

Investigation of the effects of continuous theta burst transcranial magnetic stimulation in patients with migraine

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Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) allows the non-invasive investigation of synaptic plasticity. Theta-burst stimulation (TBS) is a modified form of rTMS that induces synaptic plasticity. Our objective was to evaluate cortical excitability using paired-pulse transcranial magnetic stimulation (ppTMS) before and after continuous TBS (cTBS) in healthy controls and patients with migraine.

Methods: The study included 17 patients with migraine without aura and 18 healthy volunteers. Motor evoked potential (MEP) amplitudes, motor threshold (MT), intracortical inhibition (ICI), intracortical facilitation (ICF), and cortical silent period (CSP) were assessed using a figure-of-eight-shaped coil with a magnetic stimulator. cTBS was applied following baseline assessments; the results of ICI, ICF, and CSP at baseline and post-cTBS were compared between patients with migraine and healthy controls.

Results: There were no differences in baseline MT, CSP, and ICI parameters between patients with migraine and healthy controls; ICF was not achieved and a decrease in MEP amplitudes (80±52%) was found in most patients with migraine. After cTBS, ICF was not achieved in most subjects in both groups and a significant TIME effect (F=9.124 p=0.005) in addition to TIME x GROUP interaction (F=7.129 p=0.012) was noted, indicating a more significant decrease in the controls than in patients with migraine.

Conclusion: Baseline ICF was not achieved in patients with migraine, and after cTBS, ICF was not achieved in either group; the inhibitory effect of cTBS was absent in patients with migraine. These findings indicate impairment of glutamatergic circuits to be a major culprit in the pathogenesis of migraine.

Keywords: Migraine, transcranial magnetic stimulation, continuous theta-burst stimulation

INTRODUCTION

Patients with migraine are often considered to have an abnormal cortical activation pattern; however, it is controversial as to whether this pattern is towards hypo- or hyper-excitability, or more complex excitability changes exist. In recent years, transcranial magnetic stimulation (TMS) has been used as a good non-invasive method of in-vivo investigation of cortical excitability in migraine and several other neurologic diseases (1). Although several studies performed with a single-pulse TMS paradigm demonstrated hypoexcitability or hyperexcitability in patients with migraine, other studies found no significant excitability change between patients with migraine and normal controls (2-10). The paired-pulse TMS paradigm may reveal intracortical inhibition and facilitation of motor circuits (11). Some studies that used this paradigm suggested the presence of cortical hyperexcitability in migraineurs, whereas others reported no difference between healthy controls and migraineurs; a controversy that possibly stems from the use of different parameters for evaluating cortical excitability (9, 12-15).

Repetitive TMS (rTMS) allows the non-invasive investigation of synaptic plasticity because it can induce changes that continue after the stimulation period in cortical activity (16). Migraineurs have been shown to respond exactly oppositely to the rTMS protocol compared with healthy controls (13, 14, 17). Theta burst stimulation (TBS),

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is a modified form of the rTMS protocol that was established upon the 5 Hz theta rhythm of the hippocampus itself, which induces synaptic plasticity in animal models (16). Evidence of plastic cortical modulation has also been reported in humans (16, 18-24). The effects of continuous TBS (cTBS) in reducing migraine frequency has been investigated in only one study in the literature using 50 Hz cTBS, but cortical excitability changes have not been investigated. Recent studies have also shown that there is inter- and intra-individual variability with routinely used 50 Hz cTBS (23, 25-28). Our unpublished data of the study of the effects of different cTBS frequencies in normal individuals demonstrated less variability with 100 Hz than with 50 Hz cTBS.

The objectives of this study were to examine cortical excitability using the paired-pulse TMS protocol and to investigate the effects of cTBS on cortical excitability in patients with migraine and healthy controls.

