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Title
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Journal
Proceedings of the Annual Meeting of the Cognitive Science Society, 40(0)

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Publication Date
2018

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Dorsal Premotor Cortex and Conditional Rule Resolution: A High-Frequency TMS Investigation

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Abstract

Behavior that is contingent on conditional rules necessitates an abstraction away from concrete stimulus-response identities in order to form a rule template, but also a subsequent transformation of representation back into sensorimotor format in order to produce concrete behavior. Evidence suggests that dorsal premotor cortex (PMd) is well-positioned to mediate such an operation. We utilized repetitive transcranial magnetic stimulation, a non-invasive manner of perturbing the functioning of targeted cortical regions, to investigate the role of dorsal premotor cortex during performance of a Rapid Instructed Task Learning paradigm. The task required participants to form conditional associations between stimuli and responses carrying varying levels of abstraction. Selective interference of response times to stimuli presentation was observed only when the task necessitated the participants to resolve a conditional response referring to an internally-produced representation of a rule element with relatively abstracted quality. We conclude that PMd specifically supports conditional rule behavior through transformation of abstract representations to concrete response, when the conditional rule necessary to resolve includes abstract, internally-produced identities.

Keywords: Prefrontal Cortex; Premotor Cortex; Transcranial Magnetic Stimulation; Stimulus-Response associations; Abstract Rule Representation

Introduction

Behavior is often conditional; for instance, a dog may not be as excited to go for a walk when it is raining, and a human may take care to grab an umbrella before going on the walk. Accounting for these contingencies requires a generalization away from concrete (i.e. specific) stimulus/response (S/R) identities to a representation that considers categories of potential stimuli and responses. Categories are linked in a series of relationships, where knowledge of a specific identity in one category allows resolution of specific identity in another. To successfully guide goal-directed behaviors, effective utilization of general task rules requires a linkage between an abstract, generalizable format that allows for abstracted conditional relationships, and a concrete, direct S/R format compatible with sensorimotor systems.

Individuals are informed of many conditional relationships through instructed rules, which clarify how categories of stimuli and response are linked together. Converging lines of evidence suggest that the frontal cortex is responsible for the representation of these rules. In humans, neuroimaging studies have demonstrated that regions of prefrontal cortex (PFC) are activated while humans are learning new task rules or executing behavior in accordance with learned rules (Strange, Henson, Friston, & Dolan, 2001; Stocco, Lebiere, O'Reilly, & Anderson, 2012).

Although rule representation has been a major focus of studies of PFC functioning, relatively little is known regarding how abstract rule representations are converted into specific motor plans. Anatomically, the dorsal premotor cortex (PMd) is well-situated for carrying out such a transformation (Hanakawa, 2011). This structure receives input from frontal and sensory regions and outputs predominantly to regions within primary motor cortex (M1) that represent primary effectors (Tomassini et al., 2007; Guye et al., 2003). In particular, PMd receives input from both the dorsolateral PFC, which has been shown to encode both abstract rules and categories (Wallis, Anderson, & Miller, 2001; Wutz, Loonis, Roy, Donoghue, & Miller, 2018), and the posterior parietal cortex, a site of multisensory integration (Xing & Andersen, 2000). Accordingly, PMd has been proposed to play a role in the transformation of simple contextual cues into motor responses on the basis of present sensory information (Wise, Boussaoud, Johnson, & Caminiti, 1997). Preferential activation of PMd for conditional motor tasks in humans has been demonstrated in both PET and fMRI studies (Grafton, Fagg, & Arbib, 1998; Kurata, Tsuji, Naraki, Seino, & Abe, 2000), while humans with PMd lesions are specifically impaired in learning conditional associations between visual, tactile, or auditory cues and motor responses (Halsband & Freund, 1990). There is also evidence that PMd is involved in the processing of internal representations. For instance, transcranial magnetic stimulation (TMS) over PMd disrupts both manipulation of visuospatial information (Oshio et al., 2010) and prediction of occluded action (Stadler et al., 2012). In monkeys, inactivation of PMd degrades performance of internally generated movements, but not spatially guided ones (Ohbayashi, Picard, & Strick, 2016).

