Theta Burst Stimulation Over the Right Broca’s Homologue Induces Improvement of Naming in Aphasic Patients

Jochen Kindler, MD*; Rahel Schumacher, MSc*; Dario Cazzoli, PhD; Klemens Gutbrod, PhD; Monica Koenig; Thomas Nyffeler, MD; Thomas Dierks, MD; René M. Müri, MD

Background and Purpose—Improvements of language production in aphasic patients have been reported following repeated 1-Hz transcranial magnetic stimulation over the nondamaged right hemisphere. Most studies examined aphasic patients in the chronic phase. The effect of transcranial magnetic stimulation application in acute or subacute patients has not been systematically studied. We aimed to evaluate whether continuous theta burst stimulation, an inhibitory protocol with a shorter application time than the common 1-Hz protocol, is able to improve naming performance in aphasic patients in different poststroke phases.

Methods—Eighteen right-handed aphasic patients performed a picture naming task and a language independent alertness test before and after the application of theta burst stimulation over the intact right Broca’s homologue localized by the 10–20 electroencephalogram system in a randomized, sham-controlled, crossover trial.

Results—We found that naming performance was significantly better, and naming latency was significantly shorter, after theta burst stimulation than after the sham intervention. Patients who responded best were in the subacute phase after stroke.

Conclusions—This setting with the short theta burst stimulation application time and the simple stimulation localization procedure is suitable for clinical purposes. (Stroke. 2012;43:2175-2179.)

Key Words: aphasia ■ repetitive TMS ■ theta burst stimulation ■ right Broca’s homologue

Aphasia is a common syndrome after brain damage to the language dominant hemisphere occurs, and is characterized by partial or total loss of language functions. The most prevalent cause of aphasia is stroke.1 After stroke, 38% of the patients show aphasic symptoms and 18% develop chronic aphasia.2 Although patients usually receive intensive daily language therapy, recovery from aphasia is often not complete.3 Concerning language reorganization, functional imaging studies suggest that left perilesional activation is associated with a more favorable outcome.4–7 The role of the right, nondamaged hemisphere in recovery is less clear.8,9 Some authors suggest that right-hemispheric activations early after stroke could reflect substitution of lost left-hemispheric functions.10 Other authors suggest that right-hemispheric activation has a dysfunctional effect, which is explained within the framework of interhemispheric inhibition.11,12 This means that reduced transcallosal inhibition after brain lesion leads to a relative hyperactivity in the intact hemisphere and to an additional decrease in the neuronal activity of the damaged region.13–15 Such increased inhibition of the intact hemisphere after stroke has been described for the motor, attentional, and language systems.11,13,16,17

Noninvasive brain stimulation, such as transcranial magnetic stimulation (TMS), allows modulating cortical activity and functioning. Depending on the stimulation protocol, inhibitory or facilitatory effects can be achieved.18 A repetitive TMS protocol that has recently been introduced into clinical research is theta burst stimulation (TBS).19,20 Nyffeler et al20 showed that TBS over the contralesional hemisphere reduces neglect in stroke patients for several hours. From a clinical point of view, TBS has the advantage that the application duration is very short, compared with the often-used 1-Hz stimulation protocol.

Positive effects on language production have been reported after inhibitory 1-Hz stimulation of right frontal homologue language areas, mostly in patients with chronic aphasia.11,21–24 However, the dynamics of language recovery, such as proposed by Saur et al,25 suggest that the role of the intact right hemisphere is different depending on the time post-stroke. In their functional imaging study, they found an early upregulation of the activity of right-hemispheric homologue language areas around 2 weeks poststroke, followed by a shift back of the activation to left-hemispheric language areas in the chronic phase. The effect of TMS application over the

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From the Department of Psychiatric Neurophysiology (J.K., T.D.), University Hospital of Psychiatry, and University of Bern, Switzerland; Division of Cognitive and Restorative Neurology (R.S., D.C., K.G., T.N., R.M.M.), Department of Neurology and Department of Clinical Research, Inselspital, Bern University Hospital, and University of Bern, Switzerland; Nuffield Department of Clinical Neurosciences (D.C.), University of Oxford, United Kingdom; Logopädie (M.K.), Spitalzentrum Biel, Switzerland.

*J.K. and R.S. equally contributed to this work.

Correspondence to René Müri, Division of Cognitive and Restorative Neurology, Department of Neurology and Department of Clinical Research, Inselspital, Bern University Hospital, Freiburgstrasse 10, 3010 Bern, Switzerland; E-mail rene.mueri@insel.ch.

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Table. Clinical and Demographic Data of the Patients With Aphasia

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
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M indicates male; IS, ischemic stroke; F, female; SA, speech apraxia; HS, hemorrhagic stroke.

