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Excitability Changes in Occipital Cortex After Continuous Theta-Burst Stimulation

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ABSTRACT

Introduction: Modulation of visual cortical structures by repetitive transcranial magnetic stimulation is rarely observed in literature. In this study; the researchers aimed to investigate the neurophysiological alterations by using continuous theta burst stimulation (cTBS) protocol over the occipital cortex in healthy subjects.

Methods: Twenty-five (15 female, 10 male) (mean age 29.84±4.7 years) healthy individuals were included in sham and real cTBS occipital stimulation sessions. Before and after each session, neurophysiological studies including phosphene threshold and visual evoked potential (VEP) responses were recorded. The P100 latency values and maximum amplitude values between N75-P100 peaks of 100 responses of 1000 uninterrupted continuous visual stimuli were measured. The VEP habituation and phosphene thresholds were compared in sham and real cTBS sessions.

Results: The phosphene threshold values increased to statistically significant levels after the real cTBS session. Visual evoked potential habituation was observed in both sham and real cTBS sessions in individuals without significant differences. Also, no difference between the P100 latencies and N75-P100 amplitude values in the sham and real cTBS sessions was observed.

Conclusion: Phosphene threshold measurements demonstrated the modulation of the occipital cortex excitability via cTBS in healthy subjects.

Keywords: Occipital cortex, phosphene threshold, transcranial magnetic stimulation, VEP, visual evoked potentials

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INTRODUCTION

The visual cortical system is the endpoint of many afferent visual pathways and has more neuronal connections than the other sensory modalities. In comparison with visual processing, it is known that auditory sensory is associated with 3%, and somatosensory processing is associated with 11% of the brain (1). The role of the visual system in neurological diseases and physiological processes is being investigated with increasing interest in view of this intense connectivity. The visual system evaluation of the neurophysiological activity by transcranial magnetic stimulation (TMS) and visual evoked potentials (VEP) responses are easily applicable research methodologies. Habituation is the observance of a decrease in the responses of VEPs while the number of consecutive and uninterrupted visual stimuli is increased (2). It is known that like all other sensory modalities, the short-term plastic change mechanism in visual habituation is a defense mechanism against repetitive stimulus (3). TMS, with its diagnostic and modulatory capabilities regarding the brain, can be used as a second non-invasive tool (4). The flashes of light and scotomas that occur in the visual field in a few seconds after stimulation of the visual system are known as the phosphenes (5), which are also an excitability parameter of the visual cortex. Depending on stimulation parameters, these can be applied to human brain cortical structures with inhibitory or excitatory effects. Although applying repetitive TMS (rTMS) stimuli on the cerebral cortical structures can induce temporary inhibition or facilitation in the brain (6), permanent neuroplasticity effects can be obtained with multiple sessions. In previous studies, 1 Hz rTMS over the occipital cortex decreased VEP habituation (7) and increased phosphene thresholds (PTs) (8) in healthy subjects. In this study, the researchers aimed to inhibit visual cortical structures through continuous theta burst stimulation (cTBS) which is a relatively new rTMS protocol, and investigate the neuromodulatory after-effects including VEP habituation and PTs for the first time in healthy subjects.

Highlights

- **Visual cortex can be investigated by phosphene thresholds and VEP habituation evaluation.**
- **The excitability of the occipital cortex can be modulated by cTBS application.**
- **Single occipital cTBS session increases the phosphene thresholds.**

METHOD

Selection of Individuals

Twenty-five healthy volunteers, 15 female, and 10 male, were included in

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the study between December 2021 and June 2022. The inclusion criteria are set as being over the age of 18 and under the age of 60 without any neurological diseases. Healthy individuals were questioned in terms of the presence of any neuropsychiatric disease and drug use. Individuals with comorbidities and who use central nervous system drugs were excluded from the study. One individual was excluded due to the diagnosis of migraine during the study. All individuals were questioned in terms of TMS contraindications. Individuals with ferromagnetic implants, who had brain surgery, who had a history of syncope and epileptic seizures, or who could not tolerate TMS were excluded from the study. The previous night's sleep, cigarette, and alcohol consumption of individuals were investigated to account for their effects on brain excitability.

This study was carried out in accordance with the Declaration of Helsinki, after the approval of the Hacettepe University Clinical Research Ethics Committee's decision numbered KA-20104. All individuals were informed about the possible side effects of TMS and an informed consent form was signed after ensuring that all participants fully understood the possible side effects of TMS.

Study Design and Experiment States

All measurements of the individuals included in this study were performed in two separate sessions on different days (2–4 days) in view of the cTBS real stimulation and sham stimulation protocols. All individuals underwent neurophysiological evaluation to account for VEP habituation measurements and PT determination before and after real and sham cTBS stimulations.

Transcranial Magnetic Stimulation

Individuals were seated in a comfortable chair in a quiet and dimmed room during TMS. Phosphene threshold (PT) determination over the occipital cortex and application of the cTBS protocol was performed using a TMS (Neuro-MS/D, Russia) device with a coil figure of eight.

