One Session of Repeated Parietal Theta Burst Stimulation Trains Induces Long-Lasting Improvement of Visual Neglect

Thomas Nyffeler, MD; Dario Cazzoli, MSc; Christian W. Hess, MD; René M. Müri, MD

Background and Purpose—Visual neglect is a frequent disability in stroke and adversely affects mobility, discharge destination, and length of hospital stay. It is assumed that its severity is enhanced by a released interhemispheric inhibition from the unaffected toward the affected hemisphere. Continuous theta burst transcranial magnetic stimulation (TBS) is a new inhibitory brain stimulation protocol which has the potential to induce behavioral effects outlasting stimulation. We aimed to test whether parietal TBS over the unaffected hemisphere can induce a long-lasting improvement of visual neglect by reducing the interhemispheric inhibition.

Methods—Eleven patients with left-sided visual neglect attributable to right hemispheric stroke were tested in a visual perception task. To evaluate the specificity of the TBS effect, 3 conditions were tested: 2 TBS trains over the left contralesional posterior parietal cortex, 2 trains of sham stimulation over the contralesional posterior parietal cortex, and a control condition without any intervention. To evaluate the lifetime of repeated trains of TBS in 1 session, 4 trains were applied over the contralesional posterior parietal cortex.

Results—Two TBS trains significantly increased the number of perceived left visual targets for up to 8 hours as compared to baseline. No significant improvement was found with sham stimulation or in the control condition without any intervention. The application of 4 TBS trains significantly increased the number of perceived left targets up to 32 hours.

Conclusions—The new approach of repeating TBS at the same day may be promising for therapy of neglect. (Stroke. 2009;40:2791-2796.)

Key Words: transcranial magnetic stimulation ■ neuronal plasticity ■ recovery of function ■ stroke ■ therapy

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that allows to influence cortical activity. Depending on the frequency and discharge pattern of the magnetic pulses, inhibitory or facilitatory effects can be achieved.1 Some rTMS protocols have been shown to induce effects, which outlast stimulation to a variable extent. For the motor, language, and attention system stroke has been shown to induce an interhemispheric imbalance of mutual inhibition with an abnormal hyperactivity of the unaffected hemisphere, which is no longer inhibited from the lesioned side.2–4 As a consequence, interhemispheric inhibition from the unaffected toward the affected hemisphere is increased, which results in a further functional reduction of the neuronal activity of the damaged area. Hence, an inhibitory rTMS protocol that reduces the abnormal hyperactivity of the unaffected hemisphere may be of benefit. Until today, clinical brain stimulation protocols which produce long-lasting inhibitory effects used daily applications of 1Hz rTMS.5–7

As a novel rTMS protocol, which induces inhibitory effects, the continuous theta burst stimulation (TBS) was recently introduced into clinical research.8,9 On a neurophysiologic level, TBS has been shown to reverse the abnormally released interhemispheric inhibition of the motor cortex in stroke patients for several minutes.10

TBS is believed to induce plastic changes on cortical synapses in a long-term potentiation (LTP)-like fashion.11 Such a mechanism of action could be very attractive for therapeutic use, because in animals LTP was prolonged up to several days after repeated applications of TBS.12 In humans, we were recently able to disproportionately prolong the lifetime of the TBS effect by applying a session of repeated applications of TBS suggesting a consolidation-like mechanism: in an oculomotor task, the behavioral effect after 1, 2, or 4 trains of TBS lasted on average up to 30 minutes, 3 hours, and 11 hours, respectively.9 Interhemispheric imbalance plays a major role in neglect in humans.2,13–15 Neglect is defined as failure “to report, respond, or orient to novel or meaningful stimuli presented to the side opposite a brain lesion.”16 In stroke patients, neglect is common with an incidence of about 30%,17,18 and the outcome of rehabilitation after stroke is heavily determined by presence or absence of neglect. A neglect adversely affects mobility, the length of hospital stay, and the discharge destination (at home or institutionalized).19–23 Several approaches in neglect rehabil-
Itation have been developed, such as optokinetic stimulation; combined training of visual scanning, reading, copying, and figure description; trunk orientation plus visual scanning training; neck muscle vibration plus visual exploration training; visual scanning training alone; spatiomotor cueing with limb activation; right hemifield or right eye patching and prism adaptation training; and pharmacological treatments24–26 (see also the Cochrane review by Bowen and Lincoln27). However, to treat neglect effectively remains difficult. Hence, the search for new techniques that might be used for neglect treatment is of great importance.

