附件一

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The effect of continuous theta burst magnetic stimulation on the movement-related cortical potential in humans

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計畫主持人：蔡崇豪
共同主持人：黃英儒
計畫參與人員： 呂明桂、黃偉師、沈孟慧

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摘要

運動關聯皮質電位（Movement related cortical potential，MRCP）是一種負向位移，啟始於意志動作之前的 1.5 秒。它含括至少三項次組成：動作準備電位 (Bereitschaftspontial，BP)、負斜波(negative slope，NS')、及動作電位(motor potential，MP)。MRCP 次組成的產生源頭乃依據皮質或頭皮記錄到的波形作推論，這些理論性假設應該經由改變這些可能源頭的神經活性是否可以導致 MRCP 波形的改變來驗證。本研究採用的方法是由重複式經顱磁刺激術（repetitive transcranial magnetic stimulation，rTMS）發展出的新模式稱為θ突波磁刺激（theta burst stimulation，TBS）。實驗記錄 8 位正常受試者在接受連續θ突波磁刺激初級運動皮質區之前以及刺激之後的區段 A、B、C 的右手運動關聯皮質電位。分析記錄結果顯示實驗組在區段 C 的動作準備電位(p=0.00)、區段 B(p=0.01)和 C (p=0.00)的負斜波、及區段 C(p=0.00)的動作電位抑制現象相較於對照組有顯著統計差異。目前研究結果說明了運動關聯皮質電位可以經由抑制運動皮質來調節，同時也指出這區域對於運動關聯皮質電位的產生及傳遞極為重要。

關鍵詞：重複式經顱磁刺激術、運動關聯皮質電位、θ突波

Abstract

Movement related cortical potential (MRCP) is a negative shift starting 1.5 sec before volitional movement. It consists of 3 subcomponents, the Bereitschaftspontial (BP), the negative slope (NS'), and the motor potential (MP). The generating sources of MRCP were deduced from surface recordings and the hypothesis should be verified by determining whether functional alteration of the candidate regions can actually modulate MRCP. In this study, repetitive transcranial magnetic stimulation is adopted for this purpose with a novel suppressive paradigm, the continuous theta burst stimulation (cTBS). MRCP was recorded in 8 normal subjects before, 5'(block A), 12'(block B) and 19'(block C) after cTBS of the primary motor cortex opposite to right hand movement. Comparison between the test and sham groups reveals that the suppression of BP is at block C (p=0.00), the suppression of NS' is at block B (p=0.01) and C (p=0.00) and the suppression of MP is at block C (p=0.00). The current findings illustrate that MRCP can be modulated by the suppression of the motor cortex and imply that this region is crucial for the generation or relay of MRCP.

Key words: rTMS, movement-related cortical potential, theta burst

Introduction

Movement-related cortical potential (MRCP) is a slow negative shift starting 1-1.5 sec before volitional movement (Deecke 1990; Shibasaki et al. 1980). It is conventionally thought as a physiological signal to represent the cerebral cortical function for the preparation and initiation of the voluntary movements (Deecke 1990; Shibasaki et al. 1980). Currently it is accepted that MRCP consists of at least 3 subcomponents (Fig. 1). The Bereitschaftspotential (BP), which begins about 1.5 sec before and ends about 500 ms before the electromyography (EMG), consists of a gradually increasing bilateral widespread surface negativity centered over the vertex area (Deuschl et al. 1995). The negative slope (NS'), which follows the BP and finishes just before movement onset, is characterized by a steeper and more localized cortical negativity over the contralateral central and vertex areas, reaching its peak during the 100-ms interval before EMG onset (Deuschl et al. 1995). The highest negativity, which begins just before the onset of the movement, is the motor potential (MP). The MP reaches its peak amplitude over the frontal regions about 100 ms after the movement onset in a component called the frontal peak of the motor potential (Deuschl et al. 1995). It is generally agreed that the generator for the BP is from the mesial prefrontal cortex including the supplementary motor area and also the cingulate motor area and that for the NS' may be explained by the activation of generators in the sensorimotor cortex bilaterally (Deuschl et al. 1995; Shibasaki et al. 1980; Tarkka and Hallet 1991; Tama and Shibasaki 1985). The MP may be accounted for by