PMd may integrate abstract rule representations and current sensory information to resolve general associations into specific motor actions. However, the degree to which PMd supports conditional motor behavior remains unclear. We sought to further delineate PMd's role in translating abstract rule representation into concrete behavior by employing a Rapid Instructed Task Learning (RITL) paradigm (Cole, Laurent, & Stocco, 2013). Participants were instructed of conditional rules that allowed the resolution of a response during

stimulus presentation; however, the stimuli of a subset of trials violated the instructed contingency, requiring the participant to infer an appropriate response. During performance of this task, repetitive TMS (rTMS) was selectively applied over PMd during one of two time points during a given trial: either "early", as the participant was encoding the trial–specific rule (the "encoding phase"), or "late", while the participant was preparing a response according to the instructed or inferred contingency (the "execution phase"). In this application, rTMS induces an "informational lesion", disrupting the usual neurodynamics of the targeted cortical region throughout the stimulation periods. This disruption could either (1) *prevent* processing, in which case the targeted cortical region is unable to perform its normal function during stimulation, but resumes normal processing afterwards; or (2) *degrade* processing, in which the fidelity or quality of processing occurring during the time-course of stimulation is reduced. The first case would likely increase response times, indicating that the *speed* of processing has been affected, while the second case would likely reduce accuracy rates, indicated that the *quality* of processing has been affected.

We hypothesized that, as rules in our paradigm are explicitly instructed during the encoding phase, early rTMS should have no effect on either response times or accuracy rates during either the encoding or execution phases. Instead, late rTMS should temporarily prevent the resolution of a motor response, leading to increased response times in the execution phase. Furthermore, if PMd handles the resolution of conditional rules that refer to internal representations of stimulus identity, increased execution response times should be specific to conditions in which participants had to actively infer a valid rule.

Methods

Participants

Twelve right-handed volunteers (8 females, mean age = 24.7 $\pm$ 3.3) with no history of neurological disorder, head injury, or any other contraindications to rTMS participated in the study. Recruitment was restricted to individuals who had previously participated in neuroimaging experiments at the University of Washington, and for whom structural and functional imaging data was available. Only eight participants completed the study, as the appropriate resting motor thresholds for rTMS stimulation were unable to be determined for the remaining four. All participants received monetary compensation proportional to the total amount of time devoted to the study. The experimental protocol was approved by the University of Washington's Institutional Review Board.

Experimental Task

We constructed a RITL-based task paradigm focused on conditional motor behaviors. The progression of the task is depicted in Figure 1. Participants were instructed to determine the parity of a numeric stimulus presented on the center of the screen (restricted to the digits two through nine and randomly chosen on a trial-by-trial basis) and to respond on the basis of a trial-specific rule. Responses occurred by pressing the "left" or "right" arrow keys on a standard QWERTY keyboard with the participant's right-hand index and middle fingers, respectively.

Participants were presented with two types of rules: "concrete" rules, which indicated the association of a specific effector (either index or middle fingers of the right hand) to a specific parity; and "symbolic" rules, which indicated the association of a specific letter on the screen ("A" or "B") to a specific parity. Specific effectors in the "concrete" condition were indicated during rule presentation by a stylized hand (black on white background), with the rule-specific effector denoted by a red circle around the tip of the finger. Specific effectors in the "symbolic" condition were indicated during stimulus presentation by the placement of the letters "A" and "B", which were randomly assigned to the bottom left and right corners of the screen on a trial-by-trial basis. To make the two conditions visually comparable, these letters appeared during the stimulus presentation phase of both "concrete" and "symbolic" trials, although they only carried meaning in the "symbolic" condition. Participants were informed that the bottom left corner corresponded to the "left" arrow key, while the bottom right corner corresponded to the "right" arrow key. Due to this manipulation, participants performing during a "symbolic" rule trial could not plan a specific motor response until stimulus presentation.

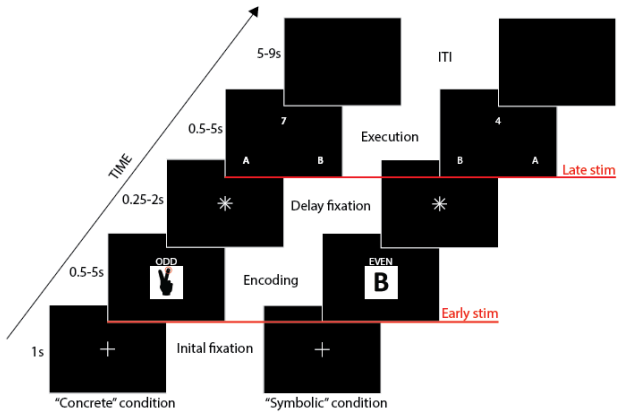


Figure 1: The task paradigm. Participants completed randomly interleaved "concrete" (*left*) and "symbolic" rule (*right*) trials. rTMS stimulation was delivered either upon presentation of the rule ("early") or upon presentation of the stimulus ("late").

