Title: Cognitive state dependent enhancement of cognitive control with transcranial magnetic stimulation

Running Head: Cognitive state dependence of TMS

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Abstract

Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment for major depressive disorder (MDD), yet variability of therapeutic responses remains high. A key contributor to this variability may be state-dependent effects of brain stimulation, where activity in underlying circuits can shape the propagation of TMS-evoked activity. Thus, pushing target circuits into a desired state by engaging cognition may sensitise those circuits to TMS-evoked plasticity. We tested whether TMS' effects on cognitive control, a transdiagnostic construct implicated across psychiatric disorders and a putative mediator of TMS efficacy, are state-dependent.

Participants (N = 25) completed a context-dependent behavioural assay of cognitive control before and after we delivered rTMS to the prefrontal cortex (PFC). During rTMS, participants performed either the cognitive control task (active-state TMS), or performed a context-independent perceptual task (control-state TMS). We assessed changes in downstream behavioural metrics of circuit function, as well as neural indices of cognitive control measured from electroencephalography (EEG).

rTMS enhanced cognitive control performance only when PFC-anchored control circuits were actively engaged during stimulation. Similarly, only active-state TMS modulated theta band oscillatory activity, which is thought to be a marker of cognitive control engagement. Moreover, modulation of those EEG indices by TMS predicted gains in behavioural performance in the cognitive control task.

These findings demonstrate that TMS' effects on cognitive control are state-dependent, in which endogenous engagement of PFC-anchored networks can shape the magnitude and functional

relevance of TMS-induced plasticity. Considering cognitive states during TMS may therefore offer a framework to enhance and/or accelerate TMS' therapeutic effects.

Cognitive state dependent enhancement of cognitive control with transcranial magnetic stimulation

Brain stimulation has emerged as an effective tool to probe and modulate function of the human brain. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive form of brain stimulation that has rapidly grown in its therapeutic use for treatment-resistant major depressive disorder (MDD; Blumberger et al., 2013). Over multiple sessions, TMS is thought to evoke persistent neuroplastic changes in the function of the stimulated neural circuitry, which may alter aberrant network activity underlying the symptoms of psychiatric disorders (Downar et al., 2024; Hernández-Sauret et al., 2024). Although considered safe and effective (Chen et al., 2025), variability in the magnitude and durability of responses to TMS remain high (Ge et al., 2024; Kaster et al., 2023; McClintock et al., 2018; McInnes et al., 2024; Sackeim et al., 2020; Taylor et al., 2017). Thus, identifying factors that govern TMS' effective engagement of its neural targets is a central challenge in improving clinical outcomes.

A critical factor that may contribute to the therapeutic variability of TMS is the dependence of neuromodulation on dynamic fluctuations of endogenous neural activity at the time of stimulation (i.e., state-dependence; Bigoni et al., 2024; Bikson & Rahman, 2013; Bradley et al., 2022; Sack et al., 2023; Silvanto et al., 2008). Adaptive sensory, motor, and cognitive function relies on dynamic neural activity across local circuits and long-range networks (Geng et al., 2024; Westlin et al., 2023), and stimulation-induced responses are shaped by those ongoing dynamics. Consistent with Hebbian (Hebb, 1949) and metaplasticity (Abraham, 2008) models of neural learning, circuits that are already active may be in a more biophysically permissive state for modification, making them prime targets for intervention-induced plasticity. In line with this notion, stimulation-induced functional reorganization of sensorimotor cortex has been shown to

depend on the underlying network structure of the brain (Bloch et al., 2022). Similarly, antidepressant responses to TMS may depend on functional connectivity of underlying networks (Fox et al., 2012). However, it remains unclear how specific manipulations of underlying circuit activity can shape the magnitude and functional specificity of TMS for MDD.

Consideration of state-dependence in brain stimulation has motivated efforts to combine TMS with psychotherapy (Neacsiu et al., 2018; Xu et al., 2023). However, administration of TMS may pose logistical barriers (Cavalerro et al., 2021) and individual differences in the effective engagement in psychotherapy exercises may introduce additional variability. An alternative strategy is to manipulate the underlying state of cognition during stimulation. The propagation of TMS-evoked activity depends on underlying function in sensorimotor (Decroix et al., 2020; McInnes et al., 2023; Silvanto et al., 2007, 2008), attention (Capotosto et al., 2017; Heinen et al., 2014; Herring et al., 2015; Kamke et al., 2014), and memory (Albouy et al., 2017; Feredoes et al., 2011; Rose et al., 2016) networks. This input selectivity raises the possibility that actively engaging target neural circuits may sensitise them to neuromodulation, while sparing quiescent non-target circuits (Bikson & Rahman, 2013). However, this premise as relevant to the application of neuromodulation in psychiatric therapeutics awaits confirmation.

Cognitive control provides a principled framework to engage the circuits commonly targeted in TMS interventions for depression. Control involves the suppression of prepotent responses in favour of more adaptive ones, and depends on distributed brain networks anchored to the prefrontal cortex (PFC; Menon & D'Esposito, 2022). PFC, in turn, is the most common target of TMS for major depressive disorder (MDD), and TMS may in part work by inducing PFC neuroplasticity that supports cognitive control (Dengler et al., 2024). Conversely, if a TMS recipient is exerting cognitive control while stimulation is delivered, that endogenous activity

might interact with and amplify the plasticity effect. A subtle, but important nuance of that hypothesis is that control is not a unitary construct. The Dual Mechanisms of Control (DMC) framework describes two distinct modes of proactive versus reactive control, each supported by partially dissociable PFC-based networks (Braver et al., 2009). The translational orientation pattern expectancy (TOPX) task (Arend, 2024) probes both these mechanisms by modifying the type of contextual information provided prior to a context-dependent response (Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996). Thus, by manipulating the engagement of cognitive control mechanisms, it becomes possible to test how the activation of those PFC-anchored networks shapes the magnitude, topology, and functional relevance of TMS-evoked activity.

Here, we tested whether TMS' effects on cognitive control are state-dependent, and hypothesised that endogenously active circuits would be more amenable to modulation by TMS. We applied the context-based TOPX task as a downstream readout of the function of cognitive control circuitry before and after applying rTMS to the PFC. During the application of rTMS, we manipulated states of cognitive control by concurrently applying the context-dependent TOPX task, or a perceptual task that was context-independent. We found that rTMS enhanced the function of PFC-anchored cognitive control circuitry, but only when those circuits were active during stimulation. rTMS tied to states of cognitive control provided functional improvements in cognitive performance, which manifested as an enhanced ability to flexibly adapt modes of proactive and reactive control based on contextual information. Moreover, neural indices of control measured from the electroencephalogram (EEG) were enhanced by rTMS applied concurrently with active control states. The modulation of those indices further predicted gains in

behavioural performance, indicating a gating mechanism in PFC by which contextual information can regulate goal-directed action.

2. Materials and Methods

2.1. Experiment One

2.1.1. Participants

Twenty-five participants were recruited (14 female, mean age = 27.65 years, SD = 9.67, range = 19 – 65). We screened participants in accordance with the TMS safety guidelines proposed by Rossi et al. (2021) to exclude participants with potential contraindications to TMS. Participants were self-reportedly free from psychiatric diagnoses, so that we could characterise typical state-dependent brain responses without influence from aberrant dorsolateral PFC (and related network) activity. The protocol was approved by the local institutional review board and all participants provided informed, written consent in accordance with the declaration of Helsinki.