the activation of a source in the contralateral central regions (Deuschl et al. 1995). The generating sources of these different subcomponents of MRCP were mainly deduced from the cortical or scalp recordings (Shibasaki et al. 1980; Tarkka and Hallet 1991; Yazawa et al. 2000) and the working hypothesis should be further verified by determining whether functional perturbation of the candidate regions could actually modulate the behavior of MRCP. At least two methods can be adopted to investigate the issue. The first would be lesion study of MRCP. In a patient with anterior cerebral arterial infarction, McNabb et al illustrated that the BP was attenuated and the NS' became asymmetric (McNabb et al. 1988). Since functional reorganization would tend to occur certain period later after a lesion and novel functional sets different from the pre-lesion state may be developed (Riecker et al. 2002; Ward et al. 2003), it is unequally footed to investigate and elucidate MRCP issue as simply based on the lesion ground. The second method is to modulate the target regions by external electrophysiological functional perturbation to see how the interference would affect the MRCP conformation. Among the external perturbing techniques, repetitive transcranial magnetic stimulation (rTMS) has been recently used to investigate the neuronal modulation of plasticity by it capability of creating 'after effect' of stimulation. At 1-Hz stimulation frequency, the rTMS usually provokes inhibitory effect on the motor cortex and at 5-Hz stimulation frequency it usually elicits excitatory effect on the cortex (Dannon et al. 2002; Gerschlager et al. 2001). Thanks to these different impacts, the 1-Hz stimulation has been adopted to treat patients with conditions where excessive cortical excitation is a pathophysiological feature (Huang et al. 2004) and 5-Hz stimulation has been used to treat patients with depression, where such changes are thought to be potentially beneficial (Dannon et al. 2002). Usually, it took a course around 20 minutes of aforementioned methods to secure the physiological effect. Recently, a novel technique, the theta burst magnetic stimulation (TBS) of the human motor cortex was introduced by Huang et al, which can swiftly produce powerful and controllable long-term changes in the excitability of cortical circuits (Huang et al. 2004). It consists of very short train stimulation which is repeated at 4-7 Hz (the theta range of frequencies in EEG terminology) for a period around 2 seconds. The basic TBS pattern is of a train containing 3 pulses at 50 Hz delivered every 200 ms. Using this basic pattern at low intensities, two different paradigms of TBS capable of swiftly producing powerful but opposite effects on the excitability of cortical motor circuits. The intermittent TBS (2 seconds of TBS repeated 20 times at 10-second intervals: 600 stimuli in total) can cultivate enhancement and the continuous TBS (cTBS, 20 seconds of TBS) can produce suppression of cortical excitability (Huang et al. 2004). Thanks to the low stimulation intensity (80% of the active motor threshold) and short stimulation duration, TBS is a paradigm of safety regards. In the current study, we adopt cTBS as the tool to modulate the human motor cortex to observe how the suppression of the human motor cortex would affect the behavior of MRCP in normal human subjects. Footing on this ground, we try to verify the role and the hypothetic accuracy of the MRCP generated regions of the brain. We hope to apply this novel technique to investigate and even to ameliorate the motor executive deficits of patients with movement disorders in the future.

Subjects and Methods

Subjects

Eight normal right handed male volunteers with mean age of 31(±4.4) years were recruited. All the subjects gave written informed consent prior to the study.

Methods

A. Research design

The study was divided into two sessions in 7 days apart. It was approved by the ethic committee of the Hospital (DMR 93-IRB-115). In test session, the subjects received MRCP recording first followed by cTBS over the left motor cortex and then another series of MRCP recording. The procedures of the Sham test were identical to those of the test session and the technique will be addressed later. The post-cTBS MRCP recordings in the test session and sham session were

divided into 3 blocks and each block lasted for 4 minutes. There was a 3-minute break between each block. The procedures is illustrated by the following diagram-

Test session: MRCP⇒5-minute break⇒ cTBS (20 sec)⇒5-minute break⇒MRCP(block A→3-minute break→block B→3-minute break→block C)

Sham session: MRCP⇒5-minute break⇒ cTBS (20 sec)⇒5-minute break⇒MRCP(block A→3-minute break→block B→3-minute break→block C)

B. Continuous theta burst stimulation (cTBS)

Throughout the study, the subjects were awake and seated with their hands resting on a manipulandum. Surface EMG recording from the right first dorsal interosseous (FDI) was made using silver/silver chloride electrodes. The EMG signal was amplified by D360 (Digitimer Ltd, UK), filtered from 5 Hz to 2.5 KHz, digitized, processed with CED 1401 plus (Cambridge Electronic Device, UK) and stored on a computer. The impedance between the cathode and anode was kept below 5 KΩ during the study.

The hand motor cortex was stimulated using a MAGSTIM 200 (Whitland, Dyfed UK) with a figure 8 coil. The threshold was determined for the tonically active muscle in force of 10% of the maximum voluntary contraction determined by a force transducer. Threshold was defined as the stimulus intensity required to produce a motor evoked potential (MEP) of at least 100 μV amplitude in at least five out of ten consecutive trials by a MAGSTIM SUPER RAPID (Whitland, Dyfed UK). Initially the stimulus intensity was adjusted in 5 % steps to secure a rough estimate of the threshold. Once this was achieved the intensity was then adjusted in 1% steps to allow precise determination of threshold. The stimulation intensity of cTBS was at 80% of the active threshold. The cTBS pattern is a train containing 3 pulses at 50 Hz delivered every 200 ms (that is 5 trains per second) for 20 seconds. The sham stimulation was conducted by holding the coil 90 degrees to the stimulating site with the skin being touched by the coil margin. The cTBS protocol was designed by Huang et. al.(Huang and Rothwell 2004). The whole process was conducted by using CED power 1401-Signal system.

