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

Running Head: Cognitive state dependence of TMS

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Abstract

Background

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, constraining the target circuits' state by engaging cognition may make TMS' effects more consistent.

Objective

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.

Methods

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).

Results

rTMS enhanced downstream readouts of cognitive control only when stimulation was delivered concurrent with the cognitive control task. Similarly, only active-state TMS modulated theta band oscillatory activity, which is thought to be a marker of cognitive control engagement

Conclusion

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

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive form of brain stimulation with established efficacy for treatment-resistant major depressive disorder (MDD)[1]. TMS is thought to evoke neuroplastic changes in the stimulated region and connected neural circuitry, altering aberrant network activity underlying the symptoms of psychiatric disorders[2,3]. TMS is safe and effective[4], but the magnitude and durability of clinical responses are highly variable[5–10]. Thus, identifying factors that govern TMS' effective engagement of its neural targets is a central challenge in improving clinical outcomes.

A candidate source of therapeutic variability is the dependence of neuromodulation on endogenous neural activity at the time of stimulation (i.e., state-dependence)[11–17]. Consistent with Hebbian[18] and metaplasticity[19] 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, functional reorganization of sensorimotor cortex by neuromodulation depends on the underlying network structure of the brain[20]. Similarly, antidepressant responses to TMS may depend on functional connectivity of underlying networks[21]. 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 has motivated efforts to combine TMS with psychotherapy[22–24], and one approved indication depends on this approach[25]. However, logistical barriers[26] and variability in patients' engagement with psychotherapy exercises may limit this approach[24]. An alternative strategy is to manipulate the underlying circuit state through computerised cognitive exercises. The propagation of TMS-evoked activity depends on

underlying function in sensorimotor[16,27–29], attention[30–33], and memory[34–36] networks. This input selectivity raises the possibility that actively engaging target neural circuits may sensitise them to neuromodulation, while sparing quiescent non-target circuits[12].

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)[37]. PFC, in turn, is the most common target of TMS for MDD, and TMS may in part work by inducing PFC neuroplasticity that supports cognitive control[38,39]. Conversely, if a TMS recipient is exerting cognitive control while stimulation is delivered, that endogenous activity might interact with and amplify the plasticity effect. 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 the cognitive-behavioural and neural effects of rTMS are state-dependent. rTMS was applied to the PFC while participants performed either a context-dependent cognitive control task, or a context-independent perceptual discrimination task. rTMS modified cognitive control performance and neural indices of control only when the underlying circuits were active during stimulation. Considering and controlling cognitive states may therefore offer a framework to enhance and/or accelerate TMS' therapeutic effects.

2. Materials and Methods

2.1. Participants

Twenty-five individuals free from potential contraindications to TMS[40] participated (14 female, mean age = 27.65 years, SD = 9.67, range = 19 – 65). We also excluded individuals who self-reported any psychiatric diagnoses so that we could characterise typical state-dependent brain responses without influence from aberrant dorsolateral PFC (and related network) activity. For our planned primary analysis of behavioural modification by rTMS as a function of the behavioural state at the time of stimulation, our sample size was determined via power analysis of (generalised) linear mixed effects models[41,42] to achieve 80% statistical power and targeting a moderate effect size ($\eta_p^2 = 0.08$) based on DLPFC-neuromodulation studies in cognition and executive function[43,44]. The protocol was approved by the local institutional review board and all participants provided informed, written consent in accordance with the declaration of Helsinki.