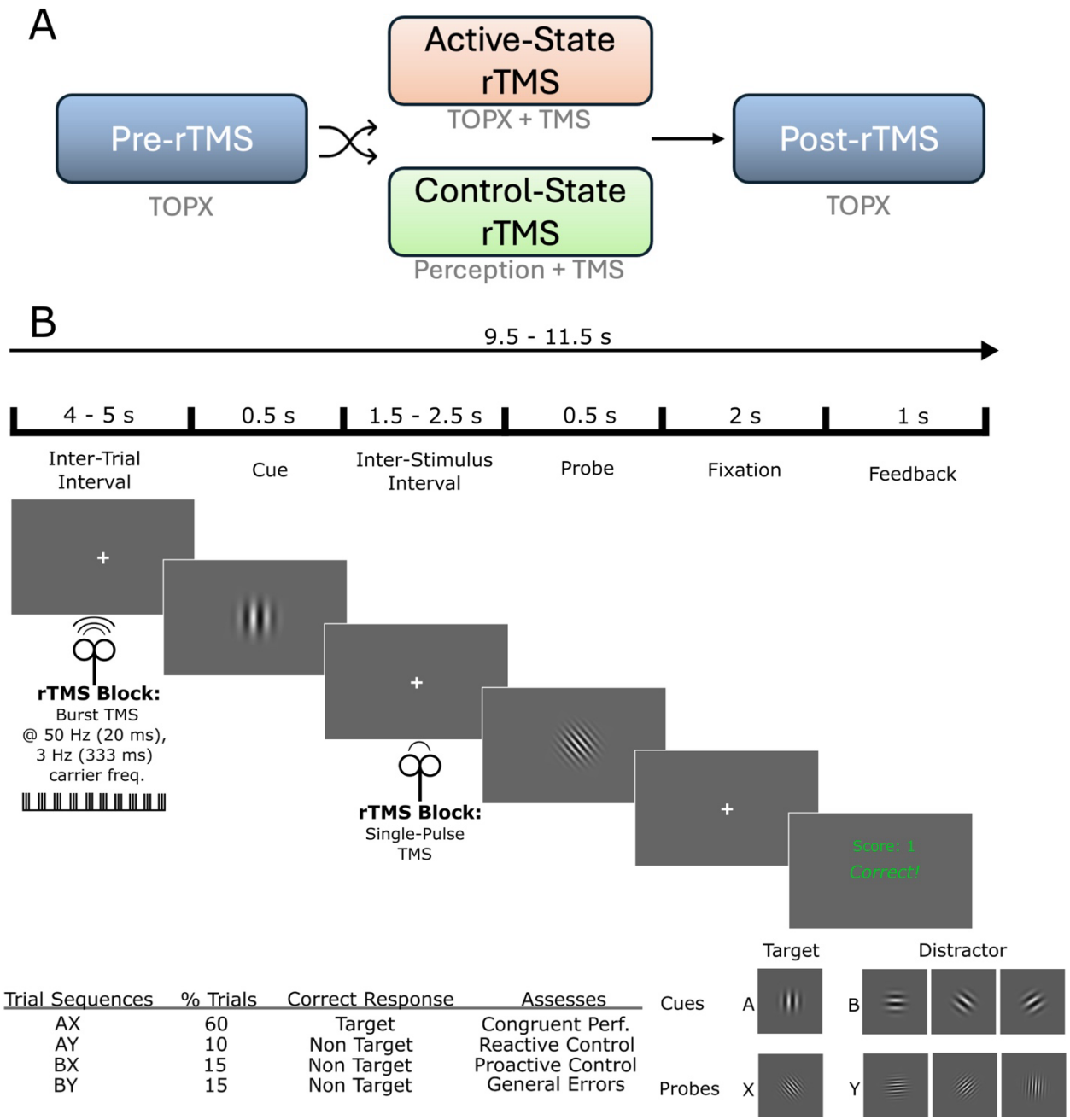
2.1.2. Procedures

To examine state dependence of prefrontal rTMS, we applied rTMS during either a PFC-dependent cognitive control task, or a perceptual task that should be less PFC-dependent, across two separate sessions, approximately one week apart, counterbalanced across participants. Prior to beginning experimental trials, we first identified the scalp location of the first dorsal interosseous (FDI) hotspot, and determined each participant's resting motor threshold (RMT) using the Rossini-Rothwell procedure (Rossini et al., 1994). This procedure involved applying single-pulse TMS over the right FDI hotspot with the muscle at rest to identify the minimum stimulation intensity (in % of maximum stimulator output) at which the TMS could elicit a motor evoked potential with an amplitude greater than 50 μV in at least 5 out of 10 trials. We recorded

the amplitude of those motor evoked potentials using an electromyography (EMG) amplifier (EMG Pod, Rogue Research Inc., Canada) with surface 8 mm Ag/AgCl sintered electrodes over the right FDI in a monopolar muscle belly-tendon montage and with a reference electrode placed over the styloid process of the right ulna. For the duration of the experiment, we recorded EEG at 1 kHz (Brain Products actiCHamp, GmbH, Munich, Germany) with 64 active electrodes in the international 10-20 EEG arrangement (Seeck et al., 2017) and with a ground electrode placed at the FPz site.

2.1.2.1. Behavioural tasks

2.1.2.2. Translational Orientation Pattern Expectancy. To measure cognitive control function (Pre-rTMS and Post-rTMS conditions), and as a means to engage cognitive control circuitry ($\text{CognitiveControl}_{\text{rTMS}}$ condition), participants completed the translational orientation pattern expectancy (TOPX) task (Arend, 2024). TOPX builds upon the AX-CPT (Cohen et al., 1997; Cohen & Servan-Schreiber, 1992; Servan-Schreiber et al., 1996) framework, which assesses context processing and goal maintenance. The task presents two visual stimuli, a cue and a probe, each requiring a behavioural response. A response is given at presentation of the target cue-probe sequence, and an alternate response is required for non-target cue-probe sequences (**Figure 1**). The target sequence is presented in a majority of trials to produce a response bias that must be countermanded in non-target trials. Due to this response bias, following target cues, there is an expectancy that the subsequent probe trial will require a target response. This target expectancy produces interference when a non-target probe is presented instead, requiring cognitive control to resolve that conflict. Similarly, when a non-target cue is presented, participants must overcome the target response bias if that non-target cue is followed by a target probe.



Trial Sequences	% Trials	Correct Response	Assesses
AX	60	Target	Congruent Perf.
AY	10	Non Target	Reactive Control
BX	15	Non Target	Proactive Control
BY	15	Non Target	General Errors

Figure 1. Sequence of events during the translational orientation pattern expectancy (TOPX) and perceptual tasks. (A) Block order of the experiment, in which participants complete a Pre- and Post-rTMS assessment of cognitive control, without TMS administered. In the rTMS block, the behavioural state is manipulated. In active-state rTMS, participants complete the context-dependent TOPX task while receiving rTMS. In the control-state rTMS

condition, participants complete a perceptual task which is context-independent while receiving rTMS. Participants complete both conditions, order counterbalanced, with a one-week washout period. (B) Sequence of events in the TOPX task. A cue and probe stimulus appear. Participants must give one response when a target (AX) sequence is presented, and an alternate response when a non-target sequence (AY, BX, BY) sequence is presented. In the perceptual task, the same stimuli are presented, but the contextual goal changes; participants respond to only the orientation of each Gabor stimulus. In the rTMS block, trains of rTMS were delivered during the inter-trial interval of TOPX (active-state TMS) or Perceptual (control-state TMS) tasks. We also administered single-pulse TMS during the cue-probe inter-stimulus interval of the TOPX and Perceptual tasks to assess cortical excitation and reactivity to TMS.

Participants completed TOPX before (baseline measure) and after (change measure) receiving rTMS. Every run of the task consisted of four blocks of 30 trials (120 trials). Participants completed 16 practice trials (four trials each of the AX, AY, BX, and BY conditions) prior to beginning experimental trials of TOPX. In the $\text{CognitiveControl}_{\text{rTMS}}$ condition, participants also completed a run of TOPX while receiving trains of prefrontal rTMS. Stimulation was applied during the inter-trial interval to avoid facial and ocular muscle contraction during stimulus presentation that may have interfered with task performance.

2.1.2.3. Perceptual Task. As a control condition, in the $\text{Perception}_{\text{rTMS}}$ condition, participants completed a perceptual task while receiving rTMS. The perceptual task had the same stimulus parameters as TOPX, but did not require context processing or inhibition of prepotent responses. Rather than responding to target/distractor stimulus sequences, participants responded according to the orientation of each stimulus that was displayed. Correct responses

required pressing the down arrow key for vertically oriented Gabor patches and the left arrow key for horizontally oriented Gabor patches. In each trial, two patches were presented, each with a 50% probability of vertical/horizontal orientation. Participants were given feedback of a correct response if they correctly identified the orientation of both Gabor patches in a trial (matching the two-stimulus cue-probe sequence of TOPX). Participants completed 16 practice trials (without TMS) of the perceptual task prior to beginning experimental trials. In $\text{Perception}_{\text{rTMS}}$ sessions, participants repeated practice of TOPX prior to beginning the post-TMS (change measure) experimental trials of TOPX. The experimental tasks were administered in MATLAB using Psychtoolbox (Kleiner et al., 2007).