C. Recording of MRCP

The subjects were seated in an arm chair in a dimly lit quite room. The electroencephalogram (EEG) was recorded with 10 gold-plated electrodes (F3, Fz, F4, FCz, C3, Cz, C4, P3, Pz, P4) affixed to the scalp according to the conventional 10-20 system. The electrode impedance was kept below 5 K and was referenced to linked ear-lobe electrodes. The electro-oculogram (EOG) was recorded from an electrode placed 1.5 cm below the left outer canthus and referenced to the linked earlobes. The EEG and EOG signals were filtered with a band pass of 0.05 to 70 Hz (Neuroscan). Brisk voluntary horizontal movement of right first dorsal interosseous (FDI) was repeated at a self-paced rate of every 7 sec. The right hand was placed on a manipulandum with bandage restraining of the thumb and third to fifth fingers and allow only index to move horizontally. The EMG of the right FDI was recorded by a pair of cup electrodes with a band pass filter of 30 to 200 Hz and the signal was rectified. The EEG segment from 2 sec before to 1 sec after the trigger movement was digitized and saved at a sampling rate of 2 KHz. Trials contaminated with eye movement or other movement artifacts and trials without a brisk EMG burst onset was excluded from the analysis. At least 70 artifact-free EEG epochs was averaged after precise alignment with the EMG burst onset. The DC off-set in each channel was removed by setting to zero the mean voltage of the interval of –2000 to –1700 ms. MRCP averages was calculated for each hand in each subject. The MRCP and cTBS studies were performed in the same position and the subjects did not have to change their spots of examination. This is important to minimize the possibility of motion confounding on the cTBS effect. In addition, the EEG electrodes were left on the scalp during magnetic stimulation to ensure the same loci of MRCP recordings before and after cTBS.

Data Analysis of electrophysiology

In the test and sham sessions of the study, the grand averages of MRCP of the right FDI before and after cTBS of the subjects were obtained. Statistical analyses were performed for each set of averaged waveforms at all electrodes during the following time intervals: -1500 to -500 ms (BP), -500 to -50 ms (NS'), and -50 to 0 ms (MP) before EMG onset. The amplitude difference by subtracting the pre-cTBS data from the post-cTBS data was calculated for each block. Multivariate analysis (MANOVA) was conducted for each block to examine any difference between the test and sham groups. Fisher's Protected Least Significant Difference (PLSD) post hoc test was then conducted to identify the significantly different electrode(s) between the two groups.

Results

BP (Fig. 2 and 3)

The mean values of BP amplitudes were shown in Table. The data of amplitude differences were calculated by subtracting the pre-cTBS from the post-cTBS BP for each block. MANOVA revealed a significant difference between the test and sham groups ($F=1.35$, $p=0.05$). Results of ANOVA for each block reveals that the significant difference was at block C ($F=2.55$, $p=0.0009$). No statistically significant difference was detected at block A (($F=0.73$, $p=0.78$) and B ($F=1.41$, $p=0.13$). By using Fisher's PLSD to examine the electrode effect in block C, the main significant different montage sites are at F3 ($p=0.01$), F4 ($p=0.0035$), FCz ($p=0.04$), C3 ($p=0.0074$), P3 ($p=0.0096$), and Pz ($p=0.04$). Fisher's PLSD was further conducted to examine the montage effect in block A and B and hope to see the evolution pattern of the BP waveform difference. In block A, only F3 was found to be significantly different ($p=0.02$). In block B, the differences were at F3 ($p=0.0043$) and F4 ($p=0.0073$).

NS' (Fig. 2 and 3)

The mean values of NS' amplitudes were shown in Table. The data of amplitude differences was calculated by subtracting the pre-cTBS NS' from the post-cTBS NS' in each block. The results of MANOVA showed a significant difference between the test and sham groups ($F=1.41$, $p=0.03$). ANOVA for each block detected that differences were at block B ($F=1.92$, $p=0.01$) and C ($F=2.89$, $p=0.0002$). There was no difference at block A between the test and sham ($F=0.59$, $p=0.90$). Fisher's PLSD was adopted to examine the montage effect in the 3 blocks separately. In block A, only F3 ($p=0.02$) was found to be significantly different between the two groups. In block B, F3 ($p=0.0017$) and F4 ($p=0.0011$) were significantly different. In block C, F3 ($p=0.0098$), Fz ($p=0.04$), F4 ($p=0.0013$), C3 ($p=0.0054$), P3 ($p=0.01$), and Pz ($p=0.02$) were found to be significantly different between the test and sham groups.

