Facilitating visuospatial attention for the contralateral hemifield by repetitive TMS on the posterior parietal cortex

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Abstract

Previous studies have demonstrated that repetitive transcranial magnetic stimulation (rTMS) could modulate the visuospatial functions. In this study, we investigated the effect of off-line high frequency subthreshold rTMS, when applied over the right or left posterior parietal cortex (PPC), on the visuospatial attention of the bilateral hemispaces. The subjects underwent visuospatial tasks before and immediately after receiving 1000 pulses of 10 Hz rTMS for a period of 20 min, and their responses were recorded. Our results demonstrated that the high frequency rTMS applied over the PPC produced facilitative effects on the visuospatial attention to the contralateral hemispace. The inhibitory effect to the ipsilateral hemispace was noticeable only in the left PPC.

Keywords: Repetitive transcranial magnetic stimulation; Visuospatial attention; Posterior parietal cortex

Hemi-spatial neglect refers to the failure to attend to one side of one’s own space. The significance of this neglect as a major source of long-term disability after such brain disease as stroke justifies further research efforts for developing an appropriate therapeutic intervention for this complex and multi-factorial syndrome. Previous studies have demonstrated that repetitive transcranial magnetic stimulation (rTMS) could modulate the visuospatial functions; however, the methods of application and the effects seen in these studies were diverse. Synchronous application of high frequency (25 Hz) rTMS applied over the right posterior parietal cortex (PPC) has been reported to induce a perceptual bias on the contralateral hemifield and it produced a transitory contralateral neglect in healthy subjects [6,7,14]. For patients suffering from hemispatial neglect as a consequence of brain damage, the high frequency or 1 Hz rTMS ameliorated contralateral visuospatial neglect when they were applied to the unaffected parietal cortex [4,10,13]. These findings were interpreted in the light of the right hemispheric dominance in the visuospatial attention model and the interhemispheric competition model [12,13]. The methods and parameters of applying...
rTMS need to be considered in order to obtain the desired effect. High frequency rTMS (5–25 Hz) has been shown to increase cortical excitability transiently beyond the period of train of stimulation [16]. Therefore, it can be postulated that the high frequency rTMS can modulate visuospatial attention, which is influenced by the increased excitability of the focal cortical area if it is applied in an appropriate manner. To the best of our knowledge, there has been no report on the effect of off-line high frequency rTMS on the visuospatial functions. In this study, we aimed to assess the effect of high frequency rTMS delivered over the right or left PPC on the visuospatial perception of the contralateral and ipsilateral hemispace by using the computerized line bisection task in normal healthy subjects.

Twenty healthy right-handed subjects (5 males and 15 females; the mean age was 22.9 years) having normal or corrected-to-normal vision participated in our study. We obtained an informed consent from all the subjects for their participation in the experiment, and the study was approved by the Institutional Research Board at Samsung Medical Center. The exclusion criteria used for the selection of subjects conformed to the current guidelines for rTMS research [18]. The subjects were informed that they could end the experiment at any moment if they found the stimulation to be uncomfortable.

The line bisection task was designed as follows: all the stimuli were presented on a 15-in. monitor driven by a Pentium-3 PC programmed with SuperLabPro 2.0 software. The stimulus consisted of a black, horizontal transected or bisected line on a white background. The horizontal lines were of five different lengths ranging from 36° to 40°. A short vertical line (2.2° long) transected the horizontal lines. All the lines were 0.1° thick. When the line was asymmetrical about the transaction, the elongated line segment was 1° longer than the shorter line segment. The stimuli were always presented with the transection mark in front of the subjects’ head and body midline.

A central fixation cross appeared for 1000 ms, and this was followed by the appearance of the stimulus for 180 ms (to limit the scanning eye movement); this was immediately followed by the mask for 1000 ms. The mask consisted of a thick horizontal line that was thicker than the horizontal line of the stimulus, and also a vertical line that had the same width as the transection mark. The mask was symmetrical around the head midline, and it covered the entire area of the previously displayed stimulus and extended to the edges of the screen (Fig. 1A).

