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State-dependent TMS effects in the visual cortex after visual adaptation: A combined TMS–EEG study

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HIGHLIGHTS

- TMS effects are modulated by the current brain state.
- TMS-evoked potentials were stronger after adaptation to high luminance.
- This study provides the first neural evidence on the interactions between TMS and visual adaptation.

ABSTRACT

Objective: The impact of transcranial magnetic stimulation (TMS) has been shown to depend on the initial brain state of the stimulated cortical region. This observation has led to the development of paradigms that aim to enhance the specificity of TMS effects by using visual/luminance adaptation to modulate brain state prior to the application of TMS. However, the neural basis of interactions between TMS and adaptation is unknown. Here, we examined these interactions by using electroencephalography (EEG) to measure the impact of TMS over the visual cortex after luminance adaptation.
Methods: Single-pulses of neuronavigated TMS (nTMS) were applied at two different intensities over the left visual cortex after adaptation to either high or low luminance. We then analyzed the effects of adaptation on the global and local cortical excitability.
Results: The analysis revealed a significant interaction between the TMS-evoked responses and the adaptation condition. In particular, when nTMS was applied with high intensity, the evoked responses were larger after adaptation to high than low luminance.
Conclusion: This result provides the first neural evidence on the interaction between TMS with visual adaptation.
Significance: TMS can activate neurons differentially as a function of their adaptation state.

1. Introduction

The effects of transcranial magnetic stimulation (TMS) are modulated by the initial activation state of the stimulated region (state-dependency). For example, suppression or facilitation of neural activity with transcranial direct current stimulation (tDCS) in the motor cortex modulates the impact of subsequent repetitive TMS (Siebner et al., 2004; Lang et al., 2004). Furthermore, TMS-evoked potentials (TEPs) depend on the state of neuronal activity in the stimulated area in the motor cortex and change in relation to preparation and execution of unilateral motor action (e.g., (Nikulin et al., 2003; Kičić et al., 2008)) with high reproducibility and sensitivity of TEPs (Lioumis et al., 2009; Casarotto et al., 2010; Kerwin et al., 2018).

In the visual domain, several studies have studied state-dependency using visual adaptation, a phenomenon in which changes in neural tuning and excitability are induced by prolonged

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exposure to sensory stimulation (Gibson and Radner, 1973; Mather et al., 1998; Grill-Spector et al., 2006). These studies have concluded that TMS is more effective in activating adapted than non-adapted perceptual representations; for example, after adaptation to a uniform colored background, phosphenes induced from the early visual cortex take on the color qualities of the adapting stimulus (Silvanto et al., 2007; Silvanto and Pascual-Leone, 2012). Furthermore, adaptation not only modulates phosphene appearance, but also increases the proportion of trials in which phosphenes are reported (Guzman-Lopez et al., 2011). Similar effects have been found in a wide range of cognitive domains, including numerical magnitude (Cohen Kadosh et al., 2010) and action encoding (Cattaneo et al., 2011, 2010), and form the basis of the TMS-adaptation paradigm.

However, the neural basis of how responses to TMS in the visual cortex are affected by adaptation has not been investigated. In the present study, we utilized electroencephalography (EEG) to investigate the neural basis of this state-dependency. Since the pioneering work of Ilmoniemi et al., (1997) (Ilmoniemi et al., 1997), the combination of TMS–EEG has become widely used in cognitive neuroscience (e.g., (Thut et al., 2003a, 2003b; Romei et al., 2007, 2010; Thut and Miniussi, 2009; Taylor et al., 2008; Reichenbach et al., 2011)). We used the behavioral paradigm of Silvanto et al. (2007), in which participants were adapted to visual stimuli prior to the application of single neuronavigated TMS (nTMS) pulses over the visual cortex. In the study of Silvanto et al. (2007), participants were presented with uniform colors. This leads to adaptation at retinal level, leading to a reduced level of input to the early visual cortex. Consequently, cortical neurons receiving input from the adapted cells are discharging less than in the absence of adaptation; this reduced activity level increases excitability (i.e., susceptibility to a TMS pulse (Siebner et al., 2009). In the present study, we used high luminance adaptation to induce a similar adaptation effect at retinal level. We hypothesized that this would increase susceptibility to TMS in the high luminance *vs*. low luminance condition, and result in larger evoked responses in the former condition. To study the interaction between adaptation and nTMS effects, we concurrently recorded EEG to examine TEPs. Furthermore, in order to explore whether such effects are stimulus intensity-dependent, nTMS was applied at either "high" (80% of maximum stimulator output, MSO) or "low" (60% of MSO) intensity.

