suppa et al., 2016), especially in heteromodal association cortices, i.e., PFC regions (Mueller et al., 2013; Padberg et al., 2021). The varying states of local brain regions will influence the remote effects through functional connectivity and neural pathways. Furthermore additional factors, such as the anatomical and physiological characteristics of participants, have been identified to influence the induction of plasticity by NIBS (Guerra et al., 2020; Ridding and Ziemann, 2010). Any of the above factors may lead to large inter- and intra-individual variability of prefrontal TMS-induced hemodynamic responses.

Regarding the interesting finding of excitatory effects being more prevalent than inhibitory effects in remote effects, the underlying mechanisms remain unclear. Several lines of evidence suggest that excitatory as well as inhibitory effects of rTMS result from the activation of N-methyl-d-aspartate (NMDA) receptors at the excitatory synapse, leading to increased post-synaptic Ca^{2+}concentration and affecting the alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. The difference lies in the "nature" of the Ca^{2+} surge: excitation effect requires a large and rapid increase in Ca^{2+} concentration to enhance the amount and sensitivity of post-synaptic AMPA receptors to glutamate, whereas inhibition results from small and slow rises in Ca^{2+} concentration that decreases the amount and sensitivity of post-synaptic AMPA receptors to glutamate (Hoogendam et al., 2010; Klomjai et al., 2015; Tang et al., 2017). It is conceivable that inhibitory effects in remote brain regions may need longer periods of low-frequency stimulation than what is applied in the studies included in our review. Indeed, concurrent TMS/fMRI and TMS/fNIRS studies always apply stimulation and measurement in a short time window. This may explain why remote effects summarized in our review are mostly excitatory in nature.

4.3. Limitations and future directions

Although our current review aims to consolidate findings from various concurrent TMS/fNIRS and TMS/fMRI studies, several limitations restrict our comparisons across studies. A major limitation of this manuscript is the grouping of studies that employ vastly divergent methodologies. The included studies utilized diverse TMS protocols with heterogeneous stimulation parameters and target sites, which likely contributed to the conflicting results. This largely precluded us from synthesizing results in a meaningful way. Studies with similar protocols and parameters are needed to allow meaningful comparison and contribute to understanding the mechanism of modulating cortical excitability with TMS. Moreover, there were limited well-powered studies and randomized controlled studies.

The relationship between neuronal modulation and clinical consequences remains unknown. Only four studies connected the TMS-

induced oxygenation changes with clinical rTMS treatment responses in depression (Ge et al., 2022; Shinba et al., 2018; Struckmann et al., 2022, 2021), and three emphasized the predictive value of acute TMS-induced functional connectivity and cortical activation changes in symptom improvement (Ge et al., 2022; Shinba et al., 2018; Struckmann et al., 2022). Therefore, we suggest future research to investigate therapeutic stimulation protocols with high quality experimental designs to associate the instantaneous effects of prefrontal TMS with clinical outcomes. It would enable us to optimize TMS treatment for neuropsychiatric disorders to achieve precision psychiatric care. However, it is critical to address the inter- and intra-variability of the instantaneous effects of TMS on brain oxygenation prior.

Taking into account the variability, further personalization of the stimulation will be critcal to maximize the effectiveness of concurrent TMS/fMRI or TMS/fNIRS approaches(Padberg et al., 2021; Zhong et al., 2021). One of the most popular personalized strategies is using personalized connectivity-guided stimulation (Cash et al., 2021; Zhong et al., 2021). Conversely, concurrent TMS/fMRI technique can also be used to verify both functional connectivity between the superficial and deep targets, as well as to determine the successful activation of deep targets (Luber et al., 2022).

5. Conclusion

Concurrent uses of neuroimaging technology are ideally suited to measure the “online” effects of TMS in non-motor regions. Here we reviewed all published concurrent TMS/fMRI and TMS/fNIRS studies that applied TMS to the PFC to investigate the instantaneous effects of TMS on brain oxygenation across the brain. Our results demonstrate that prefrontal TMS is most likely to immediately modulate the excitability of several brain networks (SN, CEN, and DMN) and their constituent nodes, i.e., the PFC (particularly DLPFC), insula cortex, striatal regions (especially caudate and putamen), ACC, and thalamus. Meanwhile, high-frequency rTMS seems robust in inducing expected facilitatory effects in those regions. However, the potential variability of target engagement and its response to TMS should not be ignored. There is still room to enhance the effects of TMS with consistent outcomes. With the simultaneous application of TMS and fNIRS or fMRI, more reliable developments and optimization of stimulation parameters can be achieved.

CRediT authorship contribution statement

Adam W.L. Xia: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Visualization. **Minxia Jin:** Methodology, Investigation, Writing – original draft, Writing – review & editing. **Penny P.I. Qin:** Methodology, Investigation, Writing – review & editing. **Rebecca L.D. Kan:** Writing – review & editing. **Bella B.B. Zhang:** Writing – review & editing. **Cristian G. Giron:** Writing – review & editing. **Tim T.Z. Lin:** Writing – review & editing. **Ami S.M. Li:** Writing – review & editing. **Georg S. Kranz:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data was used for the research described in the article.

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Supplementary materials

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