So, a "concrete" rule such as "Even:Index" indicates that, if the to-be-presented digit stimulus is even, the participant should use their index finger to respond, while a "symbolic" rule such as "Odd:B" indicates that, if the to-be-presented digit stimulus is odd, the participant should respond with the key that is assigned to the position that *B* appears in during

stimulus presentation (i.e., if the digit stimulus is 7, and *B* is in the lower left corner, the index finger should be used to press the left arrow key).

Crucially, only half of a trial's rule is displayed. That is, a participant may be given the task rule "*Even*:Index", then asked to respond to a stimulus (e.g., "7") that is *odd*. Under these circumstances, participants have to re-process the rule and mentally generate a new version that deals with the new stimulus-response configuration. This conferred to the task another level of complexity in which the operative half of the trials rule is either *instructed* (i.e., the rule instructed what to do for an even digit, and the stimulus was an even digit) or *inferred* (i.e., the rule instructed what to do for an even digit, but the stimulus was an odd digit, and the other half of the rule had to be inferred by the participant).

The task consisted of 4×60 trials, with a 5-minute break enforced between each block. Completion of the experiment, including the individualized setup for TMS and neuronavigation, took approximately three hours. Each trial began with a central fixation cross displayed for 1s. Immediately after, the rule informing the participant of the individual trial's valid associations was displayed for a maximum of 5s. Presentation of rule condition was randomized and balanced across trials within a block, while whether a trial was instructed/inferred was randomly determined on a trial-by-trial basis. Participants acknowledged understanding of the presented rule by pressing the spacebar with their *left* hand, so as to not to interfere with the activity of the *right* hand used for the response mappings. If no response occurred within 5s of rule presentation, the trial was terminated. After participants acknowledged the rule, a variable (0.25–2s) delay occurred while a fixation "asterisk" was displayed. The delay was variable in order to ensure that the participant had encoded the rule during rule presentation, rather than rely on the delay to "figure it out" while waiting for the stimulus. The fixation "asterisk" was different from the initial fixation cross so that it would assist participants in tracking the progression of the trial. Once this delay had passed, the stimulus was displayed and participants were given a 5s window to respond by pressing the left or right arrow key with the index or middle finger of their right hand. Upon response (or after 5s had passed), a variable inter-trial interval (5–9s) was enforced while a blank screen was displayed.

Event-related rTMS was delivered across two sites (left PMd, experimental; Vertex, control) in alternating blocks, the order of which was balanced across participants. There were two possible time points of stimulation during a trial, either upon presentation of the rule instruction screen (referred to as "early" stimulation), or upon presentation of the stimulus screen (referred to as "late" stimulation); however, in one third of trials in a given block, no stimulation was delivered, and in all other trials, only one instance of stimulation occurred per trial. Instances of stimulation were pseudo-randomized so that consecutive segments of three trials contained one instance of early stimulation, one instance of late stimulation, and one instance of no stimulation in randomized order. Due to the possibility of rTMS delivery either inducing an unwanted motor response or suppressing a genuine response, participants were locked out of responding to either screen for the first 0.5s of presentation, and made aware of this fact. In agreement with rTMS safety guidelines, instances of stimulation did not occur more than once every 8s.

Transcranial Magnetic Stimulation

Parameters High-frequency repetitive TMS (rTMS) was performed with a 70mm figure-of-eight coil (Double Alpha coil, Magstim, UK) connected to a biphasic magnetic stimulator (Super Rapid^2, Magstim, UK). Online rTMS consisted of a five-pulse train delivered at 10 Hz. The coil was placed over the stimulation sites tangential to the skull, with the handle pointed at 45° to the sagittal plane (in the case of left PMd stimulation) or backwards, parallel to the midline (in the case of vertex stimulation). The intensity of stimulation across both stimulation sites was set to 110% of the individual's resting motor threshold.

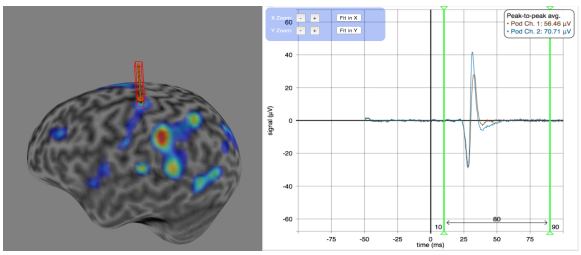


Figure 2: Screenshot of a portion of the Brainsight software display. *Left*: A 3D structural MRI with functional imaging data overlaid; the PMd target is indicated by the orange arrow in a red box. *Right*: Time course of an MEP response elicited by single pulse stimulation of M1.