*Patients with a difference higher than the median difference post-/preTBS were defined as best responders (see Methods section).

intact hemisphere in acute or subacute patients has not yet been systematically studied.

The aim of the present study is to evaluate whether continuous TBS over the intact right Broca’s homologue is able to improve naming performance in aphasic patients in different poststroke phases. To this end, we tested 18 patients with aphasia 0.5 to 57 months poststroke. Furthermore, we investigated whether the best responders to TBS can be distinguished from the other patients of the sample, depending on patient-specific parameters such as time poststroke, age, or sex.

Methods

Patients

Eighteen right-handed patients (10 women, mean age 55.0 ± 8.6 years) with aphasia after left-hemispheric stroke (13 ischemic, 5 hemorrhagic; Table and Figure 1 for further details) were included in the study. Patients with a history of previous stroke, seizure, or with metal implants in the brain were not included. Diagnosis and classification of aphasia were based on neurological examination, standardized diagnostic procedures conducted by professional language therapists, and imaging data. Lesion mapping was performed in MRICron. Magnetic resonance imaging (MRI) scans were available for 14 patients, and computed tomography scans were available for the remaining 4 patients. Maps were normalized and projected onto a standard brain. For the 14 patients with available MRI scans, the boundary of the lesions was delineated directly on the individual MRI image for every single transversal slice. For the 4 patients with computed tomography scans, lesions were mapped directly on the T1-weighted MNI single-subject template implemented in MRICron with a slice distance of 1 mm and using the closest matching transversal slice for each individual. BA44/BA45, as defined by the Wake Forest University Pickatlas (SPM 5, Wellcome Department of Imaging Neuroscience), was additionally plotted onto the normalized images.

All patients had ongoing or had already completed standard language therapy. Patients gave written informed consent before the experiment. The investigation was carried out in accordance with the latest Declaration of Helsinki and was approved by the ethical committee of the State of Bern.

Naming Task

Six different versions of a timed picture-naming task were used. The 6 versions were comparable with respect to mean word frequency class in German (13.1 ± 0.1; a word in frequency class 13 is 2^13 less frequent than is the most frequent word [in German: der]; http://wortschatz.uni-leipzig.de) and word length (mean syllables/word, 2.0 ± 0.1). Every version consisted of 31 pictures from the colored Snodgrass and Vanderwart line drawings. Within every version, the 31 pictures were presented in a fixed order with descending word frequency. The subjects saw each version once in a randomized order. Each picture was presented for 5 seconds on a computer screen using E-Prime 2.0 (Psychology Software Tools, Inc). Patients were instructed to name the pictures as accurately and as quickly as possible. Answers were recorded during the 5-second time window of picture presentation with Adobe Audition 1.5 and were analyzed offline for errors and latency by 2 trained independent raters. A white screen followed every picture presentation and the next trial was started by a key press.

Alertness Test

To control for unspecific or confounding effects of TBS on alertness, the subtest Alertness from the Test of Attentional Performance (http://www.psytest.net/) was administered. Patients were instructed to respond by key press as quickly as possible to a cross that appeared on the monitor at randomly varying time intervals. In this condition, intrinsic alertness was measured. A second condition measured phasic alertness by assessing the reaction time to the critical stimulus (cross) when it was preceded by a warning tone. The task consisted of 4 blocks (2 blocks per condition) of 20 trials each and took usually 4 to 5 minutes to be completed.
TMS Procedure

A MagPro X100 stimulator (Medtronic Functional Diagnostics) was used to generate repetitive, biphasic magnetic pulses. Magnetic pulses were delivered with a figure-of-eight-coil (MC-B70) or a placebo coil (MC-P-B70). Individual resting motor thresholds were defined by stimulating the motor cortex with single TMS pulses until a contraction of the contralateral small hand muscles was observed. TMS pulse intensity was adjusted to 90% of subjects’ individual resting motor thresholds.22–24

The TBS protocol consisted of a continuous train of 801 pulses delivered in 267 bursts.20 Each burst contained 3 pulses at 30 Hz, repeated with an interburst interval of 100 ms. Total duration of a train was 44 seconds. The stimulation was applied over the right Broca’s homologue (Brodman area BA45), using the international 10–20 electroencephalogram system for stimulation localization. The target area was the pars triangularis of the inferior frontal lobe. Münster T2T-Converter (http://wwwneuro03.uni-muenster.de/get/t2tconv/) coordinates were used to determine the specific localization. Stimulation was applied between electrodes C4 and F8 (10–20, 1.260/0.74; Talairach space x/yr/z, 58/31/22). During stimulation, the center of the coil was held tangentially to the skull with the handle pointing upwards. Following stimulation, patients were asked whether they suffered from headache, nausea, or other negative effects. Furthermore, patients were clinically observed at least 30 minutes following stimulation.

