# Associative Visuomotor Learning Using Transcranial Magnetic Stimulation Induces Stimulus–Response Interference

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## Abstract

■ Classical conditioning states that the systematic co-occurrence of a neutral stimulus with an unconditioned stimulus can cause the neutral stimulus to, over time, evoke the same response as the unconditioned stimulus. On a neural level, Hebbian learning suggests that this type of learning occurs through changes in synaptic plasticity when two neurons are simultaneously active, resulting in increased connectivity between them. Inspired by associative learning theories, we here investigated whether the mere co-activation of visual stimuli and stimulation of the primary motor cortex using TMS would result in stimulus–response associations that can impact future behavior. During a learning phase, we repeatedly paired the presentation of a specific color (but not other colors) with a TMS pulse over the motor cortex. Next, participants performed a two-alternative forced-choice task where they had to categorize simple shapes and we studied whether the shapes' task-irrelevant color (and its potentially associated involuntary motor activity) affected the required motor response. Participants showed more errors on incongruent trials for stimuli that were previously paired with high intensity TMS pulses, but only when tested on the same day. Using a drift diffusion model for conflict tasks, we further demonstrate that this interference occurred early, and gradually increased as a function of associated TMS intensity. Taken together, our findings show that the human brain can learn stimulus–response associations using externally induced motor cortex stimulation. Although we were inspired by the Hebbian learning literature, future studies should investigate whether Hebbian or other learning processes were also what brought about this effect. ■

## INTRODUCTION

Classical conditioning is a dominant theory of learning in psychology. It argues that the consistent pairing of a neutral stimulus with an unconditioned stimulus should, over time, result in the neutral stimulus eliciting the same response as the unconditioned stimulus (Pavlov, 1927). Largely inspired by Pavlov and others (Brown & Milner, 2003), this famously led to the proposal of the Hebb rule that postulates that, on a neural level, the consistent co-activation of two neurons should result in increased connectivity through changes in synaptic plasticity if one repeatedly takes part in firing the other (Keysers & Gazzola, 2014; Caporale & Dan, 2008; Bi & Poo, 2001; Hebb, 1949). As a framework, Hebbian learning inspired much of our current understanding about neural connections and has proven to be a successful tool in the computational modeling of human learning and behavior (Flesch, Saxe, & Summerfield, 2023; Verguts & Notebaert, 2008; McClelland, 2006). In this study, we sought to investigate whether we can condition stimulus–response associations using TMS, as a more general form of associative visuomotor learning based on Hebbian principles and aimed to explore associated temporal dynamics and awareness measures to get an idea about the level of learning. Evidence thereof could point at an interesting target for clinical and cognitive interventions complementing those requiring more effortful or conscious engagement.

TMS is a non-invasive technique that uses a magnetic field to generate an electric current in a targeted region of the brain. It has been used in a variety of studies, ranging from those measuring corticospinal excitability (Derosiere, Vassiliadis, & Duque, 2020), to those studying its therapeutic potential in various disorders (Lefaucheur et al., 2014; Luber & Lisanby, 2014). Another recent group of studies started using paired associative stimulation (PAS), the repeated time-locked pairing of two stimulations to induce Hebbian learning in the respective pathways. Both stimulations can be cortical, referred to as cortico-cortical TMS, which has led to the study of performance in experimental tasks relying on the co-stimulated regions such as motion detection, manual dexterity, or action reprogramming (see, e.g., Turrini, Bevacqua, Cataneo, Chiappini, Fiori, Battaglia et al., 2023; Turrini, Bevacqua, Cataneo, Chiappini, Fiori, Candidi et al., 2023; Chiappini, Sel, Hibbard, Avenanti, & Romei, 2022; Lazari

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et al., 2022; Chiappini, Silvanto, Hibbard, Avenanti, & Romei, 2018; Fiori, Chiappini, & Avenanti, 2018). Interestingly, however, the stimulation can also be of different sensory systems (cross-systems PAS; for a review, see Guidali, Roncoroni, & Bolognini, 2021) to modulate visuomotor properties of sensorimotor cortices. For example, peripheral-cortico stimulation coupling visual stimulation with TMS on primary motor cortex (M1) (Wolfe, Kaethler, & Staines, 2021; Suppa, Li Voti, Rocchi, Papazachariadis, & Berardelli, 2015) or cross-modal stimulation with stimulation of somatosensory cortex (S1; Zazio, Guidali, Maddaluno, Miniussi, & Bolognini, 2019) or M1 (Guidali, Picardi, Gramegna, & Bolognini, 2023; Guidali, Carneiro, & Bolognini, 2020) has been shown to successfully induce Hebbian plasticity. In summary, these studies provide evidence that corticospinal outcomes can be visually conditioned following Hebbian learning.

Building on this literature, the goal of this study was to test whether TMS can be used to bind and retrieve specific motor actions to certain stimulus features. Specifically, we reasoned that a consistent pairing of a single pulse TMS of the M1 hand region to a specific color; that is, conditioning, should lead to the learning of stimulus–response associations that affect performance on different tasks using the same response sets and stimulus features. Similar to the above-described protocols, single-pulse TMS stimulates the cortical-spinal tract leading to electromyography (motor evoked potentials [MEP]) activity that can be registered at the periphery. To our knowledge, few have looked into whether this activity can become a conditioned response in the absence of TMS and tested its implications for behavioral experimental paradigms.

