**On the mechanisms of Transcranial Magnetic Stimulation (TMS): How brain state and baseline performance level determine behavioral effects of TMS**

Running title: Neural excitability and facilitatory/inhibitory ranges of TMS

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**Abstract**

The behavioral effects of Transcranial Magnetic Stimulation (TMS) can change qualitatively when stimulation is preceded by initial state manipulations such as priming or adaptation. In addition, baseline performance level of the participant has been shown to play a role in modulating the impact of TMS. Here we examined the link between these two. This was done in the context of a priming paradigm, in which, at group level, TMS selectively facilitates targets incongruent with the prime while having no statistically significant effects on other prime-target congruencies. Correlation and regression analyses indicated that, for all prime-target congruencies, a significant linear relationship between baseline performance and the magnitude of the induced TMS effect was present: low levels of baseline performance were associated with TMS-induced facilitations and high baseline performance with impairments. Thus as performance level increased, TMS effects turned from facilitation to impairment. The key finding was that priming shifted the transition from facilitatory to disruptive effects for targets incongruent with the prime, such that TMS-induced facilitations were obtained until a higher level of performance than for other prime-target congruengies. Given that brain state manipulations such as priming operate via modulations of neural excitability, this result is consistent with the view that neural excitability, coupled with nonlinear neural effects, underlie behavioral effects of TMS.

## Introduction

Single pulses of Transcranial Magnetic Stimulation (TMS) applied concurrently with a visual target can either facilitate or impair detection performance, depending on factors such as stimulation intensity and brain state. Whereas TMS intensities above phosphene threshold have been found to mask visual perception when applied over the early visual cortex within a time window of 80-120 ms from stimulus onset (see e.g. Kammer, 2005, de Graaf et al, 2014, for reviews), subthreshold TMS within the same time window can facilitate behavior (e.g. Abrahamayan et al, 2011), particularly when baseline performance is low, reflecting a situation with a weak perceptual signal (e.g. Schwarzkopf et al, 2011). On the mechanistic level, such effects have been proposed to reflect the noise induced by TMS pushing weak signals above perceptual threshold (Schwarzkopf et al, 211; Miniussi et al, 2013).

Nonlinear effects are also observed when TMS is applied during a behavioral task following an initial state manipulation such as adaptation or priming. For example, in a study using orientation-contingent colour priming, suprathreshold TMS (applied within the TMS-masking time window) was found to induce a *facilitatory* effect on items incongruent with the prime, with no effects on other prime-target congruencies (Silvanto et al, 2017). Similarly, TMS induces a facilitation of adapted visual attributes while the same stimulation parameters impair performance in the absence of adaptation (Silvanto et al, 2007). Thus manipulations of initial activation state qualitatively change the nature of behavioral TMS effects.

However, the extent to which these state-dependent effects depend on the baseline performance level of the participant is unknown. This is a potentially important issue, given that, as discussed above, task difficulty has been shown to determine behavioral effect of TMS in conventional "virtual lesion" paradigms (e.g. Schwarzkopf et al, 2011). Specifically, could the facilitations observed in state-dependent paradigms be explained in terms of baseline performance level of the participants, with addition of noise by TMS pushing to weak signals pushed to perceptual threshold? We examined this issue by carrying out new analyses on our dataset from the state-dependent TMS study of Silvanto et al (2017), focusing on individual differences. In that study, participants were required to detect the colour of a briefly presented colour grating. On each trial, the target stimulus was preceded by a prime (a combination of colour and orientation) which was either fully congruent with the target (i.e. both colour and orientation matched), fully incongruent (ie. both colour and orientation of the prime and target differed), or partially congruent (i.e. either colour or orientation of the target matched that of the prime). single pulse TMS applied within the classic TMS-masking time window, 100 ms after target onset. (e.g. de Graaf et al, 2014). The results showed that, at group level, single pulse TMS applied within the classic TMS-masking time window (e.g. de Graaf et al, 2014) applied facilitated the detection of targets fully incongruent with the prime, while having no statistically significant effects on other stimulus types (see Figures 1 and 2). These effects were found on median reaction times of correct responses.