MP (Fig. 2 and 3)

The mean values of MP amplitudes were shown in Table. To calculate the amplitude difference, the pre-cTBS amplitudes were subtracted from the post-cTBS in each block. MANOVA was conducted to detect any difference between the test and sham groups and the results illustrated a significant difference between the two ($F=1.35$, $p=0.05$). ANOVA was then conducted for each block and a significant difference was detected in block C ($F=2.52$, $p=0.001$). There was no difference in block A ($F=0.52$, $p=0.94$) and block B ($F=1.36$, $p=0.15$). Fisher's PLSD was adopted to detect the montage effect of each block. There was no difference of any montage sites between the 2 groups in block A. Difference began to appear in block B at F3 ($p=0.0062$) and F4 ($p=0.0030$). Full blown different pattern was revealed in block C at F3 ($p=0.01$), Fz ($p=0.03$), F4 ($p=0.0009$) and C3 ($p=0.01$).

Discussion

The main findings of the current study are suppression of the three subcomponents of MRCP by cTBS. It is intriguing to detect that the suppression began to appear at the late phase after stimulation. In the BP session, we found that the initial cTBS effect taking place in the prefrontal regions, i.e. premotor area, and with the evolution of time the suppression spread out to involve the midline, i.e. SMA, electrodes and electrode located at primary motor cortex contralateral to the

index movement. Similar phenomenon can also be observed in NS' and MP, apart from that the overall suppression territory of MP was smaller than the former. It is amazing to find that local suppressive stimulation of primary motor cortex can modulate the MRCP waveforms at the remote SMA and premotor regions. There are two hypotheses of motor preparation and execution models. The first is the supplementary model which speculates that the SMA and primary sensorimotor areas are active in parallel with and complementary to each other in the programming, initiation and execution of the voluntary movements (Chen et al. 1991). The second is the supramotor model which speculates that the SMA initiates and regulates voluntary movements contributing to the generation of a new motor program and to the control of the execution of established movements (Matsuzaka et al. 1992). In the first model, the SMA and primary sensorimotor areas are triggered simultaneously and in parallel to each other. Thus the perturbation of either one will most likely not affect its counter part and cannot explain the observed phenomenon in the current study. In the second model, there is a chronological sequence of the motor pulses generation with its initiation from the SMA and the pulses will then be conveyed to the primary sensorimotor area. It is possible that the suppression or block of the later checkpoint, i.e. primary sensorimotor cortex, by theta burst may cause signal transmission jamming of the trail and culminate in negative effect of the SMA and the nearby regions. In addition, with the evolution of time, the territory of the affected electrodes became wider in this study and suggested the temporal sequence of the motor pulse generation. With these regards gathered, the current finding seems more compatible with the supramotor model of motor execution. Recently, a study concerning the cortical inhibitory excitability in patients with Parkinson's disease found that abnormal baseline intracortical excitability at an interstimulus interval of 5 ms could be normalized by dorsal premotor rTMS. The result was also in favor of supramotor model (Buhmann et al. 2004).

The pivotal cTBS effect on MRCP components took place in later blocks, usually more than 10 minutes after the magnetic suppression, of the tests. The phenomenon is compatible with the time course of suppressive effect of cTBS on motor cortex (Huang et al. 2005). In cTBS, it had been proposed that both the facilitatory and inhibitory effect are elicited at the synaptic transmission levels with the suppressive effect being slower but more powerful to be developed in long term (Huang et al. 2005). Thus, a simmering duration is usually required for the compromise between the facilitatory and inhibitory effect elicited by cTBS to occur. The temporally lasting after-effect of cTBS (Huang et al. 2005) mimicking in certain degree to that of neuroplasticity and calcium related pathways may be crucial for its occurrence. In the potentiation of fascilitatory situation, the calcium/calmodulin-dependent kinase II(CaMKII) and the cyclic adenosine monophosphate (cAMP)-dependent pathways are important (Cooke and Bliss 2006). In the depression or inhibitory condition, the calcium-responsive phosphatases such calcineurin and protein phosphatase-1 are implicated as effector molecules (Cooke and Bliss 2006; Morishita et al. 2005). It is currently uncertain how would the high frequency magnetic stimulation would affect these cellular mechanisms to cause the net after-effect in the human brain. In rat brain model, Kole et. al. illustrated that the number of NMDA and serotonin receptor subtype 1A (5-HT_{1A}) binding sites were increased after a train of 20 Hz magnetic stimulation for 3 seconds and the effect can be observed at the 24-hour point (Kole et al. 1999). The authors hypothesized that the phenomenon may be crucial for the strengthening of the glutamatergic synaptic connections. If the concept was adopted to the human, it is likely that the rTMS may cause after-effect of the brain through the modulation of neurochemical synaptic transmission. It yet remains to be elucidated that how will different magnetic stimulation paradigms exert different patterns of receptor or neurotransmitter changes, which in turn corresponding to either inhibitory or excitatory after-effects.