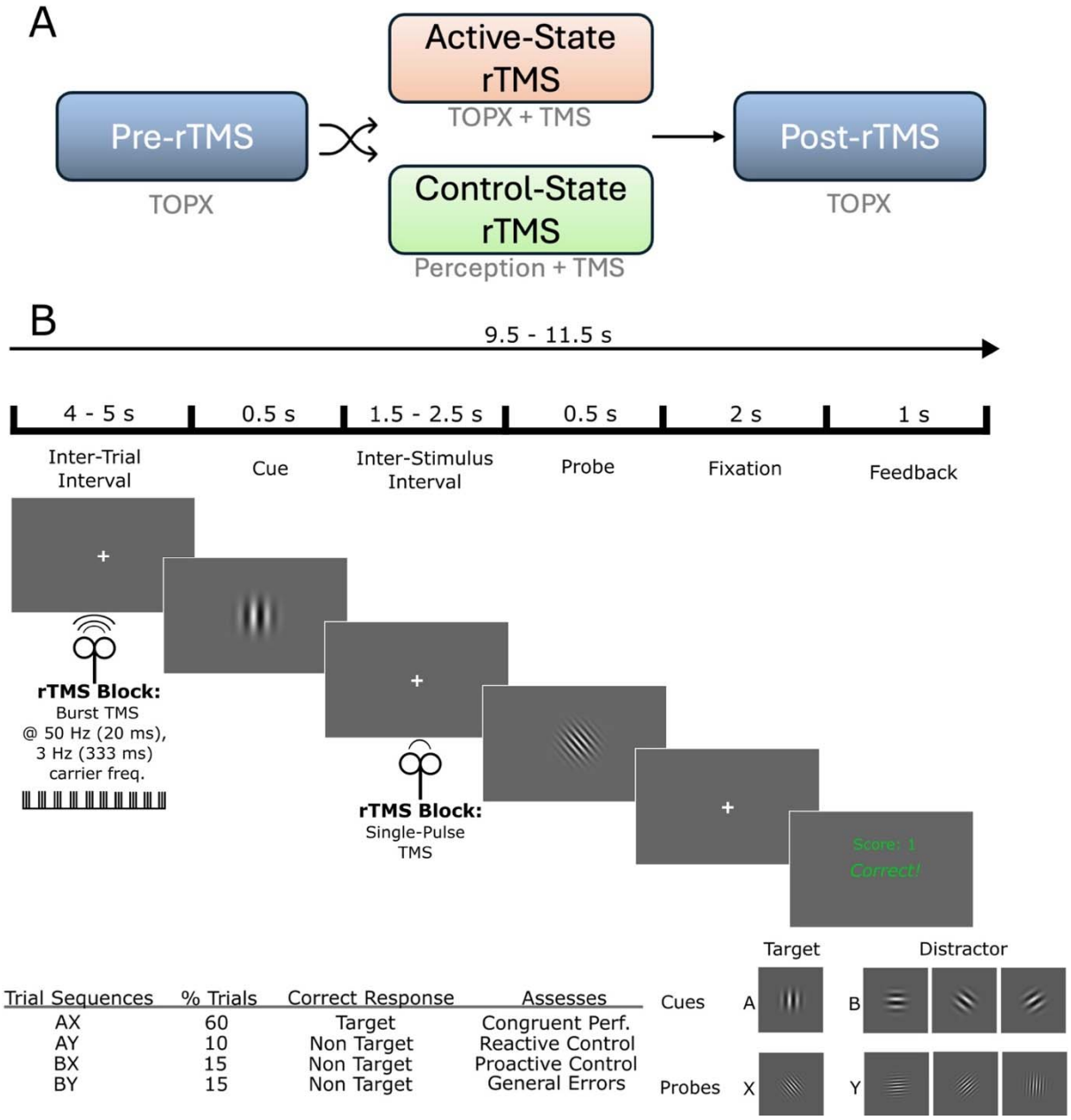
2.2. Procedures

To examine state dependence of prefrontal rTMS, we applied trains of rTMS at 100% of resting motor threshold during either a PFC-dependent cognitive control task, or a perceptual discrimination task that should be less PFC-dependent, across two separate sessions, approximately one week apart, counterbalanced across participants. A detailed description of the stimulation parameters is provided in the **Supplementary Materials**. 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 arrangement[45] and with a ground electrode placed at the FPz site.

2.2.1. Behavioural tasks

2.2.1.1. Translational Orientation Pattern Expectancy. To measure cognitive control function (Pre-rTMS and Post-rTMS), and engage cognitive control circuitry ($\text{ActiveState}_{\text{rTMS}}$),

participants completed the translational orientation pattern expectancy (TOPX) task[46]. The task presents two visual stimuli, a cue and a probe, each requiring a behavioural response. A frequent cue-probe target sequence produces a prepotent response tendency that must be countermanded in infrequent non-target sequences (**Figure 1**).