Johnson and colleagues (2010) and Luber, Balsam, Nguyen, Gross, and Lisanby (2007) studied changes in motor cortex excitability after pairing audiovisual stimuli with TMS pulses and found mixed results. For instance, these authors found prepulse inhibition rather than excitation, showing that TMS motor-evoked potentials were smaller when preceded by the paired stimulus, compared with test trials where only a pulse was given (Johnson et al., 2010; Luber et al., 2007). Notably, both studies did not use a distractor task (making participants fully aware of the setup), used high-intensity pulses (i.e., 120%–150% of resting motor threshold), stimulated rather long after the onset of the visual stimulation (400–1700 msec), and used long intertrial intervals (10–80 sec). Interestingly, when using shorter intertrial intervals (2–6 sec), Johnson and colleagues (2010) did find some elicitation of MEP signals on a percentage of test trials following the conditioning phase. However, because of a number of differences in the design between these and the long ITI trials, it is unclear what led to those opposite effects. A final crucial limitation is that they looked at the conditioning of stimulus–response associations in isolation and did not study their interaction with the use of the same versus conflicting pairings in an independent task.

In summary, we believe there is currently no clear evidence for the prediction that evoking TMS-induced unintentional MEPs at the time of presentation of a certain stimulus feature results in the formation of stimulus–response associations. Moreover, it is crucial to test if these paired stimuli affect task performance in subsequent unrelated tasks and to explore the underlying mechanisms. To test these ideas, we set up a study where participants first underwent a conditioning phase with different colors paired to one of four different TMS pulse intensities (no stimulation, low, medium, high intensity), eliciting motor responses of different magnitudes during a counting task. The side of stimulation (left/right) and respective elicitation of motor responses (right/left) was counterbalanced across participants; that is, each participant was stimulated only on one side throughout the entire experiment. Our test phase comprised an unrelated, simple shape discrimination task displayed in these same, now task-irrelevant colors, requiring either the same or competing responses as they were paired with during the conditioning phase. This way, we could evaluate whether previous color-specific stimulation of the motor cortex would interfere with behavior when incongruent with the required response. Thus, if a stimulus required responding with the nonstimulated side (hand), a trial was considered incongruent; if it required responding with the stimulated side (hand), a trial was considered congruent. Furthermore, by modeling the temporal evolution of this hypothesized response conflict using drift diffusion modeling (Ulrich, Schröter, Leuthold, & Birngruber, 2015), and linking its latency to those of other seminal cognitive control tasks, we aimed to further our understanding about the stage at which such a response interference might take place. Although this is obviously no hard proof, we reasoned that the earlier potential conflict occurs, the less likely is the additional involvement of mediating brain regions and the more likely these effects stem from more direct Hebbian-like forms of learning.

Finally, a secondary aim of our study was to also explore whether sleep (consolidation) would aid or impair associative learning in our task, by testing participants either on the same or next day after the learning phase. Although sleep consolidation is often thought to support different forms of learning, some have suggested that sleep consolidation only helps for learned behaviors that involve declarative knowledge, goal relevance, and awareness (for reviews, see Vorster & Born, 2015; Rasch & Born, 2013; Song, 2009).

## METHODS

### Participants

Data of 40 participants were collected, which should result in a sufficient number of observations per condition to assess the interaction of congruency and TMS intensity

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(Brysbaert, 2019). Of those participants, 20 were assigned to the same-day group and 20 to the next-day group, meaning that they were either assigned to the test phase on the same or next day. They were recruited via Ghent University's online recruitment system and participated for monetary compensation (25 € in the same-day group and 30 € in the next-day group). Participants' mean age in the same-day group was 22.2 (2.42) years (11 women, 9 men, 19 right-handed) and 23.15 (4.42) years (14 women, 6 men, 16 right-handed) for participants in the next-day group. Exclusion criteria included a history of psychiatric or neurologic disorders, or presence of significant medical conditions. All participants were required to have normal or corrected-to-normal vision and to meet the TMS safety measures (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). The study was approved by the Medical Ethic Review Board of the Ghent University Hospital and was conducted in accordance with the 1964 Declaration of Helsinki.

### Materials

The experiment was programmed in E-Prime v2.0 (Schneider, Eschman, & Zuccolotto, 2002). Task stimuli consisted of black and colored (purple, yellow, blue, and brown) circles in the training phase and squares and diamonds in the test phase. All stimuli were presented in the center of a white screen with 80 pixels (corresponding to a diameter/width of 4 cm). Response keys for the test phase were the Z and M keys on a QWERTY keyboard given with the left or right index finger. Stimulus-to-response mapping was counterbalanced across participants.

### TMS and Electromyography

Single-pulse TMS was applied with a biphasic magnetic stimulator (Rapid2 Magstim) that was connected to a 70-mm figure-of-eight coil. The coil was positioned tangentially over the hand area of the primary motor cortex (the stimulated hemisphere was counterbalanced across participants). The handle of the coil pointed backward and formed an angle of 45° with respect to the sagittal plane. Electromyographical (EMG) activity was recorded from the first dorsal interosseous (FDI) muscle (muscle involved in the abduction of the index finger) of the right or left hand. For this purpose, the ActiveTwo system (BioSemi) was applied, using sintered 11 × 17 mm active Ag– AgCl electrodes. Before the outset of the experiment, the hotspot within the associated primary motor cortex hand area was determined. We localized the motor cortex area activating the left or right index finger (counterbalanced across participants) and determined the resting motor threshold for each participant separately. The resting motor threshold was set to the lowest intensity needed to evoke motor potentials of at least 50 μV recorded from the FDI muscle in at least 5/10 stimulations (Rossini et al., 1994). The stimulation intensity was set at 110% of the motor threshold during the high intensity trials, at 95% for the medium-intensity trials and 80% for the low-intensity trials (see Figure 1 for mean MEP amplitudes).

