Modulation of brain activation and functional connectivity during motion perception with concurrent TMS

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Introduction

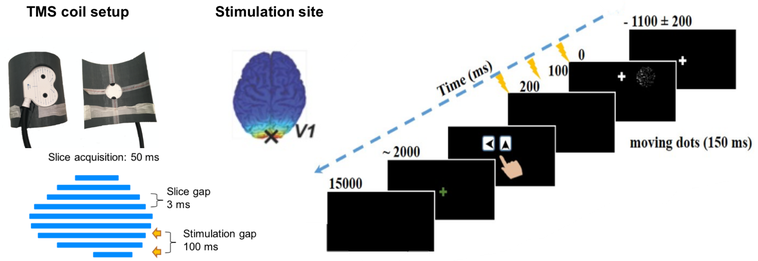
Concurrent TMS-neuroimaging research is an exciting technological development that may elucidate key dose-response relationships and guide therapies relying on neurostimulation. While TMS effects often occur at the targeted brain regions, fMRI-based experimental evidence shows otherwise. However, the global effects of TMS to a single cortical site are still not fully understood.

The state-dependency of the brain, whether it be baseline or activated, also affects the influence of TMS. For example, when rTMS is applied to middle temporal visual area (MT+), performance is hindered in tasks which require attention to visual motion and enhanced in tasks in which attention is given to non-motion visual attributes (Walsh 1998). This suggests the neural effects of TMS may depend on whether the stimulated area – and the areas functionally connect to it – are associated with task performance.

In the current study, we sought to explore the TMS effect beyond the stimulated region by investigating whole-brain univariate activation and functional connectivity during a motion-perception task under concurrent TMS.

Methods

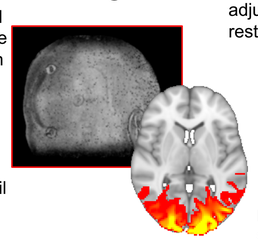
Concurrent TMS-fMRI was administered when participants performed a dot-motion direction discrimination task presented in their right visual field. A figure-8, MR-compatible coil was used to apply three-pulse, 10 Hz stimulation over the **primary visual cortex (V1)** at the onset of the dot stimuli with 4 levels of trial-randomized stimulation intensity: **20% / 40% / 80% / 120%** resting Motor Threshold (denoted as 20%MT, 40%MT, 80%MT, 120%MT).



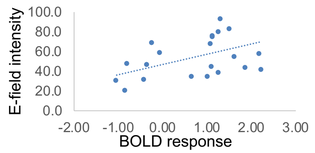
TMS pulses were delivered between the acquisition of uninterested slices of the image. ArtRepair and independent component analysis (ICA) were used to further remove TMS-related artefacts. The preprocessing pipeline is described as followed:
Raw fMRI data ➔slice timing, reslice & realign ➔ repair bad slices ➔ repair bad volumes ➔ ICA-based denoising ➔ registration, univariate & functional network analyses
Univariate activation and brain connectivity were subsequently computed from the preprocessed data.

Electric field modeling

In order to model the effective dose delivered to each participant, we first identify the stimulation location via fiducial markers placed on the coil during scanning.



Next we estimate the Electric field (E-field) and adjust the delivered (di/dt) by the individual resting motor threshold.

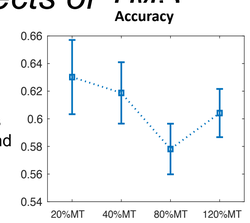


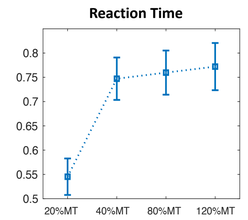
E-field intensity correlates with BOLD response and serves in our analyses as a control covariate.

Results

Behavioral Effects of TMS

TMS intensity has significant effects on response accuracy (p=0.049) as well as reaction time (p=1e-19). Across 4 levels of stimulation intensity, we found a selective deficit at 80% of Resting Motor Threshold.