PT determination

Before the TMS stimulation, participants were trained on whether any light of flash would occur concurrently with the stimulation in their visual fields. All individuals were instructed to inform the researchers on the presence or absence of these flashes during stimulation. The method previously used by Gerwing was employed to determine the optimal position for phosphene formation (9). To start the stimulation, 20% less of the single supramaximal stimulation was applied. The appropriate position of the area of phosphene development was found by placing the coil on the inion with its handle in the upward direction and advancing with 1 cm placements in succession. Then, in order to determine the PT value, TMS intensity was reduced by 2%, and the intensity level that resulted in positive 5 out of 10 consecutive responses was considered as the PT level.

Visual Evoked Potentials

Latency and amplitude measurements of VEP were obtained with Keypoint (Denmark) EMG device. Visual evoked potential assessment was also performed in a quiet, dimmed room while individuals were sitting in a comfortable chair. The distance between the screen providing VEP stimulation and the individual was set as 50 cm. The 12×16 sized Pattern VEP checkboard stimulation screen with an average luminescence level of 100 cd/m^2 was operated with a Keypoint device. The experiment started with the right eye, and the other eye was covered with a cotton patch. Individuals were instructed to look at the fixation point in the middle of the screen after stimulation started. Visual evoked potential recordings were performed with the superficial cup electrodes with Ag/AgCl. Oz was placed 1 cm above the inion as the active electrode, and Cz was placed on the midsagittal line as the reference electrode. The ground electrode was placed on the neck. Filtering was applied with a 1–100 Hz band-pass filter. The stimulation frequency was set to 3.1 Hz.

Experimental-states

Continuous Theta Burst Stimulation Session

The cTBS protocol was applied at the center in the occipital lobe where phosphene is found. The stimulation intensity was set as 80% of the PT. A total of 600 stimulations were displayed, with triplet stimulations at 50 Hz frequency (triplet stimulation at 5 Hz frequency), with 200 ms intervals, and the entire stimulation protocol ended after 40 seconds (84).

Sham TMS Stimulation Session

To induce sham stimulation, a coil was placed on the scalp of the individuals above occipital region at a 90° angle. Thus, individuals were able to hear and feel the same sound of TMS without the presence of real stimulation.

Experimental-States PT Parameters

Phosphene threshold parameters were determined before-pre (PRE-cTBS-THRESHOLD and PRE-SHAM-THRESHOLD) and after-post (POST-cTBS-THRESHOLD and POST-SHAM-THRESHOLD) cTBS and sham sessions.

Experimental-States VEP Habituation Parameters

Visual evoked potential habituation measurements were performed before and after both conditions. One thousand VEP recordings were obtained in blocks of uninterrupted 100 averaged blocks consecutively. The responses were averaged in ten blocks of 100 responses and the following measurements were carried out on the 1st, 5th, and the 10th blocks of 100 responses. In each block, P100 latencies (P100_Lat) and peak-to-peak maximal amplitude of P100 amplitudes (P100_Amp) were measured to determine pre-stimulation (PRE) and post-stimulation (POST) experimental-states of both Continuous theta-burst stimulation (cTBS)and SHAM (fake) sessions. Right (R) and left (L) eye stimulation were conducted separately as follows:

1. P100 Amplitude parameters (total 24 parameters)
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Amp-BLOCK1
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Amp-BLOCK5
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Amp-BLOCK10

2. P100 latency parameters (total 24 parameters)
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Lat-BLOCK1
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Lat-BLOCK5
[PRE/POST]-[cTBS/SHAM]-[R/L]-P100_Lat-BLOCK10

3. Researchers also calculated the ratio of BLOCK5 and BLOCK10 values to BLOCK1 values of each P100 amplitude and latency parameter as BLOCK5/BLOCK1 and BLOCK10/BLOCK1 for both PRE-stimulation and POST-stimulation experimental-states (total 32 parameters).

Statistical Analysis

IBM Statistical Package for Social Sciences (SPSS) program v.20 package program was used for statistical analysis. Shapiro-Wilk test was used for the normal distribution of parameters. Reciprocal transformation (1/x) for phosphene parameters and logarithmic transformation for VEP habituation parameters were applied to reach the normal distribution values.

ANOVA Analysis of PTs

To evaluate the modulatory effect of cTBS and SHAM treatments on PT value, analysis of variance (ANOVA) for repeated measurements with 2 levels of 2 within-subject factors [STATUS (cTBS and SHAM) and TIME (PRE and POST)] was applied.

ANOVA Analysis of VEP Habituation Parameters

Three-way repeated-measures ANOVA was used with STATE (cTBS, SHAM), BLOCK (BLOCK1, BLOCK5, BLOCK10), and TIME (PRE, POST) within-subject factors on P100 amplitude and P100 latency parameters to evaluate the significance of the VEP habituation as well as the modulatory effects of cTBS and Sham experiments. ANOVA tests were performed separately for right and left eye stimulations (total of 6 tests were conducted).

ANOVAs sphericity assumption was evaluated with the Mauchly-test, and the Greenhouse and Geisser correction was used to calculate the F values as the sphericity assumption were not met. Post hoc analyses were performed by Student's t-test pairwise comparisons with a Bonferroni correction in cases where significant main effects or interactions are observed.