2.1.2.4. Transcranial Magnetic Stimulation. Single pulse and repetitive TMS was applied using a Magstim Super Rapid^2 Plus stimulator connected to a figure-of-eight Air Film Coil with a wing diameter of 70 mm (Magstim Co. Ltd, Wales, UK). TMS was applied at 100% of the participant's RMT (to the nearest 1% of maximum stimulator output) over the left PFC using the Beam-F3 targeting method (Beam et al., 2009). The mean resting motor threshold was 65.95% of maximum stimulator output (SD = 7.35, range = 51% - 86%). Resting motor thresholds showed excellent consistency within subjects across both testing sessions, with an intraclass correlation coefficient = 0.91, $p < .001$. Throughout all TMS procedures, the stimulation coil was placed tangentially to the skull with the handle rotated clockwise 45 degrees from the midsagittal plane. Consistency in the position and orientation of the coil was maintained throughout the experiment using frameless stereotactic neuronavigation (BrainSight *v2.5.8,* Rogue Research Inc., Canada*)*. Stimulation parameters were controlled via MATLAB using the MAGIC toolbox (*v1.0*, Habibollahi Saatlou et al., 2018). To reduce auditory evoked potentials from the coil's discharge (Biabani et al., 2024), participants wore hearing protective earplugs,

and active noise-cancelling headphones (BOSE QC25) playing white noise at an amplitude of approximately 75 dBA throughout the experiment, including task blocks where no stimulation was applied.

During rTMS blocks, trains of rTMS were delivered during the inter-trial interval in a modified intermittent burst stimulation pattern (**Figure 1**). Bursts of three TMS pulses with an inter-pulse interval of 20 ms (50 Hz) were triggered every 333 ms (3 Hz) and 10 bursts were applied every trial. Trial durations resulted in an inter-train interval ranging from 9.5 – 11.5 s. The carrier frequency was slower than that of traditional intermittent theta burst stimulation, due to limitations of the stimulator in triggering bursts at shorter intervals when parameters were set externally via the MAGIC toolbox. In a subset (26.66%) of trials in both the $\text{CognitiveControl}_{\text{rTMS}}$ and $\text{Perception}_{\text{rTMS}}$ tasks, we delivered single-pulse TMS during the inter-stimulus interval to probe cortical excitability. During $\text{CognitiveControl}_{\text{rTMS}}$, single-pulse TMS was applied in 16 (22%) of AX trials, and in 8 trials (44%) each of the BX and BY trials. In the $\text{Perception}_{\text{rTMS}}$ condition, single pulse TMS was applied in an equal subset of trials presenting the cue-probe stimuli in Vertical-Vertical, Vertical-Horizontal, Horizontal-Vertical, and Horizontal-Horizontal orientations. Trial distributions were pseudorandom so that single pulse TMS was not presented in any two consecutive trials.

2.2. Data Processing and Statistical Analyses

2.2.1. Behavioural Data.

Statistical analysis was performed in R statistics (R Core Team, 2016). We screened behavioural data for blocks where response accuracy was < 70% or where the number of omitted responses was > 10. No blocks met these criteria. Two participants did not complete the second

experimental session and were excluded from analysis. To assess cognitive control performance before and after stimulation, we computed accuracy, probe reaction times (RTs), D′-Context, and the Proactive Behavioural Index of error rates (PBI_{ER}) and probe RTs (PBI_{RT}) for each run of TOPX. Accuracy was computed as the number of correct responses divided by the number of trials in each run. RTs were registered by the task as the time difference between stimulus onset and the time a valid keypress was detected. We removed probe RTs < 200 ms (indicating anticipatory responses; 0.52%) and RTs > 1500 ms (indicating lapsed attention; 0.76%) from analysis. D′-Context was calculated as a measure of context processing, as the z-score difference between the proportion of correct responses in the AX trial sequence (hit rate) and the proportion of incorrect responses in the BX trial sequence (false alarm rate); $D'\text{-}Context = z(AX_{Hit}) - z(BX_{FalseAlarm})$ (Servan-Schreiber et al., 1996). PBI_{ER} and PBI_{RT} were calculated as a measure of proactive control over reactive control, as the ratio of errors and reaction times, respectively, in proactive versus reactive trial types; $PBI = (AY - BX)/(AY + BX)$ (Braver et al., 2009). We assessed change in TOPX accuracy, D′-Context, and PBI_{ER} across blocks (Pre/Post) as a function of behavioural state at the time of TMS ($CognitiveControl_{rTMS}$, $Perception_{rTMS}$) using a series of linear mixed-effects models, including session number (1, 2) as a main effect and subject IDs as a random effect. Given their positive, right-skewed distribution, we analysed RTs using a generalised linear mixed effects model with a gamma link function and identity distribution, as in our past work (Reimer et al., 2024; Widge et al., 2019), applying the same fixed effects and random intercept as the linear mixed model. We report R^2 values alongside our statistical tests as an estimate of effect size. Linear models were run with the Satterthwaite approximation for degrees of freedom (Satterthwaite, 1946) and post-hoc tests were corrected for multiple comparisons using the false discovery rate method (Benjamini & Hochberg, 1995).

Recent work from our group (Glewwe et al., 2025; Kim & Widge, 2025; Reimer et al., 2024; Sachse et al., 2025) and others (Cole et al., 2025; Georgiev et al., 2016; Liu et al., 2025; Shen et al., 2024) suggests that neurostimulation of PFC and connected structures affects evidence accumulation processes. To assess those potential effects of our task-linked TMS intervention, we hierarchically fit Bayesian drift diffusion models (DDMs) to reaction times and response accuracy to infer latent processes of evidence accumulation towards decisions in TOPX. For each run of TOPX, we estimated the drift rate (v), decision threshold (a), non-decision time (t), and starting point bias (z) using the HDDM package (Wiecki et al., 2013). Consistent with a previous report applying hierarchical DDMs in the dot-pattern expectancy task (Shen et al., 2024), a paradigm similar to TOPX, we found the best fitting model according to posterior predictive checks and Deviance Information Criterion (DIC) permitted the v and a parameters to vary by trial sequence (AX, AY, BX, BY), while z was permitted to vary only by cue type (A Cue, B Cue), and t was held constant across conditions and estimated hierarchically with a group-level prior. We ran five independent chains per model, and we assessed model convergence by confirming that the Gelman-Rubin $\hat{R}$ (Gelman & Rubin, 1992) statistic was < 1.1.

2.2.2. Electroencephalography.

EEG data were pre-processed offline using the EEGLAB (Delorme & Makeig, 2004) and FieldTrip (Oostenveld et al., 2011) toolboxes in MATLAB (R2023a, Mathworks, USA). EEG data from -2 to +15 ms around TMS pulses were removed and interpolated to mitigate high amplitude TMS pulse artifacts, as recommended in standard TMS-EEG procedures (Rogasch et al., 2017). We resampled the data to 500 Hz and any channels showing poor signal were identified based on kurtosis and interpolated. We applied a two-step independent component

analysis (ICA) procedure to first remove TMS-evoked muscle artifacts, and a second ICA to remove remaining artifactual components (Rogasch et al., 2014, Rogasch et al., 2017). In addition, we band-pass filtered at 1 – 80 Hz, notch filtered at mains frequency (60 Hz), and re-referenced to the average of all channels.

To extract task-evoked and TMS-evoked oscillatory activity, time-frequency representations of oscillatory power were computed on single trials using a Morlet wavelet decomposition (Tallon-Baudry & Bertrand, 1999). Wavelets had frequency-dependent widths from 3 – 50 Hz, starting at 3 cycles at 3 Hz and adding 0.8 cycles for each 1 Hz. Event-related spectral perturbations (ERSPs) were computed by applying a pre-stimulus divisive baseline in the linear power domain from -500 to -100 ms relative to the target event. Those ERSPs were analysed using nonparametric cluster-based permutation tests. For task-evoked ERSPs, we analysed the difference between blocks (post-rTMS – pre-rTMS) as a function of behavioural states during rTMS (cognitive control, perception), and for each stimulus type (target, distractor). Given the known role of theta band activity in executive functioning (Ahumada-Méndez et al., 2022; Cavanagh & Frank, 2014; Q. Li et al., 2025; Y. Li et al., 2025; Soltani Zangbar et al., 2020), we primarily expected TMS to modulate activity within that band during the cognitive control task. As such, we tested for electrode clusters within the theta band (4 – 8 Hz) and within the time window 0 – 1000 ms relative to the task stimulus, applying a threshold for cluster formation of at least two electrodes. To test for spectral specificity (as opposed to broadband effects) within the derived spatially defined effects, we then performed follow-up time-frequency cluster-based permutation tests restricted to the averaged activity across electrodes in each significant cluster. We applied similar tests for TMS-evoked ERSPs, but compared the difference

between the cognitive control and perceptual tasks, using a time window of 0 – 500 ms relative to single-pulse TMS or the end of the rTMS train.

