Very low-frequency rTMS modulates SEPs over the contralateral hemisphere

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Abstract: In order to investigate the transcallosal effects of repetitive transcranial magnetic stimulation (rTMS), we studied median somatosensory evoked potentials (SEPs) before and after applying monophasic very low-frequency (0.2 Hz) subthreshold rTMS over the right motor cortex. For SEPs, median nerve was stimulated on each side. Sham rTMS served as the control. Twelve healthy subjects participated in this study. After rTMS over the right hemisphere, the amplitude of N34 component in right median SEPs recorded from the left parietal scalp (C3') increased significantly. Other components of right or left median SEPs or those after sham stimulation showed no changes. Monophasic 0.2 Hz subthreshold rTMS over the motor cortex predominantly affected the contralateral SEPs, probably through the transcallosal pathway. J. Med. Invest. 57: 109-113, February, 2010

Keywords: somatosensory evoked potential, repetitive transcranial magnetic stimulation, primary motor cortex, contralateral sensory cortex

1. INTRODUCTION

Repetitive transcranial magnetic stimulation (rTMS) over the motor cortex modifies cortical excitability that outlasts the period of stimulation (1-5). The effect of rTMS has been explored by examining the changes of motor evoked potentials (MEPs), which reflect activities of the corticospinal tract. However, only a few studies of somatosensory evoked potentials (SEPs) have been reported on the effects caused by rTMS. The right median SEP components N20-P25 and P25-N33 generated in the left hemisphere significantly decreased in amplitude after low-frequency rTMS (1 Hz, biphasic, 200 times) applied over the ipsilateral left motor cortex (6). Their study suggested sensory inhibition occurred by direct cortico-cortical connection between motor and sensory areas because the N20 component reflects an activation of the sensory cortex by thalamocortical fibers. However, our previous study (7) found no changes of these SEP components after very low-frequency rTMS (0.2 Hz, monophasic, 250 times) over the left motor cortex. The discrepancy between these studies may be due to the different stimulation parameters; frequency (1 Hz vs. 0.2 Hz) or phase (biphasic vs. monophasic) of rTMS.

Seyal et al. reported significant reduction at base-to-peak amplitude of N20 and peak-to-peak amplitude of N20-P25 after very low-frequency rTMS (0.3 Hz, monophasic, 20 min.) applied over the contralateral hemisphere, but they did not examine ipsilateral effects (8). The present study aimed at examining not only ipsilateral but also contralateral SEP changes after very low-frequency monophasic rTMS.
given over the right motor cortex. In search for
stimulus parameters suitable for this use, we used
monophasic very low-frequency (0.2 Hz) rTMS,
which was efficacious in treating writer’s cramp (9).

2. MATERIALS AND METHODS

2.1. Subjects
Twelve healthy right-handed male volunteers
(33.0 ± 9.5 years) participated in this study. All sub-
jects were free from neurological and psychiatric
diseases. They gave their informed consent for the
study, which was approved by the Ethics Commit-
tee of the University of Tokushima. Handedness was
established by a detailed questionnaire, the Edin-
burgh Handedness Inventory (10).

2.2. Experimental design
In an electrically and auditory shielded room, the
subjects relaxed on a reclining chair with their feet
on the foot-rest and were instructed to keep eyes
open. SEPs were recorded before and after applica-
tion of monophasic 0.2 Hz rTMS or sham stimula-
tion over the left cortex hand motor area. Two ses-
sions (rTMS; real vs. sham) were performed on
each separate day in a counterbalanced order at 1
week or longer intervals for each session.

2.3. rTMS
In monophasic rTMS, we used the figure-of-eight
stimulation coil (outside diameter of one half-coil,
8.7 cm; Magstim Coll Ltd., OHR Wales, UK) con-
nected to Magstim 200 Stimulator (2.2 T at the coil
surface). Magnetic stimuli of 250 times were deliv-
ered at 0.2 Hz to the right motor cortex, 2 cm ante-
rior and 3.5 cm lateral to Cz (International 10-20
System). We determined the optimal position for ac-
tivation of the left first dorsal interosseous muscle
by moving the coil in 0.5 cm steps around the pre-
sumed motor area. Motor response was recorded
using electromyography. Threshold was defined as
minimum stimulation level necessary to evoke mo-
tor response of > 50 μV peak-to-peak amplitude in
five out of ten trials. The coil was positioned tan-
gentially to the curvature of the head and handle
of the coil formed a 45° angle with subject’s body
midline. Stimulation intensity was 85% of the rest-
ing motor threshold for the motor cortex.

Sham stimulation was performed by the same
procedure as that of rTMS using a figure-of-eight
sham coil (a placebo system; Magstim Co. Ltd.,
OHR Wales, UK; the same shape as that of a true
coil) connected to Magstim 200 Stimulator (0.44
tesla at coil surface).