To examine whether these effect are driven by or modulated by participants' baseline level of performance, we carried out correlation and regression analyses to examine the relationship between baseline reaction times, priming manipulation and the induced TMS effect, as well as a new group analyses in which participants were divided into low and high baseline performance groups.

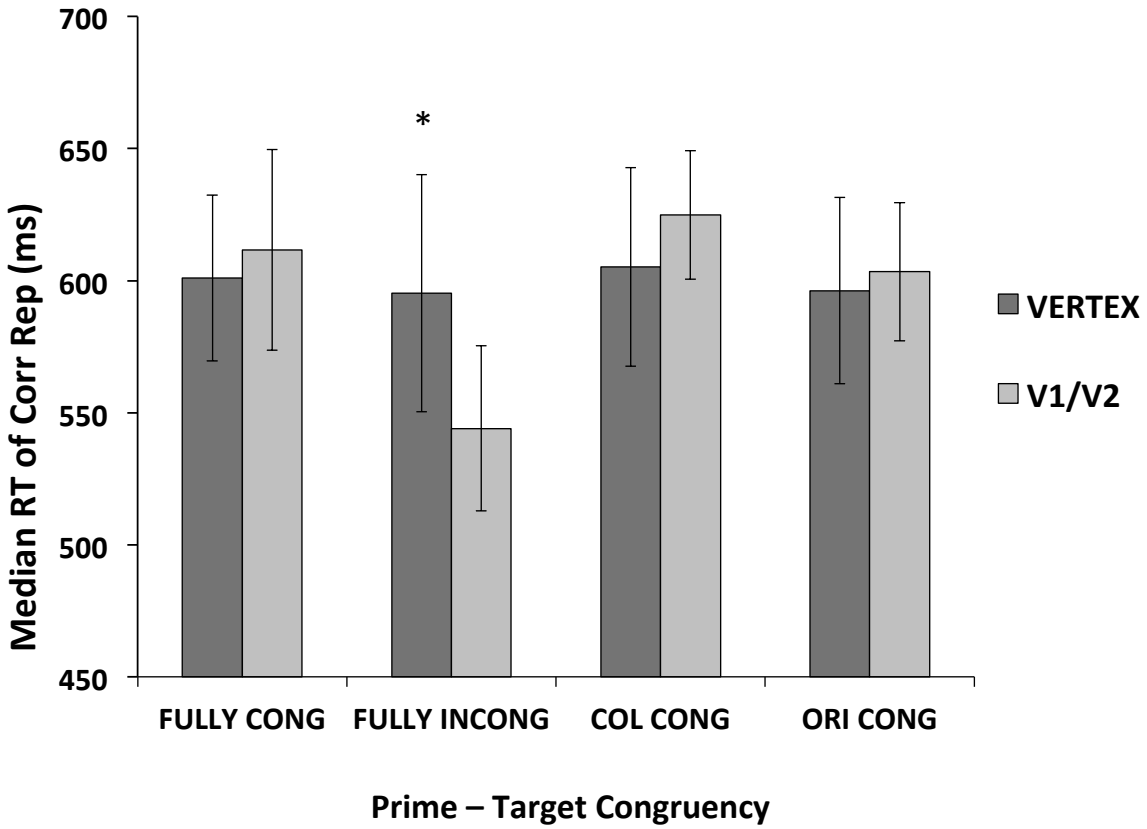


**Figure 1. Results from Silvanto et al (2017).** *Statistical analyses showed a selective facilitation of fully incongruent trials.* T*MS had no significant effect on other prime-target congruencies.*

**Methods**

The methods have been reported previously in Silvanto et al (2017) and reproduced below for the reader's convenience:

*Participants*

33 participants (12 M, mean age=23.06 years) with normal or corrected-to-normal vision volunteered to participate in the experiment, of whom 18 perceived TMS-induced phosphenes and were thus included in the main analysis. One participant was excluded due to chance-level baseline performance. Thus analyses was carried out on 17 participants. All subjects provided informed consent before participating in the study,

which had been approved by the local ethics committee of University of Pavia. All participants were naıve to the aims of the study and were treated according to the guidelines of the Declaration of Helsinki. Prior to participation, each participant was screened for contraindications to TMS.