2. Methods

2.1. Participants

Eleven healthy volunteers (mean ± standard deviation; age 27 ± 2 years, 3 women, all right-handed) participated in the study, but only seven of them completed the data collection for both TMS conditions. This resulted in a final sample of 11 participants for high TMS intensity and 7 participants for low TMS intensity. All experimental procedures were approved by the ethical committee of the Helsinki University Central Hospital and were in accordance with the Declaration of Helsinki. All participants gave their written informed consent before the experiments, and none of them had any contraindication to TMS or any neurological, psychiatric, or other relevant medical problems (Rossi et al., 2009).

2.2. Transcranial magnetic stimulation

TMS was performed with a figure-of-eight coil with a 70mm outer diameter of each wing (Nexstim Ltd, Finland). The positioning of the TMS coil was navigated with the eXimia 3.2 navigation brain system (Nexstim Ltd, Finland) using a three-dimensional reconstruction of the individual magnetic resonance images (MRI; Fig. 1**)**. TMS was applied in the vicinity of the calcarine sulcus in the left hemisphere. The coil orientation was lateral-to-medial, as this orientation is the most effective in visual cortex stimulation (Kammer et al., 2001). To ensure accurate targeting of the V1/V2 visual cortex, we applied nTMS, in which the location of the TMS coil is shown over the individual MRI reconstruction of the subject's brain in real-time. Monophasic TMS pulses were administered in the region of the calcarine sulcus, between the electrodes Oz, POz, and PO3 (Fig. 1**B)**. In experiment 1, nTMS was applied at an intensity of 80% MSO, inducing an average induced electric field (E-field) of 122 V/m (high TMS), the highest intensity well tolerated by all the participants. In experiment 2, TMS was applied at an intensity of 60% MSO with an average induced E-field of 92 V/m (low TMS). Experiments 1 and 2 were separated by at least 7 days and their order was counterbalanced across participants. 216 TMS pulses were delivered in each experiment (108 pulses for each luminance condition). We initially aimed at adjusting TMS intensity according to the individual phosphene threshold, but they were too high for comfortable stimulation. The use of the EEG cap increased the distance to the cortical surface from the coil. This reduces the stimulation strength at the cortex, decreasing the probability of phosphene induction. Our participants perceived phosphenes on average 15% of the high TMS condition trials; the intensity was thus clearly below the phosphene threshold.

2.3. EEG recordings

The TMS-evoked EEG responses were recorded with a 60-channel TMS-compatible Nexstim eXimia EEG device (Nexstim Ltd., Helsinki, Finland). The electrodes were placed according to the 10–20 system. The signals were referenced to the right mastoid; the ground electrode was over the right cheekbone. Electrooculography (EOG) was recorded from electrodes placed on the frontal process of the zygomatic bone and under the eye. The impedance of all electrodes was kept below 5 kΩ. The signals were band-pass filtered from 0.1 to 350 Hz and digitized at 1450 Hz. During the TMS pulse, the EEG amplifier was blocked by a sample-and-hold circuitry for 2 ms to remove most of the TMS-induced artifacts (Virtanen et al., 1999).

2.4. Visual stimulation protocol

The experimental setup is shown in Fig. 1. Participants were adapted (for 40 s), to a uniform computer display that was either white (high luminance; 98 cd/m^2) or black (low luminance; 0.5 cd/m^2) at the viewing distance of 57 cm to the monitor. Participants were asked to fixate their eyes close to the left edge of the screen (Fig. 1) to adapt the right visual field (as nTMS was applied over the left visual cortex). After the end of the adaptation, the screen turned to black and a fixation cross (presented for 1–1.5 sec) appeared on the screen. Each adaptation period was followed by a block of 12 TMS pulses. There was a 3 s delay between the response and the onset of the next trial. A total of 18 adaptation conditions (9 with adaptation to the high luminance display, and 9 with adaptation to the low luminance display), and a total of 108 nTMS responses were collected for each adaptation condition and each subject. Earplugs were used to attenuate the acoustic click produced by the TMS coil.