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. Participants completed 16 practice trials prior to beginning experimental trials of TOPX. In the $\text{ActiveState}_{\text{rTMS}}$ condition, participants also completed a run of TOPX while receiving trains of prefrontal rTMS.

2.2.1.2. Perceptual Task. In the $\text{ControlState}_{\text{rTMS}}$ condition, participants completed a perceptual discrimination task while receiving rTMS. The perceptual task had the same stimulus

parameters and trial structure as TOPX, but did not require context processing or inhibition of prepotent responses. Instead, participants responded according to the orientation of each stimulus. See **Supplementary Materials** for a description of the task parameters in the TOPX and perceptual tasks.

2.3. Data Processing and Statistical Analyses

2.3.1. Behavioural Data

Statistical analysis was performed in R[47]. Two participants did not complete the second experimental session and were excluded from analysis. For each TOPX run, we computed accuracy, probe reaction time (RT), D′-Context, and proactive behavioural control (PBI) indices, and quantified pre–post rTMS change using metric-appropriate difference or ratio scores (definitions in **Supplementary Materials**). Those change scores were analysed as a function of behavioural state at the time of TMS ($\text{ActiveState}_{\text{rTMS}}$, $\text{ControlState}_{\text{rTMS}}$) using a series of linear mixed-effects models, including session number (1, 2) as a fixed effect and subject IDs as a random intercept. 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[48–50].

Recent work from our group[49,51–53] and others[54–57] suggests that neurostimulation of PFC and connected structures affects evidence accumulation processes. To assess those after our task-linked intervention, we hierarchically fit drift diffusion models (DDMs) to reaction times and response accuracy to infer latent processes of evidence accumulation towards decisions in TOPX. Model specification followed prior work applying hierarchical DDMs to expectancy-based tasks[57], where the *v* and *a* parameters were permitted 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 verified that this model structure fit the data well using an information criterion analysis (Supplementary Methods).

2.3.2. Electroencephalography

EEG data were pre-processed offline using EEGLAB[58] and FieldTrip[59] 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[60]. Data were resampled 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 pulse and muscle artifacts, and a second ICA to remove remaining artifactual components[60,61]. In addition, we band-pass filtered at 1 – 50 Hz and re-referenced to the average of all channels.

To extract task-evoked and TMS-evoked oscillatory activity, we applied a Morlet wavelet decomposition on single trials[62]. 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.

We also considered that cognitive 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[63]. The TOPX task, which is based upon the AX-Continuous Performance Test (AX-CPT[64–67]) probes both these mechanisms by

modifying the type of contextual information provided prior to a context-dependent response[65,68]. For instance, distractor cues provide sufficient contextual information to indicate that the trial sequence is a non-target, allowing participants to maintain goal-relevant information in advance and deploy proactive control. In contrast, target cues provide insufficient context to determine the appropriate response until presentation of the probe stimulus, thereby evoking greater reactive control demands (**Figure 1**). Because proactive and reactive trials were expected to engage partially distinct spatial distributions of activity[69], we analysed ERSPs using cluster-based permutation tests to identify scalp-wide, data-driven regions of interest, rather than imposing a-priori electrode or source locations. 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). Theta band activity has a known role in executive functioning[70–73], and thus, we primarily expected TMS to modulate activity within that band during the cognitive control task. Therefore, 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[74] relative to single-pulse TMS or the end of the rTMS train.

3. Results

3.1. State-Dependent Enhancement of Cognitive Control

3.1.1. Accuracy

Task-linked rTMS enhanced cognitive control, but only when the target circuits were engaged by the task ($F_{(1, 45)} = 6.11$, $p = .017$, $R^2 = .121$), with ratios of accuracy significantly greater than $\mu = 1$ (baseline) for $ActiveState_{rTMS}$ ($M = 1.03$, $SD = 0.04$, $p = .005$), but not for $ControlState_{rTMS}$ ($M = 1$, $SD = 0.04$, $p = .985$; **Figure 2A**). Raw behavioural data are presented in the **Supplementary Materials Figure S1**.

