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EFFECTS OF SUBTHRESHOLD TRANSCRANIAL MAGNETIC STIMULATION ON CHOICE REACTION TIME AND CORRELATION WITH MOTOR CORTICAL ACTIVATION

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INDEXING WORDS

transcranial magnetic stimulation; choice reaction time; MRP; motor preparation; human

SYNOPSIS

To study the effect of subthreshold transcranial magnetic stimulation (TMS), we measured choice reaction time (RT), with or without TMS, in 7 healthy participants. TMS over the hand motor area was randomly delivered at variable delays after the imperative signal, while partici-

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pants performed right or left abduction of the thumb. Lateralized movement-related potentials (MRPs) were recorded in a separate session to link the TMS effect with the motor cortical circuitry. For the right hand, the coexistence of a motor specific and non-specific effects of TMS was clearly evidenced, by the RT shortening at delays of 0 and 150 ms. The response dependency of the specific TMS effect was also demonstrated through the response-locked analysis, showing a maximal shortening at 120-ms bin before EMG onset. Furthermore, the lateralized MRP commenced at about 80 ms before EMG onset, indicating that TMS influences the cortical motor circuitry around 30-40 ms before the activation of the primary motor cortex. In contrast, for the left hand, we were faced with some uncertain concepts as human handedness and hemisphere asymmetries in both measures of RT and MRP, and thus it was not possible to substantiate about the motor specific effect of subthreshold TMS.

INTRODUCTION

The remarkable and precise faculty observed in transcranial magnetic stimulation (TMS) has been widely settled about providing information of central motor pathways. [4,10] The question remaining is whether TMS can really cause some influence over the cortical motor circuitry. Pascual-Leone et al. [9] assigned to TMS the capacity of shortening simple reaction time (RT) when delivered at proper time, intensity and site. On the other hand, Terao et al. [12] considered the shortening of simple RT almost a mere result of the intersensory facilitation phenomenon, caused by the TMS local sensation and artifact sound.

Recently, we have shown that subthreshold TMS is able to shorten simple and go/no-go RTs on account of two entirely different factors. The first factor, called intersensory facilitation (IF), is not considered as being peculiar to subthreshold TMS, because it can be present when the imperative signal is accompanied by an additional stimulus in various sensory modalities. In case of TMS, it provokes auditory and somatosensory effects when the coil discharge the magnetic stimulation and both of them are capable of shortening RT. The second factor, which we regarded as the motor-specific effect of TMS, is the unique capacity of TMS in shortening simple and go/no-go RTs. The specific effect of TMS most likely appeared after the completion of stimulus evaluation but before the initiation of the required motor response. This assumption was drawn from the prolonged go/no-go RT data, in which the specific effect of TMS was delayed and dissociated from the motor non-specific IF.

Further support was obtained from the response-locked analysis of RT, which revealed that TMS is effective in shortening RT when delivered approximately 120 ms before movement onset, independently of task complexity. Moreover, our cortical potential finding revealed that the movement-related potential (MRP) commenced approximately 85 ms before movement onset regardless of simple or go/no-go RT task. Incorporating this result with the fact that TMS is effective around 120 ms before movement onset, we presumed that the specific effect of TMS is maximal around 30-40 ms before the activation of the primary motor cortex.

This investigation was performed to further study the roles of TMS over the cortical motor circuitry. The main aims were (1) to verify whether, as in simple and go/no-go RT tasks, TMS in a choice RT task sustains the two-factor hypothesis, and (2) to execute a second experiment recording cortical potentials close to the movement onset and then integrate the results with the TMS study.

MATERIALS AND METHODS

Experiment 1

Seven right-handed participants (5 men, 2 women), aged 22-52 (mean 35.8 years), including 2 of the authors, engaged in this experiment. All of them had no evidence of neurological disease and gave their written informed consent after aims and procedure of the study had been explained.