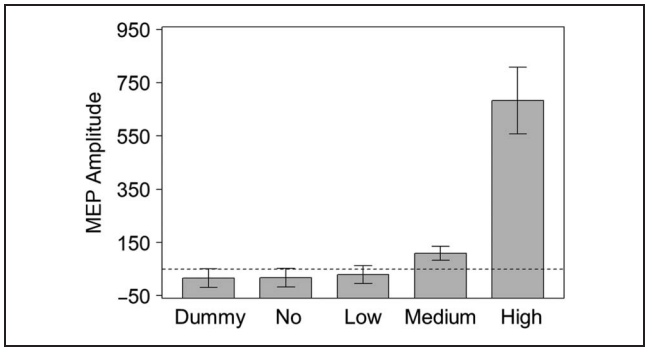


**Figure 1.** MEP amplitude as a function of no stimulation, low, medium, and high intensity. The dashed line represents the resting motor threshold (lowest intensity needed to evoke motor potentials of at least 50 μV recorded from the FDI muscle in at least 5/10 stimulations (Rossini et al., 1994). Dummy refers to the MEP recorded during the presentation of the black circles in the counting task.

### Procedure

The experiment was advertised as an experiment about the effects of brain stimulation on counting (which was used as a distractor task in the conditioning phase; see below). Participants were asked to sign a written informed consent before the start of the experiment. The experiment was divided into a learning and a test phase, which were either on the same day (same-day group) or on subsequent days (next-day group). Before starting the experiment, participants underwent the TMS protocol (see above). During the preparation phase in which the individual motor threshold was determined, participants were told that we were interested in the effects of closely neighboring brain regions on counting and that assessing the MEP was a necessary procedure to set the right intensity level.

#### *Conditioning Phase*

The total duration of the conditioning phase was around 60 min. Participants sat approximately 40 cm from a computer screen (17-in. monitor, 640 × 480 pixels). In this phase, participants completed 12 blocks of 80 trials with breaks in between. In each block, the 80 trials consisted of 40 black circles and 40 colored circles presented in a random order. Participants were instructed that their task was to count the number of stimulus repetitions, defined as two successive presentations of circles in the same color. In each block, only one color was used for the colored circles, and each of the four colors (purple, brown, yellow and blue) was used in three out of the 12 blocks.

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The order of the blocks was randomized with the restriction that every color occurred once per every four blocks. Three out of the four colored circles were systematically paired with a TMS pulse with a low, medium, or high intensity (color-to-intensity assignment counterbalanced across participants), and one was never paired with a pulse, from here on referred to as the no-intensity color. Although we expected our effect to occur only in the high-intensity condition, as only in this condition TMS stimulation is above threshold, we introduced low and medium intensity to reduce the experienced difference between the no intensity and high-intensity condition. In other words, we used these intensities to make participants less aware of our manipulation. On each trial, either the black or colored circle was presented for 500 msec, following a black fixation cross that was similarly presented for 500 msec and followed by an intertrial interval of 1000–1500 msec (see Figure 2). On each colored trial (except for those containing the no-intensity color), the associated TMS pulse was delivered 200 msec after stimulus onset, assumed to be a realistic timing for initial stimulus-evoked motor activation based on previous studies. Specifically, the beginning of the lateralization of the readiness potential following a stimulus is assumed to mark the time point where a response side is selected following sensory processing and differential lateralization of the readiness potential effects have been shown at around 200 msec (Eimer, 1998). We reasoned that delivery of the TMS pulse at this moment would maximally reinforce the according response (left or right). After each block, participants had to indicate how many repetitions they counted and received feedback on the computer screen. Because of a programming mistake, this feedback was only presented in half of the blocks (every other block).

### *Test Phase*

The conditioning phase was followed by a test phase, whose format was not announced or explained beforehand. To dissociate both phases as much as possible, the TMS coil was removed before the test phase, which was further introduced as a different experiment addressing different hypotheses. This test phase was about 30 min long and consisted of a simple categorization task with 480 trials during which no TMS stimulation was delivered. In total, participants completed 120 trials per four blocks, with the first block considered a training block. Participants were no longer presented with circles but were now asked to categorize whether they saw a diamond or a square shape, by responding as quickly and correctly as possible (see Figure 2). Importantly, the shapes were displayed in the same colors as the training stimuli (the shape color was task irrelevant), resulting in a set of eight unique combinations, appearing 15 times per block in random order. The duration of the fixation cross and ITI corresponded to the durations used in the training phase. Between each block, participants had the possibility to rest.

After this test phase, participants were provided with a pen-and-paper questionnaire to determine manipulation awareness. Specifically, participants were first asked whether they had any idea about the underlying