2.5. Data analysis

All analysis was carried out offline with Matlab (The Mathworks, Inc., Natick, Massachusetts, USA). The EEG recordings were visually inspected. The epochs with amplitudes larger than ± 100 μV or containing excessive spontaneous muscle activity

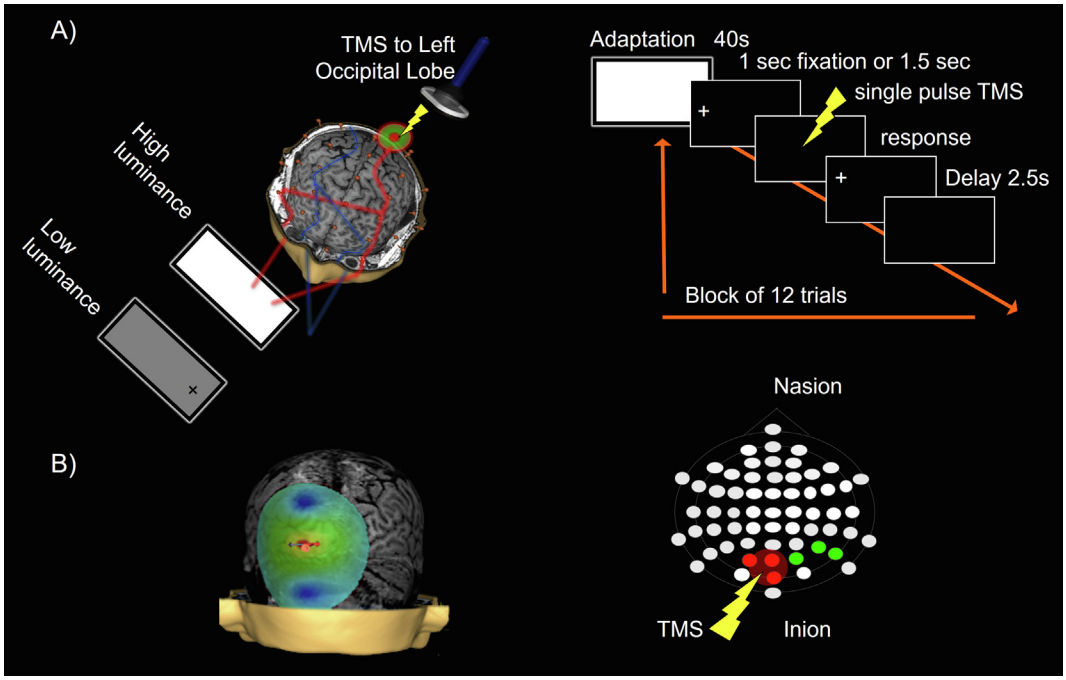

Fig. 1. Experimental setup. (A) The timeline of the experimental trial. A 40-sec period of adaptation to either high luminance (white screen) or low luminance (black screen) was followed by a block of 12 transcranial magnetic stimulation (TMS) pulses. (B) Neuronavigated TMS (nTMS) and the electroencephalography (EEG) electrode montage shows that TMS was applied in the region of the calcarine sulcus, between the cluster of electrodes Oz, POz, and PO3 (red), and the cluster of electrodes PO4, P4, and P8 that were used as a control (green). The current orientation was lateral-to-medial. The positions of the electrodes were co-registered with each participant's MRI scan. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(i.e., from the scalp, neck muscle, or blinks) were removed from the analysis. The bad channels (e.g., those with strong muscle/eye movements or poor electrode contact) were excluded from the analysis. On average, 70 trials per condition were included into the analysis for each subject. The data were baseline corrected from −300 to −10 ms, and the TMS induced artifacts were suppressed from 0 to 30 ms with a method of principal components (PCs) suppression (Hernandez-Pavon et al., 2012; Ilmoniemi et al., 2015). On average, 6 to 7 PCs were suppressed in each subject. This method has been validated in recorded and simulated TMS–EEG data and has shown to effectively suppress the artifacts' amplitude, leaving the neurophysiological signals intact. After that, the data were average referenced and filtered with a band-pass filter (1–40 Hz) and a notch filter (48–52 Hz) to remove high-frequency and the remaining power-line interference, respectively. Both filters were fourth-order, Butterworth, and zero-phase.