Participants sat comfortably in a darkened and electrically shielded room and performed the choice RT task with quick abduction of the right or left thumb. During the recording time participants were requested to make no other movements. In each trial a visual imperative signal with a 100-ms duration was preceded by an auditory 1000-Hz warning signal with a 200-ms duration at variable intervals of 1.8, 2.0 and 2.2 s. The imperative signal was presented in a square matrix (35 X 50 mm) of small light emitting diodes (LEDs), 1 m in front of the participants and placed slightly below eye level.

Participants engaged in a training session, and when they were sufficiently familiarized with the procedure, the recording session started. In order to keep participants vigilant and to encourage them to minimize the variability in RT, oral feedback was given constantly. Each participant received the recording session up to 10 blocks without errors and could recess between blocks. Each block consisted of 10 trials with 4 different experimental conditions: 20% of which were control trials for the right-hand response (right go-signal only), 30% test trials with TMS for the right hand response (right go-signal + TMS), 20% left control trials (left go-signal only) and 30% left test trial (left go-signal + TMS). These different trials were presented in random orders. The green or red LED could be either signal for the right-thumb or left-thumb abduction.

Single TMS was delivered using a Maglite TM-Dantec with an 8-shaped coil, which allows focal stimulation. The TMS threshold was referred as the minimum intensity that elicited at least 3 reproducible motor evoked potentials in 6 consecutive stimuli at rest. In this experimental protocol TMS output was fixed at 90% of the resting threshold. An optimal site of TMS was determined to elicit a maximal response in the abductor pollicis brevis (ABP) and the coil was fixed on the head by a band. The intensity and site was maintained steady during the session, although the timing of TMS delivery varied randomly in 7 delays of 0, 60, 90, 120, 150, 180 and 210 ms after the imperative signal. TMS over the left and right hand motor areas was performed in separate sessions.

The electromyogram (EMG) was recorded by two pairs of silver/silver-chloride electrodes positioned on the right and left ABP muscles. After amplification at a bandpass of 5-3000 Hz, the EMG signal was digitized with a rate of 1 kHz and stored on a magneto-optical disk along with stimulus codes. The RT for each trial was measured as the elapsed time from the imperative signal to the EMG onset. Based on median RTs that were calculated separately for each TMS delay and for the right and left stimulation in each participant, the TMS effect on RT was estimated as the RT difference between control and test trials. A signed rank sum (T) test was performed to analyze the statistical significance.

Experiment 2

The MRP data was obtained from the same participants in Experiment 1. The electroencephalogram (EEG) was recorded after scrubbing carefully the scalp and attaching the silver/silver-chloride electrodes to the scalp with a conductive paste. Recording sites were Fz, Cz and Pz, related to the International 10:20 system. Additional electrodes were placed over the left (LHM) and right (RHM) hand motor areas. All electrodes were referenced to linked earlobes. The horizontal and vertical electrooculograms (EOG) were monitored through electrodes placed at the outer canthi and a pair of electrodes placed above and below the left eye, respectively. Participants were asked to relax and to refrain from eye movements and blinking as far as possible. The EEG and EOG signals were amplified with a bandpass filter of 0.05-30 Hz, and stored together with the trigger signal in a digital format at a rate of 200 Hz. The MRP for each responding hand in each participant was obtained by averaging EEGs time-locked to EMG onsets. The averaging epoch began 3.0 s before EMG onset and lasted for 4.0 s. Epochs containing ocular or amplifier saturating artifacts were excluded from the average. The waveforms obtained were referred to the baseline, which was taken as the mean voltage between 2.5 and 3.0 s before EMG onset. The EMG was recorded from the right and left ABP muscles as in the Experiment 1.

The remaining procedures employed in this second experiment were identical to the first, except no TMS discharge.

RESULTS

Experiment 1

Reaction time in control trials

The mean (±SD) RTs across the seven participants in the control trials were 238 (± 28) ms for the right hand and 244 (± 34) ms for the left hand. There was no significant RT difference between the right hand and left hand conditions.