2.3. Experiment Two

Our within-subjects design used TOPX performance before and after TMS as a downstream readout of the function of cognitive control circuitry. With this design, it is possible that change in behavioural performance could be attributed to task switching costs or practice effects (i.e., TOPX-TOPX-TOPX in the cognitive control condition; TOPX-Perceptual-TOPX in the perceptual condition). To rule this out, we applied our experimental paradigm without administering TMS and tested for change in cognitive control performance across the first and third runs of TOPX as a function of whether a task switch occurred.

2.3.1. Participants

Based on the results of Experiment One, we ran a power analysis to determine the minimum required sample size to detect the smallest observed behavioural effect (D'-Context). The observed mean and standard deviation for each condition were used as generating parameters for a Monte Carlo simulation. For a grid of candidate sample sizes (N = 2 – 25 participants per condition), we generated synthetic datasets, and tested for a significant effect of task switching, repeating the process 1000 times per candidate N. Power was estimated as the proportion of simulations in which the effect of task switching was significant at $\alpha = .05$. This indicated a minimum of 14 participants was required to achieve 80% power. We recruited 16 participants for Experiment Two, oversampling to account for potential attrition. Participants were recruited from the online platform Prolific. Although no TMS was administered, we applied the same screening criteria as Experiment One to maintain consistency between samples.

2.3.2. Procedures

Experiment Two followed the same procedures as the initial experiment, except that no TMS was administered. Participants each completed two sessions which involved three task runs, with a one-week washout period between sessions. The experimental tasks were administered online using PsychoPy (Peirce, 2007). Parameters for the TOPX and perceptual tasks remained the same as Experiment One, but there was an enforced three-minute rest period between each task run. To maintain consistency with the previous experiment, participants were required to wear headphones, so that the masking white noise used in Experiment One could be delivered throughout the experiment. To ensure compliance, prior to each block of 30 trials, a generated audio clip instructed participants to press a randomly selected key. The experiment did not proceed without the correct input. No participants were excluded due to failing this compliance criterion. We followed the same analysis procedures as Experiment One for the behavioural data in Experiment Two. Given that we expected no effect of task switching, which relies on confirmation of the null hypothesis, to complement the frequentist tests we ran a series of Bayesian linear mixed models on the derived behavioural metrics. We report BF_{01} values to evaluate the degree of evidence for the null over the alternative hypothesis and interpreted these based on the criteria outlined by Jeffreys (2006).

3. Results

3.1. State-Dependent Enhancement of Cognitive Control

3.1.1. Accuracy

Ratios of Post/Pre TMS accuracy as a function of behavioural state during TMS indicated that task-linked rTMS enhanced cognitive control, but only when those circuits were engaged by the

task ($F_{(1, 45)} = 6.11$, $p = .017$, $R^2 = .121$), with ratios significantly greater than $\mu = 1$ (no change) for $\text{CognitiveControl}_{rTMS}$ ($M = 1.03$, $SD = 0.04$, $p = .005$), but not for Perception_{rTMS} ($M = 1$, $SD = 0.04$, $p = .985$). There was no evidence of practice effects across testing sessions for TOPX accuracy, with no significant main effect of session number on accuracy values ($p = .667$) or accuracy ratios ($p = .496$). Accuracy ratios are shown in **Figure 2A.**

3.1.2. Reaction Time

RT shortening across blocks was dependent on the behavioural state during rTMS. Differences in reaction time from pre- to post- rTMS yielded a main effect of rTMS State ($F_{(1, 22.39)} = 6.70$, $p = .017$, $R^2 = .099$), and indicated a numeric shortening of reaction time in the $\text{CognitiveControl}_{rTMS}$ condition ($M = -17.49$, $SD = 55.14$), but not the Perception_{rTMS} condition ($M = 14.52$, $SD = 51.52$). Those RT differences were not significantly different from $\mu = 0$ (no change) in either $\text{CognitiveControl}_{rTMS}$ or Perception_{rTMS} conditions, but the RT differences were significantly shortened in $\text{CognitiveControl}_{rTMS}$ relative to Perception_{rTMS} ($p = .017$). There was evidence of practice effects across testing sessions, with a main effect of session number on raw RTs ($\chi^2 = 99.67$, $p < .001$, $R^2 = .008$), but those practice effects did not explain pre- to post- rTMS RT differences ($F_{(1, 22.37)} = 0.55$, $p = .465$, $R^2 = .009$). RT differences are shown in **Figure 2B.**

3.1.3. Contextual Behavioural Performance

Contextual processing also showed a state-dependent enhancement by rTMS. Pre- to post- rTMS differences of D′-Context yielded a significant main effect of rTMS state ($F_{(1, 45)} = 4.62$, $p = .037$, $R^2 = .094$), with significantly greater TMS-evoked change for $\text{CognitiveControl}_{rTMS}$ ($M = 0.88$, $SD = 0.80$, $p < .001$) relative to $\mu = 0$ ($p < .001$) and relative to Perception_{rTMS} ($p = .043$). In contrast, Perception_{rTMS} differences were not significantly different from $\mu = 0$ ($M = 0.02$, $SD =$

1.83, p = .965). We observed evidence of inter-session change in D′-Context across testing sessions, $F_{(1, 68.58)}$ = 4.54, p = .037, R^2 = .037, with lower D′-Context in second testing sessions (M = -0.27, SD = 1.55) relative to initial ones (M = 0.13, SD = 1.21). However, inter-session change did not influence rTMS-evoked enhancement of D′-Context, with no main effect of session number in the linear model of pre- to post- rTMS D′-Context differences, $F_{(1, 45)}$ = 0.65, p = .425, R^2 = .014. D′-Context differences are shown in **Figure 2C.**

PBI_{ER} decreased from pre- to post- rTMS, $F_{(1, 67.73)}$ = 4.57, p = .036, R^2 = .009, but that effect was not state-dependent, with no interaction of Block with rTMS State, $F_{(1, 69.99)}$ = 0.27, p = .607, R^2 = .007. That change in PBI_{ER} may have been driven by practice effects, as there was also a significant effect of session number, $F_{(1, 69.91)}$ = 7.95, p = .006, R^2 = .070. There was no significant change in PBI_{RT} across blocks (p = .840) or sessions (p = .066), and no rTMS-state-dependent change across blocks (p = .612).

3.1.4. Drift Diffusion Parameters

We hierarchically fit DDMs to participants' RTs and response accuracy to estimate evidence accumulation in the TOPX task. Drift rate and boundary threshold showed no state-dependent modulation from pre- to post- rTMS. However, starting point bias showed a state-dependent modulation by rTMS which depended on contextual information (cue type with rTMS state interaction on bias ratios, $F_{(1, 68.48)}$ = 2334.45, p < .001, R^2 = .962). For A cues, the rTMS evoked change in starting point bias was significantly greater than μ = 1 for both the $CognitiveControl_{rTMS}$ (M = 1.01, SD = 0.01, p < .001) and $Perception_{rTMS}$ (M = 1.01, SD = 0.01, p < .001) conditions, but the change was not significantly different between the two conditions (p = .259). For B cues, the rTMS evoked change in starting point bias showed a significant increase relative to μ = 1 for $CognitiveControl_{rTMS}$ (M = 1.15, SD = 0.01, p < .001), a significant decrease

relative to μ = 1 for $\text{Perception}_{\text{rTMS}}$ (M = 0.98, SD = 0.01, $p < .001$), and the change was significantly different between the two conditions ($p < .001$). We did not observe evidence of practice effects influencing starting point bias across sessions, with no significant main effect of session number $F_{(1, 84.77)} = 2.90$, $p = .092$, $R^2 = .032$. Ratios of starting point bias are shown in **Figure 2D.**