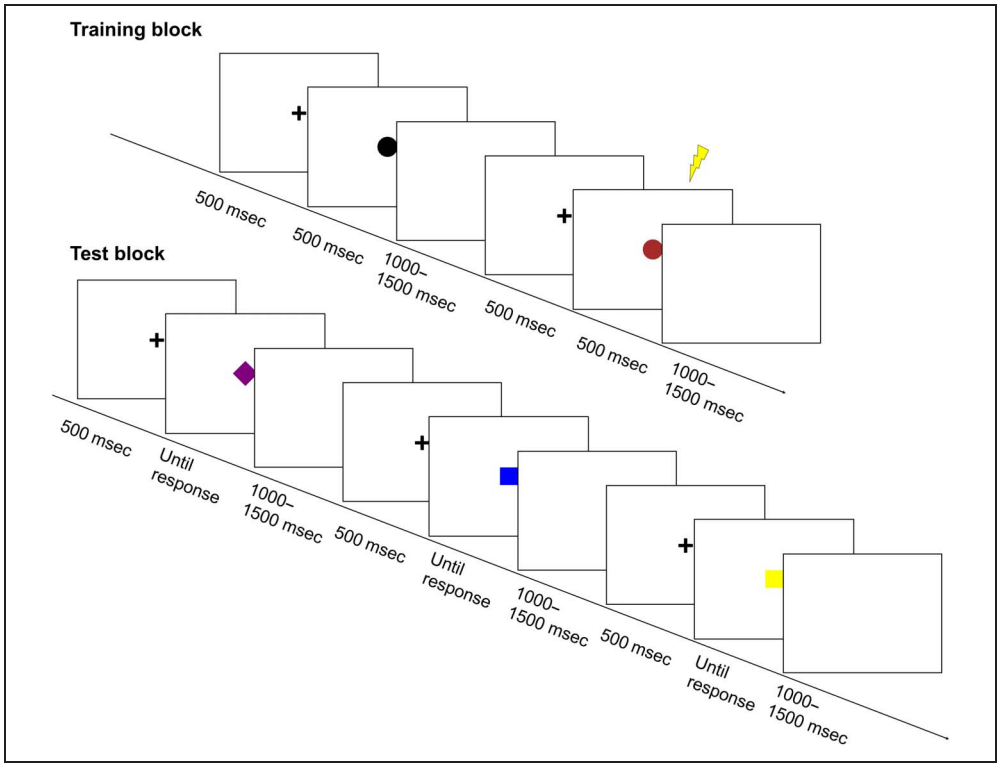


**Figure 2.** Task sequence of training blocks with TMS and test blocks. Participants underwent four separate training blocks per stimulus color in which they were instructed to count the number of colored circles paired with the four different stimulus intensities, respectively. In the four subsequent test blocks, they had to categorize shapes presented in the same colors according to being a square or a diamond.

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hypothesis and if they noticed anything specific regarding the TMS pulses and colors during the training phase. Second, they were explicitly told that different colors could be associated to different TMS intensities, and asked whether they could order the colors accordingly (or indicate which colors they thought were of similar intensity).

### Data Analysis

#### *Preprocessing*

Three participants were excluded from the final sample, because of manipulation awareness in the post experiment questionnaires ($n$ = 1; see below) or below chance-level performance ($n$ = 2), resulting in a final sample of 18 participants in the same-day group and 19 participants in the next-day group. For all remaining participants, we excluded the first (training) block of the test phase.[1] For the error analyses, we removed every trial immediately following an error and the first trial of each block. For the RT analyses, we additionally removed each trial resulting in an error and all trials with RTs 1.5 times the interquartile range above the 75th percentile and below the 25th percentile (within-subject), as well as RTs faster than 200 msec (as in Xu, Simoens, Verguts, & Braem, 2023).[2] For the main analyses, we decided to group the low- and medium-intensity level into one low level (see Figure 1), as they served the same experimental purpose, and mainly differed from the no intensity level in terms of subjective experience (tickling sensation and noise from the TMS stimulation).

#### *Mixed-effects Models Analysis*

To take trial-by-trial variability into account, data were analyzed using Bayesian mixed-effects models in brms (Bürkner, 2017) in R (R Core Team, 2022). Specifically, we ran separate models predicting accuracy and RT in the test blocks based on Group (2; same-day vs. next-day), Congruency (2; congruent vs. incongruent), and Pulse Intensity (3; high vs. low vs. no) as well as all two-way and the three-way interaction(s). We further included random participant intercepts and random slopes for congruency, pulse intensity, and their interaction per participant. Congruency was determined by comparing response side (left vs. right) to motor cortex stimulation (right vs. left) in the conditioning phase. Follow-up models were run per group to interpret three-way interaction effects of Group, Congruency, and Intensity. All categorical predictors were coded using sum-to-zero contrasts to obtain main effects and main interactions rather than simple effects for general interpretability of the omnibus models. Intensity was thus represented by two contrasts (the first comparing the no-intensity level to the grand mean and the second referring the medium intensity level to the grand mean). As we were rather interested in the congruency effect per intensity level (in each group), we performed additional post hoc tests using the emmeans package (Lenth, 2022; as in Ikink, Van Duijvenvoorde, Huizenga, Roelofs, & Figner, 2023). RTs were modeled with shifted lognormal distributions and accuracy with Bernoulli distributions (logit link), and we used weakly informative brms default priors. Significance was inferred based on whether the 95% credible intervals (CIs) included 0, a common indicator used in Bayesian frameworks (based on Kruschke, 2015).

## RESULTS

### Awareness

All participants, except for one, either reported to be unaware of the purpose of our experiment or reported hypothesized purposes that were incorrect. This one participant correctly indicated how the different colors were mapped onto the various TMS intensities, and this participant was removed from the analyses. After having explained that the different colors were, in fact, systematically paired with different TMS intensities, we asked participants to guess the intensity for each color. Here, participants could identify the color associated with the high TMS intensity (i.e., 50% of the participants) above chance level (i.e., 25%; $\chi^2[1, n = 40] = 13.33$, $p < .001$) and could almost do so for the no intensity condition (37.5%; $\chi^2[1, n = 40] = 3.33$, $p = .068$). Please note that although these results suggest that some participants could recall the stimulus-specific TMS intensity, none of the analyzed participants were aware of why we tried to induce these color–TMS pairings, let alone how we evaluated them during the test phase.

### Task Performance

#### *Accuracy*

No significant main effects or two-way interactions were found in the maximal model, that is, the model fit to the whole sample. However, we found a significant three-way interaction between Group, Pulse Intensity, and Congruency (contrast 2; b = −0.20, 95% CI [−0.35, −0.05]). Follow-up models run on each group separately showed that the interaction between Pulse Intensity and Congruency was significant in the same-day group but not in the next-day group (see Table 1 and Figure 3). Specifically, in the same-day group, the Congruency effect was significant for the high intensity level (mean = 3.32, $SD$ = 4.96), suggesting interference when the stimulation side matched the alternative response side and/or facilitation when the stimulation side matched the task-relevant motor response. It was not significant at the no-intensity (mean = −1.61, $SD$ = 3.37) and low- (mean = −0.13, $SD$ = 4.38) intensity levels (see Table 1). We further performed pairwise comparisons to test whether the effect of Congruency was significantly different between intensity levels.