Target Localization for TMS As the participants had existing structural and functional MRI data, neuronavigation was utilized in order to achieve sub-millimeter precision in the targeting of stimulation sites. The targeting of the rTMS coil was achieved through the use of a frameless stereotactic system, which tracked the location of the participant's heads relative to the coil with an IR tracker camera and co-registered these locations with the individual participant's structural and functional images using Brainsight software (Rogue Research, Montreal, QC, Canada). The location of PMd stimulation was determined by targeting the most significant voxel in a a cluster identified while the participant was making a finger response, ensuring that the location was in good agreement with published anatomical landmarks (Fig. 2, left). The location of Vertex stimulation was defined by position the rTMS coil over the sagittal midline, at the level of the postcentral gyri (location Cz in the 10-20 system). Trials in which the stimulated area was more than 3.0mm away from the designated target were excluded from all analyses.

Assessment of Resting Motor Threshold In order to determine each participant's resting motor threshold (RMT), electromyography surface electrodes were placed over the muscle belly and corresponding tendon of the right first and third dorsal interosseous (FDI) muscles in a belly-tendon montage. The software utilized for neuronavigation included an EMG interface that allowed imaging of muscle activity time-locked to a single pulse (Fig. 2, right) delivered over the left primary motor cortex (M1). Occurrences of motor evoked potentials in response to stimulation were recorded and entered into a parameter estimation algorithm (PEST: Taylor and Creelman, 1967) in order to derive the RMT. A valid MEP was defined as a muscular response to M1 stimulation of at least 50 mV peak-to-peak amplitude.

Results

All analyses and plots were generated with the R software (R Core Team, 2013) and the ggplot2 package (Wickham, 2009). Neuronavigation-guided coil targeting indicated that, for one block of one participant's data, the coil position had drifted more than 3.0mm away from the intended site of stimulation. As such, trials from that block (60 total) were excluded from analysis. On average, participants were very accurate across conditions ($M = 95\%$), and no significant differences in accuracy due to task condition or TMS application were observed. Error trials (94 out of 1860 total) were excluded from all subsequent analyses.

In both the encoding phase and the execution phase, there was no significant difference between the response times of the control conditions of early Vertex stimulation, late Vertex stimulation, and no stimulation, as revealed by two repeated-measures one-way ANOVAs (Encoding Phase: $F(2,14) = 3.21$, $p > 0.07$; Execution Phase: $F(3,21) = 0.98$, $p > 0.42$; Fig. 3). Thus, trials without stimulation were excluded from the rest of the analysis, so that more straightforward statistical comparisons between the experimental (PMd) and control (Vertex) conditions could be carried out.

For the encoding phase of early and no stimulation trials, a repeated-measures two-way ANOVA considering the effect of site of stimulation and type of rule revealed no significant main effects or interactions of these conditions on the encoding response time (Fig. 4).

A repeated-measures four-way ANOVA examining the effect of site of stimulation, timing of stimulation, type of rule, and instruction/inference of rule on execution phase response times revealed a main effect of rule ($F(1,7) = 238.30$, $p < 0.0001$) alongside a main effect of inference ($F(1,7) = 31.44$, $p < 0.001$). Across participants, response times for "symbolic" trials were 217 ± 9ms (mean $\pm$ sem) longer than "concrete" trials, while response times for "inferred" trials were 149 ± 22ms longer than response times for "instructed" trials. Additionally, a significant two–way interaction between site of stimulation and type of rule was observed ($F(1,7) = 16.70$, $p = 0.005$), while a significant three–way interaction between site of stimulation, timing of stimulation, and instruction/inference ($F(1,7) = 13.30$, $p = 0.008$) was also present.