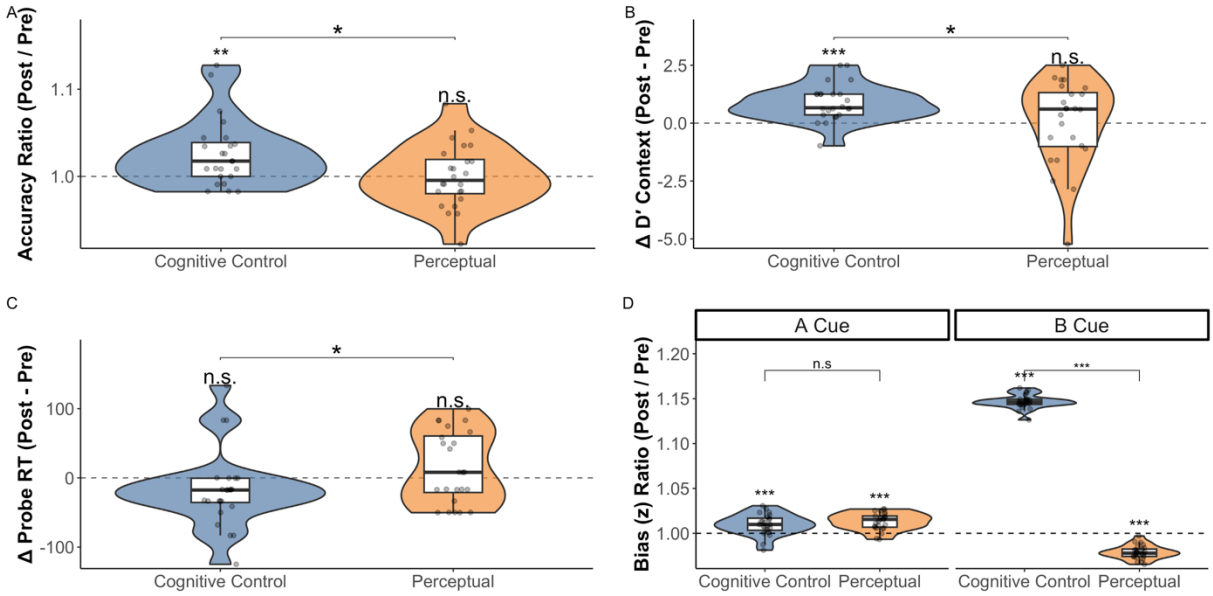


Figure 2. Enhancement of cognitive control by active-state TMS. (A) Accuracy was enhanced by TMS when cognitive control circuitry was engaged, but not when non-target circuits were engaged during TMS. (B) Contextual processing, represented by D'-Context, showed a similar state-dependent enhancement. (C) Probe RTs were numerically shortened by active state TMS, but that difference was not significantly different from μ = 0 (no change). However, RT shortening by TMS showed a significant improvement in $\text{CognitiveControl}_{\text{rTMS}}$ relative to $\text{Perception}_{\text{rTMS}}$. (D) Evidence accumulation bias estimated by drift diffusion modelling showed a state dependent modulation by TMS, particularly for non-target cues, whereby starting point bias was increased in active-state TMS, but decreased in the control-state TMS condition.

Violins depict probability density distributions for each condition; boxplots depict the between-subject median and interquartile range for each condition; points represent individual-subject change scores. Significance (FDR-corrected) is denoted above each condition with reference to mean difference = 0 or mean ratio = 1 (no change). Significance (FDR-corrected) is denoted between conditions determined by pairwise contrasts. *** = $p < .001$, ** = $p < .01$, * = $p < .05$, n.s = $p > .05$.

3.2. State Dependent Modulation of Theta Band Activity

3.2.1. Cortical Engagement by TMS Depends on Cognitive State

We examined state dependence of TMS' cortical engagement by comparing theta band ERSPs evoked after single-pulse and repetitive TMS for each of the cognitive control and perceptual tasks. Cluster-based tests did not identify statistically significant electrode clusters for either of the tasks. However, we tested for differences in theta band ERSPs specifically at the stimulation site (F3) and found that single-pulse TMS-evoked ERSPs were on average 0.58 dB larger in the cognitive control task in comparison to the perceptual one and that difference was statistically significant against a null distribution generated by shuffled task labels ($p = .014$). Similarly, following the rTMS trains, theta band ERSPs were 0.49 dB larger on average during the cognitive control task relative to the perceptual one ($p = .021$). ERSPs evoked by TMS are shown in **Figure 3**.

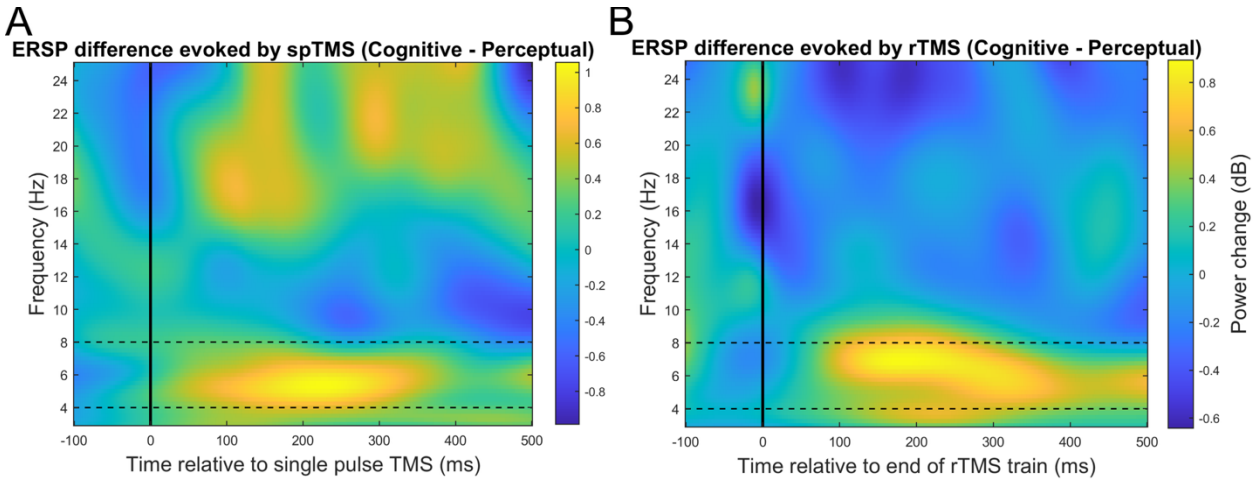


Figure 3. **State-dependent theta band activation evoked by TMS.** (A) Differences in ERSP power between TOPX and Perceptual tasks evoked by single-pulse TMS indicate an enhancement of TMS-evoked theta band oscillatory power during states of cognitive control relative to perceptual (control) states. (B) Similarly, trains of rTMS evoked stronger prefrontal oscillatory theta responses when applied during active behavioural states of cognitive control relative to perceptual states. Dashed lines represent the theta band spectral region for which we tested for condition differences via permutation tests.

3.2.2. State Dependent Modulation of Contextual EEG Responses

We examined the state dependent modulation of contextual neural processes by TMS by comparing theta band activity evoked during TOPX, at baseline and following TMS, as a function of behavioural state at the time of TMS. Spatial cluster-based statistics showed a modulation of cue-locked TOPX ERSPs from baseline after TMS, which depended on the behavioural state at the time of TMS. Specifically, when participants were engaged in cognitive control during TMS, the power of cue-locked theta-band ERSPs was significantly reduced after

TMS relative to baseline, for both TOPX target cues, $t_{(22)} = -4.13$, $p = .011$, $d = -0.95$, and distractor (non-target) cues, $t_{(22)} = -3.84$, $p = .039$, $d = -0.88$. That theta band reduction showed a frontocentral-parietal spatial distribution for target cues, and a left-prefrontal distribution for distractor cues (**Figure 4B**). In contrast, when participants were engaged in the perceptual task during TMS, cluster-based tests showed no modulation of theta band activity for either TOPX target cues, $p = .168$, or distractor cues, $p = .450$. Moreover, there was spectral specificity in the state-dependent modulation of contextual neural processing. Significant time-frequency clusters of spatial cluster activity were limited to the theta and low-alpha bands for both TOPX target (latency = 38 – 786 ms, $t_{(22)} = -7.36$, $p = .004$, $d = -1.69$) and distractor (latency = 44 – 658 ms, $t_{(22)} = -5.44$, $p = .022$, $d = -1.25$) cues (**Figure 4C**).

Spatial cluster-based tests also showed a state dependent modulation of probe-locked TOPX ERSPs from baseline after TMS. When participants were engaged in cognitive control during TMS, the power of probe-locked theta-band ERSPs were significantly reduced after TMS, relative to baseline, for TOPX target probes, $t_{(22)} = -3.87$, $p = .010$, $d = -0.89$, but not distractor probes ($p = .623$). The target probe evoked cluster showed a left prefrontal-occipital distribution (**Figure 4E**). No significant clusters were detected for cue or distractor probe-locked ERSPs when participants engaged in the perceptual task during TMS. Time-frequency cluster tests of the state-dependent modulation of target probe evoked ERSPs showed spectral specificity to the theta and low-alpha bands, latency = 0 – 598 ms, $t_{(22)} = -7.17$, $p = .010$, $d = -1.64$. (**Figure 4F**).