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**Table 1.** Coefficients ($B_{EMM}$ Values) and 95% CIs Estimated from Accuracy Follow-up Models

| | *Same-day Group* | | | | | | *Next-day Group* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Effect* | *No* | | *Low* | | *High* | | *No* | | *Low* | | *High* | |
| | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI |
| Congruency | −0.41 | −0.99, 0.11 | −0.06 | −0.50, 0.38 | 0.66* | 0.08, 1.24 | 0.36 | −0.31, 1.04 | −0.09 | −0.61, 0.43 | −0.43 | −1.18, 0.27 |

* Significant.

The tests revealed that although the Congruency effect did not significantly differ between the no- and low-intensity levels, it significantly differed both between the high- and no-intensity levels as well as between the high- and low-intensity levels. As an exploratory analysis, we also ran an additional model to test if this effect in the same-day group was modulated by awareness of the highest intensity color. However, this factor did not show a main effect or any interaction with Congruency, Pulse Intensity, or the three-way interaction.

### *RTs*

No main or interaction effects were found in the main RT model as well as in the follow-up RT models fitted per group (see Table 2 and Figure 3).

### *Diffusion Modeling of Conflict*

To obtain a better insight in the temporal dynamics of the conflict revealed in our accuracy models, we followed up

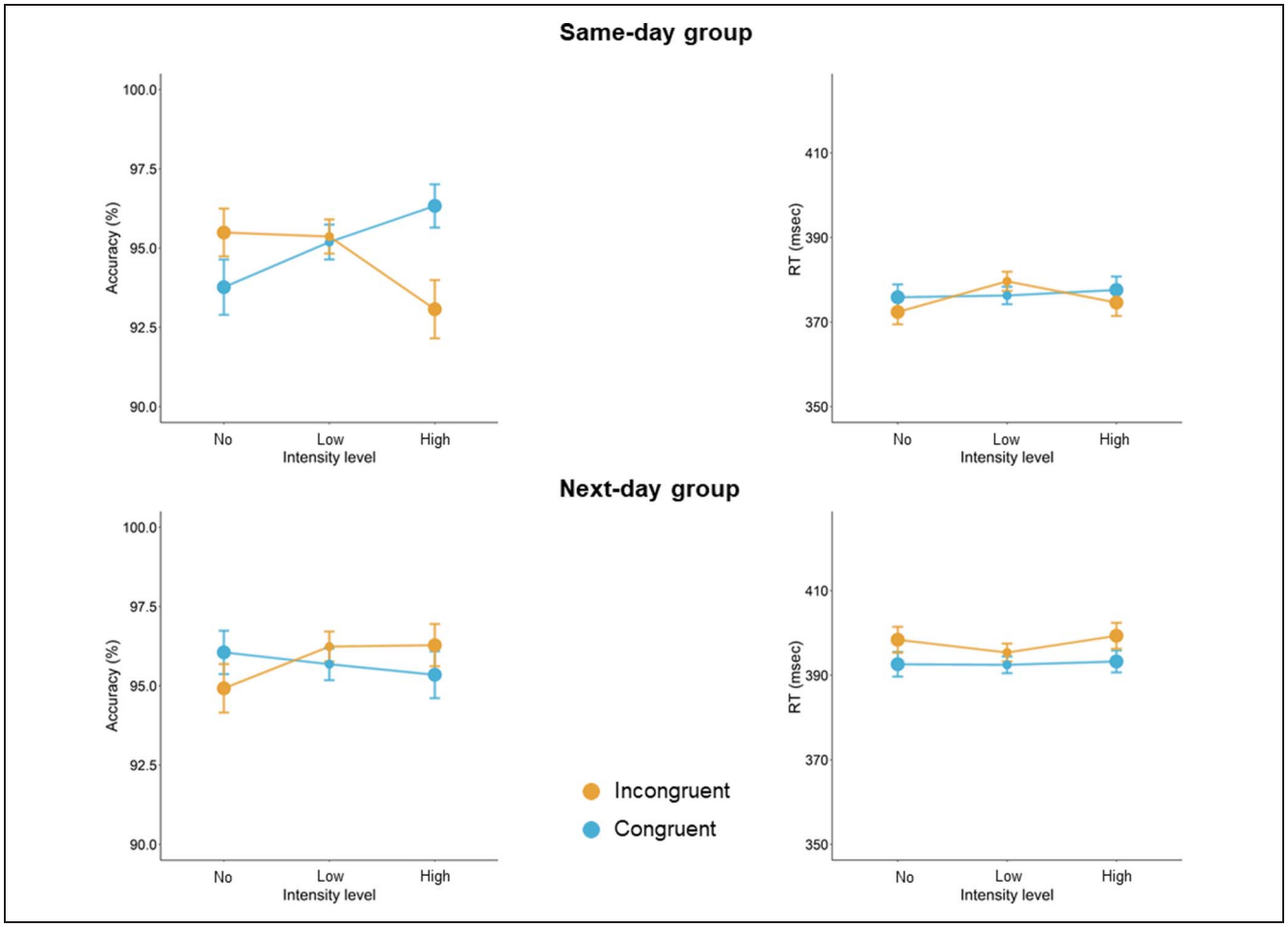


**Figure 3.** Congruency effects per intensity level in the same-day and next-day group. Plots depicting congruency effects per congruency level in accuracy and RT for the same-day and next-day groups. Bars represent error bars of the means.

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**Table 2.** Coefficients ($B_{EMM}$ Values) and 95% CIs Estimated from RT Follow-up Models

| | *Same-day Group* | | | | | | *Next-day Group* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Effect* | *No* | | *Low* | | *High* | | *No* | | *Low* | | *High* | |
| | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI | $B_{EMM}$ | 95% CI |
| Congruency | 0.01 | −0.03, 0.06 | −0.01 | −0.04, 0.03 | 0.02 | −0.03, 0.06 | −0.01 | −0.05, 0.03 | −0.01 | −0.05, 0.02 | −0.01 | −0.05, 0.03 |

on the mixed-effects models results by inspecting conditional accuracy functions for the highest intensity in the same-day group using functions of the DMCfun package (Ulrich et al., 2015). Conditional accuracy functions display the proportion of correct responses per RT quintile (or any other quantile of choice), that is, they allow us to see when interference is highest (or lowest). Both accuracy and RT patterns showed clear evidence for the presence of fast errors on incongruent trials (see Figure 4).

