Assessing brain-wide TMS-evoked responses depending on ocular and oscillatory state: a simultaneous TMS-EEG-fMRI project

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Background

Complex cognitive functions rely on communication within and between widespread brain networks. Brain-wide signal propagation can be studied using transcranial magnetic stimulation (**TMS**) as a system probe, and concurrent functional magnetic resonance imaging (**fMRI**) to measure local and remote responses [1].
However, this approach ignores the fact that brain state changes constantly, affecting how information is processed and signals propagated. Specifically, network responses can depend on:

- **Momentary neuronal oscillations** as measured with electroencephalography (**EEG**) [2];
- **Neurocognitive state** [3].

Here, we studied brain-wide signal propagation in two neurocognitive states: **eyes open,** and **eyes closed**. We applied an innovative simultaneous TMS-EEG-fMRI setup in eight participants [4,5], targeting high-level association area **right posterior parietal cortex** (PPC), a known neurocognitive network hub [6].

Methods

- ***Eye closure***: cued by auditory tone, in complete darkness (*Fig. 1*).
- ***TMS***: Supra- vs. sub-threshold (120% vs. 40% resting motor threshold) 15Hz triplets ('TMS bursts') were delivered during fMRI acquisition gaps. An MRI-compatible figure-8 coil was fixed over EEG position P4.
- ***EEG***: 64 channels, Fs: 5000Hz, ref: Cz, ground: AFz, imp: <25 kOhm.
- ***(f)MRI***: 3T data were acquired using two 4-channel MRI flex coils *(Fig. 2).* Three to eight functional runs were collected (EPI, 150 volumes, 30 slices, multiband 2, 3mm^3, TR/TE: 2500/30ms). A 3D T1-weighted anatomical scan was acquired (MPRAGE, 1mm^3, 192 slices, TR/TE: 2300/2.98ms).

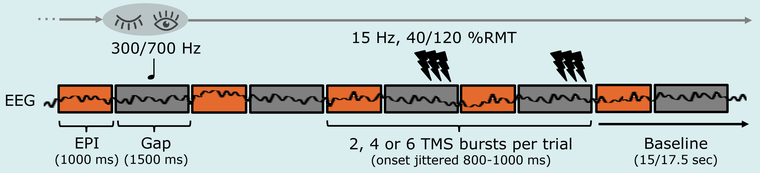

***Fig. 1*. Experimental design.** EPI = echo-planar imaging, RMT = resting motor threshold.

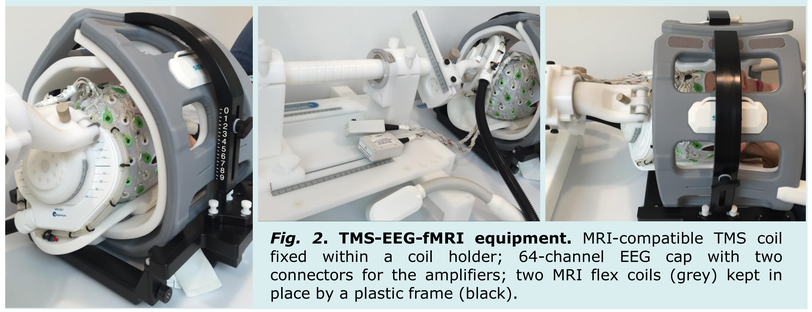

***Fig. 2*. TMS-EEG-fMRI equipment.** MRI-compatible TMS coil fixed within a coil holder; 64-channel EEG cap with two connectors for the amplifiers; two MRI flex coils (grey) kept in place by a plastic frame (black).

Analyses

- ***EEG***: Data were epoched (-500 to -5ms pre-TMS), detrended, and downsampled (500Hz). Bad channels were excluded based on visual inspection. Data were re-referenced to an average electrode, baseline corrected (-450 to -50ms), and filtered (50Hz, 0.5-40Hz). An FFT (Hanning-tapers, 1Hz resolution) was used to calculate pre-TMS alpha power (8-12Hz) as a measure of brain excitability [2]. Epochs/trials were labeled "low" vs. "high" alpha power, through median split.
- ***fMRI***: A GLM was calculated with hemodynamic response (HDR-)convolved event predictors for TMS bursts in 8 conditions (eye closure (2) x TMS intensity (2) x alpha power (2)), and the auditory cues for eyes open/closed.

Results

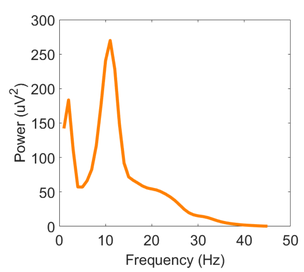

***Fig. 3*. Average power spectrum.** Power spectra were calculated for all pre-TMS epochs and averaged across participants and runs. Even though participants were in a noisy and arousing environment, an alpha power peak could be reliably detected.

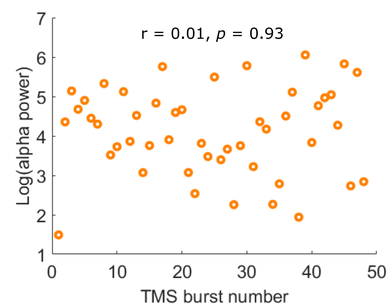

***Fig. 4*. Alpha power over time**. Alpha power can show drifts over time due to changes in vigilance/fatigue. We did not find any significant correlation between log(alpha power) and TMS burst number (i.e., time). This could be due to the fact that our runs were short and participants were not engaged in a demanding task. Data are shown for one representative subject and run.