2.6. TEPs

For the TMS-evoked potentials (TEPs), the data were averaged separately for the different TMS intensities and luminance, resulting in four data sets (high TMS intensity low luminance *vs*. high TMS intensity high luminance; low TMS intensity low luminance *vs*. low TMS intensity high luminance). To assess the effects of the TMS-evoked global cortical activity, the global mean field power (GMFP) was computed from 200 ms before to 400 ms after the TMS pulse (Lehmann and Skrandies, 1980). The local effects induced by TMS over the left occipital area were assessed by the averaged TEPs across a cluster of electrodes in a region of interest (ROI) surrounding the stimulated target. The averaged TEPs were analyzed in two ROIs, the left occipital cortex (Oz, POz, PO3), which contained the electrodes surrounding the TMS pulse, and a control area in the right occipital cortex (PO4, P4, P8) containing electrodes away from the TMS pulse. The signals from the same ROIs were averaged for each volunteer to compute the averaged TEPs. We then compared the effects of low *vs*. high luminance during high TMS intensity and low *vs*. high luminance during low TMS intensity on the GMFP and averaged TEPs. Fig. 1 depicts the experimental setup and the distribution of the electrode groups over the scalp that were grouped in the analyses. We aimed at recording each participant with two TMS intensities. Unfortunately, all participants were not available for both TMS experiments. We compared the results obtained from 11 participants in experiment 1 with 7 participants in experiment 2. We also compared the results from the 7 participants participating in both experiments 1 and 2. To increase statistical power, values at individual EEG electrodes were entered into the ANOVA.

2.7. Statistical analyses

The EEG data analysis was carried out in five-time windows: −150 to −50 ms (T0), 15–50 ms (T1), 50–150 ms (T2), 150–250 ms (T3), and 250–350 ms (T4). The time windows (T1–T4) were based on peaks visible in the grand average data and GMFP (Figs. 2 and 3**A**). Some of these responses are consistent with prior work showing brain activation in these time windows (Taylor et al., 2010). T0 was used to assess possible changes induced by the adaptation condition in the baseline, prior to TMS being applied on each trial.

We assessed the effects of adaptation conditions in the global cortical excitability by comparing the GMFP in the time windows. For this aim, we used a 2-way repeated-measures ANOVA with main factors "adaptation condition" (low luminance, high luminance) and "time window" (T0, TI, T2, T3, and T4).

The statistical analysis of averaged TEPs within the ROIs was performed for peak amplitudes, peak latencies, and area under the curves separately for each subject and condition in the time windows (T0, T1, T2, T3, and T4). A 3-way repeated-measures ANOVA analysis with main factors "adaptation condition" (low luminance *vs*. high luminance), "time window" (T0, T1, T2, T3,