3.1.2. Reaction Time

Reaction time was differentially shortened after TMS as a function of rTMS State ($F_{(1, 22.39)} = 6.70$, $p = .017$, $R^2 = .099$; **Figure 2B**), and indicated a numeric shortening of reaction time in the $ActiveState_{rTMS}$ condition ($M = -17.49$ ms, $SD = 55.14$), but not the $ControlState_{rTMS}$ condition ($M = 14.52$, $SD = 51.52$). Those RT differences were not significantly different from $\mu = 0$ (no change) in either $ActiveState_{rTMS}$ or $ControlState_{rTMS}$ conditions, but the difference between RTs from the two conditions ($ActiveState_{rTMS}$ relative to $ControlState_{rTMS}$) was significant ($p = .017$).

3.1.3. Contextual Behavioural Performance

Contextual processing as indexed by D□-Context showed a state dependent enhancement following TMS ($F_{(1, 45)} = 4.62$, $p = .037$, $R^2 = .094$; **Figure 2C**), with significantly greater TMS-evoked change for $ActiveState_{rTMS}$ ($M = 0.88$, $SD = 0.80$, $p < .001$) relative to $\mu = 0$ ($p < .001$) and relative to $ControlState_{rTMS}$ ($p = .043$). In contrast, $ControlState_{rTMS}$ differences were not significantly different from $\mu = 0$ ($M = 0.02$, $SD = 1.83$, $p = .965$). PBI measures did not significantly change after TMS (see **Supplementary Materials**).

3.1.4. Evidence accumulation

Hierarchical drift diffusion modelling revealed no modulation of drift rate or decision threshold. In contrast, starting point bias showed a state-dependent modulation by rTMS which depended on contextual information (cue type with rTMS state interaction on bias ratios, $F_{(1, 68.48)} = 2334.45$, $p < .001$, $R^2 = .962$; **Figure 2D**). For A cues, the rTMS evoked change in starting point bias was significantly greater than $\mu = 1$ for both the $\text{ActiveState}_{\text{rTMS}}$ ($M = 1.01$, $SD = 0.01$, $p < .001$) and $\text{ControlState}_{\text{rTMS}}$ ($M = 1.01$, $SD = 0.01$, $p < .001$) 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 $\mu = 1$ for $\text{ActiveState}_{\text{rTMS}}$ ($M = 1.15$, $SD = 0.01$, $p < .001$), a significant decrease relative to $\mu = 1$ for $\text{ControlState}_{\text{rTMS}}$ ($M = 0.98$, $SD = 0.01$, $p < .001$), and the change was significantly different between the two conditions ($p < .001$). In a follow-up experiment, we found that task-switching or practice effects do not explain our observed behavioural effects (see **Supplementary Materials**).

