Neuroscience and Biobehavioral Reviews 157 (2024) 105532

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Effects of transcranial magnetic stimulation on reactive response inhibition

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ARTICLE INFO

Keywords:
Reactive response inhibition
Stop-signal task
Transcranial magnetic stimulation
Right inferior frontal cortex
Pre-supplementary motor area

ABSTRACT

Reactive response inhibition cancels impending actions to enable adaptive behavior in ever-changing environments and has wide neuropsychiatric implications. A canonical paradigm to measure the covert inhibition latency is the stop-signal task (SST). To probe the cortico-subcortical network underlying motor inhibition, transcranial magnetic stimulation (TMS) has been applied over central nodes to modulate SST performance, especially to the right inferior frontal cortex and the presupplementary motor area. Since the vast parameter spaces of SST and TMS enabled diverse implementations, the insights delivered by emerging TMS-SST studies remain inconclusive. Therefore, a systematic review was conducted to account for variability and synthesize converging evidence. Results indicate certain protocol specificity through the consistent perturbations induced by online TMS, whereas offline protocols show paradoxical effects on different target regions besides numerous null effects. Ancillary neuroimaging findings have verified and dissociated the underpinning network dynamics. Sources of heterogeneity in designs and risk of bias are highlighted. Finally, we outline best-practice recommendations to bridge methodological gaps and subserve the validity as well as replicability of future work.

1. Introduction

Retracting an outstretched foot towards the crosswalk as the traffic light suddenly turns red, or suppressing a prepared joke as an unexpected threatening glance updates the behavioral priority, are considered crucial for risk avoidance and flexibility. These abilities to cancel impending but no longer appropriate action according to external triggers are termed reactive response inhibition. In contrast to proactive withholding, the reactive withdrawal of prepotent responses should be mobilized often by unforeseeable emergencies that are inherent in the real world.

In addition to its everyday relevance, reactive response inhibition possesses clinical significance that spans a spectrum of neuropsychiatric disorders. Systematic investigation thereof can advance the pathological conception of both movement-related disinhibition in tics or stuttering and more general impulse control deficits in obsessive-compulsive disorders, attention-deficit/hyperactivity disorder and schizophrenia (for a review, see Lipszyc and Schachar, 2010), and reveal potentially mediating personality traits (Avila and Parcet, 2001; Logan et al., 1997). Moreover, identifying the brain areas that malfunction in various disorders related to inhibition issues helps transcend diagnoses. This paves the way for a more unified, dimensional approach of intervention research (Insel, 2014).

1.1. SST as a robust measure of reactive response inhibition

Researchers have designed highly controlled laboratory-based experiments to operationalize the covert inhibition processes. Usually performing a standard two-choice reaction time task, shortly after the task stimulus, subjects are presented with a "stop" signal on a minority of trials, which instructs them to brake contingently (Logan et al., 1984). This Stop-Signal Task (SST) is commonly applied to quantifying the stopping latencies of simple, discrete actions, such as button presses. Though the SST has been advocated to capture the occasional and unpredictable essence of circumstances demanding reactive response inhibition, laboratory settings can hardly reconstruct the real-world

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https://doi.org/10.1016/j.neubiorev.2023.105532
Received 26 September 2023; Received in revised form 28 December 2023; Accepted 30 December 2023
Available online 8 January 2024

surprise and the instruction about potential occurrence of stop signals might engage constant, implicit anticipation (Hannah and Aron, 2021; Wessel, 2018). Still, relative to other tasks on inhibitory control (Miyake et al., 2000), SST possesses fewer proactive components and serves as a well-established paradigm for reactive response inhibition.

To orient the reader, different facets of response inhibition are briefly introduced within the task context. First, timing of the stopping message relative to action initiation distinguishes the proactive and reactive modes of response inhibition. *Proactive inhibition* involves top-down withholding prepared by a no-go cue before the action is initiated. In contrast, *reactive inhibition* is triggered in a bottom-up fashion by the presentation of an unforeseen stop signal to countermand an already elicited response. A further distinction in global or selective forms of inhibition is associated with specific contents of the stopping message. *Selective inhibition* targets designated aspects of responses and allows others to continue, while *global inhibition* engages diffuse, unspecific suppression that affects multiple systems simultaneously. Global inhibition tends to be exerted in a reactive mode, whereas selective inhibition entails recruitment of specific pathways through proactive preparation in advance. It is noteworthy that these processes are not mutually exclusive. They prove to share the essential neural substrates and co-occur during SST (Kenemans, 2015; van Belle et al., 2014; Zhang and Iwaki, 2019), since most cognitive tasks are not ideal representations of isolated concepts, as previously mentioned.

Most SST studies focused on a single outcome parameter depicting the efficiency of inhibitory control, namely the Stop-Signal Reaction Time (SSRT). The covert latency of stopping can be estimated based on an independent horse-race model (Logan and Cowan, 1984). It conceptualizes response inhibition as two independently competing processes, initiated by the primary task and the "stopping task" with stimulus onset asynchrony, respectively. The relative finishing time of both racers thus determines the probability of successful withdrawal. As the onset difference between "go" and "stop", commonly named stop-signal delay (SSD), increases, the probability of timely stopping or p(respond|signal) shrinks. The independence assumptions, despite partially paradoxical neural architecture (Verbruggen and Logan, 2009), are robustly aligned with empirical data across designs and subjects (for a review, see Logan, 1994). Therefore, several methods of SSRT estimation have been derived from the assumed horse-race model. Prevailing methods are either based on central tendency measures including mean and median (SSRTm) or grounded in integration of reaction time distribution (SSRTi). SSRTm is usually estimated by subtracting mean SSD from the averaged response time on go trials. This simple approach, however, frequently overestimates SSRT, since it is susceptible to the common right skew of the reaction time distribution and gradual slowing over the course of the experiment (Verbruggen et al., 2013). The integration method, or SSRTi, organizes the go response times in an ascending order and identifies the reaction time at which the probability of responding equals the probability of successfully stopping on a stop-signal trial. This reaction time is then subtracted from the mean SSD to estimate SSRTi, which tends to slightly underestimate SSRT.

Even though the integration method provides more reliable estimation, simulations revealed that both estimation methods are prone to deviation of p(respond|signal) from 50%, violation of the independence assumption or a high go omission rate (Band et al., 2003). Ideally, p(respond|signal) should be sustained at 50% using adaptive procedures to maintain the maximal competition of "go" and "stop" runners, ensuring reliable estimation by mean method. In realistic experimental settings, nonetheless, it's already desirable to hold p(respond|signal) within a range of 25%− 75% (Congdon et al., 2012). The SSRTi does not rely on an exact 50% assumption, proves to be less distorted by strategic waiting, and can replace go omissions with maximal go time to mitigate their impacts on SSRT estimation (Boehler et al., 2012; Verbruggen et al., 2013). Consequently, to warrant the eligibility of SSRT estimation, data validation should be performed as a precondition to detect substantial deviation from the intended p(respond|signal) or go omission rates exceeding study-specific cut-offs (Verbruggen et al., 2019). Note that usually the intended p(response|signal) is 50%, but other thresholds may be set given specific research questions. For example Tran and colleagues (2023) argue that 66.67% has some advantages such as reducing strategic behavior in participants. Due to the short-comings of both mainstream non-parametric methods, a Bayesian parametric approach has been developed (Matzke et al., 2013, 2017). Based on the race model and censored distributions, it provides an unbiased estimation of the entire SSRT distributions and the probability of trigger failures, especially in contexts like ADHD (Weigard et al., 2019).

In the vast parameter space of the SST paradigm, key design characteristics such as the SSD, probability of stop signal occurrence, trial number, task difficulty etc., were diversely implemented in previous work and could introduce hardly dissociable variability into the summary outcome. Since inhibitory control cannot manifest in direct behavioral readouts, it is thus crucial to follow consensus-based design criteria (Verbruggen et al., 2019) to optimize reliability of SSRT estimation and ensure validity of task-specific biomarkers derived from neuroimaging.

1.2. Neural correlates of reactive response inhibition

Dissecting the SST paradigm, researchers dissociate the reactive response inhibition process into a cascade of subprocesses such as "triggering" and "braking" in chronological order (Jana et al., 2020), which involves the functional interplay of cognitive control and motor cancellation. Accordingly, the underlying neural circuitries must recruit central nodes at multiple levels and specific information dynamics. Multimodal evidence converged during the last two decades to establish a prefrontal–basal ganglia–thalamocortical network involved in the classic SST (for a review, see Hannah and Aron, 2021). Sensory registration of stop signals would be fed forward to the command-generating prefrontal regions, particularly the right inferior frontal cortex (rIFC) and presupplementary motor area (preSMA), besides conventional hubs of executive function in right dorsolateral or middle frontal cortex (Depue et al., 2016). Stop commands then propagate via the hyperdirect pathway into the basal ganglia, mainly from subthalamic nucleus (STN) to globus pallidus (GP), the outputs of which subsequently inhibit the thalamic actuation towards action execution in the primary motor cortex (M1). Though effective connectivity analysis revealed that response inhibition involved both the indirect pathway via the striatum and the hyperdirect pathway (Jahfari et al., 2011), it is rather the proactive, goal-directed inhibition that implicates the indirect fronto–striato–pallido–thalamocortical pathway (Jahanshahi et al., 2015).

A consistent body of literature has established the pivotal roles of the rIFC and preSMA particularly in action-stopping, among other domain-general prefrontal regions (Aron et al., 2004, 2014; Verbruggen and Logan, 2008). Lesion studies and electrocorticography (ECoG) substantiated the causal relevance of the subregion rIFC pars opercularis for response inhibition (Aron et al., 2003; Swann et al., 2012), while its primacy in early stop command initiation still awaits evidence with sufficient temporal resolution. Likewise, the specificity of its role in the subprocess calls upon clarification. Furthermore, converging lines of evidence also implicated robust involvement of the preSMA in generating and forwarding the stop command (Rae et al., 2015). However, dissociating the individual chronometry, functional primacy and relative roles of rIFC and preSMA remains a conundrum (Jha et al., 2015; Swann et al., 2012).