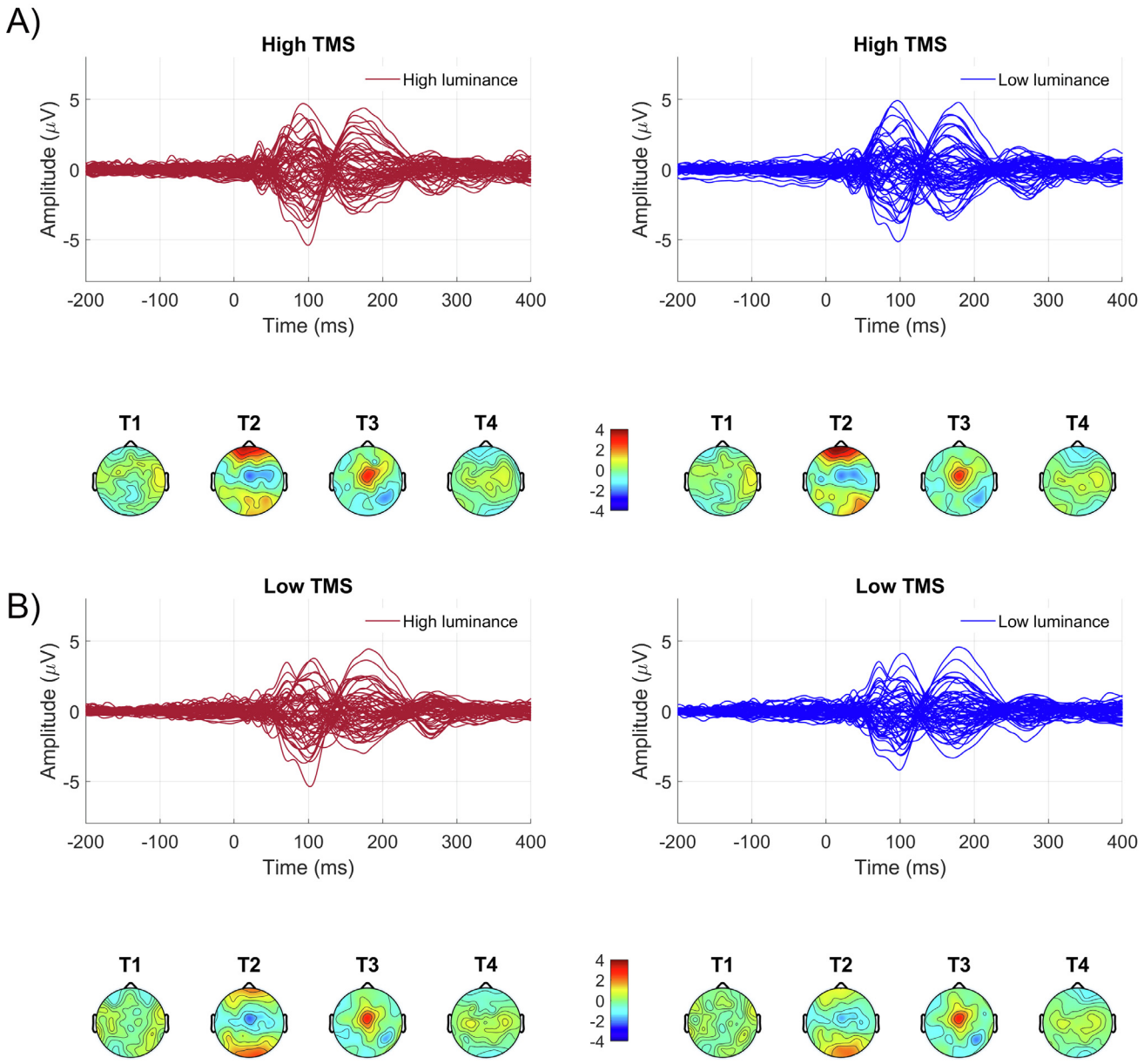

Fig. 2. Grand average transcranial magnetic stimulation (TMS)-evoked responses and topographies for high and low TMS intensity conditions the same 7 participants that completed both Visits. (A) TMS-evoked potentials from all channels in response to single TMS pulses as a function of high TMS intensity (adaptation to high luminance and adaptation to low luminance). Four peaks of activity were observed in the time windows: 15–50 ms (T1), 50–150 ms (T2), 150–250 ms (T3), and 250–350 ms (T4). The topographies were calculated in peak time windows. The topographies at T2 and T3 showed fronto-occipital and centro-parietal responses, respectively. (B) TMS-evoked potentials from all channels in response to single TMS pulses as a function of low TMS intensity (adaptation to high luminance and adaptation to low luminance). Similar peaks of activity were observed in the same time windows as in A), and the topographies at T2 and T3 displayed similar activity patterns. All topographies have the same scale.

and T4), and "ROI" (left *vs*. right occipital area) was carried out for the TEPs. All ANOVAs, for GMFP and TEPs, were performed separately for high and low TMS intensity conditions because not every participant completed both conditions. For *post-hoc* tests, pairwise comparisons were corrected by the Bonferroni method. The significance level was set at 5% ($p < 0.05$).

3. Results

3.1. Global cortical excitability

TMS to the left occipital area evoked positive and negative deflections with amplitudes lasting up to ~ 350 ms for all conditions (Fig. 2). GMFP peaks of activity were identified for both TMS intensities from the grand average GMFP within the five time windows (see Fig. 3.)

The 2-way ANOVA analyses conducted on the individual GMFP for the low and high TMS conditions revealed a main effect of adaptation in the global cortical excitability for low TMS intensity ($F_{(1,6)} = 7.98$; $p = 0.030$) but not for high intensity ($F_{(1,10)} = 0.718$; $p = 0.417$). However, most importantly, there were no significant interactions between adaptation and time intervals for either high ($F_{(4,40)} = 0.749$; $p = 0.565$) or low ($F_{(4,24)} = 1.2$; $p = 0.324$) intensity TMS condition. The same results were obtained for the GMFP for the same 7 participants who completed both TMS conditions (i.e., high TMS intensity and low TMS intensity). The main effect of