These parameters of rTMS were in accordance
with the international safety guidelines (11).

2.4. SEPs
SEPs were obtained by electric median nerve
stimulation at right or left wrist respectively in each
session. Each recording took for about 10 minutes.
Sides of stimulation were randomly assigned. Elec-
tric stimuli (0.2 ms duration) were delivered at 1
Hz through surface electrodes. Positive electrodes
were placed on distal and negative ones were on
proximal side of wrist. Intensity was adjusted just
above the motor threshold of abductor polices mus-
cle. SEPs were recorded with silver chloride disk
surface electrodes at F3, F4, 2 cm posterior to C3
(C3′) and 2 cm posterior to C4 (C4′), according to
the International 10-20 system. The linked earlobe
electrodes served as reference. The impedance of
these electrodes were kept below 5 kΩ. The electro-
oculogram (EOG) was also recorded with a pair
of silver chloride disk electrodes at 2 cm above the
left outer canthus and 2 cm below the right outer
canthus. Signals from scalp electrodes and EOG
were amplified and acquired at a sampling rate of
10 kHz and filtered at 1-5000 Hz and 0.5-1000 Hz
respectively (MEB2200 amplifier; Nihon Kohden,
Tokyo, Japan). All signals were recorded for 100
ms after the onset of median nerve stimulation and
stored on a personal computer for off-line analysis.
We collected at least 200 artifact-free sweeps and
then averaged them on off-line.

2.5. Data analysis
Components with clear peak were all analyzed.
Among SEP components from right median nerve
stimulation, P14, P22, N30 and N60 were deter-
mined at F3; P14, N20, P26, N34 and P45 at C3′;
P14, P22 and N30 at F4; P14 was at C4′. Among
left median SEP components, P14, P22, N30 and
N60 were determined at F4; P14, N20, P26, N34,
and P45 at C4′; P14, P22 and N30 at F3; P14 was at
C3′. We measured the baseline-to-peak ampli-
tudes of these components. The baseline was de-
fin ed as the segment between 2 and 6 ms after ele-
ctrical stimulation.

We analyzed the amplitudes of all SEP compo-
nents by two-way repeated measures analysis of
variance (ANOVA) with conditions (real vs. sham
rTMS stimulation) and time course (before vs.
after stimulation). When statistical significance was reached, we used two tail paired t-test to analyze the amplitude change after rTMS compared with that of before.

All data were analyzed with SPSS version 11.01 J for Windows (SPSS Japan Institute Inc., Tokyo). Significant level of all analysis were defined p < 0.05.

3. RESULTS

Figure 1 shows the grand-averaged waveforms obtained from twelve subjects. Table 1 shows the peak amplitudes of each component before and after application of rTMS and sham stimulation. In rTMS condition, only N34 amplitude at C3’ of right median SEP’s reached a significance level by repeated measures ANOVA (F=4.585, p=0.044). Post hoc analysis disclosed N34 amplitude after rTMS increased significantly (t=-3.332, p=0.007) (Fig. 2). Figure 3 shows the amplitude change after rTMS compared with that of before stimulation. When statistical significance was reached, we used two tail paired t-test to analyze the amplitude change after rTMS compared with that of before.

Table 1  Peak amplitudes of each SEP component before and after the application of rTMS and sham stimulation