*Stimuli and psychophysical task*

Stimuli were presented at a viewing distance of 60 cm on a 16-inch monitor with a display resolution of 1920 x 1080. Stimuli and task were presented by using E-prime software (Psychology Software Tools Inc., Pittsburgh, PA). Both stimulus prime and stimulus target consisted of diagonal lines at 45° to the left or right of vertical such that stimuli were made of a series of stripes. These stripes were either black and green (CIE x = 0.30, y = 0.60, luminance 20 cd/m2) or black and red (CIE x= ¼ 0.60, y = 0.35, luminance 20 cd/m2) with a stripe width of 0.25° in a stimulus subtending 6° horizontally and 3° vertically (adapted from Silvanto et al., 2007's study). Therefore, four different colour–orientation combinations were used, in which prime and target could have: a) same colour and same orientation ("fully congruent" trial); b) opposite colour and opposite orientation ("fully incongruent" trial); c) same colour but opposite orientation ("colour congruent" trial); d) same orientation but opposite colour ("orientation congruent" trial). These congruency types appeared with equal frequency within a block. The procedure is shown in Figure 2. Each trial started with a fixation cross presented in the middle of the display for 500 ms, followed by the presentation of the prime stimulus (appearing for 100 ms) and subsequently by a 300ms blank screen; after that, the target stimulus appeared on the middle of the screen for 20 ms. The target stimulus was followed by a mask (remaining of the screen till participants' response) composed of black diagonals in both possible orientations and with the gaps filled with green or red with the colour for each gap selected at random. A new randomly generated mask was used for each trial. When the mask was presented, participants had to indicate the colour of diagonals in the stimulus target display (red or green) by pressing the corresponding key on the keyboard. Both accuracy and response speed were emphasized. Each participant underwent a total of 8 experimental blocks, namely 2 blocks for each stimulation site (V1/V2, Vertex) and for each stimulation intensity (80%, 120% of PT, see below). Each block included 40 trials, 10 for each of the 4 colour-orientation combinations. The order of stimulation sites and intensities was counterbalanced across participants, as well as the orientation–colour combinations of the stimuli within each block. Before the main experiment, participants underwent a block of practice with no TMS (20 trials).

*Transcranial Magnetic Stimulation*

TMS was administered using a 70mm biphasic figure-of-eight coil connected to a Magstim stimulator (Magstim, Wales). The site of stimulation (V1/V2 region) was localized functionally in each participants by means of phosphenes search (see Walsh & Pascual-Leone, 2003, for a detailed description, see e.g. Campana et al, 2002, 2006 for examples). In this method, the coil is initially positioned 2 cm above the inion and its location is subsequently adjusted until foveal phosphenes (overlapping with the target location in the main experiment) are induced. PTs were measured, after dark adaptation, for each participant using a modified binary search algorithm (Tyrrell & Owens, 1988; Thilo et al., 2004). In the main experiment, participants

were stimulated at 90% and 120% of their PT. On each trial, a single-pulse TMS was delivered over V1/V2 or Vertex (baseline), 100 ms after onset of the target stimulus, i.e. within the classic TMS masking time window (e.g. de Graaf et al, 2014). Vertex was identified as the halfway location between the inion and the nasion and at an equal distance from the left and right inter-trachial notches and was used as control site. We included two Vertex conditions, one in which TMS was applied at 90% and the other with 120%, so that the level of possible auditory artefacts was controlled. During the stimulation, the coil was held with the handle pointing medial to lateral away from the midline and kept in place by the experimenter.