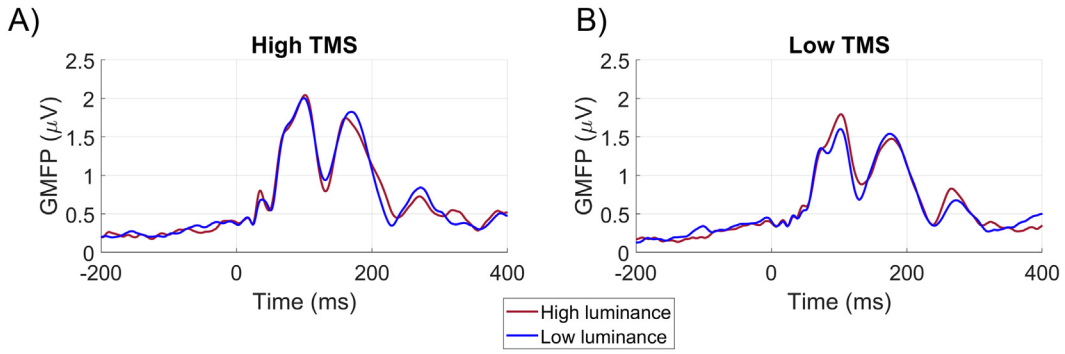

Fig. 3. Grand average global cortical excitability for high and low luminance adaptation conditions for the same 7 participants that completed both Visits. (A) Global cortical excitability for high transcranial magnetic stimulation (TMS) intensity. (B) Global cortical excitability for low TMS intensity. Non-significant differences in the adaptation condition between low and high luminance conditions or TMS intensities were observed.

adaptation in the low TMS intensity condition indicates that adaptation did have a general effect on global cortical excitability, however what is relevant for the present study is that adaptation did not interact with time window. This indicates that adaptation did not modulate TMS effects for this measure. As the analysis in the next section shows, statistically significant adaptation and time window effects are only observed in the TEPs where analysis was restricted to electrodes in the proximity of the TMS coil, indicative of relative local effects.

3.2. TEPs

The TEPs induced by stimulation of the left occipital area consisted of four peaks: N15, P100, N180, and P270. Fig. 4 shows TEPs for high and low luminance adaptation conditions as a function of the two ROIs.

The 3-way ANOVA revealed a main effect of adaptation for the area under the curve for high TMS intensity ($F_{(1,10)} = 9.3$, $p = 0.012$), but no main effect of adaptation condition for low TMS intensity ($F_{(1,6)} = 0.505$, $p = 0.504$). The key finding was that for the high intensity TMS condition there was an interaction between TEP time peak window and adaptation condition ($F_{(4,40)} = 3.6$, $p = 0.012$), but not significance between area, time peak window, and adaptation condition ($F_{(4,40)} = 1.34$, $p = 0.271$). For the low intensity condition, no such interaction was observed. This indicates that the magnitude of the TEPs is modulated by adaptation condition at the high TMS intensity.

Bonferroni-corrected *post-hoc* comparisons revealed a significant difference between the two adaptation conditions for the left ROI (i.e., the ROI where the coil was placed) in the 50 to 150 ms ($p = 0.01$) and 150 to 250 ms time windows ($p = 0.01$) but not in the other time windows (as highlighted in Fig. 4**A**). This indicates that the TMS-evoked response is larger after high luminance than low luminance condition. Fig. 4**C** illustrates the difference in the amplitude of evoked responses as a function of adaptation for this significant main window. None of the responses were significant for any TMS intensity and ROI for the peak latency and peak amplitude.

In the data of the 7 participants who completed both the low and high TMS intensity conditions, the 4-way repeated-measures ANOVA with TMS intensity, adaptation condition, electrode, and time interval showed a significant interaction between TMS intensity, time interval, and adaptation condition ($F_{(4,80)} = 8.45$, $p = 0.0001$). The presence of this interaction supports the view that TEPs are modulated by adaptation in an intensity-dependent manner.

4. Discussion

We used luminance adaptation to investigate how the activation state of the visual cortex affects TMS-evoked activity as assessed with EEG. TEPs were significantly affected by the state of the visual cortex at the time of stimulation, reflected in a significant interaction between adaptation condition and 50–150 ms and 150–250 ms time windows. Interestingly, TEPs after adaptation to high luminance were larger in amplitude than TEPs induced after dark adaptation. The effect also depended on the TMS intensity; the observed TEP enhancements were found in the high but not low TMS intensity condition (however it is important to note that this could reflect smaller sample size in this condition). Moreover, while no significant adaptation effects were observed in the TEP analysis for Low TMS intensity, GMFP did show a significant main effect of adaptation in this condition. It is difficult to conclusively explain these results. One potential explanation is in terms of lack of power; it is possible that low sample size (n = 7 for low intensity TMS) underlies the lack of significant effects in the TEP analyses. An alternative explanation is it reflects adaptation occurring outside the visual cortex, as the TEP analysis included only the electrodes surrounding the coil. However, this view is difficult to reconcile with the finding that in the high TMS intensity condition (where visual stimulation was identical), adaptation × time window interaction was observed in the TEPs (but not in the GMFP), indicative of adaptation localised to visual cortex.