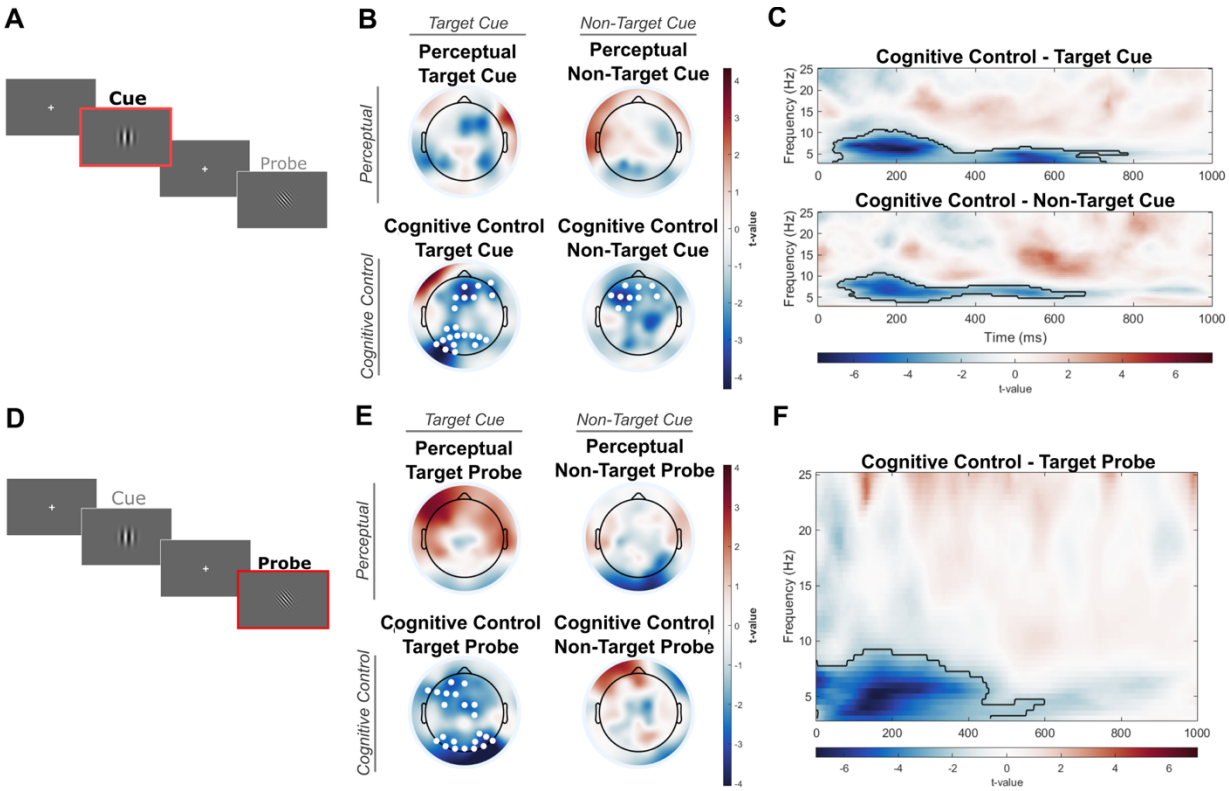


Figure 4. Modulation of goal maintenance and context processing by active-state TMS. (A) Theta-band oscillatory power evoked by cues in the TOPX task was calculated as a difference from Pre- to Post- TMS, as a function of behavioural state at the time of TMS, showing a state-dependent modulation of context processing and goal maintenance by TMS. (B) The power of theta-band oscillatory responses was reduced after active-state TMS, but not control-state TMS. That modulation of theta-band activity showed a prefrontal-parietal distribution for target cues (consistent with reactive control), and a left-prefrontal distribution for non-target cues (consistent with proactive control). White circles show significant cluster-forming electrodes in cluster-based permutation tests. (C) The modulation of cue-evoked processing by active-state TMS was specific to theta and low-alpha bands. The outlined region shows significant time-frequency clusters in cluster-based permutation tests. (D) We also computed theta-band oscillatory power evoked by probe stimuli in the TOPX task, and calculated Pre- to Post- TMS differences in those

ERSPs as a function of the behavioural state at the time of TMS. (E) The power of theta-band oscillatory responses to target probes was reduced after active-state TMS, showing a prefrontal-occipital distribution. White circles show significant cluster-forming electrodes in cluster-based permutation tests. (F) The modulation of target probe-evoked processing by active-state TMS was specific to theta and low-alpha bands. The outlined region shows significant time-frequency clusters in cluster-based permutation tests.

3.2.3. Contextual EEG Responses Predict Behavioural Performance

The physiological effects of TMS influenced an interaction of cue processing and probe processing which predicted behavioural gain. We tested whether the pre- to post- TMS change in the power of our derived ERSP clusters could predict each of our observed behavioural effects. To this end, we entered ΔRT, ΔAccuracy, ΔD'Context, and ΔBias as response variables in a series of linear models with ΔTarget Cue (A), ΔDistractor Cue (B), and ΔTarget Probe (X) ERSPs as predictors. ΔX ERSPs ($F_{(1, 18)} = 18.70$, $p < .001$, $R^2 = .033$; **Figure 5A**), but not ΔA ($p = .116$) or ΔB ($p = .642$) ERSPs predicted RT shortening by TMS. Moreover, the association between X ERSP change and RT change after TMS depended on the degree of B ERSP change (interaction of ΔX with ΔB ERSPs, $F_{(1, 18)} = 9.12$, $p = .009$, $R^2 = .421$). Given that ΔX values were generally negative (reflecting target probe-related theta suppression), greater values of ΔX (values closer to 0) in the model represent a lack of suppression. A Johnson-Neyman (D'Alonzo, 2004) analysis of this interaction indicated that a lack of X ERSP suppression predicted RT shortening, only when ΔB values were sufficiently negative (< -0.31 dB; **Figure 5C**). This suggests that the shortening of RT in TOPX after TMS was largest when rTMS modulated the

cue-evoked theta-band response which could effectively "turn off" the probe theta-band response, indicating successful contextual goal updating.

TMS-evoked modulation of ΔX and ΔB predicted the modulation of ΔD'-Context (ΔX with ΔB ERSPs interaction $F_{(1, 18)} = 7.95$, $p = .014$, $R^2 = .254$). This indicated that the effect of target probe ERSP modulation on D'-Context change depended on the degree and direction of modulation of distractor cue ERSPs (**Figure 5D**). Reductions of X ERSP suppression (values closer to 0) were predictive of improved D′-Context when B ERSPs suppressed strongly from baseline after TMS (< -0.65 dB), but impaired D′-Context when B ERSPs increased from baseline (> 0.09 dB). ΔX ERSPs were not predictive of D′-Context at intermediate values of ΔB ERSPs (-0.65 – 0.09 dB). This suggests that a lack of theta-band suppression after target probes can predict context-sensitive response accuracy only when accompanied by distractor cue theta-band suppression after TMS. In the absence of distractor cue suppression, or when distractor cue ERSPs increased after TMS, reduced target probe suppression was not beneficial, and may even impair discrimination performance. This again suggests a role of the distractor cue neural response in regulating the response to probe stimuli, reflecting contextual goal updating.

The degree of modulation of ΔA and ΔX ERSPs by TMS predicted ΔBias, which further depended on the type of cue, with a significant three-way interaction of ΔA ERSPs, ΔX ERSPs, and cue type (A/B) on ΔBias, $F_{(1, 38)} = 6.12$, $p = .020$, $R^2 = .026$. Follow up tests indicated that the interaction of ΔA ERSPs with ΔX ERSPs was significant for ΔBias in A cue trials ($p = .036$) but not B cue trials ($p = .510$). This suggests that the association between X ERSP change and bias change after TMS depended on a gating via cue-evoked responses in target-cue trials. The Johnson-Neyman procedure on this interaction indicated that a lack of X ERSP suppression predicted Bias change, only when ΔA values were sufficiently negative (< -0.66 dB; **Figure 5E**).