METHODS

Subjects

Twenty-two patients with migraine were recruited. Due to the small number of patients, we excluded 3 patients with migraine with aura. Also, 2 patients had a migraine attack within 48 hours of the rTMS procedure and were excluded. Seventeen right-handed patients with migraine without aura and 18 healthy volunteers were included in the study during the study recruitment period, pre-defined as between August 2013 and July 2014. Control patients were selected from among hospital staff and their relatives without headache or other neurologic or systemic disorders. Patients were recruited from the Headache Outpatients' Clinic of our hospital and diagnosed by a headache specialist (G.G.) according to the diagnostic criteria released by the International Headache Society in 2013 (29). All patients had episodic migraine without aura. The exclusion criteria were prophylactic medication use in the 3 months prior to the onset of the study, using drugs that could alter the excitability of the central nervous system, having other primary or secondary headaches, or other neurologic and systemic diseases. Patients were examined in the interictal period. Phone interviews were performed to ensure absence of attacks 48 hours before and after the test. Female patients were examined when they were not in the menstruation period. All patients were checked for any contraindications against TMS and written informed consents were obtained prior to the performance of any study procedures according to the Declaration of Helsinki (30).

This study was approved by the Institutional Ethics Committee on May 2nd, 2013 (protocol number: 270). The demographic and clinical data of the participants are summarized in Table 1.

Stimulation Procedures

Patients were examined in a quiet room, on a comfortable chair, and asked to relax as much as possible. A cap that allows

Table 1. Demographic and clinical features of migraine patients

	Migraine patients	Control group	p
Number of subjects	17	18	
Sex (F/M)	15/2	13/5	0.402
Age (Mean±SD)	34.06±5.2	30.56±5.4	0.058
Clinical features (Mean±SD)			
Disease duration (years)	10.7±7.2		
Attack frequency (months)	2.8±2.2		
VAS	7.6±1.4		
Clinical features (ratio)			
Nausea and/or vomiting	82%		
Photophobia	88%		
Phonophobia	82%		
Unilateral headache	65%		
Throbbing headache	94%		
Aggravation of headache by physical activity	88%		

F: female; M: male; SD: standard deviation; VAS: visual analog scale

demarcation of the stimulation site was provided. The figure-of-eight coil was attached to the Mag Pro Mag Venture Magnetic Stimulator (MagVenture A/S, Farum, Denmark), which was used to administer focal TMS over the hand area in the left motor cortex to produce a contralateral muscle response with a posteroanterior orientation (31). Electromyography (EMG) signals were recorded using the Ag-AgCl surface electrodes, with a diameter of 0.9 cm, placed at 3-cm intervals on the belly and tendon of the right adductor digiti minimi (ADM) muscle. All recordings were performed using a Dantec Keypoint 3-Channel Amplifier EMG Device (Alpine Biomed ApS, Skovlunde, Denmark) at 10 ms sweep speed, 50 µV- 1 mV sensitivity, and 2 Hz-10 kHz frequency filter band. The resting motor threshold was defined as the intensity of the lowest stimulation producing a response of 50 µV or higher in at least 5 out of 10 stimulations at rest. Participants were asked to maintain a resting status during the examination as determined using audio-visual feedback. The coil was fixed with an arm attached to the TMS device to maintain its position. Stimulation was performed taking safety guidelines into account (18).

Experimental Paradigm and Measurements

Paired-stimulus cortical excitability studies were performed by stimulating the hand motor cortex region with a figure-of-eight coil (coil number: MCF:B 65). Intracortical inhibition (ICI) was evaluated at 2 ms interstimulus intervals (ISI), and intracortical facilitation (ICF) was evaluated at 10 ms ISI. The conditioning stimulus was set at 80% intensity of the resting motor threshold, and the test stimulus intensity was determined as the stimulus intensity that produced about 1 mV motor evoked

potential (MEP) (32). Ten stimuli were administered in each study and the mean amplitude was calculated automatically by the device, as well as the baseline peak amplitude values were recorded. Additionally, the MEP amplitude produced by conditioning stimulus and test stimulus was compared with the MEP amplitude produced by the test stimulus alone. To measure the cortical silent period (CSP), subjects were asked to slowly open the fingers on their right hand, and maintain the level of muscle contraction producing 20-25% of maximal voluntary contraction as determined using audio-visual feedback. CSP was examined by administering a single stimulation at 140% intensity of the resting motor threshold. Five stimuli were administered and the shortest stimulation was used in comparisons.