Right hand RT

Table I indicates the effect of contralateral and ipsilateral subthreshold TMS on RT as a function of TMS delays. The data at a delay of 210 ms was excluded from the analysis, because of frequent observations of trials in which TMS was delivered after EMG onset. In the contralateral stimulation, the EMG response for the imperative signal was detected earlier in test

Table I. TMS effects on RTs (ms) obtained by subtracting test trials from control trials in the stimulus-locked analysis.

Response	TMS	TMS delays (ms)					
		0	60	90	120	150	180
Right hand							
	Contralateral	-22 **	-11*	7	-13	-20**	-1
	Ipsilateral	-19	-29**	-13	-10	-5	-12
Left hand							
	Contralateral	-6	3	-18	13	-22**	1
	Ipsilateral	-15 *	-18*	-2	18	-15*	-10

**p<0.05, one tailed. *0.05<p<0.10, one tailed.
Subthreshold TMS was randomly delivered at different delays to the imperative signal. TMS effect was estimated to as the RT difference between control and test trials.

trials than control trials at delays of 0 and 150 ms ($T = 0.5$, $p = 0.016$ and $T = 1$, $p = 0.016$, respectively). In the ipsilateral stimulation, substantial shortenings of RT were observed at delays of 0 and 60 ms ($T = 5.5$, $p = 0.078$; $T = 0$, $p = 0.016$, respectively).

In order to test the TMS effect referred to the movement onset, RTs were reviewed in 30-ms bins backwards from RTs on control trials. That is to say, TMS timing of the 7 TMS delay conditions was adjusted at time bins in reference to the control RT separately for each of 7 participants. Table II indicates the response (EMG)-locked effect of contralateral and ipsilateral TMS. In contralateral stimulation, a maximal shortening was observed at 120-ms bin (or 105-135 ms) before EMG onset ($T = 2$, $p = 0.023$). For ipsilateral stimulation, the test RT was significantly shorter than the control RT at 150-ms bin before EMG onset ($T = 3$, $p = 0.039$).

Table II. TMS effects on RTs (ms) obtained by subtracting test trials from control trials in the response-locked analysis .

Response	TMS	30-ms bins before EMG onset (ms)				
		180	150	120	90	60
Right hand						
	Contralateral	-6	9	-29**	-7	-3
	Ipsilateral	-21*	-17**	-19*	6	-17
Left hand						
	Contralateral	-4	-10	-2	-17*	-2
	Ipsilateral	-13	-3	2	-9	

**$p<0.05$, one tailed. *$0.05<p<0.10$, one tailed.
RTs were reanalysed in 30-ms bins backward from the EMG onset for each participant and then averaged across participants. The bins of 0 and 30 ms were excluded because there were less than 5 data filling this time window, in contralateral and ipsilateral stimulation. For the same reason, bin of 60-ms was not accounted in ipsilateral TMS.

Left hand RT

In the stimulus-locked analysis (Table I), a significant shortening was found at a delay of 150 ms ($T = 2$, $p = 0.023$) for contralateral stimulation, whereas ipsilateral TMS tended to shorten RTs at delays of 0 ($T = 3.5$, $p < 0.055$), 60 and 150 ms ($T = 4$, $p = 0.055$, for the last two comparisons). In the response-locked analysis (Table II), a tendency of shortening was noted at

90-ms bin before EMG onset for contralateral stimulation (T = 6, p = 0.078).

Experiment 2:

The lateralized MRP, which was time-locked to EMG onset, was acquired by subtracting the cortical potential at the RHM from that at the LHM, at the corresponding time points, separately for the right and left hands (Figure 1). Consequently, the lateralized negativity, reflecting the activation of the contralateral motor area to the response hand, is expressed as upward and downward deflections for the right and left hands, respectively. For the right hand, therefore, the onset time of the lateralization was determined as the first point of an upward wave