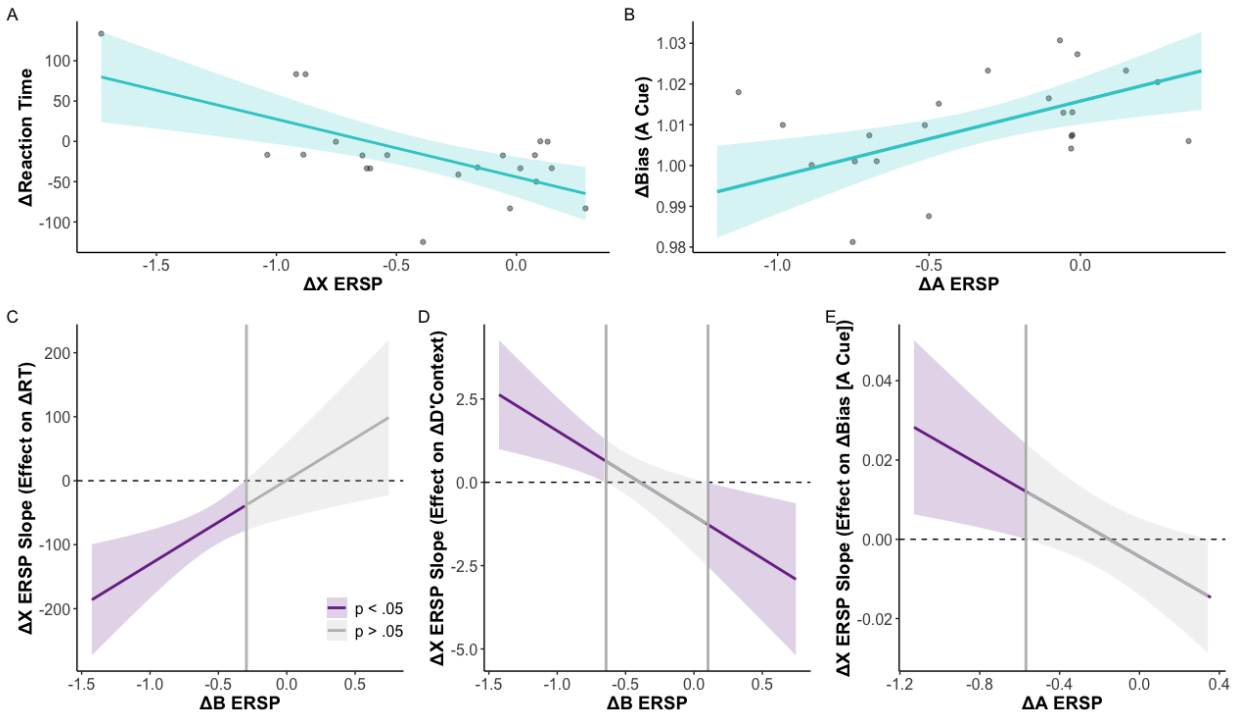


Figure 5. Modification of contextual EEG responses by active-state TMS predict downstream behavioural outcomes. (A) Modulation of target probe evoked theta band activity predicts shortening of reaction time (RT). (B) Modulation of target cue evoked theta band activity predicts change in decisional evidence bias for target probes. (C) Johnson-Neyman plot of the interaction of ΔB ERSPs with ΔX ERSPs on the shortening of RT. Suppression of distractor cue evoked theta band activity predicts reaction time shortening, when accounting for the modulation of target probe evoked activity. (D) Johnson-Neyman plot of the interaction of ΔB ERSPs with ΔX ERSPs on the enhancement of D'-Context. Suppression of distractor cue evoked theta band activity predicts enhancement of downstream contextual processing, when accounting for the modulation of target probe evoked activity. (E) Johnson-Neyman of the interaction of ΔA ERSPs with ΔX ERSPs on the enhancement of non-target cue decisional bias. Suppression of target cue evoked theta band activity predicts decisional evidence bias for target probes, when accounting for the modulation of target probe evoked activity.

3.3. Behavioural Change is not Explained by Task Switching Costs

In Experiment Two, there was no evidence of a systematic change in manifest behaviour as a function of task switching. The interaction of TOPX block number (1, 3) with task sequence (switch, no-switch) was not significant in the frequentist linear mixed model of accuracy ($F_{(1, 45.18)} = 0.90$, $p = .349$, $R^2 = .004$), D′-Context ($F_{(1, 45.07)} = 0.03$, $p = .857$, $R^2 = .00$), or probe RTs ($F_{(1, 7653.8)} = 0.21$, $p = .650$, $R^2 = .001$). In support of this, Bayesian linear models indicated strong- to very-strong evidence (Jeffreys, 2006) against an effect of task switching on the change of TOPX accuracy ($BF_{01} = 38.00$), D′-Context ($BF_{01} = 42.33$), and probe RTs ($BF_{01} = 25.76$). However, the linear mixed model of evidence accumulation bias indicated a significant interaction of block with task sequence, $F_{(1, 106.06)} = 16.01$, $p < .001$, $R^2 = .08$. We further examined bias ratios in the third TOPX run as a ratio of bias in the first. Bias ratios for target (A) cues were significantly enhanced (relative to a mean of 1) when there was a task switch ($M = 1.03$, $SD = 0.05$, $p = .012$), but decreased when there was no task switch ($M = 0.92$, $SD = 0.06$, $p < .001$). For non-target (B) cues, bias ratios showed no significant change when there was a task switch ($M = 1.01$, $SD = 0.05$, $p = .396$), but decreased when there was no task switch ($M = 0.85$, $SD = 0.03$, $p < .001$). Given that the direction of the effects are opposite from what we observed in our TMS experiment, it is unlikely that a confounding effect of task switching can explain the state dependent effects of TMS on decisional bias observed in Experiment One.

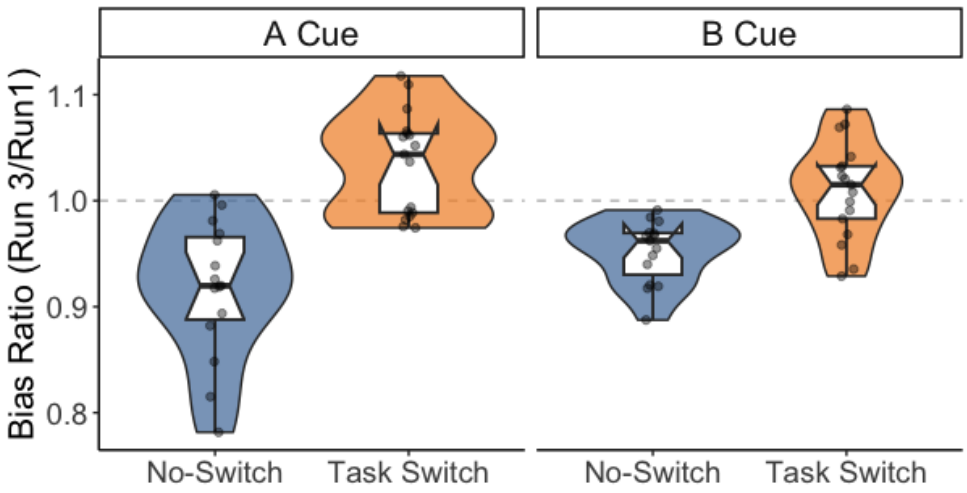


Figure 6. Change in evidence bias as a function of task-switching or practice effects does not explain the modification of bias by TMS observed in Experiment One.

4. Discussion

TMS is increasingly being adopted as a therapy for psychiatric disorders. Yet, currently, no TMS protocols systematically control or manipulate neural engagement during stimulation, which may pose a missed opportunity to leverage state-dependent plasticity mechanisms that could improve treatment reliability, speed, and/or magnitude. Here, we demonstrated that the neuromodulatory effect of TMS on PFC-anchored networks is shaped by the cognitive state in which stimulation is delivered. When TMS was paired with active engagement of cognitive control circuits, participants showed selective enhancements of behavioural and neural indices that reflect the function of those circuits. In contrast, delivering the same stimulation during a purely reactive perceptual task produced little measurable change. These findings provide direct evidence that endogenous engagement of PFC-anchored networks can shape the magnitude and functional relevance of TMS-induced plasticity.

4.1. Modulation of prefrontal cortex circuitry by TMS is state dependent

Our results align with extensive literature suggesting that neural plasticity is gated by the dynamic neural patterns and activation states of within a circuit. Hebbian learning and metaplasticity models predict that circuits already engaged in processing goal-relevant information occupy a biophysically permissive regime for modification (Abraham, 2008; Hebb, 1949). Thus, by actively engaging a target circuit toward a desired outcome, it may be possible to bias the effects of neuromodulation in a selective manner. The finding that TMS could enhance downstream readouts of cognitive control only when those circuits were concurrently active supports this view and extends prior demonstrations of state-dependent effects of TMS. The notion that the ongoing state of neural activity can shape the propagation of TMS-evoked activity has been demonstrated across sensorimotor (Decroix et al., 2020; McInnes et al., 2023; Silvanto et al., 2007, 2008), attention (Capotosto et al., 2017; Heinen et al., 2014; Herring et al., 2015; Kamke et al., 2014), and memory (Albouy et al., 2017; Feredoes et al., 2011; Rose et al., 2016) domains. Here, we have shown the state dependence of TMS effects in complex cognitive function which spans across those domains. Differential effects of TMS on affective processing have recently been observed to depend on trait-state depression severity at the time of stimulation (Paneva et al., 2025). Our results here highlight that states of cognition can be specifically manipulated to bias the effects of TMS toward clinically relevant outcomes.