Further downstream along the critical locus, the ventral STN seems to receive hyperdirect projections from both prefrontal nodes and displays the common electrophysiological marker of beta-bursting (Aron et al., 2016; Chen et al., 2020). When implementing the received stop command, the STN serves rather as a global "brake" than selective stopping control (Wessel et al., 2016; Wessel and Aron, 2017), which characterizes the emergency-like nature of reactive response inhibition

measured in the standard SST. Despite extant rodent data (Schmidt et al., 2013), a more fine-grained subcortical contribution, its interplay with top-down control from prefrontal regions and the behavioral relevance of its facets should be investigated in human subjects.

The final cortical region, to which the stopping command propagates, is the M1. As a classic TMS target, M1 is endowed with a neurophysiological readout for corticospinal excitability, namely the motor-evoked potential (MEP). Related characteristics including MEP amplitude and duration of the silent period, enable mechanistic investigation on when and how TMS shifts the excitation-inhibition balance on microcircuit level. As early as 150 ms following the stop signal (Raud and Huster, 2017), or 134 ms according to van den Wildenberg et al. (2010), inhibitory interneurons in M1 are recruited, as indicated by subthreshold electromyogram (EMG) activity. MEP was suppressed approximately 180 ms after the stop signal. Based on the neural dynamics, online TMS can be administered to precisely modulate execution of the stopping commands in M1.

In addition to the well-established nodes, emerging evidence also suggested a role of the anterior insula in reactive response inhibition, since activity in bilateral anterior insula was associated with both stopping efficiency and overall accuracy in SST (Boehler et al., 2010; Swick et al., 2011). Right anterior insula activation was dissociable from an artefact stemming from smoothed rIFG activity and was rather coupled with salience detection (Cai et al., 2014).

To add to conventional methods and address the aforementioned research gaps involving relative chronometry of central nodes or causal verification of subprocess-specific neural dynamics, transcranial magnetic stimulation (TMS) could be applied to probe the reactive response inhibition network.

1.3. TMS as investigational tool with a vast parameter space

TMS is a non-invasive brain stimulation (NIBS) technique. Transcending the correlational nature of neurophysiological recordings and complementing the temporal resolution of BOLD signals, NIBS holds promise to causally verify the putative roles of key regions at high temporal resolution, or to induce “neuro-enhancement” in recruited circuitries. Previous meta-analyses underpinned the plausibility of NIBS as investigational or therapeutic tool for reactive response inhibition. For instance, excitatory NIBS over prefrontal regions could specifically modulate inhibitory control among other executive functioning domains (de Boer et al., 2021; Friehs et al., 2021). Furthermore, both excitatory and inhibitory TMS protocols could induce a small but significant positive effect on inhibition of motor impulsivity, as manifested in SST (Yang et al., 2018).

1.3.1. Timing

To exert impacts on SSRT, TMS can either be continuously administered before the task blocks or interleaved between trials, applying “offline” or “online” approaches, respectively. In terms of mechanisms, offline TMS induces relatively durable modulation of cortical excitability via plasticity, whereas online pulses elicit transient stimulation effects and modify short-term information processing (Bergmann et al., 2016). Both methods are endowed with different advantages. The sensory ancillary effects of offline procedures do not interfere with task execution directly. In contrast, online TMS is less perplexed with compensation or network propagation and can dissociate the contribution and chronometry of individual regions with high resolution (Hartwigsen, 2018; Rossini et al., 2015). Additionally, both procedures can be combined as a “condition-and-perturb” approach to probe functional primacy and specificity among multiple regions.

1.3.2. Control conditions

Notwithstanding the versatility and potentials of TMS in principle, the complex chain of causality is laden with confounds (Bergmann and Hartwigsen, 2021). To better justify causal claims, stringent design of control conditions is paramount. Usage of sham coils is prevalent, though it might be confined to blinding TMS-naive participants. Stimulating control sites should be more effective in blinding participants throughout repeated measurements, and control better for somato-sensory side effects of active stimulation. Moreover, control sites provide more informative hints on functional specificity of targeted regions. Combining both sham and active control sites thus establish optimal grounds for drawing causal inference.

Besides timing and control conditions, rigorous interpretation of TMS effects necessitates clarifying major sources of variability such as stimulation protocols, targeting methods and dosing approaches (Caulfield and Brown, 2022). Target regions and frequencies serve as overarching foci for both online and offline protocols, exerting complex impacts on stimulation exposures and directionalities of cognitive effects (Miniussi et al., 2010; Schwarzkopf et al., 2011). Specifically, online protocols focus on precise time windows or whether the pulses are delivered at fixed intervals post-stimulus or locked to individual estimated responses. In contrast, diverse patterns and frequencies in offline protocols result in vastly different conditioning time and distinct levels of perceived discomfort (Bergmann and Hartwigsen, 2021).

1.3.3. Targeting

Targeting methods can be cost-effective if the 10–20 electroencephalography (EEG) cap is adopted or targets are defined relative to motor hotspots. Nevertheless, NIBS effects are generally susceptible to inter-individual variability in skull thickness, cortex-to-skull distance, and organization of the cortex, especially across clinical populations (Bijsterbosch et al., 2018; López-Alonso et al., 2014). Utilizing neuronavigation technology to co-register structural MR scans and the subject heads in real space helps investigators place the coil precisely in line with individual neuroanatomy and provides real-time feedback to keep it on-target despite movement. Therefore, it is crucial for TMS to employ neuronavigation instead of the cap/scalp targeting with remarkable inter-operator differences (Caulfield et al., 2022). Ideally, additional functional localizers should be applied during tasks of interest to extract regions with peak task-specific activation for individual subjects. Multimodal evidence and simulations bore out functional accuracy of fMRI-guided, individualized neuronavigation, which also yielded the strongest behavioral effects compared to conventional methods (Sack et al., 2009).

1.3.4. Dosing

Analogously, the subject responsiveness to TMS pulses could vary with individual neuroanatomy or intrinsic brain states. To calibrate the actual stimulation intensity, motor thresholding methods are employed, accounting for inter-individual variability in corticospinal excitability and sometimes in the coil-to-cortex distance (Stokes et al., 2005). The minimum stimulation intensity necessary to prompt effective neuronal depolarization in M1 is titrated by eliciting motor-evoked potentials (MEPs), and then serves as a proxy for other brain regions. However, practitioners questioning the generalizability of M1 thresholds onto higher order cognitive areas might stick to dosing at a fixed proportion of maximal stimulator output (Boroojerdi et al., 2002). More recent work emphasizes the potential of a priori electrical field modeling of the induced current flow in the target area to improve targeting and dosing outside the primary motor cortex (Numssen et al., 2023; Numssen et al., 2023).

Even if the cause-effect link between TMS and subsequent behavioral changes is established at high temporal resolution, claims on underlying mechanisms still entail auxiliary proof from concurrent neuroimaging. By correlating TMS-induced neural activity with behavioral measures, reverse inference can be drawn for task relevance of manifested network engagement or perturbed integrity of target regions. Therefore, it is strongly recommended to combine TMS with neuroimaging.

This systematic review aims to provide an overview of the heterogeneous parameter space of SST and TMS implementations, highlight

under-recognized bias and deliver consensus-based recommendations to improve the validity and replicability of future work. Additionally, the concomitant results from neuroimaging measures were synthesized to shed light on the neural mechanisms underlying TMS effects on SST performance.

2. Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Rethlefsen et al., 2021). Search for relevant articles, selection of eligible studies, data extraction and synthesis were conducted.

2.1. Literature search

To exhaustively identify English articles investigating the effects of TMS on SST performance, a comprehensive literature search was conducted in the peer-reviewed databases PubMed, Web of Science, and Scopus. The primary source search was initially run on 5th October 2022 and then rerun in August 2023 to account for publications emerging after the initial cut-off date. The search strategy combined TMS-specific keywords including "TMS", "transcranial magnetic stimulation", "rTMS", "repetitive magnetic stimulation", "cTBS", "theta burst" with terms related to the behavioral task, namely "stop-signal task" "stop signal task" "inhibitory control" "response inhibition". While defining search terms, the authors opted rather for sensitivity than for specificity.

2.2. Study selection

After removal of duplicates, the 4948 identified articles remained for manual screening. Titles and abstracts should align with the preliminary inclusion criteria for experimental studies applying both TMS and SST to healthy adults, as listed in Fig. 1. The filtered studies went through full-text assessment by independent raters. The eligibility of studies was only finalized if TMS was utilized as experimental manipulation rather than mere measurement tool of intracortical inhibition, and its impact on SST performance could be ascertained. For eligible studies, backward citation search was carried out to detect omissions in primary search.

2.3. Data extraction and synthesis

For each included study, two reviewers independently extracted data according to a predefined coding scheme, encompassing authors, year of publication, sample size, study design, TMS parameters, SST outcome measures, and concomitant neurophysiological findings. Methodological quality was assessed with respect to eight Risk of Bias domains proposed by Cochrane guidelines (Higgins et al., 2011). Disagreements on coding were resolved through discussion with a third reviewer.

The 30 studies were divided into 36 subordinate experiments with mostly, if not completely, independent samples. Codings were listed for each sub-experiment and partially synthesized in graphics.

3. Results

Extracted data on selected dimensions were enumerated in Table 1. The following sections provides a synthesis of study designs, TMS protocols and effects, SST parameters and risk of bias assessment for the 36 experiments, respectively. TMS effects on SST performance and concomitant neuroimaging results were scrutinized for qualitative insights to inform future studies.