In difference to BP, the suppression of the NS' and MP by cTBS was most obviously allocated over the primary motor cortex contralateral to the index movement. Previous hypothesis concerning the generator of NS' suggested that the wave may be explained by the activation of generators in the sensorimotor cortex bilaterally (Tarkka and Hallet 1991). On the other way, Deuschl et. al. illustrated that the NS', which follows the BP and finishes just before movement onset, is characterized by a steeper and more localized cortical negativity over the contralateral central and

vertex areas, reaching its peak during the 100-ms interval before EMG onset (Deuschl et al. 1995). This implies that NS' generating source could be more or less lateralized oppositely to the moving limb. Since the theta stimulation was focused on the hand motor spot in the current study, the lateralized suppressive effect suggests that the generator of NS' could be much more localized at the motor cortex opposite to the hand moving side than what was suggested by Tarrka et. al. Same rule can also be adopted to MP and it is conceivable that motor cortex contributes to its generation or relaying as originally believed (Deecke et al. 1969; Shibasaki et al. 1980).

The current findings were similar to those found in a previous report by using 1-Hz stimulation of the primary motor cortex for 15 minutes{Rossi et al. 2000}and suggests that the short duration paradigm, 20 seconds, can achieve a significant impact on modulating the human cortical activities. From the practical point of view, the cTBS is time economical to be adopted for the modulation of MRCP and may be hopefully used for the management of disorders with motor preparation dysfunctions, such as task specific dystonia or Parkinson's disease in the future.

Although the current results illustrated significant late after effect of cTBS on the MRCP, it is uncertain whether the effect was generated by pure local effect or by also remote effect triggered by local transcranial magnetic stimulation as proposed by Bestmann et. al. (Bestmann et al. 2004). Further work should be conducted by using functional MRI to elucidate the intriguing phenomenon observed in this study.

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Figure

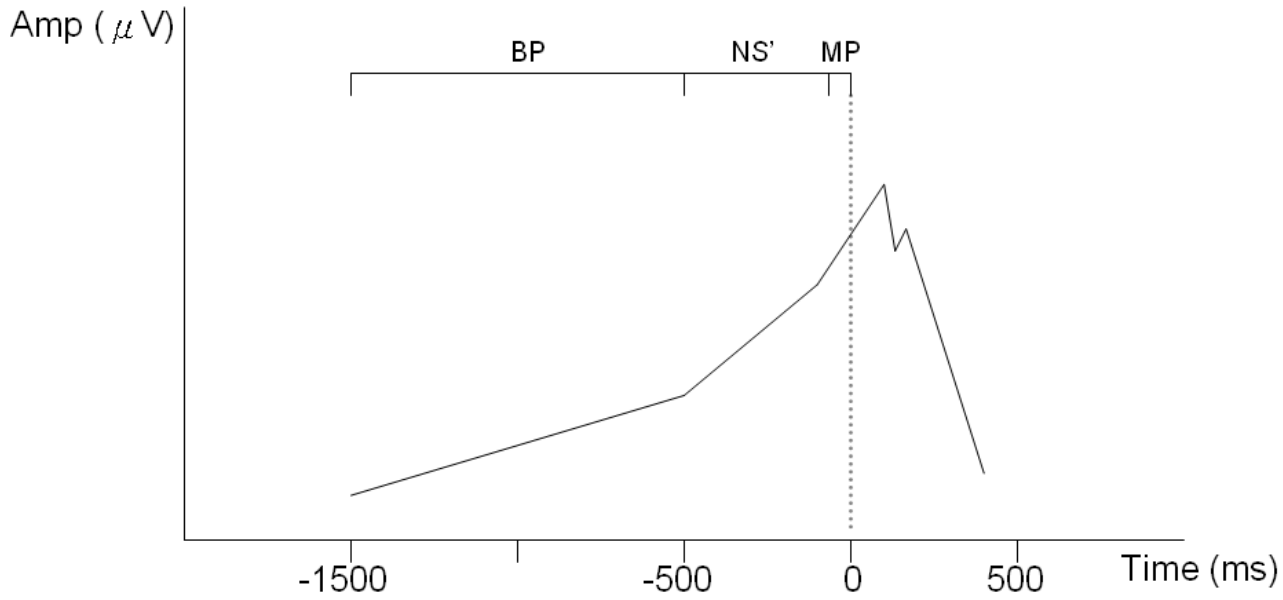


Figure 1. The figure illustrates the subcomponents of movement-related cortical potential. Bereitschaftspotential (BP) is from -1000 to -500 ms, negative slope (NS') ranges from -500 to -50 ms and motor potential (MP) is from -50 to 0 ms prior to the EMG onset.