The subjects were comfortably seated 47 cm away from the screen. All the subjects used their right index and middle fingers to make their responses to the stimulus by using a mouse. In half of the task blocks, the subject was asked to press the left or right mouse button according to whether the left or right side of the line appeared longer. In the remaining half of the task blocks, the subject pressed the mouse button that corresponded to the shorter side of the line. The subjects were asked to respond as quickly as they could, but they were instructed not to sacrifice their response accuracy for the sake of speed.

An experimental session consisted of four blocks of a task and each block contained 40 trials including 10 bisected lines, 15 left-elongated lines and 15 right-elongated lines. The stimuli were presented in a random order within each block and the four blocks were counter-balanced. The subjects performed a session having a total of 160 trials (four blocks) over a period of 7 min as a baseline assessment, and then 1000 trains of 10 Hz rTMS were applied for a period of 20 min as is described below. Immediately after the rTMS, the subjects again performed a session of 160 trials. The experiment session for one subject lasted a total of 44 min.

The resting motor threshold (RMT) was determined on the left first dorsal interosseus muscle using a Medelec Synergy system (Medelec, UK). TMS was performed using a 70 mm figure-of-eight coil by moving the coil in 1 cm steps around the presumed hand motor area of the right hemisphere to determine the optimal position for activation. The RMT intensity was approached from the supra-threshold levels by reducing the stimulus intensity initially in 5% steps, and then in 1% steps. The RMT was defined as the first stimulus intensity that failed to produce a MEP in three of six subsequent trials.

The rTMS stimulation site was individually defined for each subject within the 10–20 electroencephalogram (EEG) coordinate system, and it corresponded to the position P4 that
was localized over the right posterior parietal cortex (PPC) and to the position P3 that was localized over the left PPC. Magnetic resonance images were taken on two subjects before the experiment, and the anatomical site of stimulation was confirmed as pointing to the posterior parietal lobe by using optical tracking via a miniBIRD\textsuperscript{®} tracker (NexGen Ergonomics Inc., USA) (Fig. 1B).

rTMS was delivered on the scalp in accordance with the generally established safety recommendations by using a Magstim Rapid\textsuperscript{®} stimulator with two Booster Modules (Magstim Co. Ltd, UK). The 70 mm figure-of-eight coil was held tangentially to the skull with the handle pointing about 45° posteroilaterally in order to stimulate the parietal cortex. Fifty pulses of 10 Hz rTMS were applied over a period of 5 s with an RMT of 80% and an intertrain interval of 55 s. A total of 1000 pulses of stimulation were given during 20 min. Sham stimulation was performed using the one-wing sham method at an angle of 90° from the tangential plane to the scalp at the Pz area. Fifteen out of 20 subjects participated in the experiment two times and five subjects participated three times with an interval of 1 week between each experimental period, and the P3, P4 or sham stimulations were administered in a pseudorandomized order. For each of the stimulation conditions, data was obtained from 15 persons. The rates of correct or incorrect responses to the left- or right-elongated lines were obtained and these were used to define the accuracy and error rate for the transected lines. The correct response for the left (or right)-elongated line included the responses of both ‘left (or right)-longer’ and ‘right (or left)-shorter’. The response rates of the left- or right-longer were obtained for the bisected line as well. Response bias was calculated following the methods previously described [5]. Three-way repeated measures ANOVA was conducted using the side of the response (left and right) and the sessions (baseline and post-rTMS) as the within subject factors, and the type of stimulation (P3, P4 and sham) as the between subject factor. Differences were regarded as significant when the P values were less than 0.05.

When comparing the performances of the baseline sessions, there was no significant difference between the three rTMS conditions, the P3, P4, and the sham stimulation, in the rates of accuracy or the error responses for the transected lines, and also for the response rates for the bisected lines. Overall, the subjects responded more accurately for the left-elongated lines than the right-elongated lines \((P = 0.002)\) during the baseline session. The response rate for the ‘left-longer’ was significant higher than for the ‘right-longer’ response to bisected lines \((P < 0.001)\). These phenomena were consistent with the findings on so-called “pseudo-neglect” that have been demonstrated in normal persons [2,3].