Comparison of PRE and POST BLOCK1/BLOCK5 and BLOCK1/BLOCK10 Ratios

Researchers compared PRE-stimulation and POST-stimulation BLOCK1/BLOCK5 and BLOCK1/BLOCK10 ratios of P100 amplitude and latency parameters for both cTBS and SHAM experimental-states separately by paired sample tests.

RESULTS

Twenty-five healthy subjects with a mean age of 29.84±4.7 years were included in the study. One individual stated having a headache after VEP evaluation. No side effects were described and no complications were encountered after TMS application. While the PTs were obtained before cTBS, the values in question could not be obtained in two participants, even though the maximum TMS output value was increased to 100% after stimulation.

PRE-cTBS, POST-cTBS, PRE-SHAM, and POST-SHAM results of phosphene thresholds, P100 amplitude, and P100 latency parameters are shown in Table 1 as mean ± SEM; ANOVA results were summarized in Tables 2 and 3.

1. Two way repeated measurements showed that ANOVA is affected by both STATE [F (1.22)=18.000, p=0.000] and TIME [F (1.22)=13.101, p=0.002] factors and STATE×TIME factors [F (1.22)=59.484, p=0.000]. TIME factors were found to be statistically significant for PTs [F (1.22)=59.484, p=0.000] (Table 2). While Post-hoc pairwise comparisons with Bonferroni correction showed that phosphene threshold values after the real cTBS were significantly higher than their pre-cTBS values (72.96±2.27 vs 66.3±1.5, p=0.000) after the sham stimulation, these values were significantly lower than pre-sham values (64.13±1.57 vs 65.29±1.57, p=0.008) (Figure 1). Also, although phosphene threshold PRE-cTBS values did not differ from PRE-SHAM values (p=0.130), there was a significant difference between POST-cTBS values and POST-SHAM values (p=0.000).
2. Three-way repeated-measures ANOVA for P100 amplitude obtained by right eye stimulation did not show any significant interaction between STATE×BLOCK×TIME, STATE×TIME, or BLOCK×TIME factors (Table 3A). The main effect of BLOCK factor was significant ([F (2,48)=10.130, p=0.001] on P100 amplitude while STATE and TIME factors were not. At post-hoc pairwise comparisons with Bonferroni correction, P100_Amp-BLOCK5 values were significantly lower than P100_Amp-BLOCK1 values (7.280±0.511 μV and 7.967±0.566 respectively, p=0.002) and P100_Amp-BLOCK10 values were significantly lower than P100_Amp-BLOCK1 values (7.116±0.483 μV and

Table 1. (A) Mean ± standard error of PRE- and POST- cTBS and SHAM phosphene thresholds without reciprocal transformation. **(B)** Mean ± standard error of PRE- and POST- cTBS and SHAM P100 amplitude parameters, and BLOCK1/BLOCK5 and BLOCK1/BLOCK10 ratio parameters without logarithmic transformation. **(C)** Mean ± standard error of PRE- and POST- cTBS and SHAM P100 latency parameters, and BLOCK1/BLOCK5 and BLOCK1/BLOCK10 ratio parameters without logarithmic transformation

A	**Phosphene Thresholds (Mean ± Standard Error)**			
	cTBS		**SHAM**	
	PRE	**POST**	**PRE**	**POST**
	66.3±1.5	72.96±2.27	65.29±1.57	64.13±1.57

B	**P100 Amplitude (μV) (Mean ± Standard Error)**							
	Right Eye Stimulation				**Left Eye Stimulation**			
	PRE-cTBS	**POST-cTBS**	**PRE-SHAM**	**POST-SHAM**	**PRE-cTBS**	**POST-cTBS**	**PRE-SHAM**	**POST-SHAM**
BLOCK1	7.56±0.64	8.39±0.69	8±0.56	7.92±0.57	7.1±0.69	7.13±0.61	7.28±0.6	6.82±0.65
BLOCK5	7.22±0.62	7.34±0.62	7.18±0.48	7.38±0.61	6.86±0.69	7.5±0.71	6.92±0.71	6.35±0.58
BLOCK10	7.18±0.68	7.5±0.51	6.56±0.48	7.22±0.55	6.12±0.61	7.02±0.52	6.84±0.45	6.61±0.56
BLOCK1/BLOCK5	1.11±0.07	1.23±0.09	1.12±0.03	1.14±0.07	1.09±0.07	0.99±0.04	1.15±0.07	1.17±0.13
BLOCK1/BLOCK10	1.12±0.06	1.12±0.05	1.28±0.09	1.17±0.07	1.28±0.11	1.04±0.06	1.09±0.06	1.05±0.06