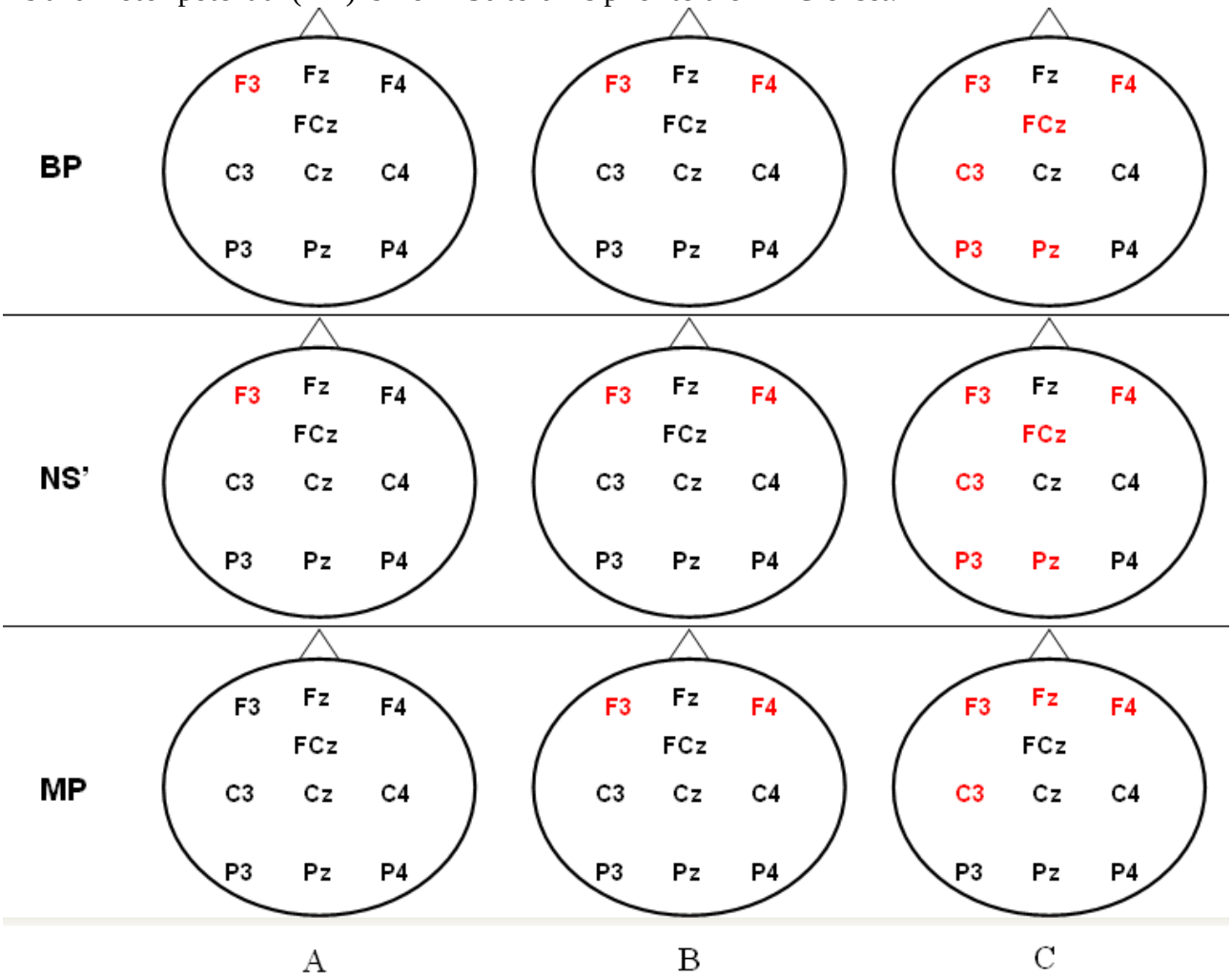
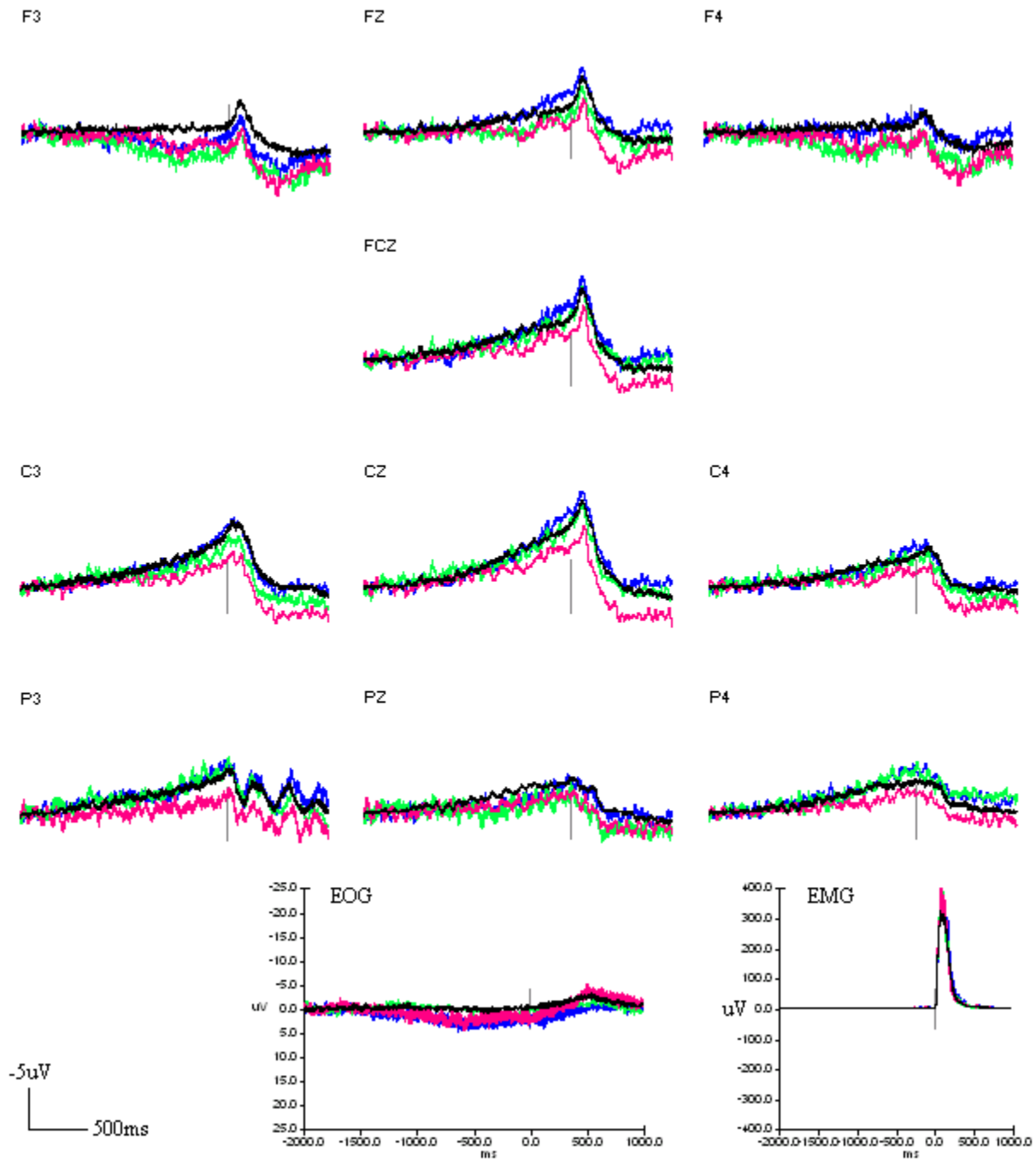