After the application of rTMS over the left posterior parietal region (P3), the accuracy for detection of the right-elongated lines was increased \((P = 0.013)\) and the error rate was decreased \((P = 0.050)\). However, the error rate for the left-elongated lines was increased \((P = 0.046)\). For the bisected lines, the number of choices of the ‘left-longer’ decreased \((P = 0.019)\) and the number of choices of the ‘right-longer’ increased \((P = 0.030)\) after rTMS application (Table 1 and Fig. 2).

After the application of rTMS over the right posterior parietal region (P4), the accuracy for the left-elongated lines increased \((P = 0.005)\) and the error rate decreased \((P = 0.013)\) as compared with the baseline session. The accuracy and error rate for the right-elongated lines showed no significant changes. For the bisected line, the subjects’ number of choices of the ‘left-longer’ increased \((P = 0.028)\) and subjects’ number of choices of the ‘right-longer’ decreased \((P = 0.045)\) after rTMS application (Table 1 and Fig. 2).

There were no significant changes in the accuracy and the error rate for the transected lines, or in the response rate for the bisected lines after sham stimulation.

The three-way repeated measures ANOVA revealed the main effect of the side (left-longer and right-longer) on the accuracy \([F(1, 42) = 11.789, P = 0.001]\) and the error rate \([F(1, 42) = 11.714, P = 0.001]\) of the transected lines, and main effect of the side (left-longer and right-longer) on the response rate of the bisected line \([F(1, 42) = 17.697, P = 0.000]\). In addition, there was an interaction between the type of stimulation (P3, P4 and sham), the session (baseline and post-rTMS), and the side on the accuracy \([F(2, 42) = 8.026, P = 0.001]\) and the error rate \([F(2, 42) = 6.862, P = 0.003]\) of the transected lines and on the response rate of the bisected lines \([F(2, \text{...})\).

Table 1

<table>
<thead>
<tr>
<th>rTMS</th>
<th>Session</th>
<th>Accuracy (%)</th>
<th>Error rate (%)</th>
<th>Response of bisected line (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Left-elongated</td>
<td>Right-elongated</td>
<td>Left-elongated</td>
</tr>
<tr>
<td>Lt. parietal</td>
<td>Baseline</td>
<td>71.78 ± 16.04</td>
<td>58.89 ± 24.06</td>
<td>22.22 ± 10.83</td>
</tr>
<tr>
<td>Post-rTMS</td>
<td>69.56 ± 16.58</td>
<td>66.67 ± 26.88</td>
<td>26.11 ± 12.95</td>
<td>26.67 ± 17.07</td>
</tr>
<tr>
<td>Rt. parietal</td>
<td>Baseline</td>
<td>72.78 ± 16.14</td>
<td>65.33 ± 18.68</td>
<td>23.89 ± 13.33</td>
</tr>
<tr>
<td>Post-rTMS</td>
<td>80.11 ± 11.71</td>
<td>64.67 ± 16.38</td>
<td>18.11 ± 10.44</td>
<td>33.56 ± 15.69</td>
</tr>
<tr>
<td>Sham</td>
<td>Baseline</td>
<td>72.22 ± 16.14</td>
<td>63.45 ± 12.59</td>
<td>25.22 ± 10.25</td>
</tr>
<tr>
<td>Post-rTMS</td>
<td>70.44 ± 16.79</td>
<td>59.78 ± 22.15</td>
<td>26.44 ± 14.92</td>
<td>37.44 ± 19.39</td>
</tr>
</tbody>
</table>

Values are mean ± S.D.

*p ≤ 0.05; comparison between the baseline and post-rTMS sessions.

**p ≤ 0.01; comparison between the baseline and post-rTMS sessions.
Fig. 2. Effects of rTMS on the subjects’ responses in the three stimulation conditions (left parietal cortex, P3 rTMS; right parietal cortex, P4 rTMS; and sham stimulation). Three-way repeated measures ANOVA revealed that there was a significant interaction between the sides, the sessions and the type of stimulation on the accuracy for correctly detecting the transected lines (A) and on the error rate (B). There was also a significant interaction between the sides, the sessions and the type of stimulation on the response rate for the bisected lines (C).