Recently, we tested the model of interhemispheric imbalance in healthy subjects using TBS. We were able to show that TBS over the right posterior parietal cortex (PPC) induced “neglect-like” visual exploration behavior,28 which could be corrected by subsequently stimulating the left PPC.29 The aim of the present study was to apply TBS in neglect patients. We expected that parietal stimulation with inhibitory TBS over the unaffected contralesional hemisphere reduces its abnormal hyperactivity thereby decreasing the transcallosal inhibition of the affected hemisphere, resulting in an improvement of neglect signs. Furthermore, we expected that repeated TBS applications at the same day substantially prolong the improvement of neglect signs.

Materials and Methods

Patients

Eleven right-handed patients with left-sided visual neglect attributable to right hemisphere damage (9 ischemic strokes, 2 hemorrhagic strokes) were tested. Diagnosis of neglect was based on neurological examinations, including line bisection task,30 Bells Test,31 and drawing and reading performance. In all patients the central 30° of the visual field was intact measured by perimetry. Clinical and demographic data of the patients are presented in the Table. Figure 1 shows individual cerebral lesions and the overlap map.

Four experiments were performed, each time including 5 patients. Therefore, 3 patients participated in 2 experiments and 3 patients in 3 experiments. The control group included patient 5, 6, 8, 9, and 10. The sham group included patient 3, 7, 9, 10, and 11. The 2×TBS group included patient 1, 3, 4, 7, and 8. The 4×TBS group included patient 1, 2, 3, 7, and 10. There were no significant differences between the 4 patient groups in severity of neglect, age, and time since lesion onset. For each patient, the time interval between the different experiments was at least 3 weeks.

All participants had normal or corrected-to-normal vision and gave written informed consent before the experiment. The investigation was carried out in accordance with the latest Declaration of Helsinki and approved by the ethical committee of the State of Bern.

TBS Procedure

TBS was applied using a MagPro R30 stimulator (Medtronic Functional Diagnostics), connected to a round coil (outer radius of 60 mm, Magnetic Coil Transducer MC-125, Medtronic Functional Diagnostics) or to a sham coil (Magnetic Coil Transducer MC-P-B70). The same TBS protocol was used as described previously.28 In brief, it consisted of a continuous train of 801 pulses delivered in 267 bursts. Each burst contained 3 pulses at 30 Hz, repeated with an interburst interval of 100 ms. Total duration of 1 single TBS train was 44 seconds.

Stimulation was applied over P3, which, according to the international 10 to 20 EEG system, overlies the left PPC close to the intraparietal sulcus.32 The coil was held over the target location P3 tangentially to the scalp, with the handle pointing backwards and the current flowing in a clockwise direction as viewed from above. Subjects were asked to keep their eyes closed during the stimulation.

Table. Clinical and Demographic Data of the Patients With Left-Sided Neglect

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Time Post (Months)</th>
<th>Lesion Volume (cm³)</th>
<th>Left Motor Deficits</th>
<th>Visual Extinction</th>
<th>Bell Cancellation (Left Omissions, of 15)</th>
<th>Line Bisection (% Bias to the Right)</th>
<th>Drawing Neglect (Score)*</th>
<th>Reading (Word Omissions on the Left)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44</td>
<td>2.1</td>
<td>210</td>
<td>Plegia</td>
<td>No</td>
<td>8</td>
<td>7</td>
<td>2</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>0.4</td>
<td>25</td>
<td>Paresis</td>
<td>No</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>30.4</td>
<td>147</td>
<td>Paresis</td>
<td>No</td>
<td>15</td>
<td>11</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>1.8</td>
<td>184</td>
<td>Plegia</td>
<td>No</td>
<td>15</td>
<td>13</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
<td>3.5</td>
<td>149</td>
<td>Plegia</td>
<td>Yes</td>
<td>10</td>
<td>33</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>36.1</td>
<td>98</td>
<td>Paresis</td>
<td>No</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>0.9</td>
<td>139</td>
<td>Plegia</td>
<td>No</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>0.8</td>
<td>31</td>
<td>Paresis</td>
<td>No</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>61</td>
<td>0.8</td>
<td>10</td>
<td>Paresis</td>
<td>No</td>
<td>4</td>
<td>N/A</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>0.7</td>
<td>171</td>
<td>Plegia</td>
<td>No</td>
<td>14</td>
<td>27</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>11</td>
<td>44</td>
<td>0.6</td>
<td>149</td>
<td>Paresis</td>
<td>No</td>
<td>7</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A = not available.

*Drawing performance was scored as: 0 = flagrant omissions on the left side; 1 = distorted left side; 2 = intact.
TBS was delivered at 100% of subjects’ individual rest motor threshold.