3.1. Sample size and study design

Sample sizes were compiled separately for each sub-experiment, ranging from 8 to 33. All included studies except for one employed a within-subject design. Only McNeill et al. (2022) recruited 80 participants and assigned 20 to each TMS condition. For better comparability and an overview of distribution, the solitary data point was integrated

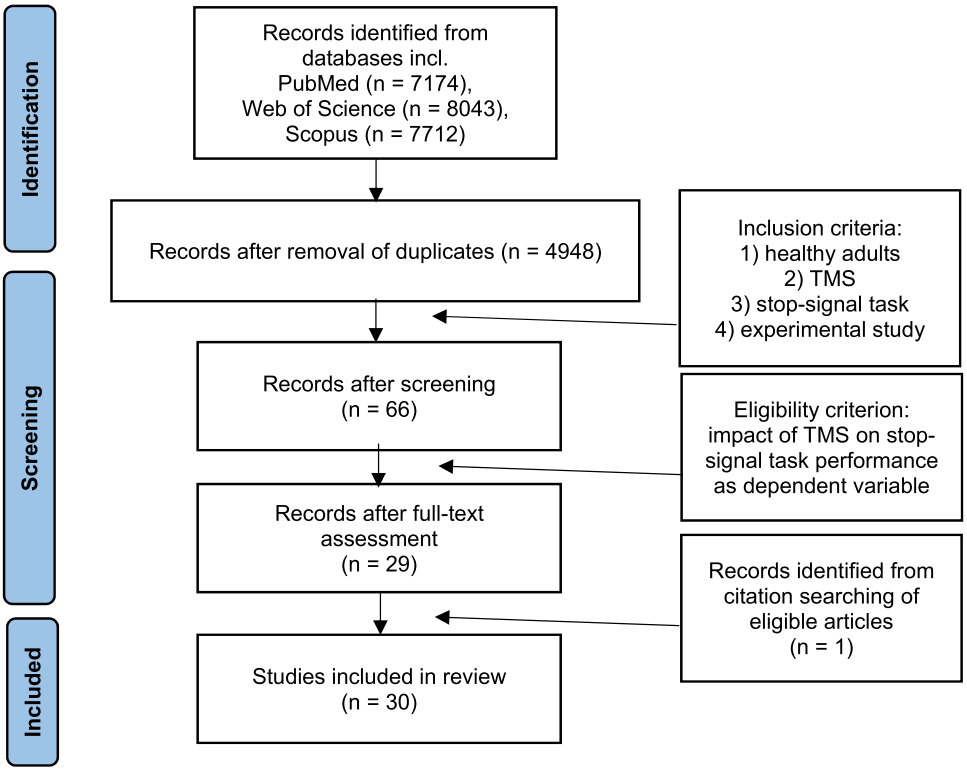

Fig. 1. PRISMA flow chart. The initial cut-off date for the publication of studies was October 2022 and search was rerun in August 2023 to account for newly emerging publications.

Table 1
N: size of the analyzed sample adhering to each TMS condition. n.r., not reported.

			TMS					Stop-Signal Task					
Author, Date	N	areas (effect)	procedures		dosing	targeting	control condition	SST variant	SS modality	response modality	trials (SS%)	SSD	SSRT method
Allen et al. (2018)	18	r. IFC->preSMA (–), preSMA->r. IFC (–)	online	pp	110%	MEG	sham	classic	visual	unimanual	960 (33%)	staircase	QC + integration
Cai et al. (2012)	Exp1:16	r. preSMA (–)	online	40 Hz dp	110%	MRI	control site; noTMS	conditional	visual	unimanual	192 * (33%)	staircase	mean
	Exp2:16	r. preSMA (–)	online	40 Hz dp	96%	MRI	control site; noTMS	conditional	visual	bimanual	720 (33%)	staircase	mean
Cardellicchio et al. (2021)	15	l. PMd (+)	offline	cTBS	80%AMT	hotspot	control site	additional	auditory	bimanual	312 (33%)	staircase	integration
Chambers et al. (2007)	16	r. IFG (-), l. IFG (0), r. PMd (0), l. PMd (0)	offline	1 Hz	92%	MRI	sham	additional	visual	bimanual	432 (25%)	fixed	mean
Chambers et al. (2006)	16	r. IFG (-), r. MFG (0), r. AG (0)	offline	1 Hz	92%	MRI	sham	classic	visual	bimanual	256 (25%)	fixed	mean
Chen et al. (2009)	9	l. preSMA (–)	online	10 Hz dp	fixed	MRI	control site; noTMS	classic	visual	bimanual	960 (25%)	fixed	integration
Dambacher et al. (2014)	8	r. AI (0), r. SFG (0), r. MFG (0), r. preSMA (0)	offline	cTBS	100% AMT	fMRI	sham; control site	simple	visual	unimanual	320 (25%)	staircase	QC + median
Dippel and Beste (2015)	18	r. IFG (0)	offline	iTBS/ cTBS	70%	MRI	sham	additional	visual	unimanual*	864 (33%)	staircase	n.r.
Friehs et al. (2023)	23	r. dlPFC (0), r. IFG (0)	offline	1 Hz	110%	MRI	sham; control site	classic	auditory	manual	450 (25%)	staircase	QC + integration
Hannah et al. (2020)	20	r. IFC (0)	online	sp	120%	fMRI	sham	classic	visual	unimanual	576 (25%)	staircase	integration
Hiwaki et al. (2011)	n.r.	M1 (no SSRT due to non-dual reponse)	online	sp	fixed	hotspot	noTMS	simple	visual	finger-reaching	n.r.	fixed	not allowed
Ji et al. (2019)	Exp1:20	r. preSMA (++iTBS/ 0 5 Hz/0 25 Hz)	offline	5/25 Hz /iTBS	110% (5/ 25 Hz) 70% (iTBS)	MRI	sham	classic	visual	bimanual	200 (25%)	staircase	mean
	Exp2:18	r. preSMA (0)	offline	iTBS	70%	MRI	sham	classic	visual	bimanual	200 (25%)	staircase	mean
Kohl et al. (2019)	25	preSMA+ 10->r. IFC (-), r. IFC+ 4->preSMA (+), preSMA+ 4->r. IFC (0), r. IFC+ 10->preSMA (0)	offline	pp	120%	MRI	no control	classic	auditory	bimanual	n.r.	staircase	median
Lee et al. (2016)	24	r. preSMA (0), r. IFG (0)	offline	cTBS	fixed	MRI	sham	conditional	visual	bimanual	300 (20%)	staircase	QC + mean
Lowe et al. (2014)	21	l. dlPFC (no SSRT due to single, fixed SSD)	offline	cTBS	80%	10-20	sham	classic	auditory	n.r.	96 (25%)	fixed	not allowed
McNeill et al. (2018)	20	r. dlPFC (–)	offline	cTBS	80%	10-20	control site	classic	auditory	manual	192 (25%)	staircase	integration
McNeill et al. (2022)	80	r. dlPFC (–), l. dlPFC (–), mOFC (0), vertex (0)	offline	cTBS	80%	10-20	no control	classic	auditory	manual	192 (25%)	staircase	integration
Muggleton et al. (2010)	Exp1:9	r. FEF (–)	online	10 Hz dp	fixed	MRI	control site; noTMS	classic	visual	bimanual	960 (25%)	fixed	integration
	Exp2:9	r. FEF (–)	online	10 Hz dp	fixed	MRI	noTMS	classic	visual	bimanual	960 (25%)	fixed	integration
Obeso, Robles et al. (2013)	16	r. IFG (++cTBS|no sp) r. preSMA (–sp|sham cTBS)	both	cTBS & sp	80%AMT (cTBS) fixed (sp)	MRI	control site	additional	visual	unimanual	432 * (17%)	staircase	integration
Obeso, Cho et al. (2013)	Exp1:16	r. preSMA (+)	offline	cTBS	80%AMT	MRI	sham	classic	visual	unimanual (switched)	384 (25%)	staircase	mean
	Exp2:8	r. preSMA (+)	offline	cTBS	80%AMT	MRI	sham	classic	visual		384 (25%)	staircase	mean

(*continued on next page*)

Table 1 (*continued*)

Author, Date	N	areas (effect)	TMS					Stop-Signal Task					
			procedures		dosing	targeting	control condition	SST variant	SS modality	response modality	trials (SS%)	SSD	SSRT method
Obeso et al. (2017)	14	r. pre-SMA (++) r. IFG (0)	offline	cTBS	80%AMT	MRI	control site	conditional	visual	unimanual	192 * (25%)	staircase	mean
Osada et al. (2019)	Exp2:12	r. IPS (–)	online	sp	120%	fMRI	control site; noTMS	classic	visual	unimanual	600 (33%)	staircase	QC + integration
	Exp3:10	r. IPS (–)	online	sp	120%	fMRI	control site; noTMS	classic	visual	unimanual	600 (33%)	staircase	QC + integration
Osada et al. (2021)	20	r. IPS (–sp), r. vpIFC (–sp), r. dpIFC (–sp/–sp|cTBS), r. preSMA (–sp/++sp|cTBS)	online/ both	sp/ cTBS & sp	120% (sp) 80%AMT (cTBS)	fMRI	noTMS	classic	visual	unimanual	600 (33%)	staircase	QC + integration
Parmigiani and Cattaneo (2018)	Exp1:20	l. PMd (no SSRT due to single, fixed SSD)	online	sp	100%	MRI	sham	classic	visual	lip	120 (50%)	fixed	not allowed
	Exp2:15	l. SMA-proper (no SSRT due to single, fixed SSD)	online	sp	100%	MRI	sham	classic	visual	lip	120 (50%)	fixed	not allowed
Sundby et al. (2021)	33	r. IFG (-)	offline	1 Hz	110%	fMRI	sham	classic	visual	unimanual	320 (25%)	staircase	QC + integration
Upton et al. (2010)	14	l.&r. dlPFC (no SSRT due to single, fixed SSD)	offline	1 Hz	110%	hotspot	sham	classic	auditory	unimanual	120 (30%)	fixed	QC + not allowed
Verbruggen et al. (2010)	18	r. IFG (–), r. IFJ (–) l. preSMA (0)	offline	cTBS	70%	MRI	sham	additional	visual	unimanual *	576 * (33%)	staircase	integration
Watanabe et al. (2015)	9	preSMA (++50 Hz qp/ -–5 Hz qp)	offline	50/5 Hz qp	90% AMT	MRI	sham	classic	visual	unimanual	433 (20%)	staircase	integration
Yang, Khalifa et al. (2018)	20	r. IFG (0)	offline	10 Hz	100%	scalp	sham	classic	auditory	bimanual	320 (25%)	staircase	mean
Zandbelt et al. (2013)	24	r. IFC (++), r. SMC (++)	offline	6 & 1 Hz	90% (6 Hz) 110% (1 Hz)	MRI	control site	classic	visual	unimanual	474 (13%)	staircase	QC + integration

Areas (effects): stimulated areas with respective TMS effects on SSRT. + +/–, significantly improved/impaired inhibition compared to sham or active control sites, indicated by shortened or prolonged SSRT; + /-, conditional (e.g. only interaction effects with irrelevant subgroup variables such as age, involved hand etc.) improvement/impairment; 0, no effect. r., right; l., left; (vp/dp)IFC/IFG/IFJ, (ventral posterior/dorsal posterior) inferior frontal cortex/gyrus/junction; preSMA, presupplementary motor area; PMd, dorsal premotor cortex; MFG, middle frontal gyrus; AG, angular gyrus; AI, anterior insula; SFG, superior frontal gyrus; dlPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; mOFC, medial orbitofrontal cortex; FEF, frontal eye field; IPS, intraparietal sulcus; SMA-proper, supplementary motor area proper; SMC, supplementary motor complex.