Following the baseline evaluations, cTBS was initiated over the left primary motor cortex using the figure-of-eight magnetic stimulator coil attached to the Mag Pro repetitive magnetic stimulator. Throughout this process, three pulses of stimulation were given at 100 Hz (ISI 10 milliseconds), and repeated every 200 milliseconds (5 Hz) in an uninterrupted fashion for 40 seconds (cTBS). The stimulation intensity was determined as 80% intensity of MT. Baseline and post-cTBS values of ICI and ICF and CSP durations were recorded and compared between patients with migraine and healthy controls.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Version 22 (IBM Corp.; Armonk, NY, USA). Frequency distribution for categorical variables and definitive statistics (mean \pm standard deviation, median) for numeric variables are given for the study data. A normality test was performed for numeric variables before starting analysis. The Shapiro-Wilk test showed that age, MEP, ICF, and CSP before and after cTBS assured the assumption of normality ($p < 0.05$), whereas duration of illness, frequency of attacks, MT, visual analog scale (VAS) scores, ICI before and after cTBS did not ($p > 0.05$). For this reason, parametric tests were used to compare variables that were normally distributed, and non-parametric tests were used to compare variables without normal distribution. Parametric tests including the independent t-test and repeated measures ANOVA analysis (rmANOVA) and non-parametric tests including the Mann-Whitney U test

and Wilcoxon test were used to compare numeric variables. The Chi-square test was used with 95% confidence levels to compare categorical variables.

RESULTS

All thirty-five participants completed the planned cortical excitability measurements including the measurement of MT, ICI, ICF, and CSP. Experimental procedures were well tolerated. Only one healthy control defined sensitivity on the examination area, lasting half an hour.

Seventeen right-handed patients with migraine (15 F/2 M, mean age: 33.9 ± 5.5 years) and 18 healthy volunteers (13 F/5 M, mean age: 30.6 ± 5.7 years) were included in the study. The mean disease duration was 10.7 ± 7.2 years, attack frequency was 2.5 ± 2.1 /month, and pain score on VAS was 7.7 ± 1.4 in patients with migraine. The clinical features of the patients were as follows: nausea and/or vomiting was found in 82%, photophobia in 88%, phonophobia in 82%, unilateral headache in 65%, throbbing headache in 94%, and aggravation of headache with physical activity in 88% of patients. There was no difference in the parameters of age, sex, and resting MT between patients with migraine and healthy controls (Table 1, 2).

Baseline MEP amplitude, which was achieved using a test stimulus only, was 0.89 ± 0.181 mV in patients with migraine and 1.01 ± 0.096 mV in controls. The difference was statistically significant ($p = 0.034$).

Baseline ICI studies did not differ between patients with migraine and controls ($p = 0.898$) (Table 2). Following cTBS, in all migraine patients and controls evaluated together, there was a significant decrease in ICI compared with baseline ($z = -5.160$, $p < 0.001$), but this difference was not significant between patients with migraine and controls ($z = -1.123$, $p = 0.273$).