<table>
<thead>
<tr>
<th>Component</th>
<th>F3</th>
<th>P14</th>
<th>P22</th>
<th>N30</th>
<th>N60</th>
<th>F4</th>
<th>P14</th>
<th>P22</th>
<th>N30</th>
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</thead>
<tbody>
<tr>
<td>Before</td>
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<td>before</td>
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<td>before</td>
<td>after</td>
<td>before</td>
<td>after</td>
<td>after</td>
</tr>
<tr>
<td>rTMS</td>
<td>1.34 ± 0.39</td>
<td>1.30 ± 0.33</td>
<td>1.13 ± 0.69</td>
<td>1.01 ± 0.92</td>
<td>2.44 ± 1.53</td>
<td>2.52 ± 1.41</td>
<td>2.28 ± 1.02</td>
<td>2.27 ± 1.51</td>
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<tr>
<td>Sham</td>
<td>1.40 ± 0.34</td>
<td>1.33 ± 0.29</td>
<td>1.02 ± 0.92</td>
<td>1.11 ± 0.36</td>
<td>2.22 ± 1.29</td>
<td>2.43 ± 1.70</td>
<td>2.51 ± 1.37</td>
<td>2.12 ± 1.51</td>
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<tr>
<td>Lt median nerve stimulation</td>
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<td>Before</td>
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<td>after</td>
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<tr>
<td>rTMS</td>
<td>1.36 ± 0.24</td>
<td>1.30 ± 0.36</td>
<td>0.30 ± 0.59</td>
<td>0.56 ± 0.42</td>
<td>2.52 ± 0.97</td>
<td>2.30 ± 1.18</td>
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<tr>
<td>Sham</td>
<td>1.43 ± 0.31</td>
<td>1.30 ± 0.38</td>
<td>0.49 ± 0.58</td>
<td>0.41 ± 0.51</td>
<td>2.21 ± 0.76</td>
<td>2.38 ± 0.90</td>
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<tr>
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</tr>
<tr>
<td>rTMS</td>
<td>1.29 ± 0.12</td>
<td>1.20 ± 0.23</td>
<td>1.29 ± 0.34</td>
<td>2.58 ± 1.30</td>
<td>2.52 ± 1.55</td>
<td>2.44 ± 2.30</td>
<td>2.99 ± 3.04</td>
<td>0.66 ± 0.65</td>
<td>0.49 ± 0.79</td>
</tr>
<tr>
<td>Sham</td>
<td>1.06 ± 0.19</td>
<td>1.26 ± 0.30</td>
<td>1.45 ± 0.34</td>
<td>1.45 ± 0.33</td>
<td>2.48 ± 1.30</td>
<td>2.35 ± 1.19</td>
<td>3.08 ± 2.93</td>
<td>3.21 ± 2.95</td>
<td>0.37 ± 1.00</td>
</tr>
</tbody>
</table>

Values are expressed mean ± SD. Bold figures show the significantly increased value after than before rTMS by paired t-test (p<0.05).
component of SEPs by right and left median nerve stimulation before and after rTMS in each subject. Right median nerve stimulation disclosed significant change of N34 amplitude though left median nerve stimulation showed no significant change. Any components of left median SEPs did not change, or sham stimulation showed no changes of SEPs in each stimulation side.

4. DISCUSSION

Our results showed that monophasic very low-frequency (0.2 Hz) rTMS over the right motor cortex increased the amplitude of N34 component recorded from the left scalp (C3') after right median nerve stimulation. In previous studies, rTMS over the primary motor cortex modified the excitability of the contralateral primary motor cortex (12, 13). This study for the first time showed the rTMS predominantly affects the contralateral SEP component, while leaving the ipsilateral ones unaffected.

Bilateral motor cortices are basically considered to transfer inhibitory effect upon each other (transcallosal inhibition) (14-16). In our study, rTMS applied over the right motor cortex might exert an influence on the contralateral left motor cortex through the mechanism of inter-hemispheric inhibition, which may secondarily affect the contralateral sensory cortex.

Because no significant change was found in P14 or N20 component, we considered that the change of N34 component occurred, not at the sensory pathway up to the primary sensory cortex, but through the interactions between sensory-motor cortices of both hemispheres. It was argued that the increased amplitude of an SEP component reflects inhibition rather than facilitation (7).

Seyal et al. already reported this contralateral effect on N20-P25, but did not investigate the effect of the ipsilateral sensory cortex. Our study is the first to show this contralateral SEP effects with no ipsilateral changes. Although the stimulation condition of rTMS used by Seyal et al. was a monophasic pulse of 0.3 Hz just as we used, their stimulation intensity was 10% above the intensity of visual muscle contraction, being much stronger than ours (85% of resting motor threshold). The difference of intensity may mainly the reason of different influence on contralateral sensory cortex. We suspect the decreased amplitude by strong rTMS stimulation may relate with a kind of gating through contralateral motor cortex. On the other hand increased amplitude by weak rTMS stimulation in our result may originate mainly from contralateral sensory cortex probably through opposite mechanism of gating.

Left median nerve stimulation did not disclose any significant change of SEP components. The previous studies reported significant decrease of both N20a-P25 amplitude and P25-N33 amplitude (6) or no significant change (7). This difference may be due to the stimulation condition of rTMS. Urushihara’s and our study used 0.2 Hz monophasic pulse whereas Enomoto’s 1 Hz biphasic pulse. Recent study reported that phase was more important than frequency to induce SEP change (17).
right rather than left median nerve stimulation and the finite change of N34 component on the left hemisphere was sensitively detected through right median nerve stimulation. It supports our result that sensory modification predominantly occurs on the contralateral side of rTMS.

In conclusion, monophasic very low-frequency rTMS over the motor cortex significantly increased the amplitude of N34 component generated on the contralateral hemisphere. Our results suggests that rTMS parameters used in this study could modify the cortical sensory processing predominantly on the contralateral hemisphere, possibly through the transcallosal pathways.

REFERENCE