Procedures: sp, simple pulse; dp, dual-pulse; pp, paired-pulse; cTBS/iTBS, continuous/intermittent Theta Burst Stimulation; qp, quadri-pulse.

Dosing: TMS intensity related to resting motor threshold by default; AMT, active motor threshold; fixed, fixed amplitude dosing related to maximal output of the employed stimulator.

Targeting: fMRI/MEG, additional functional localization in conjunction to MRI.

SST variant: conditional, stop only if pre-cue indicates a critical condition; additional, stop followed by additional action such as hand switch.

SS modality: modality of stop signal presentation.

Trials (SS%): SST trials per session with stop probability. *Uncritical trials that did not engage reactive inhibition were excluded.

SSRT method: QC, data quality check regarding horse-race model prior to SSRT estimation; estimation of SSRT based on mean/median or integration method

into "analyzed sample size per condition" (mean = 17.1, SD = 5.4), as depicted in Fig. 2A. The bimodal, right-skewed distribution indicates diverging scales of samples and an overall tendency towards insufficient statistical power.

Considering the vitality of control conditions for TMS studies, the present review dissected the control comparators among other design features. The observed control conditions were sorted by methodological stringency along the horizontal axis in Fig. 2B. Only a minority of studies left out persuasive control conditions or utilized noTMS trials for comparison. Usage of a sham coil was the most widespread approach. Despite its potential of further disambiguation, active stimulation of irrelevant scalp sites, such as vertex, was less commonly utilized. The optimal implementation of both sham and control site combined remained a rarity.

3.2. TMS parameters and effects

Differences in TMS parameters are summarized in Fig. 3, encompassing heterogeneous timing, targeting and dosing parameters. Figs. 4 and 5 synthesize the inconsistent TMS effects on reactive response inhibition, highlighting key regions and specific protocol as sources of variability.

3.2.1. Timing of administration

As displayed in Table 1, about two-thirds of experiments employed offline procedures, and the other one third utilized online TMS or a combination of both. Forty-four different protocols were identified in terms of stimulation frequency and patterns. Among the 29 offline protocols, continuous theta burst stimulation (cTBS) accounted for almost one half, and the "classic" 1-Hz repetitive TMS (rTMS) accounted for one fifth. The majority of online TMS studies delivered one single pulse in a stimulus-locked or response-locked manner, and one third of the protocols applied two subsequent pulses per trial to the same target, while the other two protocols administered two contingent pulses to the paired target regions, probing potential directions of information flows.

3.2.2. Targeting method

More than half of the studies acquired anatomical MR scans in a pre-session to allow for frameless stereotactic optical tracking neuronavigation during the TMS sessions. Canonical softwares could register T1-weighted structural images to the subjects' heads in real space, encompassing Brainsight (Rogue Research Inc., Montreal, Canada), Localite (Sankt Augustin, Germany) and BrainVoyager (Brain Innovation, Maastricht, The Netherlands). One noteworthy exception was observed in the work by Chambers et al., (2006, 2007) and Verbruggen et al. (2010), where a less common magnetic tracking device named miniBird 500 (Ascension Tech, Burlington, USA) was applied in conjunction with the coregistration software MRIReg to define scalp locations of targets. As illustrated in Fig. 4B.C, the resulting coordinates seemed ostensibly out of the bounds of the template when displayed in MNI space.

To optimize the relevance of targets, one fifth of studies additionally integrated fMRI or magnetoencephalography (MEG) findings during SST in the pre-session without TMS as functional localizers, extracting peak voxels for task-specific activation to individualize TMS target sites. In contrast, more cost-effective targeting methods were employed by the other one fifth of studies. Targets were either defined topologically relative to motor hotspots, which merged procedures of determining TMS dosing and localization into one step, or simply adopted from the conventional 10–20 EEG system regardless of individual neuroanatomy.

3.2.3. Dosing approach

Two-thirds of TMS intensities were dosed in proportion to the individual resting motor threshold (RMT). One fifth of dosing relied on active motor thresholds (AMT), and seven out of eight experiments applying AMT were dosing cTBS, following the recommendations of

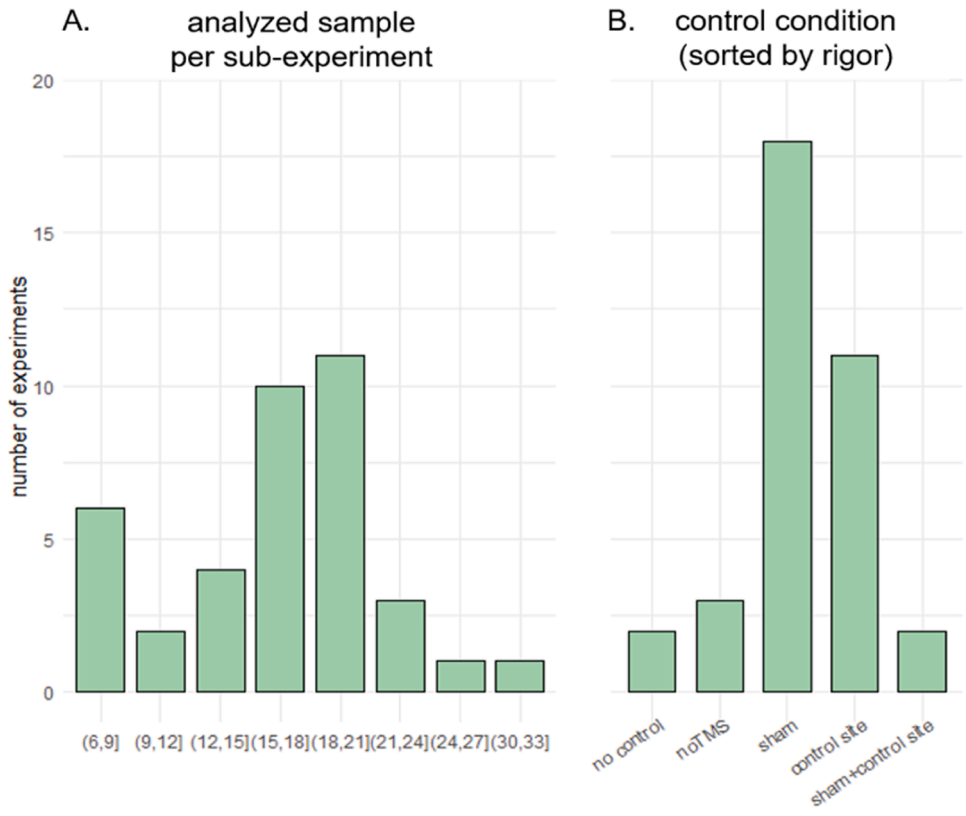

Fig. 2. Distributions are displayed for sub-experiments with independent samples. (A) histogram of analyzed sample size per condition, (B) control conditions sorted by methodological rigor.

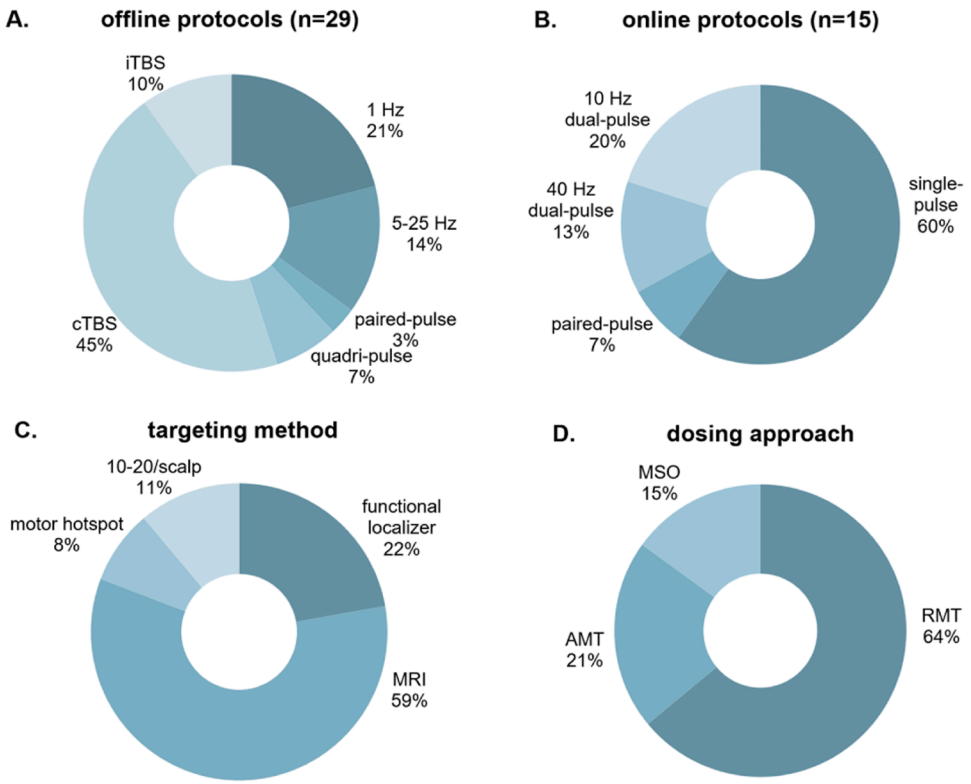

Fig. 3. (A.B) Stimulation frequency and pulses per train of offline & online TMS protocols. (C) Targeting methods. Functional localizers include fMRI and MEG; 10–20 refers to EEG cap targeting. (D) Dosing approaches. RMT, resting motor threshold; AMT, active motor threshold; MSO, maximal stimulator output.

Huang et al. (2009) to avoid that the aftereffects of TBS could be confounded by muscle contraction. The rest of the experiments set stimulation intensity at a fixed percent of maximal stimulator output without adjusting for inter-individual variability in responsiveness to TMS.

3.2.4. *Stimulation target*

As illustrated in Fig. 4A, approximately 90% of the targets pertain to the frontal lobe, exhibiting dual foci on both rIFC and dorsomedial frontal areas encompassing the preSMA. The distribution of target regions largely conformed to the posited underpinning network for motor inhibitory control (Aron et al., 2014; Hannah and Aron, 2021; Verbruggen and Logan, 2008), with nascent exploration of emerging subcortical, temporal or parietal key regions.