Baseline ICF was not achieved and a decrease in MEP amplitude ($80 \pm 52\%$) was found in most patients with migraine, whereas ICF ($128 \pm 47\%$) was achieved in most controls ($p = 0.008$). After cTBS, rmANOVA revealed a significant effect of TIME ($F = 9.124$, $p = 0.005$) as well as significant TIME X GROUP interaction ($F = 7.129$, $p = 0.012$). Although both TIME

Table 2. Baseline and post cTBS findings of transcranial magnetic stimulation examination in migraine patients and controls

	Baseline			Post cTBS		
	Migraine (n=17)	Controls (n=18)	p	Migraine (n=17)	Controls (n=18)	p
MT (%)	52.0 \pm 5.2	50.6 \pm 5.0	0.408			
Change in MEP amplitude (%) after 2 ms ISI paired pulse (ICI)	25 \pm 22	24 \pm 18	0.898	36 \pm 45	18 \pm 11	0.119
Change in MEP amplitude (%) after 10 ms ISI paired pulse (ICF*)	80 \pm 52	128 \pm 47	0.008	78 \pm 47	85 \pm 35	0.585
CSP (ms)	81.94 \pm 40.3	90.33 \pm 34.8	0.513	92.82 \pm 41.38	93.39 \pm 35.6	0.966

MT: motor threshold; ICI: intracortical inhibition; ICF: intracortical facilitation; CSP: cortical silent period; ISI: interstimulus interval; ms: milliseconds

*The procedure which was supposed to create ICF did not result in ICF but instead resulted in a decrease in MEP amplitude in most of the study subjects in both groups

Figure 1. Comparison of motor unit potentials elicited by a paired pulse with 2 ms and 10 ms ISIs obtained before and after continuous theta burst stimulation in patients with migraine and control subjects. mV: millivolts; ms: milliseconds; cTBS: continuous theta burst stimulation; ISI: interstimulus interval

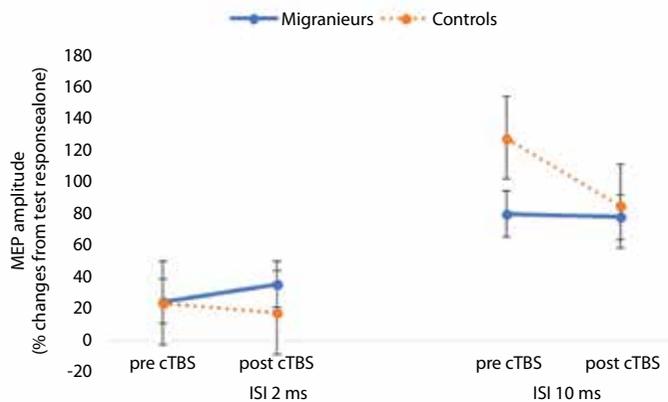
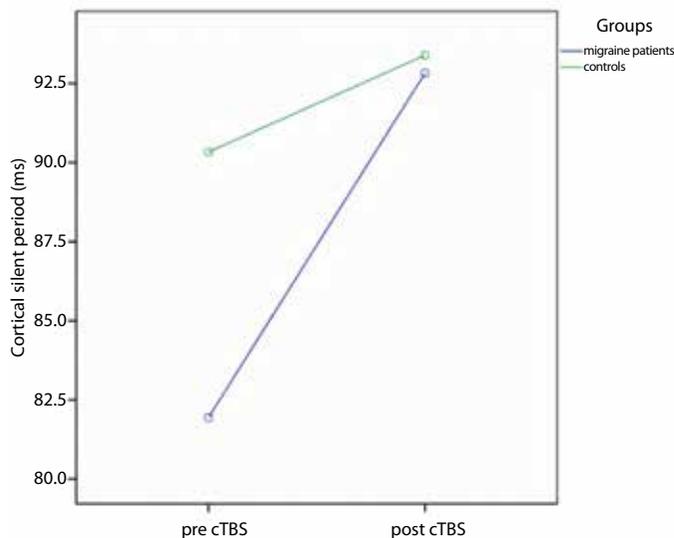


Figure 2. Comparison of cortical silent period obtained before and after continuous theta burst stimulation in patients with migraine and control subjects (p=0.002).