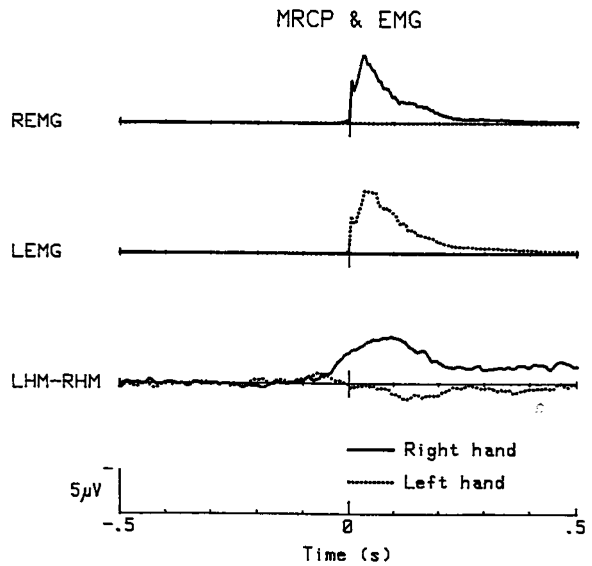

Figure 1: Grand average records (n = 7) of response-locked MRPs for the right (solid line) and left (dotted line) hands. REMG and LEMG indicate rectified averages of the abductor pollicis brevis activities in the right and left thumbs, respectively. The waveforms subtracting the cortical potentials at RHM from the potentials at LHM are shown on the bottom (LHM-RHM). Zero of the time scale points out the trigger point of EMG onset. Voltage calibration of 5μ is applicable for the cortical potentials. Note a commencement of the upward deflection at about 80 ms before EMG onset for the right hand, whereas there is no defined onset of the lateralized potentials for the left hand.

exceeding a value of 1.5 SD, calculated over the period between 300 and 500 ms before EMG onset, and lasting more than a 50 ms consecutive period. For the left hand responding, using the identical criterion, the first downward point in the subtraction wave was searched for the onset time of lateralization. A clear defined lateralized MRP was recorded for the right hand, whereas only a small deflection with fits to the lateralization was obtained for the left hand. Figure 2 illustrates the variation of the lateralized potential among participants. A homogeneous and consistent pattern of waveforms was obtained for the right hand responding. Conversely, the pattern of lateralization varied widely among participants for the left hand.The overall means (± SD) of the onset time across participants was 77.9 (± 47.1) ms for the right hand. The lateralized MRP onset was not possible to determine for the left hand because of the inter-individual variation.

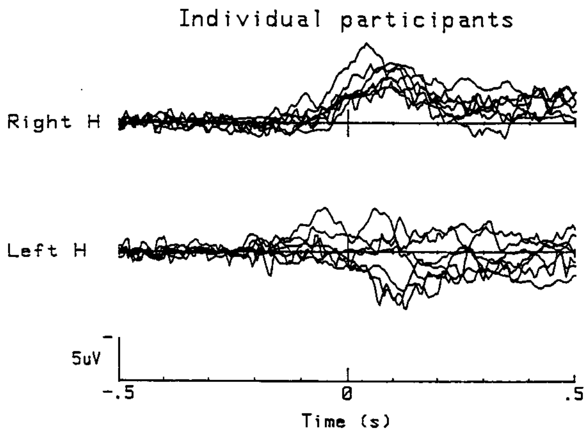

Figure 2: Superimposition of lateralized MRPs from 7 participants for the right and left hands. Note that the lateralized potentials for the right hand are much more homogeneous than the potentials for the left hand.

DISCUSSION

The aim of the present investigation was to consolidate the two-factor hypothesis of the motor specific and non-specific effects of TMS on RT. A different pattern of TMS effects was observed between RTs of the right and left hands.