Next, we fit the drift diffusion model for conflict tasks (DMC) (Ulrich et al., 2015) to this subset of data. This model models decision making in conflict tasks by assuming an evidence accumulation process until one of two decision boundaries is reached, corresponding to the relevant and irrelevant (conflict) dimension. Compared with other evidence accumulation models, it is suitable to capture tasks with a conflict dimension, by superimposing activations of a controlled and automatic process modeled with a gamma density function. Thus, a decider can initially drift toward the conflicting response, before drifting to the correct controlled decision. Using this model, we estimated the amplitude of automatic activation, the time of peak automatic activation, the drift rate of the controlled activation, the decision boundary, the mean of the normal distribution of the residual stage (nondecision time), and the standard deviation of the normal distribution of the residual stage.

We used the default parameter bounds with the exception of the peak amplitude and tau, for which we set the minimum to 0 and 1, respectively, as estimates were at the bounds with the default settings. Other parameters of noninterest were fixed as has been done in previous studies (see, e.g., Koob, Mackenzie, Ulrich, Leuthold, & Janczyk, 2023; Liesefeld & Janczyk, 2022/2023; Rastelli, Greco, Kenett, Finocchiaro, & De Pisapia, 2022; Ulrich et al., 2015). Specifically, the shape parameter of the gamma distribution for tau was fixed to 2, the shape parameter of the beta distribution for starting point variability was fixed to 3, and the scaling parameter of the drift diffusion process was fixed to 4. The model was fitted through minimizing the root-mean-square error between the predicted and observed accuracy and RT distributions using the differential evolution algorithm implemented in the package. The resulting parameter estimates are displayed in Table 3. To investigate which parameter was most affected by our conditioning procedure using TMS, we fitted the diffusion modeling of conflict (DMC) to the highest and lowest intensity levels separately, in the same-day group, and compared the difference between intensity levels based on regression models predicting parameters based on

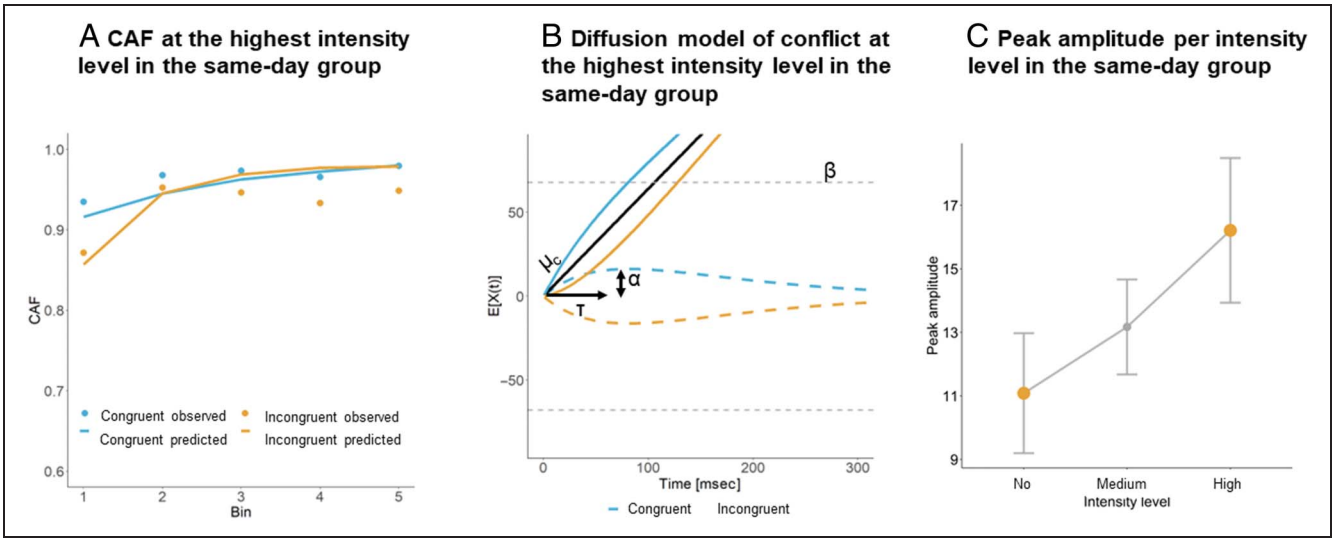


**Figure 4.** Conditional accuracy functions and model-estimated data in the same-day group. (A) Conditional accuracies per RT bin (quintiles). Observed values reflect the raw data, and the predicted values are based on the DMC, both on the group level. (B) DMC, simulations based on the averaged individual participant-level parameters. $\mu_c$ = drift rate of the controlled activation; $\tau$ = peak latency; $\alpha$ = peak amplitude; $\beta$ = decision bound. (C) Mean peak amplitude per intensity level with error bars based on the averaged individual participant parameters. Plots A and B are generated with functions from the DMCfun package.