mV: millivolts; ms: milliseconds; cTBS: continuous theta burst stimulation, ISI: interstimulus interval



and TIME X GROUP interaction had strong effects ($n^2=0.22$, $n^2=0.18$, respectively), TIME effect (0.217) was stronger than TIME X GROUP effect (0.178). According to TIME, baseline ICF ($105\pm 54\%$) was higher than post cTBS ICF ($82\pm 41\%$) in all study subjects, but the procedure that was supposed to create ICF did not result in ICF and resulted in a decrease in MEP amplitude in most study subjects. Reviewing the TIME X GROUP interaction, baseline ICF was higher than post cTBS ICF in both groups, which was reduced by 0.02 and 0.43 in patients with migraine and controls, respectively, and again, the procedure that was supposed to create ICF did not result in ICF but instead resulted in a decrease in MEP amplitude in

most subjects in each group. These results suggested a more significant decrease in controls than in patients with migraine. On the other hand, when comparing the two groups, there was a significant difference between patients with migraine and controls ($p=0.049$) and the GROUP effect was moderate ($n^2=0.11$) (Figure 1).

Baseline CSP duration was similar in patients with migraine and controls ($p=0.513$) (Table 2). When comparing post cTBS CSP durations, rmANOVA showed a significant main effect of TIME ($F=4.343$, $p=0.045$) but the TIME X GROUP interaction was not significant ($F=1.370$, $p=0.250$) and the TIME effect was moderate ($n^2=0.12$). According to the TIME parameter, baseline CSP durations (86.25) were shorter than post cTBS (93.11) across the entire study population. The TIME X GROUP interaction was not significant ($F=1.370$, $p=0.250$). Moreover, there was no significant difference in CSP durations between patients with migraine and controls ($F=0.130$, $p=0.721$) (Figure 2).

DISCUSSION

In rTMS applications, low-frequency (1 Hz) stimulations tend to reduce corticospinal excitability [an effect similar to long-term depression (LTD)], while high-frequency (5 Hz and over) stimulations tend to increase excitability [similar to long-term potentiation (LTP)] (16). Nevertheless, high-frequency rTMS leads to a threshold that induces LTD in intracortical circuits in patients with migraine, contrary to the induction of LTP in healthy controls (15). However, the TBS protocol does not appear to follow the rule of frequency in rTMS. In human motor cortex, TBS may rapidly produce effects similar to LTP or LTD, experimentally, by using bursts at the same frequency and intensity without altering other factors (20-22). The directions of the effects produced by TBS vary based on continuous (cTBS produces effects similar to LTD) or intermittent (iTBS produces effects similar to LTP) administration of bursts (20-22). In a recent review, Chung et al. reported that iTBS increased cortical excitability but had no effect on short ICI (SICI) and ICF, and that cTBS reduced corticospinal excitability and SICI, but had no effect on ICF, emphasizing the importance of other factors including stimulation frequency, number of pulses, and brain-derived neurotrophic factor (BDNF) polymorphism in determining the pattern of effect (24). In terms of longer than the conventional stimulation protocols, Gamboa et al. found a complete reversal of the effects of cTBS resulting in strong potentiation lasting up to 60 min when 1200 pulses were administered (cTBS1200), whereas other studies found that 1200 pulses iTBS (iTBS1200) and cTBS1200 induced similar, but slightly longer lasting effects in comparison with iTBS600 and cTBS600; further emphasizing the intrinsic variability of TBS paradigms and potential involvement of multiple factors in the efficacy of TBS (23, 33).

Although most studies that used theta burst stimulation pattern focused on the 50 Hz protocol with an ISI of 20 milliseconds, slightly different paradigms have also been tested. Goldsworthy et al. studied 30-Hz TBS and reported a longer

lasting after-effect and less inter-individual variability compared with 50-Hz TBS (27). Investigating the effects of 100-Hz TBS in a biologically realistic simulation model, Jedlicka et al. demonstrated a mild LTP in addition to a concurrent LTD effect (34). Also, Hamada et al. studied quadripulse stimulation (QPS) with 100 Hz in healthy volunteers and found potentiating effect on synaptic plasticity (28). In our unpublished study of the effects of different cTBS frequencies in normal individuals, we found that 100 Hz had less variability than 50 Hz TBS.