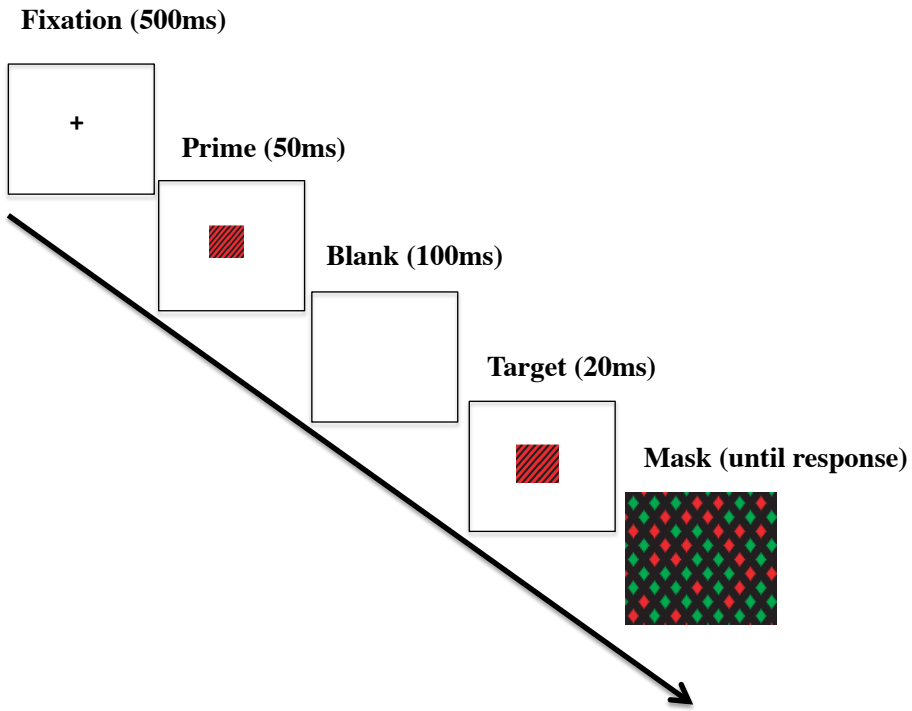


***Figure 2. Timeline of an experimental trial.*** *On each trial, participants were presented with a prime that was either a red-black or green-black grating, tilted either clockwise or counterclockwise. This was followed by a target which could be either fully congruent with the prime (i.e. the same stimulus), fully incongruent (i.e. both colour and orientation differed), or partially congruent (either colour or orientation matched the prime). Participants had to indicate the colour of diagonals of the stimulus target (red or green). In this figure, a fully congruent trial (i.e prime and target matched for both colour and orientation) is depicted. Single pulse TMS was delivered at 100 ms after target onset over either V1/V2 region or over the Vertex (baseline) Adapted from Silvanto et al (2017).*

**Results**

Statistical analyses were carried out on median reaction times of correct responses, as analyses on this variable showed statistically significant effects Silvanto et al (2017), with a selective facilitation of fully incongruent targets while no effects were found on other stimulus types. Furthermore, we focused on the suprathreshold TMS intensity, as no TMS effects were observed with subthreshold intensity in Silvanto et al (2017; see Figure 1).

Data were analysed as a function of congruency between the prime stimulus and the target – there were thus 4 trial types: congruent trials (i.e., prime and target are identical); incongruent trials (i.e., prime and target differ in both colour and orientation); colour congruent trials (i.e., target colour but not orientation matches the prime) and orientation congruent (i.e., orientation but not colour matches the prime).

Correlation/regression analyses

We first examined the correlations between baseline (Vertex) level of performance (median RT of correct responses) and the magnitude of the induced TMS effect (defined as performance in baseline (Vertex) condition subtracted from the TMS condition). These are summarized in the scatterplots shown in Figure 3.

For all prime-target congruencies, correlation (Pearson's r) between baseline performance and the TMS effect was significant (*Fully congruent*: r= -0.741, p=0.001; *fully incongruent*: = r=-0.814; p<0.001; *colour congruent*: r= -0.772; p<0.001; *orientation congruent*: r= -0.703; p=0.002). These indicate a negative relationship between baseline level of performance and the TMS effect, such that low baseline performance is associated with a facilitatory effect of TMS and high baseline performance with impairments. A multiple linear regression was then calculated to predict the TMS effect based on baseline RT and prime-target congruency. An analysis of standard residuals and collinearity were performed, which showed no outliers and lack of multicollinearity. The regression showed that baseline RT and prime-target congruency explain a significant amount of the variance of the TMS effect (F(2,65)=39.518; p<0.0001), adjusted R squared= 0.535). Further analysis showed that both baseline RT (Beta= -0.707; t(14)=-8.481; p<0.001) and congruency (Beta = -0.226; t(14)= -2.717; p=0.008) predicted the TMS effect.