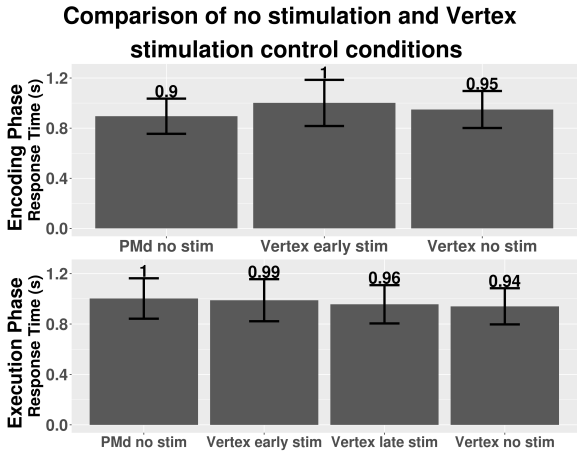


Figure 3: *Top:* Response times during the encoding phase, across control conditions. *Bottom:* Response times during the execution phase, across control conditions. Error bars represent standard errors, numbers are mean values.

Due to the significant two- and three-way interactions, we separately investigated the four subconditions (Inferred-Early stimulation; Inferred-Late; Instructed–Early, Instructed–Late) within which the two-way interaction occurred. Repeated-measures two-way ANOVAs considering the site of stimulation and type of rule again revealed a main effect for rule in all four subconditions ($F(1,7) > 16.9$, $p > 0.004$). This main effect was driven by the rule type, with symbolic rules ("Even:A") taking predictably longer than concrete rules ("Even:Index") in all cases. The Inferred–Late subcondition was the only subcondition to carry a significant interaction between site of stimulation and type of rule ($F(1,7) = 10.11$, $p = 0.015$).

As the Inferred–Late subcondition seemed to be driving the significant two-way interaction between site of stimulation and type of rule within the four-way ANOVA, we examined the differences in response times between PMd and Vertex stimulation within the rule types ("symbolic" and "concrete") specifically for this subcondition. Paired t-tests revealed there to be no difference in mean response times between PMd and Vertex stimulation on "concrete" trials (paired $t(7) = 0.12$, $p > 0.90$), but a significant difference in mean response times between PMd and Vertex stimulation on "symbolic" trials was observed (Paired $t(7) = 3.21$, $p = 0.015$) (Fig. 5B). Subsequent t-tests between PMd and Vertex stimulation within the rule types of the other three subconditions revealed no significant differences in mean response times (Fig. 5A,C,D). This pattern of results indicates that the significant interactions revealed by the above ANOVAs were driven by an effect within the Symbolic-Inferred-Late sub-condition.

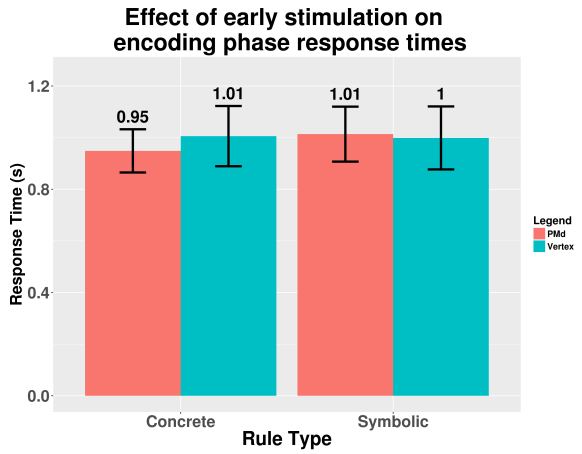


Figure 4: Response times in the Encoding phase, across rule type and stimulation site. Error bars represent standard errors, numbers are mean values.

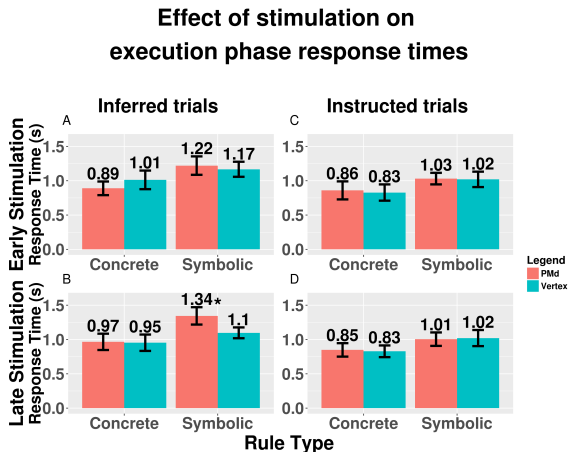


Figure 5: Response times in the Execution phase, across rule type in stimulation site. Error bars rule represent of standard errors, numbers are mean values.