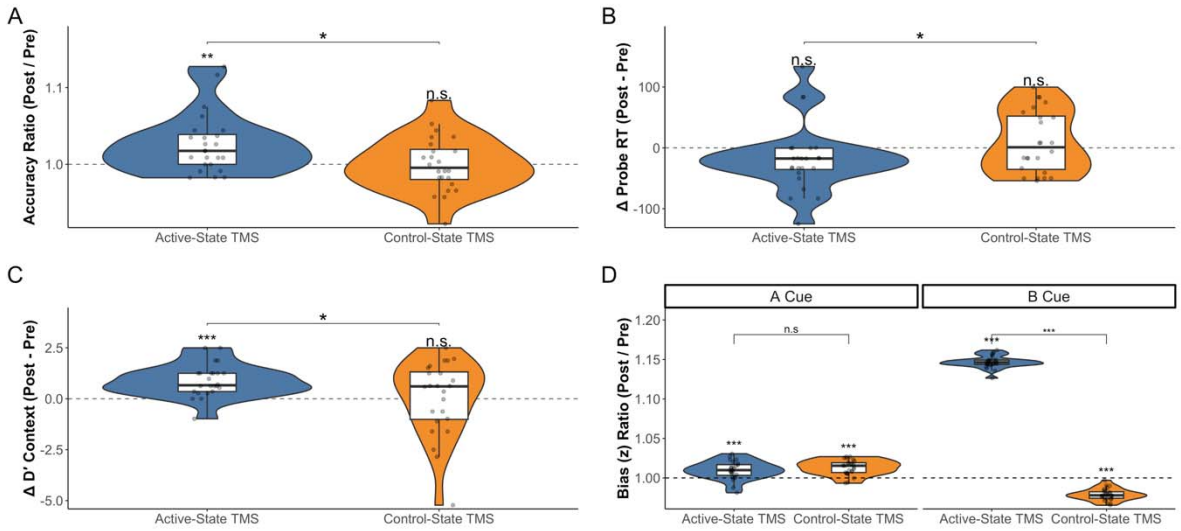


Figure 2. Enhancement of cognitive control by active-state TMS. (A) Accuracy was enhanced by TMS when cognitive control circuitry was engaged, but not when non-target circuits were engaged during TMS. (B) Probe RTs were numerically shortened by Active-State

TMS, but that difference was not significantly different from μ = 0 (no change). However, RT shortening showed a significant improvement after Active-State TMS relative to Control-State TMS. (C) Contextual processing, represented by D'-Context, showed a similar state-dependent enhancement after Active-State TMS, but not Control-State TMS. (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 that differed as a function of the behavioural state during stimulation. 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**.

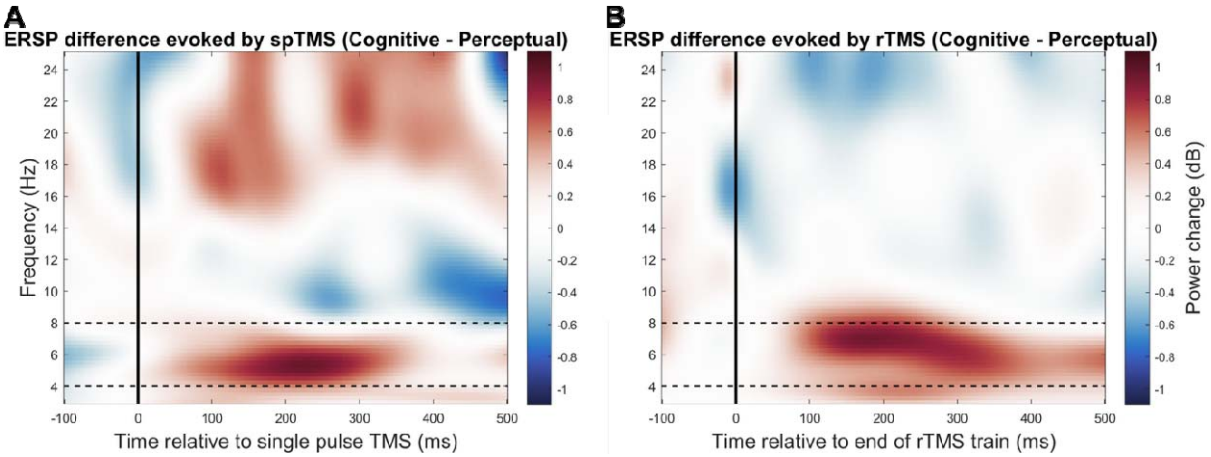


Figure 3. **State-dependent theta band activation evoked by TMS.** (A) Differences in ERSP power between TOPX and Perceptual tasks evoked by single-pulse TMS indicate an enhancement of TMS-evoked theta band oscillatory power during states of cognitive control relative to perceptual (control) states. (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. Power is computed against a divisive baseline in the linear power domain from -500 to -100 ms relative to the target event.

3.2.2. State Dependent Modulation of Contextual EEG Responses

Cue-locked TOPX ERSPs were selectively modulated after TMS as a function of the behavioural state during TMS. Following $\text{ActiveState}_{\text{rTMS}}$, the power of cue-locked theta-band ERSPs was

significantly reduced 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. The effect was expressed over frontocentral and parietal electrodes for target cues, and left-prefrontal electrodes 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**).