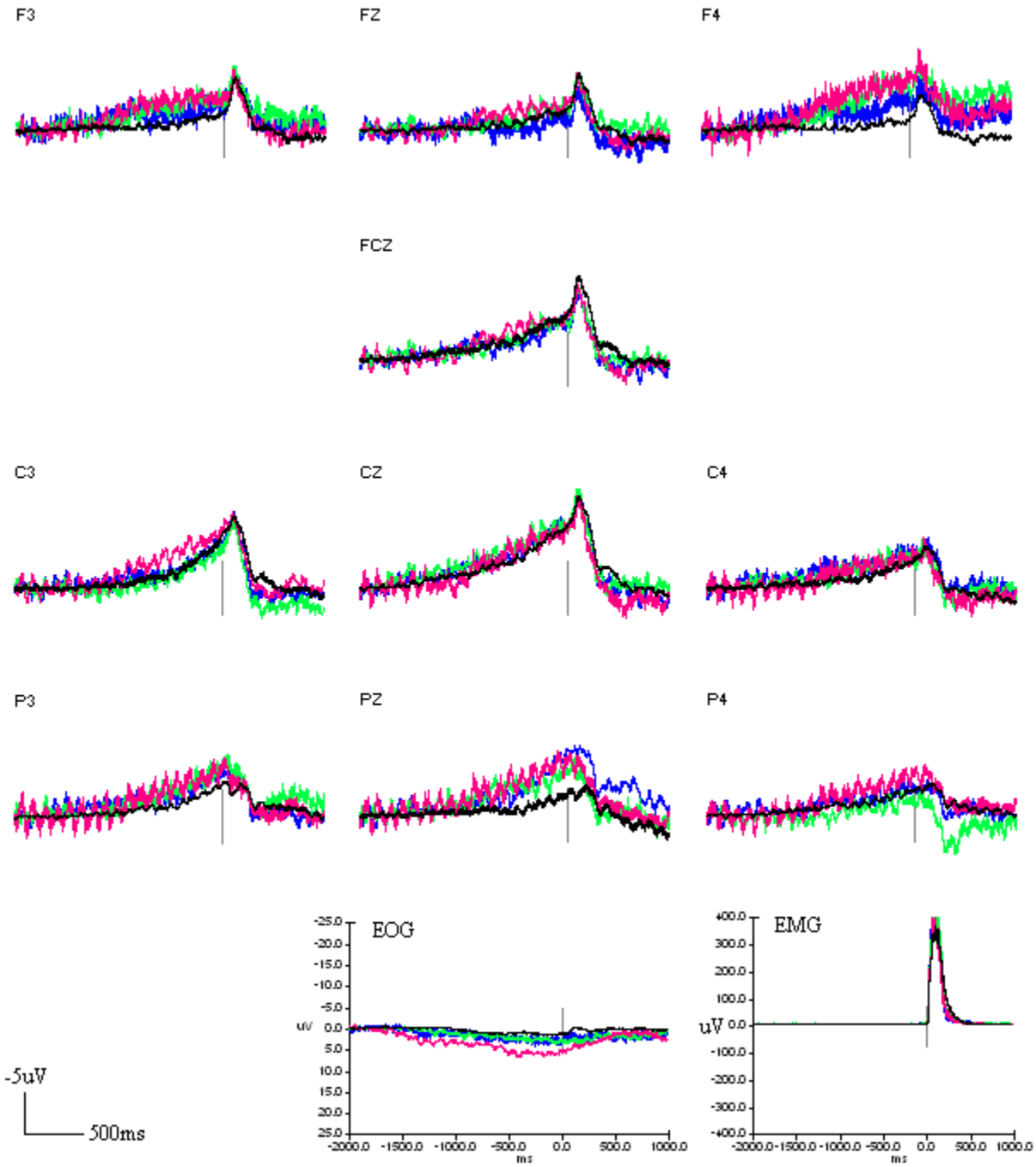