Fig. 4B and C highlight inconsistencies in actual stimulation locations under the same term for intended targets by projecting reported coordinates for rIFC and preSMA into MNI space. On-target clusters could be observed owing to protocol allegiance to own preceding studies and collaborators. Still, outliers such as the rIFG target from Obeso, Robles et al. (2013) clearly land in middle frontal gyrus of the template.

3.2.5. *Effects on behavioral and neural measures*

TMS effects on response inhibition indicated by SSRT are color-coded in Fig. 4B and C, which display various combinations of evidence strength and effect directionality. “Improved/Impaired STOP” refers to significant effects of shortening or prolonging SSRT compared to sham or active control conditions, while mere interaction effects in relation to additional subgroup variables such as age or the involved hand are termed “conditional improvement/impairment”. Overall, TMS over the preSMA induced more pronounced effects in the behavioral measure compared to TMS over rIFC. Among the scattered rIFC targets, perturbing the ventral pars opercularis of rIFG tended to impair SST performance more significantly.

Besides stimulation targets, a multitude of other factors in the vast space of TMS parameters could account for the effect variability. After holistic appraisal of unbalanced stratum sizes within each factor and its informative potential, we chose to parse effect directionality with respect to online/offline procedures. Sixty-two different TMS protocols in terms of procedures and targets were dissociated and the directionality of accordant effects was compiled in Fig. 5. The online procedures consistently perturbed inhibitory control, since the only facilitating effect stemmed from combined offline and online stimulation. In contrast, mixed effects were observed for offline protocols, and the number of offline protocols inducing non-differential effects in experimental and sham groups was remarkable despite the larger base number. Scrutinizing the effects on both pivotal nodes, we found delicate bifurcation of directionality. Offline stimulation of the preSMA resulted rather in improvement in reactive stopping, while rIFC protocols did not display any clear tendency. Only a few studies clearly predefined putative directions of applied protocols to allow knowledge update (Ji et al., 2019; Watanabe et al., 2015; Yang, Khalifa et al., 2018). To promote cumulative science, we also incorporated effect size measure. Since most studies neither reported effect size nor specific group means and standard deviations, we could only utilize the commonly available t-values and sample sizes to calculate standardized mean differences (Cohen’s d_z:Lakens, 2013). Cohen’s d_z allows cross-study comparisons among within-subject designs, which aligns well with our review. Due to the heterogeneity of protocols, we refrain from conducting a meta-analysis with the effect sizes and display their distribution in specific target and protocol combinations in Fig. 5 instead.

Adding to behavioral effects, concomitant neuroimaging provided pivotal junctures to putative mechanisms. Specificity of all offline TMS effects was substantiated by virtue of pre-post imaging contrasts, since none of the neuro-recordings were applied concurrently during online TMS despite their diverse modalities. EEG evidence revealed that in contrast with sham, offline TMS precisely administered on rIFG pars opercularis could disrupt early beta-bursting, the posited functional marker of action stopping, and had no impact on the sensorimotor mu/

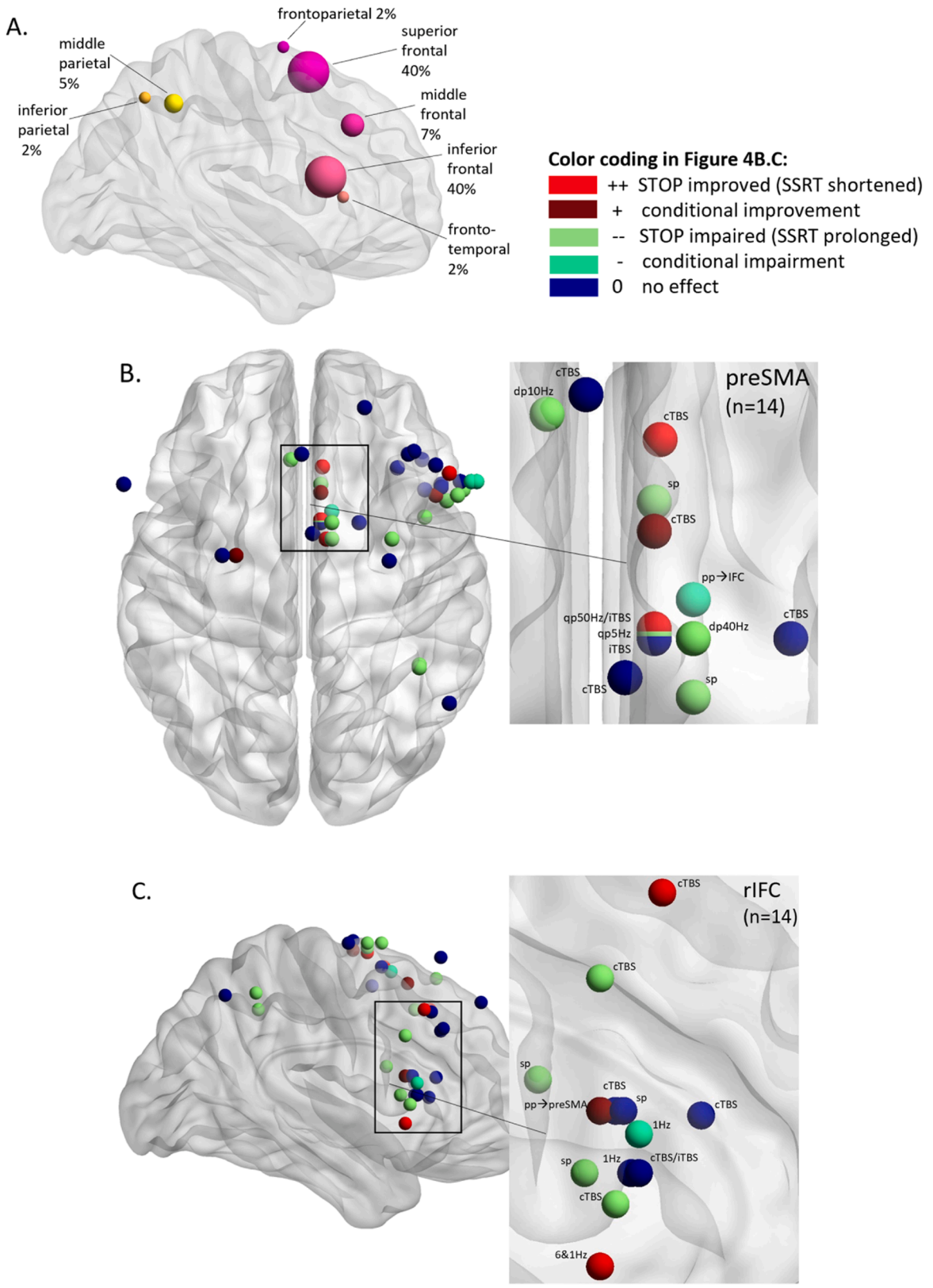

Fig. 4. (A) Distribution of stimulation targets (globe centers stemming from mean MNI coordinates projected onto the right hemisphere). (B.C) Color-coded TMS effects on SST performance, stimulation procedures specified, zoomed in for the most frequent targets–preSMA and rIFC (right IFG, IFJ, vpIFC, dpIFC summarized into rIFC for overview). Red or Green globes, corresponding to + + or – in Table 1, code improved or impaired inhibition compared to control conditions, indicated by shortened or prolonged SSRT, respectively. Burgundy or Cyan, corresponding to + or - in Table 1, code mere interaction effects in relation to specific subgroup variables like age or involved hand. Navy corresponds to 0 in Table 1, coding absence of significant TMS effects.

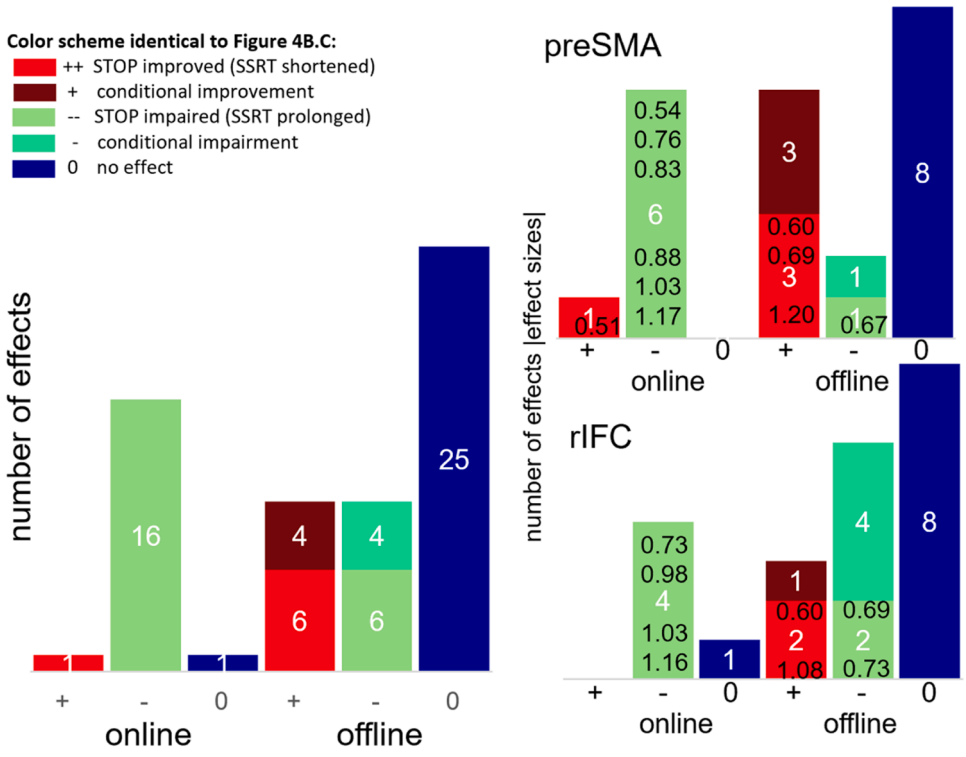

Fig. 5. Effect directionality of each dissociated protocol with distinct stimulating procedures and areas. For simplicity, the only offline-online combination was included in the "online" category. Paired-pulse protocols involving both preSMA and rIFC were assigned to the initial target respectively. Color coding follows the same scheme as in Fig. 4. For significant main effects, we calculated effect sizes (Cohen's d_z) and incorporated their absolute values into each cell.