The impact of TMS has been shown to depend on the level of visual adaptation in the visual system. Luminance adaptation (or light adaptation) modifies the gain and dynamics of retinal neurons to maintain visual sensitivity and avoid response saturation when the mean illumination level changes (e.g., (Shapley and Enroth-Cugell, 1984; Walraven et al., 1990)). This logarithmic process normalizes local variations of ambient light intensity so that the retinal output faithfully represents the contrast of objects viewed in different lightings (Troy and Enroth-Cugell, 1993). The mechanisms responsible for this sensitivity adjustment exist both within the photoreceptor cells and the retinal network (e.g., (Purpura et al., 1990; Pugh et al., 1999)). Although some adaptation involving static stimuli occur in regions of the V1/V2 visual cortex (McLelland et al., 2010; Wade and Wandell, 2002), we assume that the main adaptation in our experiment occurred in the retina. However, in turn, this adaptation also then modifies the activity of higher visual relays.

The TMS results of the present study mirror those found in the behavioral domain, where TMS has been shown to facilitate attributes encoded by adapted neural populations (Silvanto et al., 2007) and to increase neural susceptibility to TMS (Guzman-

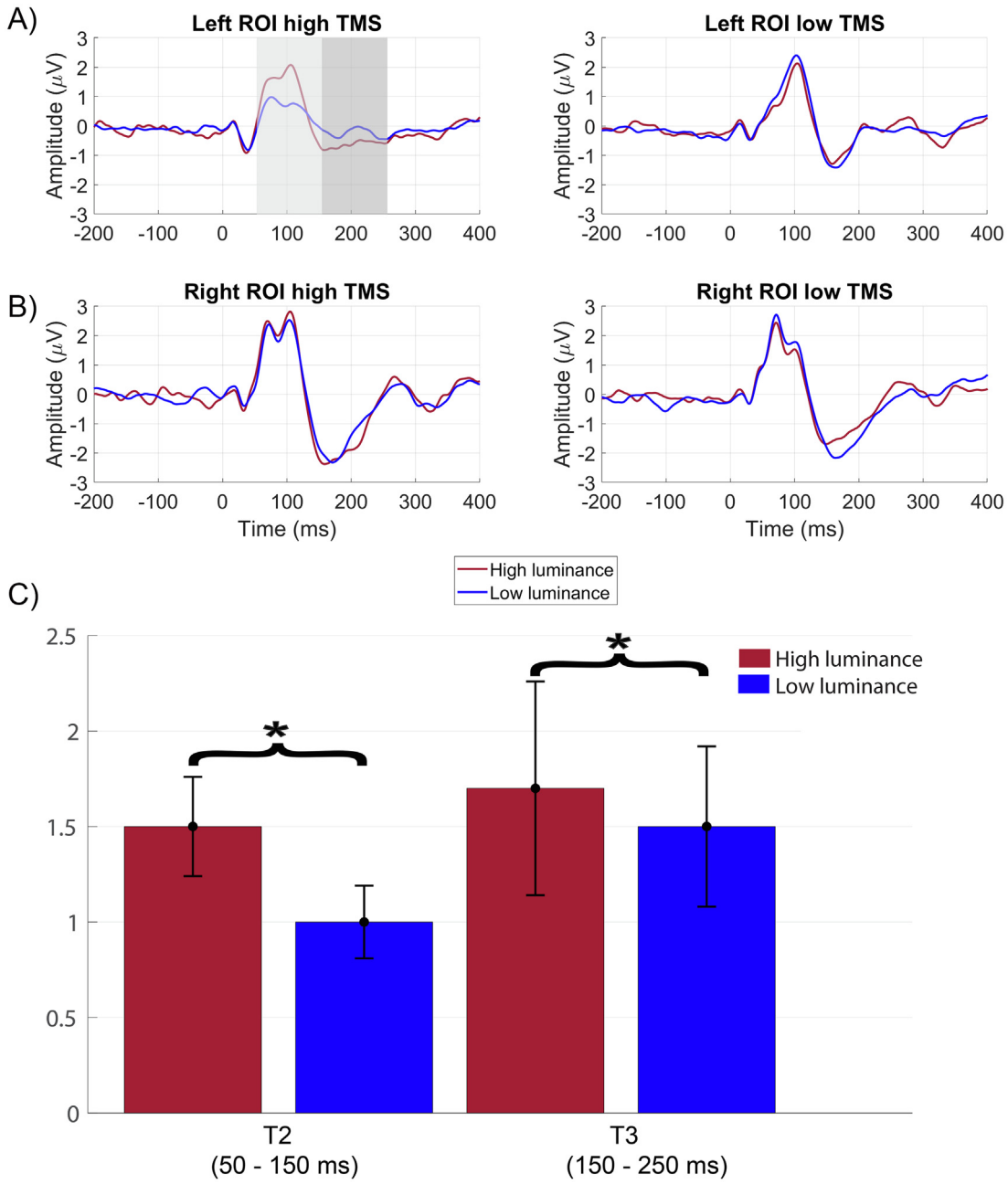

Fig. 4. Grand average amplitudes of transcranial magnetic stimulation (TMS)-evoked potentials (TEPs) as a function of adaptation condition and region of interest (ROI) for high and low TMS intensities across the same 7 participants that completed both Visits. (A) TEPs in the left ROI for high and low TMS intensities and high and low luminance. The grey shaded area depicts the time windows where the area under the curve values were statistically significant different (50–150 ms, and 150–250 ms). (B) TEPs in the right ROI for high and low TMS intensities and high and low luminance. (C) Area under the curve values for the grey shaded area depicted for left ROI at high TMS intensity (means with standard error of the mean (SEM) error bars), the areas were statistically different for times T2 (50–150 ms) and T3 (150–250 ms).

Lopez et al., 2011). To understand our results, the impact of this adaptation at the cortical level needs to be considered. Although the actual adaptation is likely to reflect retinal processes, it also modulates the input to the early visual cortex V1/V2. At the end of adaptation, the high luminance adapter is turned off, and the participants are viewing the "baseline" display (i.e., a dark screen with a fixation cross). The luminance range in which the visual system operates after light adaptation is out of range for the post-adaptation visual environment. In this circumstance, the activity of the retinal network will be lower, and less input will be transmitted to the visual cortex