Experimental Procedures
A subtask of the Vienna Test System (PVT, Dr G. Schuhfried GmbH, Mödling, Austria) was used. This test measures peripheral visual attention during a simultaneous central tracking task. On a central screen, patients were requested to keep a dot between 2 parallel moving lines using a steering knob. At the same time, they had to respond to the appearance of peripheral light bands using a foot pedal. The light bands started either from the far left or the far right visual periphery and extended over 9 seconds to the center of the visual field. Thirty light bands (15 from the right and 15 from the left side) were presented in a random order at unpredictable time intervals. Missed targets were defined as no reaction during 9 seconds to a peripheral light band. The task lasted about 15 minutes.

In the control experiment, the subtask of the Vienna Test System was performed 3 times (initial testing, 1 hour and 8 hours later). In the sham and the 2×TBS experiment, the same time schedule of the testing was used. In the sham experiment 2 trains of sham stimulation with an interval of 15 minutes were applied over the left unaffected PPC after the initial testing. In the 2×TBS experiment 2 trains of TBS with an interval of 15 minutes were applied over the left unaffected PPC after the initial testing.

The 4×TBS experiment differed in terms of the time schedule of the testing: the subtask of the Vienna Test System was performed 7 times (initial testing, 1, 3, 8, 24, 32, and 96 hours later). After an initial testing, 2 TBS trains were applied with an interval of 15 minutes. The third and fourth train was applied 60 and 75 minutes after the first TBS train.

Data Analysis
In each patient, the number of perceived left and right visual targets, ie, light bands, was calculated for each test. Furthermore, mean reaction time for target detection was calculated. For each group, statistical analysis was performed with a repeated-measures ANOVA with a within factor “time.”

Results
All patients tolerated TBS without side effects, such as headache, pain, vertigo, or paraesthesia. Most of the patients did not comment spontaneously on the stimulation procedure. After asking the patients, they frequently replied that they did not perceive anything during and after stimulation. All patients were not aware of the behavioral effect of TBS during performance of the subtask of the Vienna Test System.

In all 4 experiments patients perceived all 15 targets appearing at the right side. False-positive responses were rare events. On average, 4% (range: 0% to 11%) of all key presses were false-positive responses. The rate did not significantly vary across experiments.

Figure 2 shows the mean number (error bar: SEM) of perceived visual targets presented on the left side. In the 2×TBS experiment (Figure 2A), repeated-measures ANOVA revealed a significant effect for within-factor “time” (repeated-measures ANOVA [F(2,8)=6.392; P=0.022]). Posthoc testing was significant for the number of perceived targets after 1 hour (mean: 12.6 targets [SEM: 0.8 targets]; P=0.04) and after 8 hours (11.4 [1.8] targets; P<0.01) compared to the initial test (7.0 [2.0] targets). In 2 patients an additional measurement was also performed 24 hours after stimulation, showing that the number of perceived targets dropped down to values of initial testing.

In the sham stimulation experiment (Figure 2B), there was no significant effect for within-factor “time” (F[2,8]=0.516; P=0.615). In the control experiment (Figure 2C), there was also no significant effect for within-factor “time” (F[2,8]=0.6864; P=0.531).

In the experiment applying 4 trains of TBS (Figure 3), for targets on the left side, there was a significant effect for the within-factor “time” (F[6,24]=6.125; P=0.0005). In the initial test mean number of perceived targets was 7.4 (2.0). Posthoc testing showed a significant increase of the mean number after 1 hour (10.6 [1.4] targets; P=0.048), 3 hours (12.6 [0.6] targets; P=0.03), 8 hours (13.0 [0.7] targets; P=0.04), 24 hours (12.6 [0.6] targets; P=0.04), and after 32
hours (13.2 [0.8] targets; \( P = 0.02 \)) compared to the number before TBS application. After 96 hours, there was no significant difference (9.7 [1.2] targets) anymore.

The results of the reaction time analysis are shown in Figure 4 and 5. In the 2×TBS experiment (Figure 4A), a significant effect for within-factor “time” for left-sided targets was found (\( F[2,8] = 5.297; \ P = 0.034 \)). Posthoc testing was significant for the decrease of reaction time after 1 hour (mean: 5.2 seconds [SEM: 0.52 seconds]; \( P = 0.03 \)) and after 8 hours (5.4 [0.85] sec; \( P < 0.01 \)) compared to the initial test (6.8 [0.71] sec). For right-sided targets, there was no significant effect (\( F[2,8] = 1.750 \ P = 0.234 \)).