How does congruency modulate the TMS effect? As is apparent in the scatterplots in Figure 3, the main difference between the different congruent conditions appears to be the intercept, as indicated by separate regressions carried out for each congruency (intercepts: *congruent:* 613 ms; *fully incongruent:* 499 ms; *colour congruent:* 629 ms; *orientation congruent:* 606 ms; in contrast, the slope is similar across conditions:

*congruent:* -0.485; *incongruent:* -0.353; *colour congruent:* -0.501; *orientation congruent:* -0.350). The intercept here reflects transition from facilitatory to inhibitory effects of TMS. This means that for the incongruent condition, the transition from TMS facilitating performance to impairing it, as a function of baseline performance level, occurs at a higher level of baseline performance (appr. 500 ms vs 600 ms for other conditions). In other words, incongruent trials are facilitated until a higher level of performance than other trial types - effectively widening the facilitatory range of TMS effects.

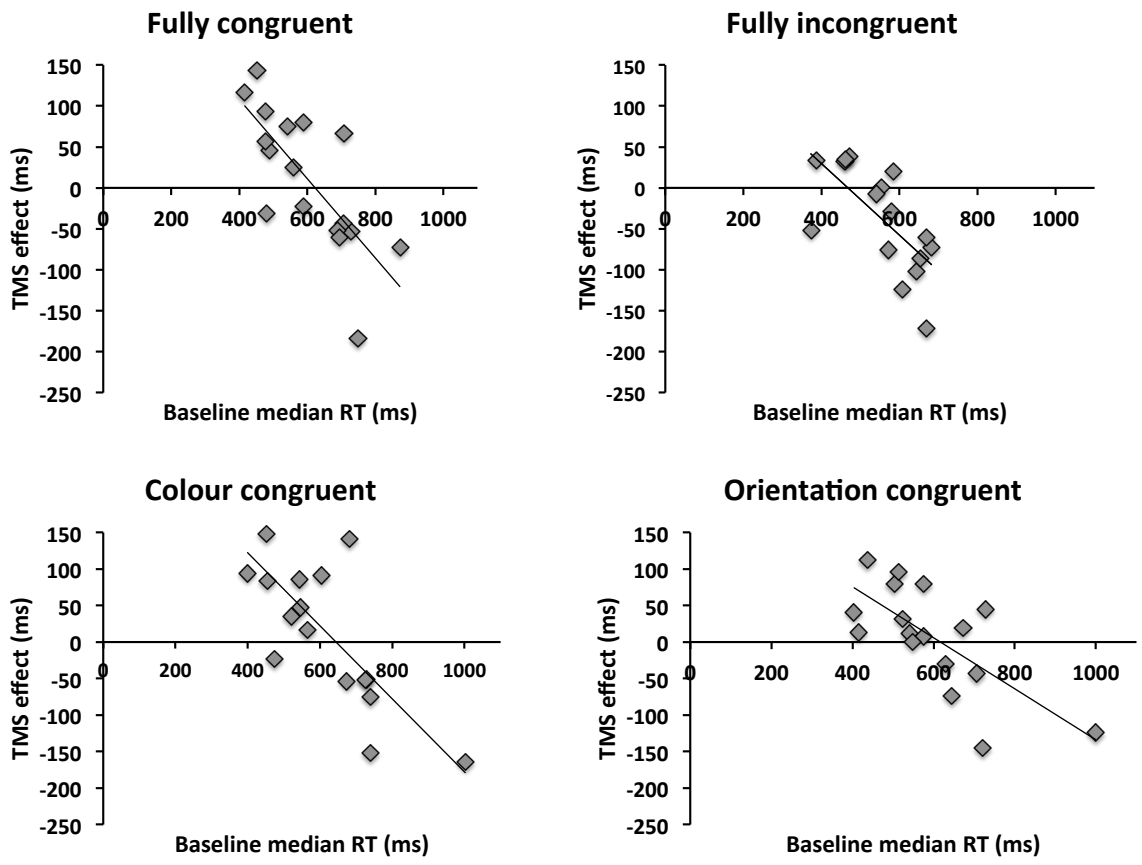


**Figure 3. Relationship between baseline reaction time and the induced TMS effect.** *The TMS effect reflects the difference between V1/V2 TMS and Vertex TMS conditions. Values above the x-axis indicate impairment of behavior, whereas values underneath it reflect facilitation. A significant correlation was present for all congruencies. Incongruent condition appears to differ from other conditions in terms of the intercept the x-axis which reflects transition from inhibitory to facilitatory effects of TMS. The intercept for congruent condition is in the region of 500 ms whereas it is above 600 ms for other congruencies. The implication is that, for incongruent trials, facilitations are observed until higher levels of performance (i.e. at lower RTs) than for other congruency types. Thus the facilitatory range of TMS effects is wider for the incongruent stimuli.*

ANOVAs on low and high baseline performers