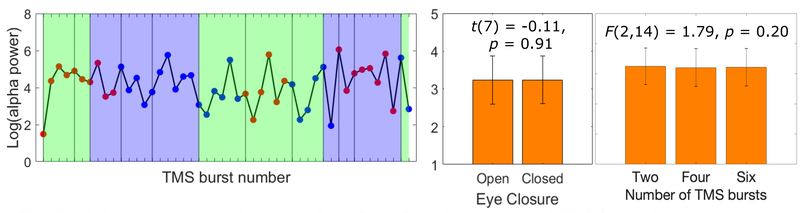

***Fig. 5*. Alpha power over time as a function of ocular state and TMS intensity.**
Left: pre-TMS alpha power within and between blocks over the course of one representative run. Background shading indicates eye closure (green: open, blue: closed). Dot color indicates TMS intensity (red: supra-, blue: sub-threshold). Ticks indicate TMS bursts. Vertical lines indicate block starts. Alpha power fluctuates spontaneously over time, within and between trials and conditions.
Middle: average pre-TMS alpha power does not significantly differ between eyes open and closed (i.e. no "Berger effect"). This finding is somewhat surprising, although we previously observed that prolonged blindfolding causes a reduction in the classic EEG Berger effect [7].
Right: average pre-TMS alpha power does not significantly differ between blocks with two, four or six TMS bursts.

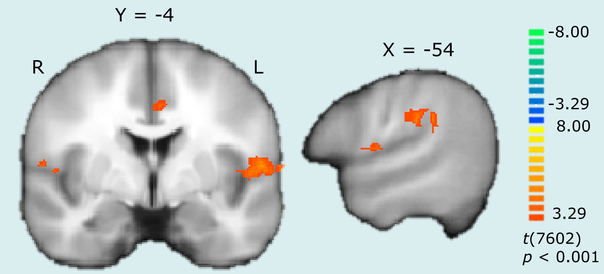

***Fig. 6*. BOLD activity time-locked to TMS events as a function of TMS intensity.** Multi-subject fixed-effects GLM results for the effect of TMS intensity (contrast: [supra-threshold > sub-threshold], cluster-level statistical thresholding at p < 0.001). Results are projected onto an MNI template brain (transformed into TAL space), coordinates are in TAL space. As expected, supra- compared to sub-threshold TMS induced higher fMRI activation in bilateral auditory (*figure: left*) and sensorimotor areas (*figure: right*), due to louder noise and stronger sensation associated with TMS bursts at a higher intensity.

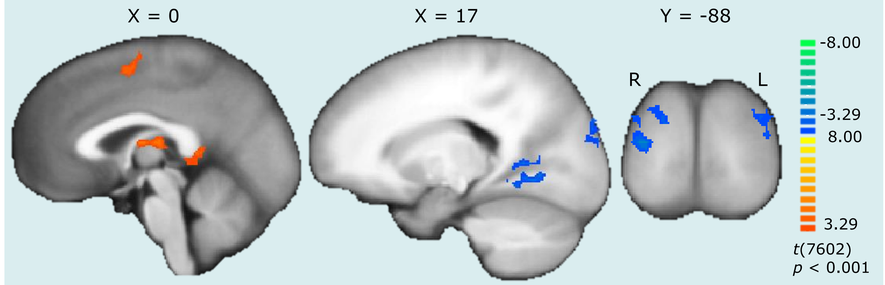

***Fig. 7*. BOLD activity time-locked to TMS events as a function of eye closure.** Multi-subject fixed-effects GLM results for the effect of eye closure (contrast: [eyes open > closed], cluster-level statistical thresholding at p < 0.001). Results are projected onto an MNI template brain (transformed into TAL space), coordinates are in TAL space. The (de-)activations in several (sub-)cortical areas indicate that BOLD responses time-locked to TMS pulses delivered to PCC depend on neurocognitive state at the time of TMS. These effects are independent of alpha power (see *Fig. 5*). *Left*: bilateral activations in supplementary motor area (SMA), thalamus, and posterior cingulate cortex (PCC), an area of the default mode network (DMN). *Middle/right:* bilateral deactivations in visual cortices.

Conclusion

- TMS-time-locked BOLD responses in **visual cortex, thalamus, SMA and PCC** depend on **neurocognitive state** (eye closure) at the time of TMS;
- These effects were **independent of alpha power**, since alpha power did not systematically differ between eyes open vs. closed;
- Supra- compared to sub-threshold TMS is associated with higher fMRI responses in **sensorimotor areas**;
- These preliminary (fixed-effects) findings **confirm the potential** of our novel concurrent TMS-EEG-fMRI setup and open the door to the investigation of state-dependent brain-wide signal propagation.

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[1] Sack (2007). Cerebral Cortex, *17*(12).
[2] Romei (2007). Cerebral Cortex, *18*(9).
[3] Blankenburg (2010). Cerebral Cortex, *20*(11).
[4] Peters (2013). J. Neurophysiol., *109*(4).
[5] Peters (2020). Commun. Biol. *3.*
[6] van den Heuvel (2013). Trends.Cogn.Sci., *17*(12).
[7] de Graaf (2017). Brain Stimulation, *10*(4).