Probe-locked theta-band ERSPs were also reduced after $\text{ActiveState}_{\text{rTMS}}$ 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**) and spectral specificity to the theta and low-alpha bands (latency = 0 – 598 ms, $t_{(22)}$ = -7.17, p = .010, d = -1.64; **Figure 4F**). In contrast, no significant clusters were detected for cue or distractor probe-locked ERSPs after $\text{ControlState}_{\text{rTMS}}$.

Because sustained changes in pre-stimulus oscillatory activity could drive the observed state-dependent attenuation of theta ERSPs, we examined power spectral densities of the baseline periods used during computation of the ERSPs. Broadband spectral power increased on average after active-state TMS, but not control-state TMS (see **Supplementary Figure S3**). However, at the level of individual subjects, those broadband power spectral shifts did not explain the magnitude of theta ERSP attenuation (see **Supplementary Materials** for a more

detailed analysis). Therefore, the data suggest that TMS specifically modulated stimulus-locked theta activity in a state-dependent manner.

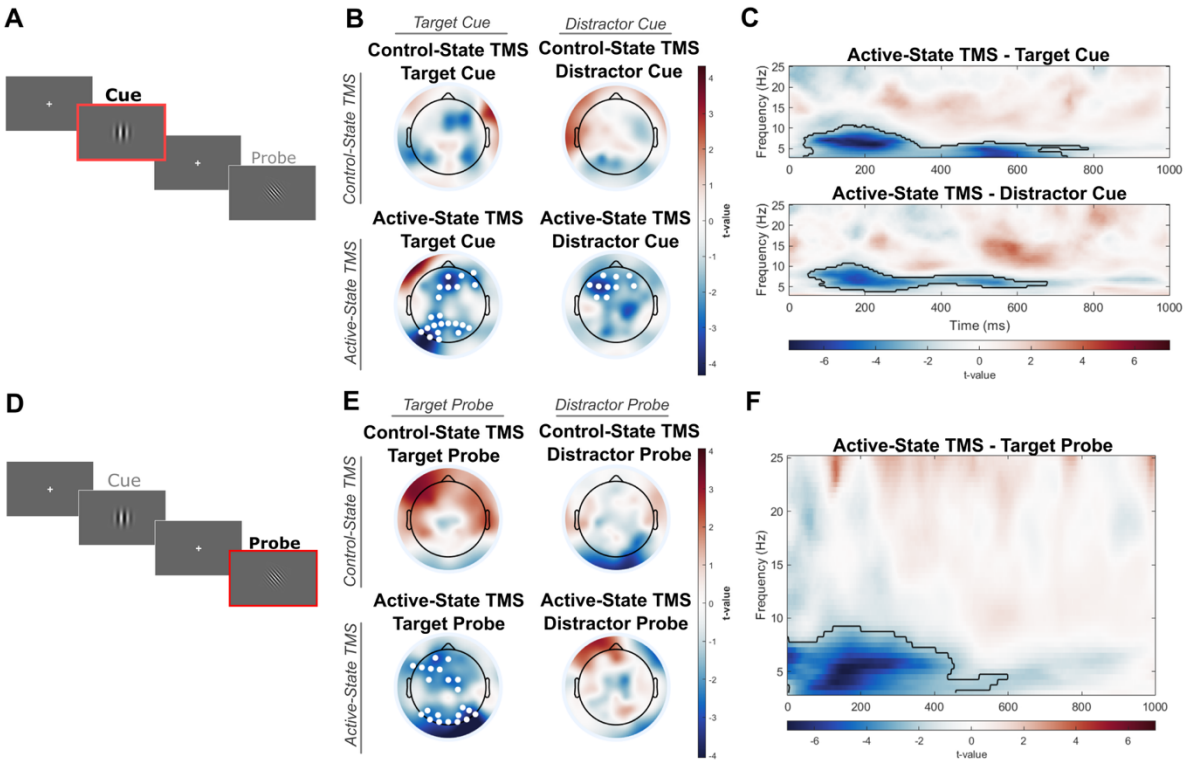


Figure 4. Modulation of goal maintenance and context processing by active-state TMS. (A) Theta-band oscillatory power evoked by TOPX cues was calculated as a difference from Pre- to Post- TMS, as a function of behavioural state at the time of TMS, showing a state-dependent modulation of context processing 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 distractor 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.