The above analysis indicates that TMS may facilitate performance in the incongruent condition until a higher baseline performance levels than for other congruency types. To examine this further, we divided participants into two baseline performance groups ("low" and "high"). The results are shown in Figure 4 (see Figure 1 for the same results when data are not divided by baseline performance). For both groups, we carried out an ANOVA with congruency (fully congruent, fully incongruent, colour congruent, orientation congruent) and TMS site (Vertex, V1/V2) as within-subject factors.

For low *performers,* the main effect for TMS site was borderline significant ($F(1,7)=5.107$; $p=0.058$; $\eta_p^2=0.422$), with the main effect of congruency ($F(3,21)=1.264$;$p=0.312$; $\eta_p^2=0.153$) and interaction between site and congruency being non-significant ($F(3,21)=2.293$; $p=0.11$; $\eta_p^2= 0.247$). The borderline significant main effect of TMS indicates that the impact of V1/V2 TMS was to induce a weak general facilitation relative to Vertex TMS, regardless of congruency (see figure 3). A planned t-test indicated that this facilitation reached significance only for the incongruent condition $t(7)=3.766$; $p=0.007$) – driving the effect reported in Silvanto et al (2017). For other prime-target congruencies, this facilitation was not close to statistical significance (lowest p-value 0.21).

In contrast, *for high performers,* there was a significant main effect of TMS site ($F(1, 8)=12.602$; $p=0.008$; $\eta_p^2=0.612$), a borderline significant effect of congruency ($(F)3,24)=2.769$; $p=0.064$; $\eta_p^2=0.257$) and a highly significant interaction between site and congruency ($F(3,24)=5.068$; $p=0.007$; $\eta_p^2=0.388$). Thus for high performers, congruency did significantly modulate the impact of TMS. Pairwise comparisons showed that V1/V2 TMS impaired performance relative to Vertex TMS for all other congruencies except for fully incongruent trials (*fully congruent:* $t(8)=2.830$; $p=0.022$); *colour congruent:* $t(8)=3.611$; $p=0.007$); *orientation congruent*: $t(8)=3.120$; $p=0.014$); *fully incongruent:* $t(8)=-0.199$; $p=0.847$).

In short, this analysis showed the following: for low performers, TMS induced a borderline-significant general facilitation regardless of prime-target congruency. (Planned pairwise comparisons indicated that for the incongruent trials there was a significant facilitation, driving the effect reported in Silvanto et al, 2017). For high performers, TMS impaired all congruency types expect incongruent trials.