C	**P100 Latency (ms) (Mean ± Standard Error)**							
	Right Eye Stimulation				**Left Eye Stimulation**			
	PRE-cTBS	**POST-cTBS**	**PRE-SHAM**	**POST-SHAM**	**PRE-cTBS**	**POST-cTBS**	**PRE-SHAM**	**POST-SHAM**
BLOCK1	103.8±1.28	103.46±1.3	105.82±1.82	104.78±1.71	103±1.26	103.76±1.19	106.17±1.54	106.03±1.53
BLOCK5	104.53±1.27	104.1±1.39	105.36±1.44	104.93±1.48	105.76±1.33	104.2±1.03	106.14±1.41	104.87±1.4
BLOCK10	104.2±1.48	104.73±1.33	105.96±1.44	105.59±1.43	104.69±1.4	103.39±1.43	105.46±1.57	105.5±1.51
BLOCK1/BLOCK5	0.99±0.01	1±0.01	1±0.01	1±0.01	0.97±0.01	1±0.01	1±0.01	1.01±0.01
BLOCK1/BLOCK10	1±0.01	0.99±0.01	1±0.01	0.99±0.01	0.99±0.01	1.01±0.01	1.01±0.01	1.01±0.01

cTBS: Continuous Theta Burst Stimulation; POST: Post-stimulation; PRE: Pre-stimulation.

Table 2. Two-way repeated-measures ANOVA result for the modulatory effects of cTBS and SHAM experimental-states on the PTs. Statistically significant test results after the Bonferroni correction are indicated by bold font.

	Anova Resutls for Phosphene Thresholds		
	Main Effects of Factors		**Factor Interactions**
	State (cTBS, SHAM)	**Time (PRE, POST)**	**State×Time**
ANOVA	[F (1.22)=18.0, **p=0.000**]	[F (1.22)=13.101, **p=0.002**]	[F (1.22)=59.484, **p=0.000**]
			cTBS (PRE×POST)
Post-hoc analysis			**p=0.000**
			SHAM (PRE×POST)
			p=0.008
			PRE (cTBS×SHAM)
			p=0.130
			POST (cTBS×SHAM)
			p=0.000

cTBS: continuous theta burst stimulation; POST: post-stimulation; PRE: pre-stimulation.

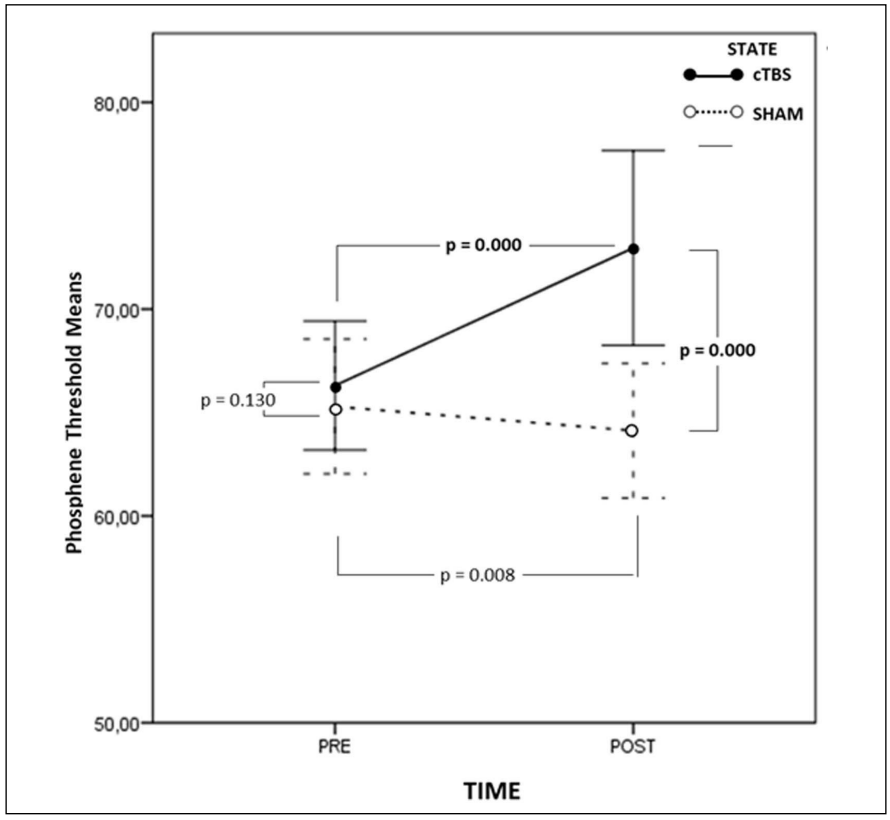

Figure 1. Post-hoc pairwise comparisons with Bonferroni correction after two-way repeated measures ANOVA for PTs. POST-cTBS-THRESHOLD values were significantly higher than PRE-cTBS-THRESHOLD values (72.96±2.27 vs 66.3±1.5, p=0.000) while POST-SHAM-THRESHOLD values were significantly lower than PRE-SHAM-THRESHOLD values (64.13±1.57 vs 65.29±1.57, p=0.008). Also, although PRE-cTBS-THRESHOLD values did not differ from PRE-SHAM-THRESHOLD values (p=0.130), there was a significant difference between POST-cTBS-THRESHOLD values and POST-SHAM-THRESHOLD values (p=0.000). Solid lines indicate cTBS-stimulation, and dotted lines SHAM-stimulation. Error bars represent ±1 the standard error of the mean (SEM). Statistically significant test results after the Bonferroni correction are indicated in bold font (cTBS: continuous theta burst stimulation; POST: post-stimulation; PRE: pre-stimulation).