resulting in reduced baseline activity in V1/V2. Thus, neurons in the early visual cortex are less likely to be firing after visual adaptation and are thus more likely to be activated by TMS. Consequently, TMS is likely to activate a large population of neurons (as a larger proportion of neurons is likely to be in a state ready to be activated). A similar explanation has been previously put forward to explain the effects of color adaptation on TMS-induced phosphenes (Guzman-Lopez et al., 2011). Neuronal adaptation increases the susceptibility to TMS-induced facilitation, and the effects on visual adaptation are observed only when TMS and the adapting stimulus overlap spatially (Guzman-Lopez et al., 2011). TMS–EEG studies have also investigated the

neural basis of longer-lasting adaptation protocols, such as dark adaptation, where participants undergo 30 minutes of adaptation (e.g., (Zazio et al., 2019)). Such long adaptations are likely to differ from those generally used in state-dependent TMS studies, where the period of adaptation is usually up to 60 seconds.

The effect of adaptation on TMS-induced neural activity depended on the TMS intensity (although this may have been partly due to the lower number of participants in the low TMS intensity condition). Such an effect would not be surprising in light of a prior TMS–EEG study that reported such effects in TMS interaction- and visual evoked potentials (Reichenbach et al., 2011). Furthermore, the presence of nonlinearities in behavioral effects of TMS have been demonstrated by distinct intensity ranges for facilitatory and suppressive behavioral effects of TMS which are shifted by state manipulations such as adaptation (Silvanto and Cattaneo, 2017, 2008). Moreover, the facilitatory effect of TMS on adaptation would only occur at specific TMS intensities – with very low intensities unable to activate adapted neurons and very high intensities inducing their suppression. Future studies are needed to parametrically examine the interaction between adaptation state and TMS intensity to test this idea explicitly.

5. Conclusion

Our study provides neural evidence for the view that TMS-induced neural activity is modulated by neural adaptation (in this case, high luminance *vs.* low luminance adaptation). This supports the view that adaptation of the visual system can increase the susceptibility of the cortex to a TMS pulse. Specifically, this is likely to occur due to a reduction in neural discharge in the visual cortex, increasing the likelihood of a TMS pulse to induce action potentials (Siebner et al., 2009). An implication of this finding is that any protocol (e.g., in the clinical domain) aiming to maximize the impact of TMS should consider the initial neural activation state.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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