4. Discussion

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 perceptual discrimination task produced little measurable change. These findings provide direct evidence that endogenous engagement of PFC-anchored networks can sensitise those circuits to shape the magnitude and functional relevance of TMS-induced plasticity.

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

Hebbian learning and metaplasticity models predict that active circuits are more receptive to modification[18,19]. Thus, actively engaging a target circuit in a desired state may bias the effects of neuromodulation. The notion that the ongoing state of neural activity can shape the propagation

of TMS-evoked activity has been demonstrated across sensorimotor[16,27,29,75], attention[30–33], and memory[34–36] domains. Here, we have shown the state dependence of TMS effects in complex cognitive function which spans across those domains. Relatedly, differential effects of TMS on affective processing have recently been observed to depend on trait-state depression severity at the time of stimulation[76]. Our results here highlight that states of cognition can be specifically manipulated to bias the effects of TMS toward clinically relevant outcomes. The effect on RT was smaller than we have previously reported with deep brain stimulation using a different cognitive control task[50], but this might be expected for a non-invasive intervention.

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[77–82] and downstream readouts of that function can provide an objective measure of target circuit engagement[83,84]. State-dependent circuit sensitisation 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). Moreover, we specifically showed in a follow-up experiment that practice/switching effects do not explain our results (see **Supplementary Materials**). An additional consideration is that we did not perform electric field modelling, which provides estimates of TMS-induced current distribution[85,86]. Importantly, such models do not specify which neural populations or networks are functionally engaged. Given that

TMS-induced fields are relatively distributed across the cortex[87,88], our study was not designed to rely on precise spatial localisation. Rather, we aimed to demonstrate that state-dependent circuit sensitisation plays a prominent role in stimulation outcomes. Together, our results suggest that TMS might be paired with structured cognitive exercises/training to increase the chance of response. 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[52].

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[63,89]. 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[90]. Those biases are postulated to originate from anticipatory lateral PFC activity and a gating mechanism operating through corticostriatal circuits[89,91]. 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[90]. This process is thought to occur via a distinct and broader fronto-parietal network[91,92]. 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[37,71,92,93]. The spatial distribution and modulation within the theta band induced by $ActiveState_{rTMS}$ is consistent with the above. Responses to non-target Distractor cues (which provide contextual

information that permits proactive control) were modulated by active-state TMS, showing a reduction in theta band oscillatory power in a region over the 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 control mechanisms may have been modified by active-state TMS.

We were surprised to observe a decrease, rather than an increase, in the power of task-evoked EEG responses after active-state TMS. For non-target cues, one interpretation is that this may reflect more active gating of PFC from subcortical regions, consistent with a proactive mode of control[89]. However, this does not explain the reduction of oscillatory theta power after (reactive) target cues and target probes. Given that behavioural metrics of control improved, a more parsimonious 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[71,92,94]. Higher theta band oscillatory power may reflect compensatory recruitment of control resources when conflict is high or processing is inefficient. Thus, the attenuated 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. This may reflect less effortful cognitive demands during conflict resolution, for instance, if prepotent responses are more easily inhibited after modulation of the underlying control networks. Additional peripheral measures of arousal associated with effort[95,96] may help to delineate this further in the future.

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. Strategies to 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 our sample consisted 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 improvements in cognitive control relate to clinical symptom improvement[50,52,97–100], 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 inflexible or overly reactive thought and behaviour patterns. For example, impaired context sensitivity may contribute to persistent negative thinking and impaired expectation updating in individuals living with depression[101]. Anxiety and phobias may involve exaggerated threat responses that persist even in the absence of contextual safety cues[102]. Similarly, obsessive-compulsive disorders may involve difficulty in using contextual information to suppress habitual behaviours[103]. As such, enhancing the function of circuits that support context processing and flexible control has broad potential to remediate a transdiagnostic marker of impairment[104].

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-dependent circuit sensitisation in prefrontal TMS can offer a path toward more reliable brain stimulation interventions.

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Declaration of Competing Interests

ASW reports consulting income from Abbott Laboratories, equity in Resilient Neurotherapeutics, and multiple unlicensed patents in the area of neurostimulation. All other 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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