Discussion

A Rapid Instructed Task Learning paradigm was utilized in conjunction with repetitive TMS in order to determine if dorsal premotor cortex mediates between abstract rule representation and concrete behavior. The paradigm required participants to quickly encode a rule indicating a stimulus–response association between the parity of a digit stimulus and either the index/middle finger of the right hand ("concrete"), or a placeholder letter that would be later associated with a finger ("symbolic"). Only one of the two possible parity judgments was associated with a finger response or placeholder, requiring participants to infer the S/R association if the parity of the presented digit did not match that which was instructed. It was observed that 10–Hz rTMS over PMd increased response times relative to controls only when the stimulation occurred while participants were actively inferring a "symbolic" rule.

One possible explanation for this finding is that PMd is involved in the formation of abstract rule representations. Dorsolateral PFC, a site of abstract rule representation, possesses bidirectional connectivity with PMd, while PMd itself has been implicated in "binding" operations, which formation of conditional associations most likely necessitates (Lu, Preston, & Strick, 1994; Hanakawa, 2011). If PMd served a role in forming the rule representations required by our task, it would be expected that early rTMS (i.e., during the encoding phase of the trial) would either disrupt the participant's ability to form the conditional association instructed by the rule, thereby increasing encoding phase response times, or degrade the fidelity with which that rule is represented, increasing execution phase response times and/or error rates. As dlPFC appears to handle relatively "high–level" abstractions (Wutz et al., 2018), this effect could be specific to "symbolic" trials. Despite this, we observed there to be no effect of "early" rTMS perturbation of PMd on either response times during the "encoding phase" or the "execution phase", for both "concrete" and "symbolic" trials. However, this does not necessarily rule out a role of PMd formation of abstract rule representations. Note that as PMd is also implicated in operations involving internal representations (Oshio et al., 2010; Stadler et al., 2012), it may preferentially bind stimulus and response identities that have been produced by internal operations, rather than informed by extrinsic sources. Since the rules in our task always explicitly instructed concrete identities, no inference was required during the encoding phase, and all information that was available to be bound into a S/R association was extrinsically informed.

Alternatively, if PMd is involved in the execution of behavior in accordance with a previously-formed rule representation, late rTMS should have a specific effect on execution phase response times, when present stimuli provide the necessary information to resolve a proper response. Again, this effect could be differential between "concrete" and "symbolic" trials, if involvement of PMd is dictated by highly-abstracted rule representations in dlPFC. We observed that rTMS had no effect on "concrete" trials, regardless of whether the trial was "instructed" or "inferred". Late rTMS did have a specific effect for "symbolic" trials, but only when the parity instructed by the trial's rule was invalid. So, late rTMS did not have an effect on execution response times across "instructed" trials, indicating that it was not involved in the resolution of a response on the basis of formerly created rule representations and present environmental stimuli. Instead, it did have an effect specifically within "inferred symbolic" trials.

What does this very specific effect imply about PMd functioning? If rTMS interfered with judgment of the digit's parity, it would be expected that late rTMS would increase response times in all execution phase response times, relative to controls. However, inferred "concrete" and instructed "concrete" and "symbolic" trials remain unaffected. Likewise, late rTMS cannot be significantly affecting the visual search for the "placeholder" on "symbolic" trials, otherwise

instructed "symbolic" trials should be affected similarly to inferred "symbolic" trials. The execution phase of "inferred symbolic", trials, however, is the only point within our task paradigm that requires the resolution of a rule that refers to an internally–produced representation of an abstracted response (i.e., the placeholder *A* or *B*). When the stimulus parity does not match that instructed by the rule, across both "concrete" and "symbolic" conditions, the participant must calculate what to do in response to the evident parity. In "concrete" trials, inference does occur, but the result of that inference is a concrete motor effector, carrying little to no abstraction. In "symbolic" trials, the result of inference is a secondary abstraction (i.e., the placeholder letter) that, through lack of alternatives, must be bound to the apparent parity. PMd rTMS specifically increased response times while resolution of conditional associations between abstract and internally–produced representations was occurring, but not while similar resolution operations between relatively concrete or externally instructed stimuli were necessary.

In conclusion, noninvasive stimulation of the dorsal premotor cortex, a brain region implicated in conditional motor behavior, was found to selectively interfere with responses when task conditions required a resolution of a conditional association referring to abstracted, internally-produced representations, but not when resolution between concrete or externally-informed representations was necessary. This result suggests that PMd does subserve conditional rule-based behavior, but only when it is reliant on internally-produced representations that are abstracted away from concrete motor effectors.

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