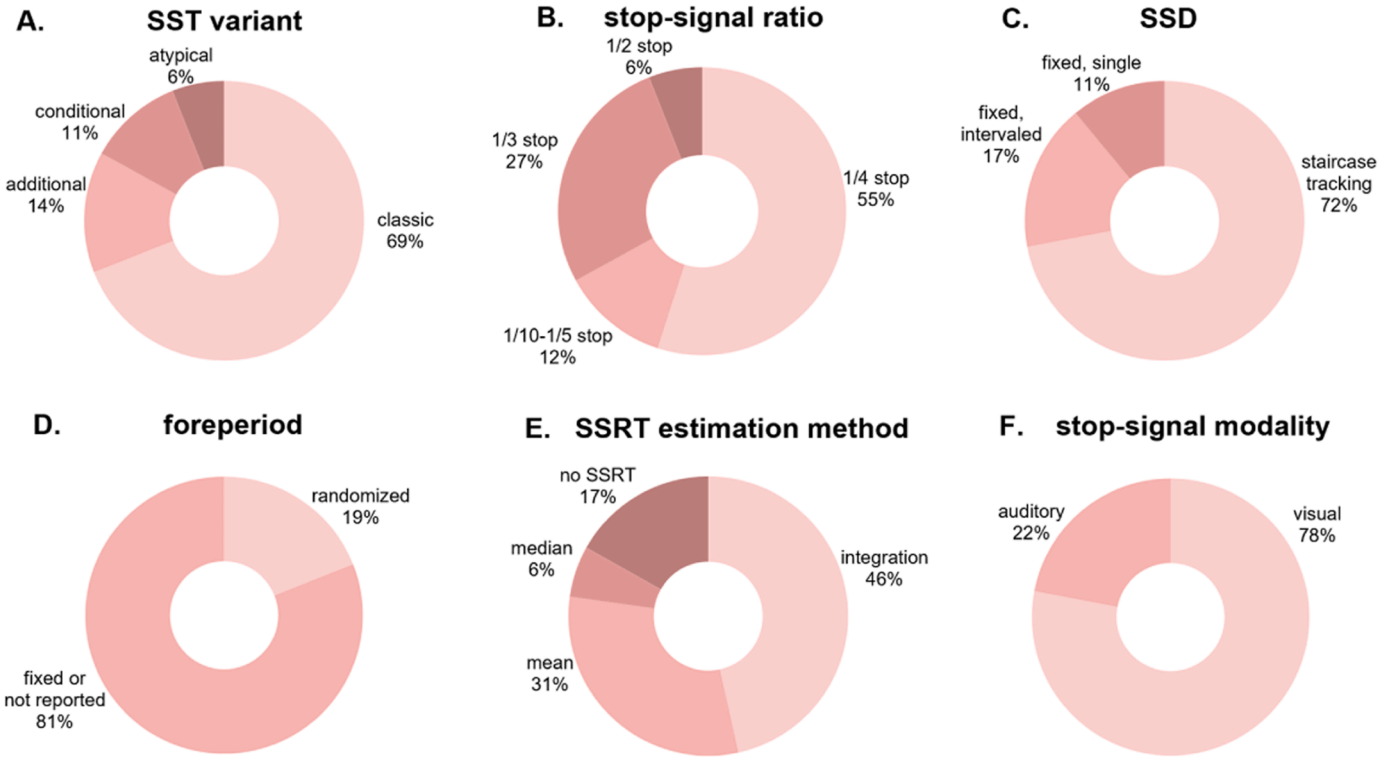

Fig. 6. Key features in SST design, recommended design displayed as the faintest color in A-E. (A) SST variants: conditional, stop only if pre-cue indicates a critical condition; additional, stop followed by additional action such as hand switch. (B) probability of presentation of stop-signals (C) Stop-signal delay (D) fixation period, (E) SSRT estimation method, (F) modality of presentation of stop-signals.

beta accompanying Go process (Hannah et al., 2020; Sundby et al., 2021). Apart from beta band oscillations, ERP components have been associated with response inhibition as well. TBS on rIFG bidirectionally modulated the P3 and the associated strategy selection in a multi-component paradigm, without affecting perceptual selection represented in P1 and N1 (Dippel and Beste, 2015). In contrast, N2 and P3 during SST with fixed SSD were not affected by TMS on dlPFC (Upton et al., 2010). Besides the focus on rIFG, contribution of other nodes in the circuitries related to response inhibition as well as network effects of TMS have been depicted by task or resting-state fMRI (Watanabe et al., 2015). TMS over the preSMA could alter task-specific BOLD-signals in the STN and GP and modulate functional connectivity between preSMA and the subcortical areas. Combining TMS with fMRI could determine the possible direction of information flow between critical regions, indicating functional primacy of rIFG over SMC (Zandbelt et al., 2013). In contrast, primary outcome measures from MEG implicated parallel, simultaneous activation of preSMA and IFC (Allen et al., 2018).

3.3. SST parameters

Fig. 6 delineates the heterogenous implementations of key features of SST protocols. To highlight how well the designs of extant studies aligned with consensus-based recommendations (Verbruggen et al., 2019), the representation of methodologically superior alternatives along each dimension was unified as the lightest color.

3.3.1. SST variant & involved modality

Two thirds of experiments conformed to the classic SST paradigm, implementing a standard two-choice reaction time task. Despite the ubiquity of highly controlled, minimalist visualization across laboratories, new attempt was made to apply a validated gamified version of the classic task (Friehs et al., 2023), which could be advantageous to maintaining the attention of subjects and enhance ecological validity. Multi-component SST variants were utilized by one fourth of experiments, either demanding additional action switching after stopping or further specifying conditions for valid stop signals. Other than the categorized variants, a few studies applied atypical task formats. Dambacher et al. (2014) employed a simple reaction task with risk of assumption violation for SSRT estimation, since trivial task requirements and short SSD caused interference between perception of go and stop signals. Instead of discrete button presses, Hiwaki et al. (2011) recorded the terminal finger positions as outcomes of a naturalistic finger-reaching task. The kinematics-based readout of every single trial might allow conclusions with better applicability to real-world movement inhibition while somewhat perplexing the SSRT approximation.

As exhibited in Fig. 6F, more than three fourths of the implemented tasks employed same presentation modality for stop signals as the go stimuli. A minority of studies delivered auditory stop signals.

3.3.2. Stop-signal ratio

Following recommendations of Verbruggen et al. (2019), more than half of experiments set the probability of stop signal occurrence at 25%. A higher ratio of 33% was adopted by one fourth of experiments, which still presented stop signal on a minority of trials. In contrast, stop signals would appear every other trial in three studies, encouraging strategic response slowing in participants. The rest of the studies required stop on merely 10–20% trials, which might result in insufficient stop trials for behavioral modeling.

3.3.3. Stop-signal delay

The majority of studies applied staircase tracking procedures to adapt SSD to performance levels from trial to trial in a dynamic fashion, titrating the task difficulty to individual levels. Taking one-up one-down tracking procedure as example: every successful inhibition prolongs the SSD by 50 ms, handicapping the next stop signal trial, while every commission error results decrease of SSD by 50 ms, ensuring maximum competition between response and inhibition processes according to the horse-race model (Logan et al., 1984). One sixth of experiments applied variable fixed SSD intervals for each SST block, which could also enable SSRT calculation, but with lower efficiency and more trials. The rest few studies applied a single, fixed SSD, which renders the SSRT estimation less sensitive, even when individually adjusted in a pre-session (Lowe et al., 2014; Parmigiani and Cattaneo, 2018).

3.3.4. Foreperiod

Merely one fifth of experiments have randomly jittered duration of the foreperiods between onsets of the fixation cross and the go signal, whereas the majority settled with invariable fixation periods or employed variable inter-trial intervals as an alternative that, however, could not discourage anticipatory response or ensure the validity of SST.

3.3.5. SSRT estimation and data validation

Almost half of the experiments estimated SSRT with the recommended integration method, while one third relied on central tendency measures of Go reaction time for convenient calculation of SSRT. Noteworthy, one sixth of the studies were not able to estimate SSRT due to deficiency in study designs. No study implemented parametric estimation methods yet for more comprehensive measures and higher reliability. As displayed in Table 1, less than one third of studies checked the quality of data regarding assumption validity of the horse-race model, before applying them to SSRT estimation.

3.4. Risk of bias assessment

Risk of bias varied across domains proposed by Cochrane guidelines (Higgins et al., 2011), as suggested by Fig. 7 & Table S1. Most studies used cross-over design, reporting counter-balanced orders of TMS conditions and randomized subject assignment. Allocation concealment till the moment of assignment, however, was not explicitly reported, leaving it unclear whether unblinded investigators manipulated allocation and undermined the random sequence later. While blinding of personnel received limited attention due to infeasibility and merely one study reported double-blind design (Sundby et al., 2021), blinding participants was stressed in most studies by virtue of sham coils or stimulation over control sites. Despite various attempts, sham TMS might not achieve comparable auditory and tactile effects as active TMS, and thus blinding success was evaluated with supplementary questionnaires on perceived discomfort and naivety of treatment, or through comparisons between subgroups with reversed treatment order. Only a few studies utilized intermixed noTMS trials as comparators, or even noTMS sessions. Moreover, blinding of outcome assessors was largely ignored despite its cost effectiveness in avoiding investigator bias.

The majority of studies reported outcome data with sufficient details and comprehensive analysis proposed by the consensus guide (Verbruggen et al., 2019), whereas a few older studies left out critical aspects of the horse-race model. However, for drop-outs due to intolerable discomfort of TMS effects, all involved studies simply excluded these subjects deviating from completion of protocols and did not carry out or report an intent-to-treat analysis. Nevertheless, high attrition rate could indicate comparatively intensive side effects of certain protocols that might impinge on task performance and confound the neuromodulation effects.

4. Discussion

This systematic review evaluated extant work addressing modulatory effects of TMS on SST performance and revealed the heterogeneity in methodology as well as inconsistencies in observations of the included studies. The scrutinized parameter selection in SST and TMS exhibited considerable scope for optimization. In addition to behavioral measures, concomitant neuroimaging extended the current understanding into underlying prefrontal-basal ganglia-thalamocortical network dynamics.