7.967±0.566 μV, respectively, p=0.000), when the STATE and TIME factors are ignored.

3. For P100 amplitude obtained by left eye stimulation, three-way repeated-measures ANOVA did not show any significant interaction between STATE×BLOCK×TIME or BLOCK×TIME factors or main effect of factors (Table 3B). Although the interaction of STATE×TIME factors were significant ([F (1.24)=6.663, p=0.016], post-hoc pairwise comparisons, P100 amplitude differences between the POST-cTBS and PRE-cTBS values as well as POST-SHAM and SHAM-L values were not statistically significant.
4. Factors or their interaction thereof had no significant main effect on P100 latencies obtained through right and left eye stimulation (Table 3C-D).

There were no significant differences between the pre-stimulation and post-stimulation BLOCK1/BLOCK5 and BLOCK1/BLOCK10 ratio values for both cTBS and SHAM experimental-states at paired sample tests (p>0.05).

Table 3. Three-way repeated-measures ANOVA result for the modulatory effects of cTBS and SHAM experimental-states on the P100 amplitude and P100 latency parameters obtained by right and left eye stimulation. Statistically significant test results after the Bonferroni correction are indicated by bold font. **(A)** For P100 amplitude obtained by right eye stimulation, The main effect of the BLOCK factor was significant ([F (2.48)=10.130, p=0.001] on P100 amplitude. P100_Amp-BLOCK5 values were significantly lower than P100_Amp-BLOCK1 values and P100_Amp-BLOCK10 values were significantly lower than P100_Amp-BLOCK1 values. **(B)** For P100 amplitude obtained by left eye stimulation, three-way repeated-measures ANOVA did not show any significant interaction between STATE×BLOCK×TIME or BLOCK×TIME factors or in view of the main effect of factors. **(C)** For P100 latencies obtained by right and left eye stimulation, there was no significant main effect of factors or their interaction.

A	**Anova Resutls for P100 Amplitude with Right Eye Stimulation (R-P100_AMP)**						
	Main Effects of Factors			**Factor Interactions**			
	State (cTBS, SHAM)	**Block (BLOCK1, BLOCK5, BLOCK10)**	**Time (PRE, POST)**	**State×Block**	**State×Time**	**Block×Time**	**State×Block×Time**
ANOVA	[F (1.24)=0.02, p=0.964]	[F (2.48)=10.130, **p=0.001**]	[F (1.24)=2.998, p=0.096]	[F (2.48)=1.650, p=0.203]	[F (1.24)=1.217, p=0.281]	[F (2.48)=0.938, p=0.398]	[F (2.48)=0.150, p=0.640]
Post-hoc analysis		BLOCK1×BLOCK5					
		p=0.002					
		BLOCK 1×BLOCK10					
		p=0.000					
B	**Anova Resutls for P100 Amplitude with Left Eye Stimulation (L-P100_AMP)**						
	Main Effects of Factors			**Factor Interactions**			
	State (cTBS, SHAM)	**Block (BLOCK1, BLOCK5, BLOCK10)**	**Time (PRE, POST)**	**State×Block**	**State×Time**	**Block×Time**	**State×Block×Time**
ANOVA	[F (1.24)=0.102, p=0.752]	[F (2.48)=1.347, p=0.270]	[F (1.24)=0.321, p=0.576]	[F (2.48)=1.884, p=0.163]	[F (1.24)=0.112, **p=0.016**]	[F (2.48)=1.480, p=0.138]	[F (2.48)=0.639, p=0.532]
Post-hoc analysis					cTBS (PRE×POST)		
					p=0.061		
					SHAM (PRE×POST)		
					p=0.069		
C	**Anova Resutls for P100 Latency with Right Eye Stimulation (R-P100_LAT)**						
	Main Effects of Factors			**Factor Interactions**			
	State (cTBS, SHAM)	**Block (BLOCK1, BLOCK5, BLOCK10)**	**Time (PRE, POST)**	**State×Block**	**State×Time**	**Block×Time**	**State×Block×Time**
ANOVA	[F (1.24)=1.665, p=0.209]	[F (2.48)=1.066, p=0.353]	[F (1.24)=0.376, p=0.546]	[F (2.48)=0.248, p=0.782]	[F (1.24)=0.302, p=0.588]	[F (2.48)=0.304, p=0.739]	[F (2.48)=0.147, p=0.864]
D	**Anova Resutls for P100 Latency with Left Eye Stimulation (L-P100_lat)**						
	Main Effects of Factors			**Factor Interactions**			
	State (cTBS, SHAM)	**Block (BLOCK1, BLOCK5, BLOCK10)**	**Time (PRE, POST)**	**State×Block**	**State×Time**	**Block×Time**	**State×Block×Time**
ANOVA	[F (1.24)=2.971, p=0.098]	[F (1.48)=0.415, p=0.663]	[F (1.24)=1.266, p=0.272]	[F (2.48)=1.914, p=0.159]	[F (1.24)=0.058, p=0.812]	[F (2.48)=1.470, p=0.240]	[F (2.48)=0.455, p=0.637]

cTBS: continuous theta burst stimulation; L: left; P100_Amp: P100 amplitude; P100_Lat: P100 latency; POST: post-stimulation; PRE: pre-stimulation; R: right.