Experimental Procedures

A randomized, sham-controlled, crossover design was applied. Two sessions on 2 different days, separated by 1 week, were conducted per patient. Patients were randomly assigned to 1 of the 2 groups (TBS or sham as the first session). The experimental procedure is depicted in Figure 2. Each session started with a naming task that was used for training and was not included in the analysis. After training, the alertness test and another version of the naming task was performed. Then, TBS or the sham was applied. After intervention, the alertness test and another version of the naming task were performed.

Data Analysis

For each task version and patient, a naming score was computed by subtracting the errors (semantic or phonematic paraphasias, anomas, or unidentifiable utterances) from the total of 31 trials. Naming latencies (interval from the start of the image presentation to the start of the utterance) were determined for correct answers using WavePad Audio Editor Software (v 4.47, www.nch.com.au/wavepad/de). For the alertness test, mean reaction time and the sum of errors (anticipations and omissions) were calculated.

To control whether the 6 versions of the naming task had the same difficulty, a repeated measures ANOVA with version as within-subject factor and accuracy as dependent variable was performed. Then, separate repeated measures ANCOVAs with the within-factor Intervention (TBS, sham) were computed for the dependent variables naming score, naming latency, alertness test reaction time, and alertness test errors. The respective baseline measure was included as covariate as suggested by Senn.34 Statistical analysis was conducted in SPSS 18.0 software, with statistical significance level set at P<0.05.

The median difference of the naming scores post-/preTBS was calculated and a median split of the group was performed. Patients with a difference higher than the median were defined as best responders. Patients’ characteristics (sex, age, and time poststroke) were then compared between the 2 groups using the Mann-Whitney U Test.

Results

TBS was well tolerated in all patients without any side effects.

Naming Task

Overall, there were no significant differences in naming scores between the 6 versions (F(5,66), 1.327; P=0.264). The baseline naming score was 23.1±1.5 (SEM), the naming score postTBS was 24.2±1.2, and postsham, 23.6±1.6. The baseline naming latency was 1240±83 ms, the latency postTBS was 1214±70 ms, and postsham was 1235±110 ms. Statistical analysis revealed a significant effect of the factor Intervention on the naming score (F(1,16), 7.72; P<0.013; r=0.56). The naming scores between the 6 versions (F(5,66), 1.327; P=0.264). The baseline naming score was 23.1±1.5 (SEM), the naming score postTBS was 24.2±1.2, and postsham, 23.6±1.6. The baseline naming latency was 1240±83 ms, the latency postTBS was 1214±70 ms, and postsham was 1235±110 ms. Statistical analysis revealed a significant effect of the factor Intervention on the naming score (F(1,16), 7.72; P=0.013; r=0.56) and on the naming latency (F(1,16), 7.559; P=0.014; r=0.56). Patients scored significantly higher and were significantly faster after TBS than after the sham intervention (Figure 3).

Alertness Test

Alertness data of 1 patient were missing. Statistical analysis revealed no differences between reaction times postTBS

Figure 2. Experimental procedure, tasks, and sequence of events. The lightning bolt symbolizes the TBS intervention, the no symbol stands for the sham intervention.

Figure 3. Mean naming scores (left) and naming latencies (right) postintervention. The horizontal line indicates the baseline value. Error bars denote 1 SEM.
(275±8.2 ms) and postsham (266±6.8 ms; baseline, 273±15.3 ms; F(1,15), 2.314; P=0.149). Furthermore, no effect was found for errors (anticipations and omissions; F(1,15), 1.615; P=0.223).

**Best Responders**
Median difference of naming scores post-/preTBS was +1.5 items. Comparison of patients’ characteristics between the best responders and the rest of the sample yielded a significant difference in the time poststroke (Mann-Whitney U Test, P=0.009). This interval was shorter (4.7±1.9 months) in the group of the best responders than in the rest of the sample (29.0±6.2 months). No significant differences were found for the parameters sex and age.

**Discussion**
The present study evaluated the effect of 1 continuous TBS train over the right Broca’s homologue on naming performance in aphasic patients. We showed that naming performance was significantly better, and reaction time was significantly shorter, after TBS than after sham intervention. Furthermore, the effect observed after TBS is language-specific and not the result of an unspecific effect on arousal, because patients showed no significant improvement in the language-independent alertness test.

Our findings confirm previously described effects of inhibitory TMS (1Hz protocol) over the right intact Broca’s homologue. The advantage of the TBS is that its application lasts only 44 seconds and that patients support it without discomfort. Indeed, none of the patients complained about pain or any side effects after TBS.