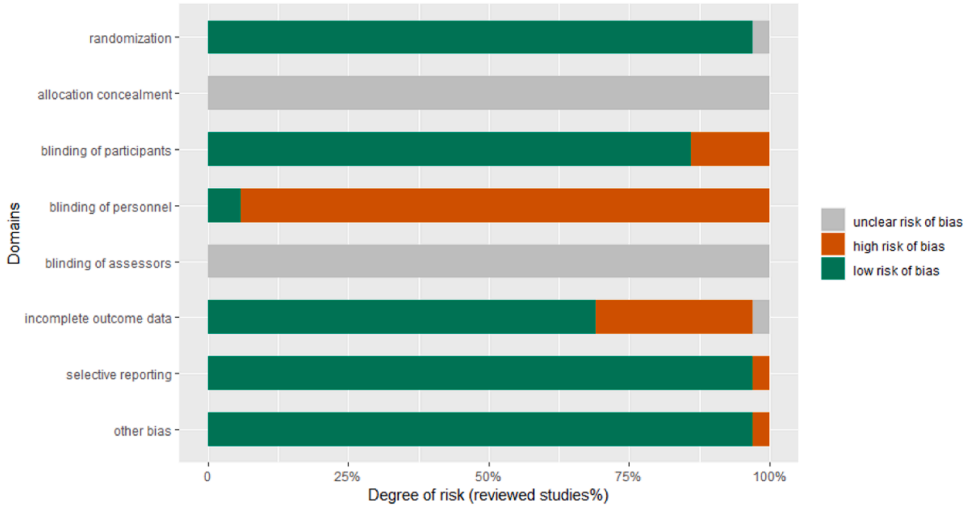

Fig. 7. Risk of bias in domains proposed by Cochrane guidelines (Higgins et al., 2011), assessed across all sub-experiments. The original assessment table was attached in appendix as Table S1.

The following discussion sections further dissect the attained insights and synthesize recommendations to facilitate future research.

4.1. risk of bias in study design and sample

The sample sizes of studies included in the current review were small-to-modest considering the overall small effect sizes of TMS treatment (e.g. Beynel et al., 2019), displaying risk of scant statistical power. The remarkable number of null effects might be attributed to the underpowered combination of study design and performed tests, which tend to yield uninformative results (Button et al., 2013). Applying pre-registered directional hypotheses instead of two-tailed t-tests might improve the sensitivity to detect intended effects of interest. Among the 30 reviewed papers, only one sixth have pre-registered their studies (Allen et al., 2018; Friehs et al., 2023; Hannah et al., 2020; McNeill et al., 2022; Sundby et al., 2021). These studies have reported pre-registered and explorative analyses separately, which effectively averts p-hacking suspicions. However, a priori specification of the study intent is not trivial. Without converging prior knowledge, ambiguity due to stochastic resonance, potential compensation mechanisms or network effects hampers deriving the directionality of primary neuromodulation (Hartwigsen, 2018; Luber and Lisanby, 2014; Schwarzkopf et al., 2011), even from robustly manifested behavioral changes (Miniussi et al., 2010). The currently reviewed experiments also exhibited conflicting results in directionality, which could not be systematized according to the duality of frequency-dependent inhibitory-excitatory heuristics (Fitzgerald et al., 2006). Therefore, in addition to contribution to statistical power, results from pre-registered studies can explicitly update the belief about protocol directionality. For Bayesian analyses, pre-registration helps warrant the selection of specific, informed priors (see Allen et al., 2018). Future studies should pre-register informed directional hypotheses to avoid circularity bias, subserve knowledge update and enable subsequent work with adequate positive predictive value (Ioannidis, 2005).

Furthermore, to proactively prevent frequently occurring drop-outs from exacerbating the power problem, the relatively intolerable discomfort and high attrition rate of specific TMS procedures should be derived from previous studies and considered during recruitment planning (Han et al., 2019). Moreover, due to the resource intensity of proper TMS studies, within-subject design should be preferably employed for its power advantages (Charness et al., 2012).

Nevertheless, multiple exposures to treatments in within-subject design render the participant blinding more challenging due to the discernible perceptual differences. It is thus crucial to perform post-session assessment of blinding success (Giustiniani et al., 2022) or comparisons of subgroups receiving treatments in converse orders. Besides, double blinding can be achieved by using mechanical arm to perform the stimulation at optimized coil orientation on fixed subject heads, or more cost-effectively, by blinding outcome assessors. Among the included studies, these measures to minimize investigator bias were not ubiquitously reported.

Apart from blinding, the validity of causal inference in TMS studies relies on effective control conditions that should surpass mere noTMS comparators. As the prevalent method to control for ancillary sensory effects, sham TMS has been implemented with varying stringency under the same term. Thereinto, electrical skin stimulation inducing comparable somato-auditory effects was proposed as the “gold standard” for sham (Duecker and Sack, 2015). Still, sham over the target does not suffice as a control condition. To demonstrate the functional specificity of anatomical and temporal targets, active stimulation should be administered at control sites or during posited noncritical time windows, additionally.

4.2. TMS optimization

To promote reliability of the neuromodulation effects, precision and personalization have been pursued in TMS procedures to minimize intra- and inter-subject variability. In comparative studies, individual fMRI-guided neuronavigation proves to yield the strongest behavioral effects, whereas the effect sizes are suboptimal with meta-analytic targets and shrink with the 10–20 EEG cap targeting (Sack et al., 2009). Therefore, more precise targeting results in more readily detectable effects and entails smaller samples. Though most included studies applied MR-guided neuronavigation for targeting, the target coordinates were often derived from meta-analyses, among which some evidently deviated from the underlying anatomical structure. A few studies complemented MR scans with functional localizers, which robustly extracts target regions with peak task-specific activation for individual subjects. Alternatively, optimal target within the ROI can also be identified as network hub by connectivity analysis (Siddiqi et al., 2022). Both temporal and spatial targets can be explored by interleaved TMS-fMRI at high resolution (Caulfield and Brown, 2022).

The majority of studies dosed TMS at certain proportions of individual RMT to implement the wide range of absolute intensity required for comparable stimulation exposure. Note that the reviewed cTBS studies employed AMT as the canonical dosing method. Though the aftereffects of TBS over M1 were prone to interference of muscle contraction (Huang et al., 2008), it might not necessarily generalize to

higher-order cognitive functions pertinent to the current review (Boroojerdi et al., 2002; Stewart et al., 2001), and the uncontrolled variability introduced by the process of determining AMT could have been bypassed. Transcending the primary cortex thresholding with single-pulse TMS as questionable proxy, recent simulations indicate that employing a-priori e-field modeling to optimize TMS stimulus intensity outperforms conventional methods in effect consistency, since it accounts for both region-specific cytoarchitecture and subject-specific physiological factors (Numssen, Kuhnke et al., 2023; Numssen, van der Burght et al., 2023).

Targeting and dosing at high spatial or temporal resolution could enable further dissection of the functional architecture of key regions. In terms of targeting, Osada et al. (2021) parceled the ventral and dorsal posterior IFC into distinct processing streams for response inhibition, which belong to the cingulo-opercular network and fronto-parietal network, respectively. In terms of timing, online TMS can be administered in a series of time windows in response-locked or stimulus-locked fashion, and the effect of neuromodulation should depend on the specific process that has been targeted by the pulses among the temporal cascades of stopping (Jana et al., 2020). Osada et al. (2021) defined the endpoint of SSRT tracked on NoTMS trials as the null point for the the timing of single-pulse TMS and set up time windows with fixed lengths. If the pulse was given in the time window of − 90 to − 60 ms over vpIFC, transient disruption of response inhibition could be observed. The dpIFC and preSMA could both be perturbed in the subsequent time window, namely − 60 to − 30 ms. The intraparietal sulcus (IPS) was disrupted by the single-pulse TMS given in the time window of − 30 to 0 ms, replicating the previous finding (Osada et al., 2019). Simultaneous activation of IFC and preSMA was also found by Allen et al. (2018) with a different timing approach, which targets at certain proportions of individualized core period for inhibitory control. 50 ms were first stripped from both ends of SSRT to eliminate the time for sensory register and motor execution. It is noteworthy that the preceding period entailed by sensory register and semantic processing of the stopping command might vary with complexity of the rules. Adaptively, the 50 ms period might need to be extended if selective inhibition is signaled. The remaining time window was considered relevant for inhibitory control. Paired TMS pulses were given at 12.5% and 62.5% of the individual core period over IFC and preSMA and SSRT were comparably prolonged, suggesting no functional primacy between both nodes. For future studies, the time interval between the paired pulses should be determined with regards to balance between efficacy of pulses and independence of conditions.

Compared to the response-locked approaches, stimulus-locked timing is simpler and thus widely applied. Dual-pulse TMS at 10 Hz over the preSMA or the frontal eye field concurrent with and at 100 ms after the go stimulus onset also led to perturbation (Chen et al., 2009; Muggleton et al., 2010). Single-pulse TMS over preSMA at 100 ms after the go stimulus showed disruptive effects (Obeso, Robles et al., 2013). Cai et al. (2012) has compared the effectiveness of different time windows and timing approaches. Dual-pulse TMS at 40 Hz over preSMA delivered at 100/75 ms or 50/25 ms prior to the go stimulus had no significant effect on SSRT, while pulse given at 125/150 ms or at 175/200 ms after the go signal as well as after the stop signal could elongate SSRT. Effect sizes were larger when stimulated after the stop signal.

Despite the inconsistency of parameters directly or indirectly related to timing, we tentatively draw inferences about online TMS to inform future studies of the existing evidence. Pulses given before the go stimulus might lose efficacy at early stages and can hardly manifest in changes of behavioral measures. Effective time windows in the reviewed studies encompass around 100 ms after the go signal and 60–150 ms after the stop signal for single pulses over a region. For dual-pulse TMS on the same target, effects have been observed during 0–200 ms after either go or stop signals, converging with the assumed stronger disruption potential of dual pulses. Critical time windows should be target-specific and appear to be earliest for vpIFC, followed by parallel activation of preSMA and dpIFC. IPS could be perturbed as late as 0–30 ms prior to termination of normal SSRT. To systematically validate the inferred neural dynamics, concurrent TMS-fMRI studies are called upon.