4.2. Cognitive control as a mechanism for neural state manipulation

The finding that cognitive control can be selectively enhanced by TMS has direct clinical implications. Deficits in cognitive control are prevalent transdiagnostically (Breukelaar et al., 2020; Dalley et al., 2011; McTeague et al., 2016, 2017; Widge et al., 2019) and downstream readouts of that function can provide an objective measure of target circuit engagement (Nagrale

et al., 2023). Biasing neuromodulatory effects toward those underlying circuits by leveraging state dependence might increase the clinical efficacy of neuromodulation and/or help target it to specific circuit deficits. Following active-state TMS, several downstream outputs of cognitive control were enhanced. Specifically, accuracy was higher, reflecting improved capacity for control, and probe RTs were shorter, suggesting enhanced computational efficiency. In addition, participants had a greater ability to use contextual information in support of goal-directed action – D'-Context was enhanced and decisional evidence was biased by sufficient contextual information (non-target cues). Although our study design has potential for confounded influence of task-switching and/or practice effects, we specifically showed in Experiment Two that these effects do not explain Experiment One's results. Together, our results suggest that active-state TMS could enhance flexible processes of cognitive control. Moreover, we observed an improvement of contextual processing, as manifested by D'-Context scores, but not in the index of proactive control (PBI_{ER}, PBI_{RT}). This suggests that active-state TMS did not push individuals into a more restrictive proactive/reactive regime, but enhanced the ability to flexibly adapt between modes of control. In other recent work, we showed that similar flexible switching may be a mechanism of recovery from depression (Kim & Widge, 2025).

4.3. Mechanisms of cognitive control modulation

By using the context-dependent TOPX task to manipulate states of control, we leveraged a well-characterised mechanism for altering prefrontal activation and gating dynamics (Braver et al., 2009; Chiew & Braver, 2017a). The two modes of control proposed by the DMC framework suggest flexible, context-dependent mechanisms that support goal directed behaviour. Proactive control actively sustains goal representations that bias attention and action systems (Etzel et al., 2022). Those biases are postulated to originate from anticipatory lateral PFC activity and a

gating mechanism operating through corticostriatal circuits (Chiew & Braver, 2017a; Kwashie et al., 2023). On the other hand, reactive control is transiently activated on an as-needed basis at the detection of conflict, triggering the retrieval and reorganisation of goal representations (Etzel et al., 2022). This process is thought to occur under a distinct and broader fronto-parietal network (Cooper et al., 2015; Kwashie et al., 2023). In addition, cognitive control is thought to operate through theta band activity which synchronises neural assemblies to integrate contextual information and enable flexible goal-directed control (Cavanagh & Frank, 2014; Cooper et al., 2015; Menon & D'Esposito, 2022; Riddle et al., 2020). The pattern of neural modulation we observed by active-state TMS here is consistent with the above. Non-target cues provide contextual information, enabling proactive control before the probe stimulus. Responses to those cues were modulated by active-state TMS, showing a reduction in theta band oscillatory power over left dorsolateral PFC. Moreover, we observed an increase in decisional evidence bias for non-target cues, which may reflect the effective engagement of proactive control. In contrast, target cues, for which reactive control may be required, evoked a fronto-parietal theta band modulation after active-state TMS. This suggests that both proactive and reactive modes of control may have been modified by active-state TMS.

However, a surprising point is that there was a decrease, rather than an increase, in the power of task-evoked EEG responses after active-state TMS. For non-target cues, this may reflect more active gating of PFC from subcortical regions, consistent with a proactive mode of control (Chiew & Braver, 2017a). However, this does not explain the reduction of oscillatory theta power after target cues and target probes. Given that behavioural metrics of control (accuracy, probe RT, and D'-Context) improved, an alternative explanation is that reductions in theta band power may reflect an increase in the efficiency of the underlying computations. For

example, prefrontal theta has been posed as a marker of the cognitive control demand or effort, rather than control ability (Cavanagh & Frank, 2014; Cooper et al., 2015, McFerren et al., 2021). Higher theta band oscillatory power may reflect compensatory recruitment of control resources when conflict is high or processing is inefficient. Thus, the reduced theta band oscillatory power we observed, coupled with improved performance in downstream readouts of control, may suggest that active-state TMS was able to shift the system into a regime where less oscillatory drive was required to support goal-directed behaviour. Alternatively, the reduced prefrontal theta may be functionally analogous to the reduction of alpha and beta power in motor cortex during action preparation as those circuits shift to a more excitable state (Jasper & Penfield, 1949; Meirovitch et al., 2015). This explanation is supported by the increased local theta band oscillatory power evoked by single-pulse and repetitive TMS during the cognitive control task, which may reflect increased excitability of those theta generators.

Supporting the idea that active-state TMS increased the computational efficiency of the underlying circuits, individual differences in the magnitude of theta band power reduction predicted behavioural outcomes. Larger reductions in theta band responses to non-target cues predicted improvement in probe RTs and D'-Context, when accounting for the target probe response. The interaction of the cue response with the probe response suggests that effective processing of the cue was able to regulate the response to probes, supporting goal-directed action. Specifically, decreased probe-evoked suppression predicted enhanced behavioural performance, only when the cue-evoked response was sufficiently suppressed. This may reflect a gating mechanism in PFC whereby contextual information can provide a top-down regulation of goal maintenance, which can enhance behavioural performance.

4.4. Implications for understanding variability in the efficacy of TMS therapies

Our findings have implications for the mechanistic understanding of neuromodulation and its use clinically. Therapeutic TMS protocols typically administer stimulation without considering the neural state of the targeted circuits. This may be a contributing factor to heterogeneity in treatment outcomes (Sack et al., 2023). Here, we have shown experimental evidence that aligning stimulation with active engagement of the targeted network can increase the magnitude and specificity of TMS' neuroplastic effects. Strategies which prime target circuits, such as engaging cognitive states, could improve treatment efficacy by increasing the physiologic receptivity of the target circuit. A limitation here is that we applied our paradigm in a sample of individuals without psychiatric disorders, to limit potential influence of heterogeneous or aberrant network processing. A key step forward would be to confirm that the same effects are observed in target populations, such as treatment resistant depression. Moreover, although cognitive control is implicated transdiagnostically, and improvements in cognitive control relate to clinical symptom improvement (Crane et al., 2017; Hack et al., 2023; Kim & Widge, 2025; Koster et al., 2017; Widge et al., 2019), it remains to be tested whether the enhancement of control we observed can translate to clinically meaningful modifications of network function. Despite this, the modification of context processing by active-state TMS holds broad relevance as a therapeutic strategy across a range of disorders. Many conditions are characterised by impairments in maintaining or updating goal-relevant context, leading to rigid, inflexible, or overly reactive thought and behaviour patterns. For example, impaired context sensitivity may contribute to persistent negative thinking, impaired expectation updating, and limited ability to modify maladaptive thought and behavioural patterns in individuals living with depression (Stange et al., 2016). Anxiety and phobias may involve exaggerated threat responses that persist even in the absence of contextual safety cues (Abend, 2023). Similarly, obsessive-compulsive

disorders may involve difficulty in using contextual information to suppress habitual behaviours (Weiss et al., 2024). As such, enhancing the function of circuits that support context processing and flexible control has broad potential to remediate a transdiagnostic marker of impairment.

4.5. Conclusion

In summary, we have shown that the effects of prefrontal TMS are shaped by the ongoing state of cognition during stimulation. Actively engaging processes of cognitive control may sensitise underlying circuits to modification, which may bias the neuromodulatory effects to provide functional improvements in targeted neural circuits. Specifically, active-state TMS provided enhancements in downstream behavioural readouts and neural indices of PFC circuit function, which outlasted the period of stimulation. In contrast, TMS delivered during a non-active control state did not provide meaningful modification of those indices. This demonstration of state dependence in prefrontal TMS can offer a path toward more reliable brain stimulation interventions.

Disclosure Statement

ASW reports consulting income from Abbott Laboratories, and multiple unlicensed patents in the area of neurostimulation. All other authors report no relevant financial interests.

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Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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