DISCUSSION

Visual evoked potential parameters and PT values before and after cTBS over the occipital cortex were investigated in healthy individuals. For this purpose, VEP habituation, VEP amplitude, P100 latency, and PT measurements were obtained before and after cTBS real and sham stimulation sessions.

cTBS Effect on VEP Habituation

Regardless of both the experimental-state factor (cTBS, SHAM application) and the time factor (PRE, POST) (i. e., without interaction with these factors), the main effect of the BLOCK factor (BLOCK1, BLOCK5, BLOCK10) on the R-P100_AMP parameter in ANOVA was significant. R-P100_AMP-BLOCK5 values were found to be significantly lower than R-P100_AMP-BLOCK1 values and R-P100_AMP-BLOCK10 values were significantly lower than R-P100_AMP-BLOCK1 values which indicate VEP habituation. The STATE and TIME factors did not cause a difference. Again, the fact that the values of VEP habituation rate parameters (BLOCK1/BLOCK5 and BLOCK1/BLOCK10) before cTBS did not differ significantly compared to the values of the same parameters after cTBS, which supports the finding that cTBS application has no effect on VEP habituation.

Visual evoked potential amplitudes and habituation ratio were observed as an evaluation of the excitability of visual cortical activity. Since the VEP latencies have high inter and intra individual variance (10), the researchers evaluated habituation rate and amplitude parameters. In a study conducted with long-term visual stimuli, it was stated that VEP habituation was evident starting from the 6th block, and habituation occurred in the 10th and 15th repetitive blocks (11). In healthy individuals, a decrease in lactate levels was observed with VEP habituation in the occipital cortex in magnetic resonance spectroscopy images after 10–12 minutes of stimulation with a visual checkerboard screen that continues sequentially (12). Basically, it is known that in series of VEP stimuli lead to metabolic changes and the VEP habituation is a protection of sensory overload of cerebral cortical mechanisms against repetitive long-term sensory stimulation. Abnormal cortical information triggers brain parenchymal hemostasis. Visual photic stimulation causes a rapid and transient increase in glycolysis and lactate levels (2). In a previous study, a decrease in VEP first block amplitudes was observed when occipital TMS pulse was induced in addition to visual stimulation at 25 ms intervals (+25 msec) in pairs (13). Noninvasive neuromodulator tools, transcranial direct current stimulation (tDCS) and TMS can alter specific visual functions (14). Interestingly, there are only a few studies within which various protocols are employed to investigate the use of the basic rTMS protocols which alter the visual function (15,16). To the best of our knowledge; this is the first study that provides VEP response data after occipital cTBS. In a previous study, in which 1 Hz rTMS protocol over the occipital cortex were applied showed a reduction in amplitudes of first blocks and habituation in healthy subjects (7). However, there was no sham group included in this study, so it is difficult to discuss the real inhibitory effect of rTMS.

The habituation loss in neurological diseases such as migraine, and epilepsy may be considered as the potential neurophysiological follow-up parameter in further cTBS studies (17,18). In migraine, repetitive stimulation triggers cortically spreading depression by accumulation of lactate in the occipital cortex, and cortical information processes by serotonergic cells in the raphe nucleus which result in a metabolic instability of physiological habituation (19–21). It has been observed that habituation alterations may be improved in patients with migraine by anodal transcranial direct current stimulation (22), and pharmacological prophylaxis drugs restore the pathological deterioration in VEP habituation (23). Loss of VEP habituation is also defined in idiopathic generalized epilepsy patients with photo paroxysmal response which has been improved with antiepileptic drugs (24). In the current study; a single session of cTBS did not provide sufficient modulation in VEP habituation when compared to the sham. Multiple sessions of rTMS may be more appropriate for providing significant habituation improvements such as preventive treatments in migraine and epilepsy.