The discussion revealed that most reviewed experiments preferred to probe the established prefrontal nodes of preSMA and rIFC. Exploration of emerging critical regions including the anterior insula, adjacent to IFC, and deeper structures such as STN seemed to be confined partially by technical challenges regarding TMS focality, range and precision of distal network effects. The feasibility should be assessed by a priori e-field simulation, and the behavioral relevance of protocol-specific stimulation exposure can be ascertained by correlating task performance with the post-hoc mapped effective e-field (Numssen, van der Burght et al., 2023).

A multitude of TMS protocols, repetitive or patterned, continuous or intervaled, were applied either before or during SST. Due to the diverse sources of variability in the vast TMS parameter space and their respective interactions with SST variants, direct comparisons of protocol efficacy in SSRT modulation were precluded. Still, a coarse dissection of online/offline procedures revealed certain protocol specificity in terms of effect directions. Online stimulation, either dual-pulse or single-pulse, induced consistent perturbations of response inhibition. The only facilitatory exception might be introduced by the preconditioning with offline cTBS (Osada et al., 2021). In contrast, offline effects often did not manifest in behavioral measures at all, since the number of null effects far exceeded the sum of significant effects. The several detected effects of offline procedures also appeared in inconsistent directions. Even though offline protocols could induce effects either resembling long-term potentiation or depression, the observed directions did not align with the common duality divided by frequencies and patterns (Quartarone et al., 2006). For instance, cTBS over M1 generally suppresses motor evoked potentials (MEPs), while iTBS tends to increase them (Di Lazzaro et al., 2008; Huang et al., 2005). With the robust neurophysiological evidence, cTBS and iTBS are established as canonical inhibitory and facilitatory protocols, respectively. However, their effect directionality varies with target regions and brain states when applied outside of M1. The most frequent targets covered in the current review are two higher-order, domain-general control regions, namely preSMA and right IFC. Both cTBS and iTBS over preSMA showed facilitatory effects (Ji et al., 2019; Obeso, Cho et al., 2013; Obeso et al., 2017), while cTBS over right IFC displayed bidirectional effects (Obeso, Robles et al., 2013; Verbruggen et al., 2010). The inter-study variability for the same target partially stems from the diverging MNI coordinates determined by differential localization approaches. Challenged by the paradoxical observations, a priori generalization of offline protocol directionality from M1 to non-motor areas should be treated cautiously in future study design. Moreover, relative to other subregions of right IFC, TMS over the pars opercularis is more likely to disrupt response inhibition (Chambers et al., 2006, 2007; Osada et al., 2021; Verbruggen et al., 2010). This observation converges with previous work on functional segregation of right IFG, which associated the activation of the ventral, posterior part of the right IFG with action inhibition (Hartwigsen et al., 2019). Given that higher-order regions lack direct, physiological readouts, validation through concurrent neuroimaging is desirable. Systematic research should be conducted to deepen mechanistic understandings and clarify sources of variability along the causality chain for effect directions (Bergmann and Hartwigsen, 2021). Region-specific and state-dependent insights can inform future applications in investigative or interventional contexts and promote reliability.

Apart from mixed behavioral outcomes under TMS, ancillary findings from neuroimaging accompanying SST before or after TMS could provide conclusive insights. Converging evidence from EEG corroborated the relevance of phasic beta-bursting at early stages as robust electrophysiological markers for inhibitory control (Hannah et al., 2020; Sundby et al., 2021), in line with crossmodal proofs (Castiglione et al.,

2019; Chen et al., 2020; Wessel, 2020). Moreover, the task specificity of prefrontal-basal ganglia-thalamocortical network was again substantiated by functional imaging during SST following TMS, though the intra-network dynamics remained ambiguous with contradictory findings (Allen et al., 2018; Watanabe et al., 2015; Zandbelt et al., 2013). Regrettably, no concurrent neuroimaging with interleaved online TMS was utilized yet, which holds promise to map the uncompensated network dynamics underlying reactive response inhibition and could examine the potentially accumulating modulation of online TMS pulses through split-half contrasts.

4.3. SST

As for key design features including the stop-signal ratio, SSD and SSRT estimation method, the majority of SST implementations complied with recommendations of the consensus guide (Verbruggen et al., 2019). Scope for improvement consists primarily in data validation prior to SSRT estimation and foreperiod randomization. As precondition for SSRT calculation, data quality and assumption intactness should be inspected with regards to the independent horse-race model (Logan et al., 1984). For validity, randomized fixation periods should be preferred to render the event onsets less predictable so that less proactive control such as preparation and planning would be engaged.

One fourth of the reviewed studies applied multi-component design rather than the standard SST to interrogate various facets of response inhibition. For instance, additional components demanded "change" after stopping, or conditional components required stopping only after selective cues. As for estimation of the stopping latencies, the SST variants stuck to the horse-race model and adopted cognitive subtraction. However, the proactive components accentuated in these variants as well as task complexity per se could impinge on physiological, neural and behavioral dimensions throughout the task (Wessel, 2018). Combined TMS and EMG revealed that stop preparation could attenuate the global suppression of corticospinal excitability (Duque et al., 2017; Greenhouse et al., 2012), and selectively exert the control on targeted response effector (Cai et al., 2011). In terms of neural engagement, goal-attaining, selective inhibition rather recruits indirect pathway via the striatum, while stimulus-driven, global inhibition takes the hyperdirect shortcut (Jahanshahi et al., 2015). More subtle differences could hardly be dissociated in dichotomy, as the preSMA and rIFC could be recruited to different extent regarding the accentuated subprocesses in design. The preSMA is preferentially sensitive to the conditions of stopping, whereas rIFG activity is rather associated with the mechanics of its execution (Jha et al., 2015). Moreover, both stopping mechanisms could share the behavioral cost, as proactive control manifests in preparation or strategic slowing to minimize demand for reactive inhibition (Chikazoe et al., 2009). Additional task switching in the stop-change variant might invalidate the independence assumption, since the race could occur between two homologous but contradictory go tasks instead of parallel go and stop runners (Verbruggen and Logan, 2009). Besides, tasks of considerably high demand and complexity per se could distort the reaction time distribution, and the conventional horse-race model fails to account for errors on go trials (Matzke et al., 2019). In sum, since the altered brain states of subjects during stimulation could influence TMS-mediated modulation, and the mathematical assumptions of behavior could be violated, the outcome measure in the multi-component SST variants should be interpreted with caution.

To probe the sub-aspects of reactive response inhibition with validity, parametric methods could be applied, compared to which even the best non-parametric methods are more prone to bias (Verbruggen et al., 2019). Parametric Bayesian modeling holds promise to dissociate "trigger failures" from "brake failures" and address the potential underestimation of SSRT (Matzke et al., 2013, 2017). The former proves to be ubiquitously present in SST studies, especially in populations with ADHD (Weigard et al., 2019), and even infrequent trigger failures could lead to distortion of stopping latency. Furthermore, parametric methods extended the conventional horse-race model to account for go errors, rendering the stop-signal paradigm informative enough to study response inhibition in complex tasks (Matzke et al., 2019). Besides, parametric modeling can estimate the entire SSRT distribution and enable group comparisons. The shape of reaction time distributions might differ between treatment groups, while differences in the mean reaction time are not necessarily detectable (Heathcote et al., 1991). Despite the methodological advantages, parametric estimation requires a larger number of SST trials, and could thus introduce extra noise if applied to patients with constrained attention span.

It remains controversial how much ecological validity and realistic relevance the highly controlled laboratory-based SST possesses. Wessel (2018) criticized the instructions inhering in SST for introducing proactive components, but the reactive response inhibition entailed in real-world might not be purely automatic or habitual, either. Hannah and Aron (2021) systematically categorized the action stopping experiments into four classes according to their naturalistic values in terms of stopping conditions and response modalities. With the help of virtual reality or gamification of the task (Friehs et al., 2023), SST could deliver more hints with real-world applicability and subserve studies of inhibition deficits under the framework of psychiatry or traffic psychology.

4.4. Recommendations for future TMS-SST studies

To improve validity and replicability of future practices, this systematic review concludes with a list of recommendations for the TMS-SST community. Instead of stemming from mere inferences based on mixed data influx, the following recommendations synthesize consensus papers and converging theoretical updates established by multimodal evidence (Bergmann and Hartwigsen, 2021; Verbruggen et al., 2019), aiming at informed design and improved data quality in future studies.

-Pre-register your study! Prespecify the hypothesized effect directionality of the selected TMS protocol.

-Ensure statistical power! Collect sufficient subjects and SST trials by running a priori power analysis to attain reliable individual estimates and maximize sensitivity for group effect detection. Take potential subject drop-outs and invalid task trials into account.

-Include effective control conditions! Combine sham stimulation and active control site or control time window to approximate perceptual side effects, improve blinding success and substantiate specificity of spatial or temporal targets.

-Pinpoint your target! Identify task-specific targets with individualized fMRI-guided neuronavigation and use a priori e-field modeling to optimize targeting and dosing.

-Utilize multimodal measures! Supplement the behavioral outcome with neuroimaging to obtain converging evidence, reveal neural correlates and verify the intended TMS exposure. Concurrent EEG or fMRI with online TMS are most desirable to map network dynamics at a high resolution.

-Implement valid SST! Conforming to the consensus guide by Verbruggen et al. (2019), use task variants of appropriate complexity and randomized intervals; use easily detectable stop signals; include sufficient trials and present stop signals on a minority (e.g. 200 trials with a 25% stop-signal ratio); use dynamic tracking to adapt SSD trial-wise; instruct participants not to wait and include block-based feedback.--Estimate SSRT properly! Check the quality of individual data under each condition before estimation; do not estimate the SSRT when the independence assumption of the race model is violated (RT on unsuccessful stop trials > RT on go trials) / when p(respond|signal) is lower than 0.25 or higher than 0.75 / when go omission rate exceeds 5%; estimate the SSRT with the integration method or, more preferably, parametric methods if data quality suffices.

Best-practice recommendations are outlined above for optimal signal-to-noise ratio. However, trade-off between cost-effectiveness and scientific rigor remains inevitable for future studies. We consider general principles for "least-worst" practices to be standardized

implementations and transparent reporting. Furthermore, if compromise is made to spare individualized neuronavigation, more subjects should be recruited. The larger sample size improves power and compensates for the signal-to-noise ratio by canceling out the fluctuations that stem from off-target localisation. On the other hand, if the sample size is restricted, stricter rules should apply to data quality check and estimation of SSRT to avoid distortion of effects.

Declaration of Competing Interest

The authors have no conflicts of interests to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105532.

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