Aimed at investigating cortical excitability using TMS and the effects of 100-Hz cTBS, the results of our study demonstrated that baseline ICF is absent in patients with migraine. We did not achieve ICF in most subjects in both groups after cTBS, but we observed a greater reduction in MEP amplitude following cTBS in normal controls; no changes were recorded in patients with migraine.

The absence of ICF in our study contradicts the related literature reporting normal or increased intracortical facilitation in migraineurs. Siniatchkin et al. found higher ICF in patients with migraine compared with controls; most other studies reported no difference (5, 9, 12-14). Similarly controversially, ICI has been demonstrated to be lower in migraineurs (13, 14), or similar between migraineurs and controls (5, 9). Cortical hypoexcitability has also been suggested via the demonstration of higher MT in patients with migraine compared with healthy individuals (4-7). Also in our study, patients with migraine tended to have higher MT compared with controls, although not to a statistically significant level. Our finding of absence of ICF in patients with migraine could be caused by methodologic differences. In some of these studies, ICF and ICI measurements were performed in patients with migraine with aura or familial hemiplegic migraine, whereas our patients had migraine without aura (9, 13, 14). Afra et al. found no difference between patients with migraine with aura and healthy subjects in terms of ICI and ICF but they used a circular coil, which could cause different results (5). Siniatchkin et al. found higher ICF in patients with migraine compared with controls, but they used 20-ms ISI for ICF, whereas we used 10-ms ISI; their patients' mean age was lower compared with ours (24.2 ± 7.9 vs. 33.9 ± 5.5 years), and their study group comprised women only, whereas we had both male and female participants (12). Test stimulus was defined differently in other studies. For example, Brighina et al. used 120% of MT as the test stimulus (13), Kujirai et al. used the test stimulus as the supramotor threshold, producing an EMG response of about 1.5 mV peak-to-peak amplitude, and we used about 1 mV peak-to-peak amplitude (35). Also the low baseline MEP amplitude and absence of ICF in patients with migraine might be explained by an insufficient stimulation intensity in our study.

One potential hypothesis to explain this discrepancy in cortical excitability parameters is the disturbance of facilitatory circuits resulting in failure to produce the required facilitation response in patients with migraine, thereby suggesting the presence of cortical hypoexcitability in migraine. In light of recent reports as

sociating SICI with GABAergic ICF with glutamatergic circuits, our findings indicate impairment of glutamatergic circuits to be a major culprit in the pathogenesis migraine (15, 19). Also, an alternative hypothesis is the activation of control homeostatic inhibitory mechanisms during the examination of hyperactive facilitatory circuits of migraineurs. Indeed, we agree with Cosentino et al. who deduced that these controversial results might be related to the different stimulation intensities used for conditioning and test stimuli (15). Certainly, further studies would be worthwhile to test different test pulse intensities systematically to elucidate the potential role of homeostatic mechanisms.

There are several limitations to our study that need to be addressed. Although study examinations were performed outside the menstrual period of female patients, a selection criterion to only include patients in the same phase of the cycle was missing, thus creating a potential bias posed by the hormonal differences between follicular and luteal phases. Also, the relatively small sample size was a limitation.

Nevertheless, our study appears to be the first to report the absence of ICF in patients migraine and investigate the effects of the cTBS protocol in migraine. Our results support recent TMS literature by demonstrating diminished intracortical facilitation suggestive of impairment of glutamatergic circuits, and it might be worth investigating different TBS protocols to normalize the dysexcitability observed in patients with migraine. To the best of our knowledge, this study is the first to demonstrate reduced baseline activity of intracortical facilitatory circuits in inter-ictal migraine patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bakırköy Training and Research Hospital for Psychiatric and Neurological Diseases / 270.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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