Right hand RT with contralateral TMS

The results showed an entire agreement with the two-factor hypothesis. In the stimulus-locked analysis, we obtained significant shortenings at delays of 0 and 150 ms. The RT shortening at a delay of 0 ms follows the expected pattern of the motor non-specific IF, whereas the shortening at a delay of 150 ms favors the advent of the motor-specific TMS effect. Figure 3 joins up our previous results of simple and go/no-go RTs [11] and the present result for the right-hand RT with contralateral TMS. In control trials, the task complexity gradually prolonged RTs, whose means (± SD) RT were 172 (± 29), 213 (± 29) and 238 (± 28) ms for simple, go/no-go and choice RT tasks, respectively. It is evident that the IF effect occurred when TMS is almost concurrently delivered with the imperative signal (delay = 0), in spite of task complexity. In contrast, the motor specific effect of TMS delayed gradually with the enhancement of task complexity. The two motor specific and non-specific factors appear to overlap due to the short RT in the simple RT task, whereas in the go/no-go and choice RT tasks, the two factors can be dissociated from each other. The motor specific TMS effect on go/no-go and choice RTs is shown at delays of 90 and 150 ms, respectively. The response dependency of the specific TMS effect is verified by the response-locked analysis, which represents the maximal shortening at 120-ms bin (or 105-145 ms) before EMG onset, irrespective of task complexity (see Figure 4). Moreover, a clearly lateralized MRP was recorded for the right hand. It revealed a plain negative-going potential in the contralateral hand motor area and it was consistent through the individual recordings. As noted in our previous investigation, [11] the time-course of the development is correspondent with the curve of the motor cortex activity. [9] According to the literature, [2,5] the lateralized MRP is closely associated with the activation of the primary motor cortex at the very

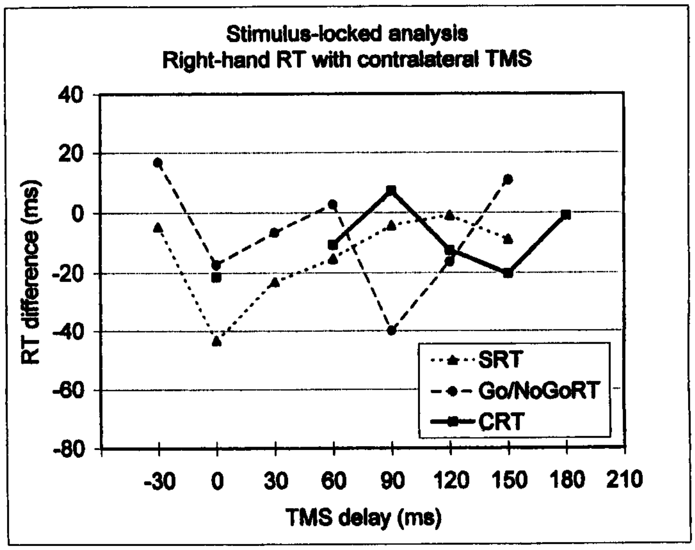

Figure 3: Comparison of the subthreshold TMS effects on simple (triangle, dotted line), go/no-go (circle, dashed line) and choice (square, thick solid line) RTs for the right hand. Simple and go/no-go RT data were imported from our previous study. [11] Note the enhancement of RT shortening at a delay of 90 ms for go/no-go RT and at a delay of 150 ms for choice RT, in addition to the RT shortening common to all of the tasks. The second period of shortening fits with the time expected for the motor specific effect of TMS, which was found overlapped with intersensory facilitation in simple RT.

moment of motor command. The lateralized MRP is also used as an index of the response activation system. [2,5] In our study, the onset of lateralized MRP was obtained around 80 ms before EMG onset. The above-mentioned findings of the specific TMS effect and the lateralized MRP onset confirm that TMS is effective when delivered around 30-40 ms before the activation of the primary motor cortex. It comes to give the consistency to the hypothesis that subthreshold TMS is capable of shortening RT by influencing the transferring process on the cortical motor circuitry without acting on the stimulus evaluation system. [9]

Right-hand RT with ipsilateral TMS

The results are consistent with the two-factor hypothesis. A motor non-specific effect of TMS was observed at a delay of 60 ms, and there was no motor specific RT shortening in the stimulus-locked analysis as well as in the response-locked analysis. The only questionable finding was concerned with the sustained TMS effect, which is typically observed as RT shortenings of 17-21 ms over bins of 120-150 ms before EMG onset. Here, it is possible to conjecture that the stimulus-response compatibility occurred. Kornblum et al. [7] studied extensively the concept that participant tend to respond automatically with the hand that corresponds to the side of stimulus presentation. In other words, we presume that the right ipsilateral TMS stimulation facilitated the right hand.