Figure 2. The temporal and spacial suppressive effects of cTBS on the subcomponents of movement-related cortical potential elicited by right index horizontal movement in 8 normal human subjects.



(A) the true test



(B) the sham test

Figure 3. The temporal sequence of cTBS after-effect on the movement-related cortical potentials triggered by right index horizontal movement in 8 normal human subjects. (A) the true test (B) the sham test.

Table. The mean amplitude of Bereitschaftspotential, NS' and MP of different blocks in each montage.

Montage	BP				NS'				MP			
	Pre-cTBS	Post-cTBS			Pre-cTBS	Post-cTBS			Pre-cTBS	Post-cTBS		
		A	B	C		A	B	C		A	B	C
F3	-.51	-1.63	-1.54	-1.77	-1.36	-2.69	-3.75	-3.86	-2.13	-3.60	-4.50	-4.53
Fz	-.48	-.92	-1.11	-1.30	-1.79	-1.54	-3.74	-3.67	-2.50	-2.97	-4.83	-4.66
F4	-.44	-1.85	-1.48	-2.06	-.97	-2.21	-4.43	-4.61	-1.24	-3.05	-5.10	-5.48
FCz	-1.32	-1.42	-2.23	-2.30	-4.03	-3.51	-6.02	-5.86	-5.42	-4.96	-7.21	-7.17
C3	-.65	-1.14	-1.26	-2.31	-3.44	-3.73	-4.98	-6.22	-6.02	-5.99	-6.72	-8.11
Cz	-2.05	-2.09	-2.90	-2.42	-5.57	-5.12	-7.44	-6.56	-7.57	-6.93	-8.54	-8.07
C4	-.80	-1.13	-1.42	-1.90	-2.41	-3.13	-3.93	-4.38	-3.44	-4.28	-4.18	-5.43
P3	-.75	-1.32	-.84	-1.73	-2.47	-2.74	-3.70	-4.36	-3.95	-3.98	-4.58	-5.32
Pz	-.51	-.77	-.75	-1.70	-1.45	-2.71	-2.98	-4.08	-2.45	-4.41	-3.34	-4.63
P4	-.93	-1.00	-.47	-1.43	-2.27	-2.13	-2.28	-3.59	-3.09	-2.84	-2.51	-4.38
F3	-.38	.77	1.94	.94	-.47	1.77	3.44	1.95	-.71	.94	3.02	2.34
Fz	-1.01	-1.08	.12	.02	-2.50	-3.42	-.97	-.63	-3.26	-5.08	-2.03	-.71
F4	-.51	-1.10	1.59	.88	-.79	-.52	2.29	1.74	-.82	-1.59	1.96	2.27
FCz	-1.88	-1.62	-1.67	-.81	-4.22	-4.98	-3.78	-2.44	-5.10	-7.03	-5.10	-3.01
C3	-1.86	-1.74	-1.56	-.75	-4.56	-4.58	-3.27	-2.03	-6.42	-7.33	-5.05	-3.30
Cz	-2.20	-2.09	-2.41	-1.37	-6.05	-6.68	-5.58	-3.85	-7.65	-9.56	-7.48	-4.79

(Table 1 continued)

C4	-1.30	-1.13	-1.17	-.79	-3.22	-3.22	-2.63	-1.49	-3.91	-5.24	-3.47	-1.73
P3	-1.92	-2.18	-1.97	-.23	-3.86	-4.37	-4.69	-1.19	-5.10	-6.20	-5.53	-2.34
Pz	-1.59	-.84	-.35	-.69	-3.47	-2.67	-1.51	-1.74	-3.96	-4.27	-2.10	-2.31
P4	-1.51	-1.85	-1.56	-.68	-3.52	-4.32	-4.32	-1.89	-3.86	-5.75	-5.18	-2.58

(Upper panel:sham group, lower panel:test group; data in the parenthesis =post-cTBS-pre-cTBS; A(5-minute), B(12-minute), C(19-minute): blocks after cTBS)