In the sham stimulation experiment (Figure 4B), there was no significant effect for within-factor “time” for both left- \( (F[2,8] = 2.901; \ P = 0.113) \) and right-sided targets \( (F[2,8] = 0.696; \ P = 0.526) \). In the control experiment (Figure 4C), there was also no significant effect for within-factor “time” for left-sided targets \( (F[2,8] = 2.332; \ P = 0.159) \) and for right-sided targets \( (F[2,8] = 1.070; \ P = 0.387) \).

In the 4×TBS experiment (Figure 5), there was a significant effect for the within-factor “time” for left-sided targets \( (F[6,24] = 2.651; \ P = 0.0407) \). Posthoc testing was significant for the decrease of reaction time after 3 hours (mean: 5.4 [0.82] sec; \( P = 0.03 \)), 8 hours (5.5 [0.47]; \( P = 0.03 \)), 24 hours (5.6 [0.83] sec; \( P = 0.03 \)), and 32 hours (4.6 [0.64] sec; \( P = 0.03 \)). After 96 hours, there was no significant difference, compared to the initial test (7.4 [0.56] sec; \( P = 0.15 \)). There was no significant effect for within-factor “time” for right-sided targets \( (F[6,24] = 2.446; \ P = 0.0547) \).

**Discussion**

The present study shows that patients with left-sided neglect benefit from the parietal application of TBS over the unaffected hemisphere. TBS significantly improved the perception of targets presented on the left side. The TBS effect was specific because sham stimulation or just repeating the test without intervention did not improve neglect symptoms. Furthermore, TBS significantly decreased reaction time only for left-sided targets. Right-sided reaction time remained unaffected suggesting that the TBS effect was not attributable to an unspecific increase of alertness.

An improvement of neglect signs after stimulating the unaffected PPC corroborates the model of interhemispheric imbalance of attention causing the neglect. The hypothesis that the TBS effect in our patients was induced by attenuation of the assumed abnormal hyperactivity of the unaffected PPC is supported by data from recent functional MRI studies: In patients with neglect attributable to right hemispheric lesions, the activity of the left unaffected PPC was abnormally increased.\(^3\) Furthermore, the authors showed that neglect recovery was accompanied by a decrease of the hyperactivity of the unaffected PPC and hence restoration of the interhemispheric balance.

The application of 4 trains of TBS significantly improved the perception of targets presented on the left side for up to 32 hours. The lifetime of this effect is much longer than what has been observed in healthy subjects.\(^9\) One might speculate that the repetition of TBS trains has a different influence on the cortical network whether it is healthy and balanced or damaged and imbalanced. It is, eg, conceivable that a cortical area that is abnormally hyperactive because of an interhemi-
spheric imbalance may be more susceptible to the repetition of TBS trains.

The physiological changes which occur in humans after TBS are under investigation. The present finding that 1 session of 4 repeated TBS trains induces a long-lasting improvement of visual neglect probably reflects consolidation mechanisms of synaptic plasticity as observed in animals.\textsuperscript{12,33,34} Such an assumption is supported by another recent TBS study in humans, where the suppressive effect of inhibitory TBS could be blocked when memantine, a N-methyl-D-aspartate receptor (NMDAR) antagonist, was given beforehand.\textsuperscript{11} The activation of both pre- and postsynaptic NMDARs is known to play a key role in the induction of LTP.

The application of repeated TBS trains at the same day has advantages for future interventions in neurorehabilitation. The duration of TBS application is very short with a train lasting only 44 seconds, and TBS was well tolerated in all patients without any side effects. Future studies will have to find out whether the combination of TBS and other rehabilitative interventions improve the outcome in a synergistic way. Several rehabilitation procedures have shown encouraging results in neglect (see the Cochrane review by Bowen and Lincoln\textsuperscript{27}). Hence, there is hope that the combination of TBS and traditional neglect therapies in neurorehabilitation might substantially improve the outcome of neglect patients.

Summary

It is assumed that the severity of visual neglect is enhanced by a released interhemispheric inhibition from the unaffected toward the affected hemisphere. We show that repeated applications of TBS over the contralesional PPC at the same day specifically and significantly improved the perception of visual targets presented on the left side up to 32 hours as compared to baseline testing. This new approach may be promising for therapy of neglect.

Sources of Funding

This study was supported by the Swiss National Science Foundation, Grant No. 3200BO-116074/1.

Disclosures

None.

References

One Session of Repeated Parietal Theta Burst Stimulation Trains Induces Long-Lasting Improvement of Visual Neglect

Thomas Nyffeler, Dario Cazzoli, Christian W. Hess and René M. Müri

Stroke. 2009;40:2791-2796; originally published online June 11, 2009;
doi: 10.1161/STROKEAHA.109.552323

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/8/2791