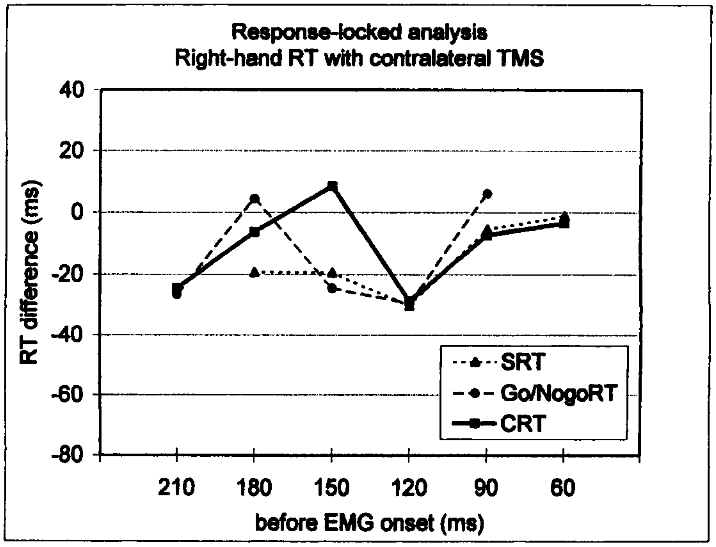

Figure 4: Comparison of the subthreshold TMS effects in 30-ms bin backward from EMG onset on simple (triangle, dotted line), go/no-go (circle, dashed line) and choice (square, thick solid line) RTs. Simple and go/no-go data were imported from our previous study. [11] Note that the maximal RT shortening converges at a bin of 120 ms before EMG onset irrespective of task complexity.

Left hand RT

The results regarding the left hand showed some peculiarities. First, ipsilateral as well as contralateral TMS induced the substantial RT shortening at a delay of 150 ms. Second, no significant TMS effect was observed at 120-ms bin prior EMG onset, although contralateral TMS tended to shorten RTs at a bin of 90 ms. And, third, the onset of lateralized MRP was unsettled and unsteady for the left hand, reflecting the wide variation encountered among participants. These observations might be due to the hemispheric asymmetries and human handedness, which have been matters of debate, but still remain as an open question in the literature. Okuda et al [8] showed that some clinical cases of patients with left hemisphere injury presented right and left clumsiness, whereas patients with right hemisphere injury presented disturbance only in the contralateral left hand. Using a nuclear magnetic resonance imaging, Kim et al. [6] demonstrated that the left hemisphere was activated for ipsilateral as well as contralateral movements. Chen et al. [1] observed through repetitive TMS that ipsilateral primary motor cortex is related to the hand movements, although the left hemisphere showed a higher participation than the right hemisphere. Further evidence indicates that right-handed persons presented larger cerebral potentials over the dominant hemisphere regardless of contralateral or ipsilateral responding hand. [3] Moreover, a lower TMS threshold was reported for the writing hand than the non-writing hand, inferring that the dominant hand has a larger motor cortical representation. [13] In our case, the motor specific effect of TMS was obtained at a delay of 150 ms in the stimulus-locked analysis, but it could not be ratified in the response-locked analysis. Furthermore, examining the inconsistent pattern of our individual cortical potentials, it is possible to infer that the primary motor cortex was activated in quite different manners depending of the given participant. Thus the present investigation could not be conclusive for the left hand investigation. It is necessary to gain more neurophysiological bases about the hemisphere asymmetries and conduct further studies in order to clarify the functional interpretation of human handedness.

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