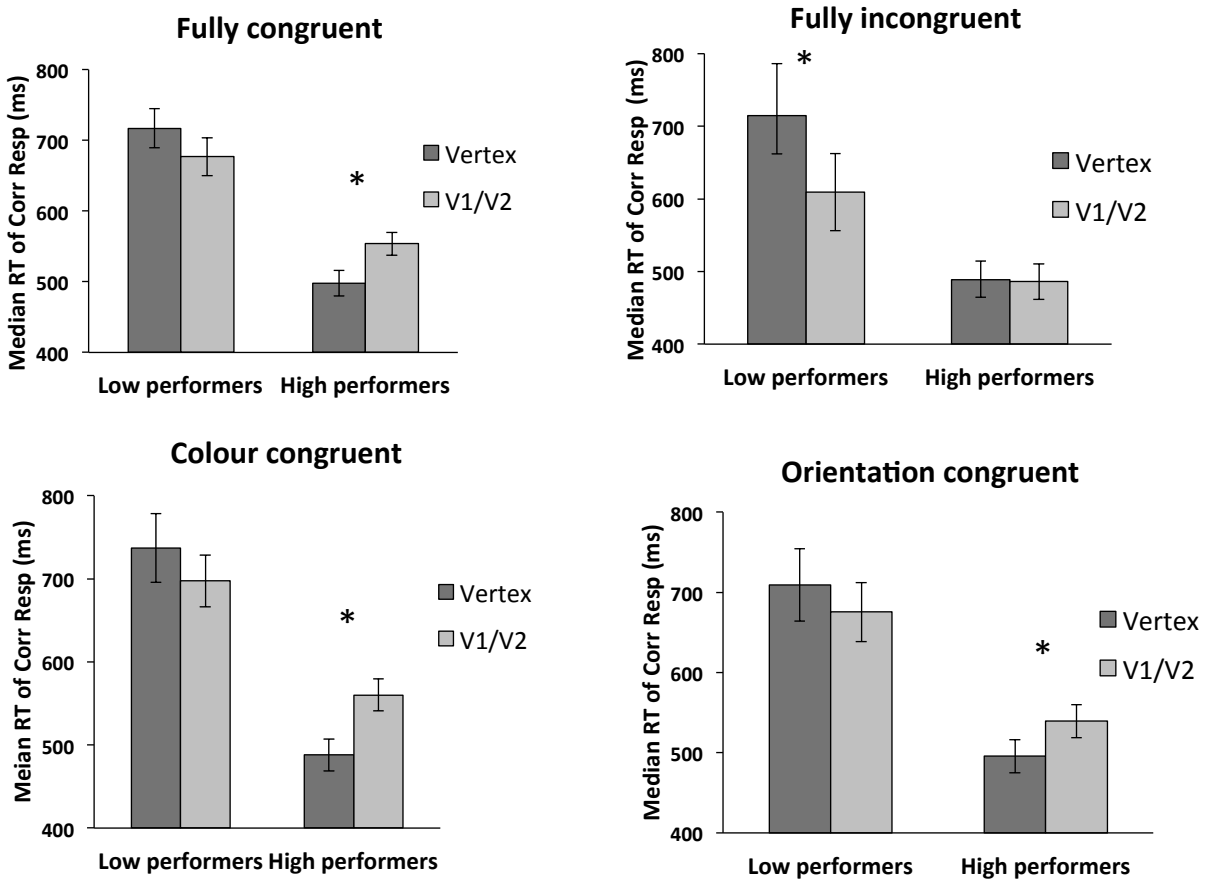


**Figure 4. Performance of low and high baseline performers as a function of prime-target congruency and TMS site.** *for low performers, TMS induced a borderline-significant general facilitation regardless of prime-target congruency. (Planned pairwise comparisons indicated that for the incongruent trials there was a significant facilitation, driving the effect reported in Silvanto et al, 2017; contrast with Figure 1). For high performers, TMS impaired all congruency types expect incongruent trials.*

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**Discussion**

Our findings indicate that baseline performance level and initial brain state combine to produce behavioral effects of TMS. Firstly, our results showed that a relationship between performance at baseline and the magnitude of the induced TMS effect was present for *all* prime-target congruencies. Thus, even though at group level TMS was found to modulate performance only for fully incongruent targets (see Silvanto et al, 2017), an analysis focusing on individual differences revealed the operation of a TMS effect at all levels of congruency. Specifically, there was a negative relationship between baseline performance level and the induced TMS effect, such that, as baseline performance level increased (i.e. RTs decreased), TMS effects turned from facilitatory to inhibitory.