cTBS Effect on PTs

Main finding of the study is the significant increase in PT after cTBS application. Phosphene threshold values after cTBS were found to be significantly higher than the threshold values before cTBS in the matched sample test (66.3±1.5 and 72.96±2.27, p=0.000) was also confirmed by the ANOVA test. Phosphene threshold values after SHAM were found to be significantly lower than pre-SHAM PT values in the paired sample test and ANOVA. Although the decrease in the PT value after SHAM was quite lower than cTBS (65.29±1.57 and 64.13±1.57), a statistical significance is also observed. The physiological relevance of this fractional, but statistically significant effect in SHAM administration versus cTBS administration is uncertain. On the other hand, while no significant difference between PT values before cTBS and PT values before SHAM was observed, it was thought that the significant difference between PT values after cTBS and PT values after SHAM could be mainly caused by the effect of cTBS. Also, the fact that the PT values not being different before the cTBS and SHAM applications may further prove consistency of the measurements and confirm the reliability of the experimental-states. Phosphenes are obtained by applying TMS stimuli over the occipital cortex with two important mechanisms. Firstly, TMS pulses develop by activating thalamo-cortical axons in optical radiation by stimulating cortical circuits in the visual cortex or targeting neurons in the primary visual cortex and protruding fibers originating from extrastriatal areas (25,26). The lowest TMS intensity that produces phosphene is determined as the PT value, which is evaluated as an excitability parameter like the MEP thresholds of the motor cortex (27,28). Previously, migraine, visual snow syndrome, amyotrophic lateral sclerosis, and idiopathic generalized epilepsy were the hyperexcitable neurological diseases related to the lower phosphene thresholds (17,29–31).

There are certain studies which include the PT value changes by tDCS (transcranial direct current stimulation) (32,33) and rTMS (repetitive transcranial magnetic stimulation) (8,34). In a study including 8 healthy individuals, an increase in PT values was observed after 1 Hz rTMS (8). In a study where iTBS and cTBS are applied to the occipital cortex in healthy individuals, cTBS increased the PT by 10% while the effect of iTBS application did not result in significant values (35). In our study, an increase in the PT value was detected as a result of real cTBS stimulation compared to sham application. These findings indicate that the PT value is affected by a single session modulation by cTBS when compared to VEP habituation. Interestingly, a statistically significant decrease was found in the PT values after the sham application, which may have occurred due to the duration of VEP and the sham process. In a study, in which light deprivation was applied to healthy individuals, a decrease in PT values was observed after 45 minutes of light deprivation. It has also been shown that PT values return to normal 120 minutes after re-exposing the individuals to the pre-deprivation level. An fMRG activation in the visual cortex after 60 minutes of light deprivation was observed, which returned to normal with 30 minutes of re-exposure to light in the same study (36).

In conclusion; the researchers have demonstrated that the cTBS protocol over the visual cortex alters the excitability of this cortical region. Disorders of this site with abnormal cortical activity may be restored noninvasively by rTMS. Further studies where multiple sessions of cTBS are included may target the visual system in larger patient and healthy individual groups.

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Informed Consent: After ensuring that all participants fully understood the possible side effects of TMS, an informed consent form was signed.