Our results demonstrated that the high frequency rTMS applied over the right or left PPC produced the hemispatial modulation of the visuospatial attention. The effect on the visuospatial function of the contralateral hemisphere was facilitative for both sides; stimulation of the right PPC increased visuospatial attention to the left hemispace and it also increased the leftward bias in healthy subjects. Stimulation of the left PPC increased the attention to the right hemispace and it reduced the leftward bias. The inhibitory effect to the ipsilateral hemispace was noticeable only for the left PPC. There was no detectable adverse effect of rTMS in all the subjects. We would like to discuss two issues that are in line with previous researches to help interpreting our results: one is the effect of high frequency rTMS on cortical function and the other is the asymmetry of the two hemispheres and their interaction on the visuospatial attention.

In the previous studies, the synchronous application of high frequency rTMS (25 Hz) produced inhibitory effects on the processing of visuospatial stimuli and it also induced contralateral neglect [5–7]. Bjoertomt et al. have reported that stimulation of the right PPC, when delivered 150 ms after a visual stimulus, produced a relative transitory rightward bias in the perceived midpoint of the bisected lines [3]. In contrast, we implemented the visuospatial task after applying high frequency rTMS. This off-line application may have produced a residual facilitative effect on the cortical excitation, and then this resulted in improvement of the visuospatial function for the contralateral hemisphere. The effect of high frequency rTMS for increasing the cortical excitability and the size of the MEP was well demonstrated by previous studies when it was applied on the motor cortex [1,17]. This facilitative
The effect of off-line high frequency rTMS on the visuospatial function, however, has not been described previously. The temporal relationship between the magnetic stimulation and behavioral task seems to be important in predicting the effect of high frequency stimulation.

In our study, the effect of high frequency rTMS to the ipsilateral hemispace was different for the bilateral PPCs. Stimulation of the left PPC increased the error rate of the ipsilateral hemispace, however, stimulation of the right PPC did not produce ipsilateral spatial error. These findings can be interpreted in line with the two best-known neural models of spatial attention: inter-hemispheric inhibition and right hemispheric specialization. Experimental studies and models of spatial attention have investigated the representation of external attentional space across the two cortical hemispheres, and these studies and models have suggested the involvement of reciprocal inter-hemispheric inhibition [4,10,15]. According to this model, the inhibition of one side of the parietal cortex may suppress the reciprocal inhibition to the opposite hemisphere, and then this increases the spatial attention for the ipsilateral hemisphere. These phenomena were previously well reported on healthy subjects and for patients with brain damage [4,10,13,15]. According to this view, facilitation of one side of the PPC may decrease the spatial attention to the ipsilateral hemisphere. However, our results have shown evidence of ipsilateral dysfunction (an increased error rate) not in both hemispheres, but in only the left PPC. Interpretation of these findings is somewhat puzzling; however, including consideration of the right hemispheric specialization model can solve this question. The right hemispheric specialization model is based on the assumption that the left hemisphere directs attention predominantly to the contralateral right side, whereas the right hemisphere directs attention to both hemispheres [12]. This model also postulates that the right hemisphere devotes more neuronal resources to spatial attention, and this has been confirmed in the course of previous clinical observations and functional imaging experiments that used a variety of behavioral tasks [9,9,11,12]. If these ideas are all true, increasing the activity of the right PPC not only increases the reciprocal inhibition to the left PPC, but it also enhances the neural apparatus to both hemispheres; therefore, the effect for the right hemisphere can be cancelled out. These findings are congruent with the clinical observation of the infrequent and less severe right-side neglect seen for patients with brain damage [12]. Further studies using different parameters of rTMS may give us more information on this issue.

Our present study has contributed crucial information concerning the effect of high frequency off-line rTMS applied over the parietal cortex on the facilitation of visuospatial attention for the contralateral hemisphere. These findings may well help to promote the further methodological trials for studying the effect of high frequency rTMS, and the findings may spur therapeutic trials for those patients having unilateral visuospatial neglect following brain injury.

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