Secondly (and what is the key finding), the incongruent condition differed from other congruency conditions in terms of the transition point from facilitatory to disruptive effects of TMS (reflected as intercepts in Figure 3). As Figure 3 indicates, the effect of TMS was such that performance of participants with relatively slow baseline RTs was facilitated by TMS, whereas those with faster baseline RTs were impaired. Interestingly, for incongruent trials the transition from facilitatory TMS to inhibitory TMS was shifted relative to other congruency types, *such that TMS induced facilitations until a higher level of performance*. Specifically, while for the incongruent condition the transition from facilitation to impairment occured at appr. 500 ms, for other congruencies this occurred at lower performance levels, at appr. 600 ms. This shift in the intercept can explain why group-level analyses such as those carried out by Silvanto et al (2017) tend to reveal significant facilitatory effects only on incongruent trial types: as the "window" for facilitatory effects of TMS is wider (i.e. such effects are obtained with a large range of baseline performance), more participants will fall within this range. In contrast, for other congruencies the transition from facilitation to inhibition occurs with lower level of baseline performance, increasing the likelihood of observing group level *impairments* for these congruency types. The existence of a wider facilitatory vs disruptive TMS window for incongruent vs other trial types is supported by the results of the ANOVA in which participants were divided into low and high baseline groups. In these analyses, TMS impaired high performers for all prime-target congruencies other than incongruent trials. In contrast, for low performers there was a borderline-significant main effect of stimulation site, indicating that TMS tended to facilitate performance for all stimulus congruencies; however, the facilitation was strongest for incongruent trials, due to the reasons discussed above.

Prior studies have shown that TMS can have a facilitatory effect on near-threshold stimuli (e.g. Abrahamyan et al, 2011, 2015; Schwarzkopf et al, 2011). The present results show that baseline performance level its own is insufficient to account for TMS effects, given that the same TMS parameters can have a different consequence despite similar baseline performance, as a function of brain state manipulations. While baseline performance (or "signal strength") clearly plays a role, this does not provide the complete picture. The key issue is that state manipulations such as priming modulate *neuronal excitability* (i.e. susceptibility to external

input such as TMS). Priming is likely to reduce excitability of neural representations incongruent with the prime and therefore a higher TMS intensity is needed to drive these neurons. How can this explain the shift in facilitatory/inhibitory range found here?

We have previously proposed (see Silvanto et al, 2017; Silvanto & Cattaneo, under revision) that behavioral TMS effects can be explained in terms of changes in neural excitability interacting with nonlinear neural effects, as a function of TMS intensity. The latter have been reported by Moliazde et al (2003), who found that low intensity TMS induced a facilitation in neural activity and visually-induced neural firing lasting up to 200 milliseconds, followed by longer lasting neural suppression. In contrast, with high TMS intensities the early facilitation was replaced by a suppression of neural activity. This early facilitation vs inhibition of neural activity has been linked to behavioral facilitations vs impairments, which also occur at low vs high TMS intensities (i.e. at group level, subthreshold TMS facilitates and suprathreshold TMS impairs perception (see Silvanto et al, 2017; Silvanto & Cattaneo, in review, for more detailed discussions of this view). The key point is that, changes in neural excitability, by modifying susceptibility to TMS, shift the intensities with which facilitatory and inhibitory effects of TMS are observed. This occurs because the same TMS parameters have a stronger or weaker effect when excitability has been increased/decreased. In a simplified sense, reduction in excitability (as is the case here with incongruent trials), turns inhibitory *high* intensity TMS to facilitatory *low* intensity stimulation - as the same stimulation intensity has a weaker neural effect after priming. The consequence is a shift in the transition point from facilitatory to disruptive effects of TMS for incongruent trials. In this view, why does baseline performance level matter? It matters because it also reflects neural excitability, in terms of the efficacy with which the incoming stimulus is processed by visual system. Slower reaction times would be indicative of lower excitability, which in terms of the above model increases the likelihood of a facilitatory effect of TMS. In contrast, higher reaction times would indicate higher level of excitability and therefore an inhibitory effect of TMS is likely. This is consistent with the present results.

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