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**Table 3.** Parameter Estimates of the DMC Fitted to the Highest Intensity in the Same-day Group

| | | *Participant-level Estimates* | | | | |
|---|---|---|---|---|---|---|
| *Parameter* | *Group Level Estimates* | *Mean* | *SD* | *Median Estimate* | *25$^{tb}$ Percentile* | *75$^{tb}$ Percentile* |
| Amplitude of automatic activation α | 3.44 | 16.21 | 9.66 | 13.37 | 8.89 | 24.02 |
| Time of peak automatic activation τ | 13.89 | 81.97 | 118.45 | 7.24 | 3.11 | 197.50 |
| Drift rate of the controlled activation μc | 0.53 | 0.64 | 0.20 | 0.58 | 0.51 | 0.75 |
| Decision boundary β | 56.89 | 67.79 | 27.00 | 57.74 | 47.19 | 81.85 |
| Mean of the normal distribution of the residual stage | 284.52 | 278.36 | 26.15 | 281.40 | 256.99 | 292.17 |
| Standard deviation of the normal distribution of the residual stage | 17.66 | 20.18 | 12.43 | 15.07 | 10.92 | 32.88 |
| root-mean-square error (RMSE) | 10.86 | 28.81 | 8.32 | 28.09 | | |

Shape parameter of the gamma distribution for tau was fixed to 2, shape parameter of the beta distribution for starting point variability was fixed to 3, and scaling parameter of the drift diffusion process was set to 4.

intensity and post hoc tests. Of main interest were the peak amplitude of the automatic process, which is hypothesized to measure the degree of interfering motor activation induced by the stimulus, as we expected this parameter to be most affected by the conditioning.

In line with our hypotheses, we observed a significant difference in amplitude between the high (mean = 16.21, *SD* = 9.66) and no intensity (mean = 11.09, *SD* = 8.01; $B_{EMM}$ = −5.09, 95% CI [−9.62, −0.5130]; see Figure 4). We did not see a difference between the high- and low-intensity (mean = 13.17, *SD* = 6.34; $B_{EMM}$ = −3.04, 95% CI [−7.43, 1.58]) and between the no- and low-intensity levels ($B_{EMM}$ = −2.08, 95% CI [−6.26, 2.41]). Importantly, none of the other model parameters, being the controlled drift rate, peak latency, or boundary, varied as a function of conditioned TMS intensity (all CIs included 0), suggesting our conditioning phase mostly influenced early, automatic, stimulus-specific motor activation, which is further supported by the early latency (τ) of the peak at 360.33 msec. For comparison, Ulrich and colleagues (2015) noted latencies of 358 msec in a classic Simon, known for similarly showing early interference, as opposed to 450 msec in a flanker task.

## DISCUSSION

The current study aimed to test if pairing hand muscle stimulation with different stimulus colors leads to learning of stimulus–response associations, by studying its impact in a subsequent, unrelated categorization task relying on these same colors and left/right responses. Concretely, we trained participants on a supposed counting task in which each of four colors was presented with zero, low and high TMS pulse intensities, followed by a shape discrimination phase in which stimuli were presented in these same colors. Interestingly, and in line with our hypothesis, we found that participants were less accurate when responding required the nonstimulated versus stimulated response at the highest TMS pulse intensity, but only in the group of participants who performed the test phase on the same day as the training phase. Interestingly, a significant difference in congruency effect was not only observed between the no- and high-intensity levels, but also between the low- and high-intensity levels, suggesting it did not merely occur as a function of the qualitatively different experience in sensation between the absence and presence of TMS in and of itself, but rather as a function of pulse intensity. The finding that these new stimulus–response associations exerted a lasting influence on performance during other, irrelevant tasks extends previous studies (Johnson et al., 2010; Luber et al., 2007) and suggests that learning may have occurred through the formation of more direct connections. This was further corroborated by computational modeling, which showed that conditioning with TMS likely affected evidence accumulation at a very early stage. That is, the peak amplitude of the automatic activation occurred at around 360 msec similar to 358 msec in the Simon, but considerably earlier than 450 msec in the flanker task, as reported by Ulrich and colleagues (2015). This would be consistent with the idea that our TMS manipulation effectively induced early visuomotor learning as the Simon effect is typically thought to be caused by a fast, short-lived interference because of a more direct association between (task-irrelevant) stimulus location and response side. To investigate if such learning was Hebbian, it would be interesting for future research to investigate different delays between the visual stimulus and TMS pulse as Hebbian learning follows clear temporal constraints (Guidali et al., 2021; Keysers & Gazzola, 2014; Caporale & Dan, 2008; Bi & Poo, 2001). As timing dependency is particularly challenging to derive with cross-systems PAS because of the potential bidirectional interplays between visual cortex and M1, establishing best practice delays will be all

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the more relevant (Guidali et al., 2021). In a similar vein, it would be interesting for future research to also incorporate neurophysiological measures of excitability of the cortico-spinal tract (i.e., MEPs) during the test phase to study if associative learning and, hence, synaptic plasticity were restricted to the motor cortex, that is, more low-level sensorimotor networks, or whether it encompassed higher-order networks, such as attention networks. As participants were engaged in a counting task during the conditioning phase and associative learning is highly state and task dependent (Nitsche et al., 2007), we may expect some evidence for the latter case, which would impede a more purist account of our effect. Although demonstrating higher-order processing with EMG is difficult as it is largely determined by response preparation and execution, a more indirect approach could be to test if we see activation of the alternative response early during incongruent trials, which would provide more evidence for early involvement of low-level processing at the level of motor cortex (Van Campen, Keuken, Van Den Wildenberg, & Ridderinkhof, 2014). In either case, it would be interesting to contrast the counting task and associated EMG timings with a conditioning phase in which participants are not actively engaged. In summary, further research is needed to delve deeper into the underlying mechanisms (to which the DMC itself is agnostic) and to assess whether levels of mediation represent qualitative differences between these tasks (see also Töbel, Hübner, & Stürmer, 2014, for comparable discussions on different versions of the Simon task).

Notably, in addition to the early latency of conflict, we also found the amplitude of the automatic activation to significantly increase with increasing stimulation intensity (i.e., participants experienced stronger conflict, or were drawn more strongly to the incongruent conditioned response if the stimulus color was previously paired with higher coil intensities; see Figure 3).