The definition of the optimal time poststroke for a TMS intervention in aphasia rehabilitation is of major importance. A dynamic model of recovery after stroke has been proposed based on functional imaging data. It states that the acute phase is characterized by the loss of activation followed by an upregulation of the language network (including right-hemispheric areas) in the subacute phase and by a consolidation and normalization of activation in the chronic phase. The model is based on data of patients in the very early poststroke phase (up to 0.5 months) and of the chronic phase (around 10 months). Most studies applying TMS in aphasic patients examined the chronic phase, based on the hypothesis that the language network is by that time settled in a pathological imbalance with an overactivated right hemisphere. Some authors even suggested that TMS intervention in the acute/subacute phase may have a negative influence or may even disrupt functional activations. For instance, Winhuisen et al. studied patients in the very early poststroke phase and found disruptive effects on a naming task in half of the patients after 4-Hz TMS to the right inferior frontal gyrus. Weiduschat et al. examined patients in a later phase (0.6–3.2 months) and reported positive effects of repeated TMS sessions on a global measure of aphasia.

Taking the literature together, few studies using TMS in aphasia focused on the time poststroke between 0.5 and 10 months, and no study included subacute as well as chronic patients. The time poststroke of the patients included in our study ranged from 0.5 to 57 months. We found that the time poststroke of the best responders to TBS was on average 4.7 months, suggesting that aphasic patients in the subacute phase may benefit most from TBS. No effect of sex or age on TBS responsiveness was found. Hence, TMS application in aphasic patients may not be limited by these factors.

The mechanisms leading to the effects of TBS are still under investigation. Huang et al. showed that TBS seems to be able to induce plastic changes in cortical synapses in a long-term potentiation or long-term depression-like fashion. In particular, they assume that the processes leading to long-term depression depend on the amount of Ca2+ entry, whereas the processes leading to long-term potentiation depend on the rate of Ca2+ entry. According to Huang et al., continuous TBS, as it was used in our study, tends to produce long-term-depression-like results.

From a practical point of view, it is noteworthy that naming improvements could be achieved by means of the simple stimulation localization procedure using the 10–20 electroencephalogram system. This suggests that, at least for clinical purposes, a neuronavigation system for TMS coil positioning is not pivotal. Some authors have found that only the stimulation of a specific site within the right Broca’s homologue successfully improves language performance. That a very precise and focalized localization of parts of Broca’s area homologue in the right hemisphere may not be crucial for a significant amelioration of language performance is also supported by the results obtained by transcranial direct current stimulation. With this method, large cortical areas in the order of 4 to 5 cm² are stimulated. A simple stimulation localization procedure for TMS application facilitates the clinical use of TMS in aphasia treatment, given that most rehabilitation clinics do not have direct access to structural MRI and neuronavigation systems.

Because of its proof-of-concept character, the present study has some limitations. The lack of long-term data does not allow conclusions about the duration of the effect. However, as we applied only 1 train of TBS, we did not expect long-term effects. Previous studies demonstrated that the TBS effects can be disproportionately prolonged and increased when the stimulation is repeatedly applied. The long-term effect of repeated applications on aphasia should thus be evaluated in future studies with a therapeutic scope. Moreover, possible confounding factors, such as ongoing language therapy, medication, or depression, should be taken into account. Finally, as our primary inclusion criterion referred to the presence of aphasic symptoms (ie, naming deficits), this resulted in a diversity of lesion etiologies and localizations.

In conclusion, the results of our study show positive effects of TBS in aphasic patients. Patients showed a specific improvement in the naming performance after TBS application over the right Broca’s homologue. Patients who responded best were in the subacute phase of the recovery process. Other patient-specific parameters distinguishing best responders could not be identified. The stimulation localization procedure using the international 10–20 electroencephalogram system is sufficient to obtain significant TBS effects. Finally, the TBS protocol has the advantage of a short application time, which makes it suitable for clinical application.
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Disclosures
None.

References
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Supplemental Methods

To evaluate the 10-20 EEG system localization procedure, we compared it with a frameless stereotaxic neuronavigation procedure (Brainsight™ 2, Rogue Research Inc., Montreal): A neuroanatomical mesh was created from MRI data of one healthy subject. The stimulation localization (10/20: 1.26/0.74) was marked on the subject’s head (Figure S1, left). The corresponding landmark was projected on the underlying cerebral cortex (Figure S1, right). The target area lay within the frontal part of the inferior frontal gyrus (pars triangularis).

Figure S1. Anatomical reconstruction of a subject’s head and brain to illustrate the accuracy of the 10-20 EEG system localization procedure. The stimulation localization (BA 45, right hemisphere) is marked with a green circle.