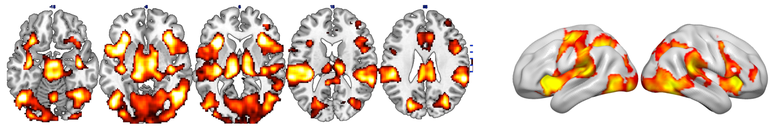




Univariate Effects of TMS

Whole-brain effects

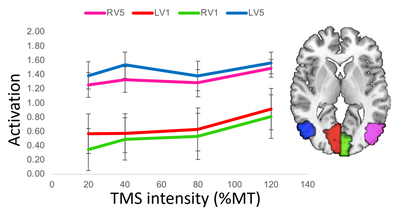
We observed widespread effects of TMS Intensity. Many of these effects are unsurprising and not interesting—e.g., increased activity in auditory or motor cortices reflecting the sensory components of increased TMS intensity. But importantly, such intensity effect also appeared in visual areas including left MT+



Region of Interest Analysis

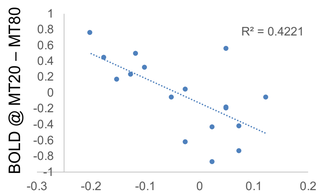
We define specific regions of interest to examine the local effects of TMS intensity on the visual system:

- Bilateral primary visual ROIs as defined "V1" by NeuroSynth
- Bilateral MT+ ROIs as defined "motion" by NeuroSynth



Higher activations were observed in the left hemisphere V1 and MT+ as expected, given the visual stimuli were presented at the right visual field

Furthermore, the selective performance deficit at 80%MT showed neural correlate in **left MT+** region, as subjects who showed a greater decrease in BOLD activity (20%MT minus 80%MT) are those to show a greater behavioral impairment (20%MT accuracy minus 80%MT accuracy), r = 0.65, p < 0.05. No neural-behavioral correlation was found in other regions.

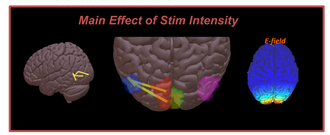


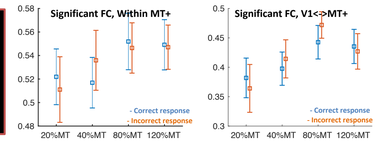
Connectivity Effects of TMS

Brain networks were constructed on a sub-parcellated HOA atlas. FC was estimated with partial correlation between PPI timeseries (BOLD x condition-specific task regressor) in two ROIs, controlling for the covariance from task activation and BOLD signal.

Intensity Effects on V1 ~ MT+ functional connectivity

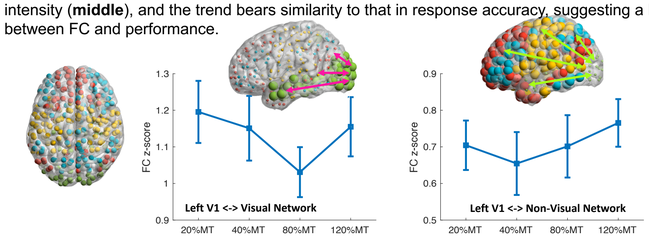
Localized analysis on a subnetwork of bilateral V1 & MT+ ROIs revealed a cluster of significant FC showing TMS intensity effect at the left hemisphere (corresponding to the side of visual stimuli) but absent in the right hemisphere, suggesting TMS selectively affects connectivity in the task-related side of brain.



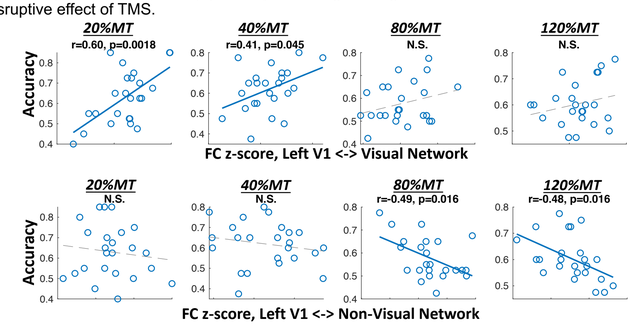


Intensity Effects on whole-brain functional connectivity

FC from the stimulated region to the whole brain was further investigated. A data-driven modularity analysis parsed the ROIs into four sub-networks (**left**), including the visual network (**green**). The FC from left V1 to other regions within visual network showed an effect of TMS intensity (**middle**), and the trend bears similarity to that in response accuracy, suggesting a link between FC and performance.



We then explored the relationship between response accuracy and FC in left V1. The FC between left V1 and other visual regions positively predicted performance at lower TMS intensity (**upper**). In comparison, at higher TMS intensity, FC between left V1 and other brain systems negatively predicted performance (**lower**), probably indicating some global network level mechanisms of the disruptive effect of TMS.



Conclusions

- The global effects of localized stimulation are evident in both univariate activity and functional connectivity
- TMS propogates in a functionally-specific (or state-depedent) manner, such that the hemisphere engaged with the motion task showed the most pronounced neuro-modulatory effect
- These findings provide evidence that TMS can modulate the activity and connectivity beyond stimulated location in an intensity-dependent manner.

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