Interestingly, it seemed that the effects of our TMS manipulation expressed themselves in accuracy, but not RTs; that is, participants were not quicker or slower when the required response matched or did not match the conditioned response. This might again be explained by the short time scale during which the effect unfolds, as can be seen in the conditional accuracy functions and the relatively short latency of the peak amplitude as compared with nondecision time. Perhaps behavioral analyses alone could not capture these separate processes as reliably and precisely as the conflict diffusion model, which is a major advantage of the joint modeling of accuracy and RTs (see, e.g., Ballard & McClure, 2019; Shahar et al., 2019).

The effects of our conditioning procedure were observed when tested immediately after training, but not after one day of sleep. This suggests sleep consolidation did not occur in this study. This finding differs from an earlier study by Luber and colleagues (2007) who found differences in MEP (as a function of paring stimuli with TMS) between a baseline condition on a first training day and the first conditioning trials of a second session on the next day. However, their training effect showed a compensatory conditioned response rather than an excitatory response and the study design differed in other crucial aspects, for example, concerning manipulation awareness, which probably led to mediated processes (see Introduction section). In contrast, conditioned responses to the stimulus color in our study may have been acquired as nondeclarative memories, which have shown to be learned more slowly and to benefit less from sleep consolidation as compared with declarative knowledge (Vorster & Born, 2015; Rasch & Born, 2013; Song, 2009).

In a similar vein, although formations of simple stimulus–response associations in this study may have been rapidly acquired in both groups, this knowledge may, similarly, have been rapidly overwritten again between testing sessions in the next-day group (in line with the stability–plasticity dilemma; see Rasch & Born, 2013; Abraham & Robins, 2005). It would be interesting to test if conditioning with TMS can lead to more long-lasting effects when using more days and training sessions or when participants are made aware of the manipulation. Importantly though, one notable limitation of our study is that our power analysis was set up towards detecting an effect of our conditioning procedure across both groups. Therefore, we were likely underpowered for group comparisons and the effects in the same-day group and lack of results in the next-day group should be taken with a grain of salt. Future studies are clearly needed to replicate our findings in a larger sample with more statistical power. Another potential limitation is that stimulation site was counterbalanced across participants which may have induced differences in hemisphere excitability depending on the participants' handedness (see, e.g., Daligadu, Murphy, Brown, Rae, & Yielder, 2013). However, as TMS intensity was calibrated individually and as we did not seek to make inferences on absolute excitability, this should not have affected our results and conclusions.

Taken together, some may infer from our findings that this learning must have occurred in absence of awareness. However, we believe our findings do not offer proof for (or against) this conclusion. Clearly, participants were aware of the TMS stimulation, which is hard to mask, and could, on a group level, link the high-intensity stimulation to the associated color. Our explorative analyses suggested that awareness of these pairings did not mediate the congruency effects. Furthermore, our questionnaire data suggested that participants were unaware of our research hypothesis, let alone how we evaluated it in the test phase. However, even if awareness was important during the formation of these stimulus–response associations, this does not challenge our other observations that the here-observed learning resulted in a relatively automatic impact on behavior (i.e., on irrelevant tasks), through rather direct associations (i.e., causing early interference on behavior).

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We would like to end with an outlook for future studies and interventions, first reiterating some key points on how our current study may inform future (cross-system) PAS protocols in the domain of experimental and cognitive psychology and, second, suggesting directions for (clinical) interventions. First, providing evidence that pairing visual stimuli with TMS can lead to behavioral changes in a subsequent decision-making task opens the door to the study of research questions involving different hierarchical levels of the control hierarchy, unlike within-system or cortico-cortical paired associative stimulation, which are commonly restricted to lower levels of this hierarchy (see also a discussion by Guidali et al., 2021). Combining thoroughly designed experiments targeting their interactions, here between controlled and automatic action tendencies, with neurophysiological measures as stated earlier, will contribute to a more mechanistic insight on more abstract behaviors.

Second, if future research demonstrates that the effect of TMS on (lasting) stimulus response learnings is reliable, this could be of great interest for both clinical and cognitive interventions, for example, by replacing expensive cortical stimulation with stimuli conditioned to this stimulation, that could even be experienced outside the laboratory. Taking this one step further, associated benefits may not even be limited to the learning of stimulus response mappings through stimulation of motor cortex as tested in the present study but may extend to other brain regions as well. For instance, one could test if certain features previously paired with stimulation over pFC could lead to improved performance of processes shown to benefit from stimulation, such as analogic reasoning (Boroojerdi et al., 2001), choice RT (Evers, Böckermann, & Nyhuis, 2001), episodic memory (Köhler, Paus, Buckner, & Milner, 2004) or semantic fluency (Esposito et al., 2022).

In summary, our findings show that associative learning through stimulation of motor cortex in humans can affect responses in a subsequent cognitive task, but only immediately after conditioning. Interestingly, more fine-grained analyses and computational modeling suggest that this effect seemed to arise at earlier stages than typical conflict tasks and likely occurs through a stronger initial drift toward the irrelevant conditioned response. These findings offer an important tool for the study of associative learning in both fundamental research and more applied clinical psychology, as they point at an interesting target for treatment and interventions.

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## Data Availability Statement

All data and materials are available on OSF (OSF | Associative visuomotor learning using transcranial magnetic stimulation induces stimulus-response interference).

## Author Contributions

L. B., M. B., E. L. A., & S. B. developed the experiment idea and designed the study. Elio C. & S. B. programmed the experiment. Emiel C., L. B., M. K., Elio C., & S. B. collected the data. L. K. H., Emiel C., M. K., Elio C., & S. B. analyzed the data. L. K. H. did the computational modeling. L. K. H. wrote the first draft. L. K. H., Emiel C., L. B., M. B., E. L. A., & S. B. made final revisions and notes on the final draft.

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## Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance. The authors of this paper report its proportions of citations by gender category to be: M/M = .537; W/M = .195; M/W = .22; W/W = .049.

## Notes

1. Note that the main effects held when performing the main analyses on the data set including this block.
2. Note that here, too, the main effects held when including the entire RT distribution.

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