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REFERENCES

1. Felleman DJ, Van Essen DC. Distributed hierarchical processing in the primate cerebral cortex. Cereb Cortex. 1991;1(1):1–47. [Crossref]
2. Phelps ME, Kuhl DE, Mazziota JC. Metabolic mapping of the brain's response to visual stimulation: studies in humans. Science. 1981;211(4489):1445–1448. [Crossref]
3. Groves PM, Thompson RF. Habituation: a dual-process theory. Psychol Rev. 1970;77(5):419–450. [Crossref]
4. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;1(8437):1106–1107. [Crossref]
5. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell AP, Eberle L. Transcranial magnetic stimulation in study of the visual pathway. J Clin Neurophysiol. 1998;15(4):288–304. [Crossref]
6. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I. F. C. N. Committee. Clin Neurophysiol. 2015;126(6):1071–1107. [Crossref]
7. Fumal A, Bohotin V, Vandenheede M, Seidel L, de Pasqua V, de Noordhout AM, et al. Effects of repetitive transcranial magnetic stimulation on visual evoked potentials: new insights in healthy subjects. Exp Brain Res. 2003;150(3):332–340. [Crossref]
8. Boroojerdi B, Prager A, Muellbacher W, Cohen LG. Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. Neurology. 2000;54(7):1529–1531. [Crossref]
9. Gerwig M, Kastrup O, Meyer BU, Niehaus L. Evaluation of cortical excitability by motor and phosphene thresholds in transcranial magnetic stimulation. J Neurol Sci. 2003;215(1-2):75–78. [Crossref]
10. Aminoff MJ. Evoked-Potentials in Clinical Medicine. Q J Med. 1986;59(228):345–362. Available at: https://pubmed.ncbi.nlm.nih.gov/3749441/
11. Afra J, Cecchini AP, De Pasqua V, Albert A, Schoenen J. Visual evoked potentials during long periods of pattern-reversal stimulation in migraine. Brain. 1998;121:233–241. [Crossref]
12. Sappeymarinier D, Calabrese G, Fein G, Hugg JW, Biggins C, Weiner MW. Effect of Photic-Stimulation on Human Visual-Cortex Lactate and Phosphates Using H-1 and P-31 Magnetic-Resonance Spectroscopy. J Cerebr Blood F Met. 1992;12(4):584–592. [Crossref]
13. Ranieri F, Coppola G, Musumeci G, Capone F, Di Pino G, Parisi V, et al. Evidence for associative plasticity in the human visual cortex. Brain Stimul. 2019;12(3):705–713. [Crossref]
14. Bello UM, Wang J, Park ASY, Tan KWS, Cheung BWS, Thompson B, et al. Can visual cortex non-invasive brain stimulation improve normal visual function? A systematic review and meta-analysis. Front Neurosci. 2023;17:1119200. [Crossref]
15. Thompson B, Aaen-Stockdale C, Koski L, Hess RF. A double dissociation between striate and extrastriate visual cortex for pattern motion perception revealed using rTMS. Hum Brain Mapp. 2009;30(10):3115–3126. [Crossref]
16. Clavagnier S, Thompson B, Hess RF. Long lasting effects of daily theta burst rTMS sessions in the human amblyopic cortex. Brain Stimul. 2013;6(6):860–867. [Crossref]
17. Yildiz FG, Turkyilmaz U, Unal-Cevik I. The Clinical Characteristics and Neurophysiological Assessments of the Occipital Cortex in Visual Snow Syndrome With or Without Migraine. Headache. 2019;59(4):484–494. [Crossref]
18. Algin DI, Erdinc OO. Impaired Visual Habituation in Idiopathic Generalized Epilepsy with Photosensitivity Patients. Noro Psikiyatr Ars. 2020;57(2):108–112. [Crossref]
19. Olsen TS. Pathophysiology of the migraine aura: the spreading depression theory. Brain. 1995;118(Pt 1):307–308. [Crossref]
20. Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. Physiol Rev. 1992;72(1):165–229. [Crossref]
21. Schoenen J. Cortical electrophysiology in migraine and possible pathogenetic implications. Clin Neurosci. 1998;5(1):10–17. Available at: https://pubmed.ncbi.nlm.nih.gov/9523052/
22. Cortese F, Pierelli F, Bove I, Di Lorenzo C, Evangelista M, Perrotta A, et al. Anodal transcranial direct current stimulation over the left temporal pole restores normal visual evoked potential habituation in interictal migraineurs. J Headache Pain. 2017;18(1):70. [Crossref]
23. Unal-Cevik I, Yildiz FG. Visual Snow in Migraine With Aura: Further Characterization by Brain Imaging, Electrophysiology, and Treatment--Case Report. Headache. 2015;55(10):1436–1441. [Crossref]
24. Ince F, Erdogan-Bakar E, Unal-Cevik I. Preventive drugs restore visual evoked habituation and attention in migraineurs. Acta Neurol Belg. 2017;117(2):523–530. [Crossref]
25. Kammer T, Beck S, Erb M, Grodd W. The influence of current direction on phosphene thresholds evoked by transcranial magnetic stimulation. Clin Neurophysiol. 2001;112(11):2015–2021. [Crossref]
26. Pascual-Leone A, Walsh V. Fast backprojections from the motion to the primary visual area necessary for visual awareness. Science. 2001;292(5516):510–512. [Crossref]
27. Aurora SK, Ahmad BK, Welch KM, Bhardhwaj P, Ramadan NM. Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. Neurology. 1998;50(4):1111–1114. [Crossref]
28. Afra J, Mascia A, Gerard P, Maertens de Noordhout A, Schoenen J. Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. Ann Neurol. 1998;44(2):209–215. [Crossref]
29. Brigo F, Bongiovanni LG, Nardone R, Trinka E, Tezzon F, Fiaschi A, Manganotti P. Visual cortex hyperexcitability in idiopathic generalized epilepsies with photosensitivity: a TMS pilot study. Epilepsy Behav. 2013;27(2):301–306. [Crossref]
30. Cengiz B, Fidanci H, Baltaci H, Turksoy E, Kuruoglu R. Reduced Occipital Cortex Excitability in Amyotrophic Lateral Sclerosis. J Clin Neurophysiol. 2022;39(6):486–491. [Crossref]
31. Coppola G, Di Lorenzo C, Parisi V, Lisicki M, Serrao M, Pierelli F. Clinical neurophysiology of migraine with aura. J Headache Pain. 2019;20(1):42. [Crossref]
32. Antal A, Kincses TZ, Nitsche MA, Paulus W. Modulation of moving phosphene thresholds by transcranial direct current stimulation of V1 in human. Neuropsychologia. 2003;41(13):1802–1807. [Crossref]
33. Antal A, Kincses TZ, Nitsche MA, Bartfai O, Paulus W. Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. Invest Ophthalmol Vis Sci. 2004;45(2):702–707. [Crossref]
34. Fierro B, Brighina F, Vitello G, Piazza A, Scalia S, Giglia G, et al. Modulatory effects of low- and high-frequency repetitive transcranial magnetic stimulation on visual cortex of healthy subjects undergoing light deprivation. J Physiol. 2005;565(Pt 2):659–665. [Crossref]
35. Franca M, Koch G, Mochizuki H, Huang YZ, Rothwell JC. Effects of theta burst stimulation protocols on phosphene threshold. Clin Neurophysiol. 2006;117(8):1808–1813. [Crossref]
36. Boroojerdi B, Bushara KO, Corwell B, Immisch I, Battaglia F, Muellbacher W, et al. Enhanced excitability of the human visual cortex induced by short-term light deprivation. Cereb Cortex. 2000;10(5):529–534. [Crossref]