Effects of Repetitive Transcranial Magnetic Stimulation in Aphasic Stroke  
A Randomized Controlled Pilot Study

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Background and Purpose—Although functional imaging studies suggest that recruitment of contralesional areas hinders optimal functional reorganization in patients with aphasic stroke, only limited evidence is available on the efficacy of noninvasive brain stimulation such as repetitive transcranial magnetic stimulation aimed at suppression of contralateral overactivation.

Methods—In this randomized, controlled, blinded pilot study, the effect of 1-Hz repetitive transcranial magnetic stimulation over right-hemispheric Broca homolog in subjects with poststroke aphasia in the subacute stage was examined. According to their group allocation, patients received, in addition to conventional speech and language therapy, multiple sessions of repetitive transcranial magnetic stimulation either over the right-hemispheric inferior frontal gyrus (intervention group) or over the vertex (control group). The primary outcome parameter was the change in laterality indices as quantified by activation positron emission tomography before and after the 2-week intervention period. The clinical efficacy was evaluated with the Aachen Aphasia Test.

Results—At baseline, no group differences were discovered for age, laterality indices, or mean Aachen Aphasia Test scores. Four patients were lost to follow-up, but none due to side effects of the transcranial magnetic stimulation. Positron emission tomography revealed an activation shift toward the right hemisphere in the control group ($P=0.0165$), which was absent in the intervention group. Furthermore, the latter improved significantly clinically by a mean of 19.8 points in the Aachen Aphasia Test total score ($P=0.002$), whereas the control group did not. There was however no clear linear relationship between the extent of laterality shift and clinical improvement ($r=0.193$, $P$=nonsignificant).

Conclusions—Repetitive transcranial magnetic stimulation might be an effective, safe, and feasible complementary therapy for poststroke aphasia. (Stroke. 2011;42:00-00.)

Key Words: plasticity ■ recovery ■ stroke ■ transcranial magnetic stimulation ■ treatment
infarction, recruitment within 16 weeks poststroke, right-handedness (as determined by the Laterality Questionnaire by Salmaso and Longoni), age between 55 and 85 years, and German as the first language. Exclusion criteria were symptomatic prior cerebrovascular accident, neurodegenerative or psychiatric disease, epilepsy or electroencephalography-documented epileptic discharges, insulin-dependent diabetes mellitus, renal or liver failure, metal parts in the body, life-threatening diseases, and auditory or visual deficits that might impair testing. Medication that alters brain excitability was not exclusionary. Written informed consent was obtained from all subjects. The Ethics Committee of the University of Cologne and the Federal Office for Radiation Protection approved the study protocol. Due to the pilot character of the study, no sample size calculation was performed.

Language Performance and Positron Emission Tomographic Imaging

Each subject was examined with the Aachen Aphasia Test (AAT) battery by experienced speech and language therapists. In German-speaking countries, the AAT is a commonly used assessment tool for aphasic patients, which includes evaluations of spontaneous language production (communicative behavior, automatized language, articulation and prosody, semantics, phonetics and syntax); general comprehension (Token test); oral repetition of phonemes, words, and sentences; written language (reading and writing functions); capability of describing objects, situations, and actions (confrontation naming); and comprehension of spoken and written language. Obtained scores can be transformed into standardized scores (t values) and percentile ranks.

The activation condition during H2O15 positron emission tomography (PET) consisted of a silent verb-generation task. During the activation condition, patients had to generate semantically matching verbs to high-frequency German nouns presented over headphones at a fixed rate of 1 noun every 5 seconds. Before the scans, patients were extensively trained in and outside the scanner room as well as with and without headphones, being confronted with different nouns every time. Participants were scanned with eyes closed. The activation and the resting condition were each presented 4 times in a balanced sequence. Each condition was started simultaneously with injection and continued until scan completion.

The PET scans measuring the regional cerebral blood flow at rest and during the activation condition were performed on a CTI/Siemens ECAT EXACT HR Scanner in 3-dimensional mode. PET sessions consisted of 8 subsequent scans each with an intravenous bolus injection of 370 MBq of H2O15 and a waiting time of 10 minutes between injections. Data acquisition started automatically, when the number of true counts exceeded the baseline level for >5 kcounts and lasted for 45 seconds. After corrections for random coincidences, scatter, and measured attenuation, each scan was reconstructed to 47 slices (3.125-mm thickness and 2.2-mm pixel size) using 3-dimensional filtered backprojection yielding images of relative cerebral blood flow. After the 2-week rehabilitation period including rTMS and speech and language therapy, the AAT was repeated and further PET scans were obtained using the same verb-generation paradigm with different nouns (Figure 1).

Repetitive rTMS Sessions

After the baseline examinations, sealed envelopes with the random group allocation were sent to the rehabilitation facility. According to this allocation, subjects received either inhibitory 1-Hz rTMS over the right triangular part of the inferior frontal gyrus (IFG; TMS group) or over the vertex (sham group) using a Magstim Rapid® stimulator with a double 70-mm coil. Choosing the right triangular part of the IFG as a target structure was based on previous studies demonstrating its significance in patients with chronic poststroke aphasia. T1-weighted, high-resolution MR scans were obtained to determine the optimal position for the TMS coil according to the surface distance measurements method. The distance measurements to localize the IFG were applied with a marker in both groups, although this target structure was only stimulated in the intervention group. Following Naeser et al., treatment and sham stimulation sessions were conducted 5 days per week for a 2-week period, yielding 8 to 10 sessions per subject (mean, 9.2). Not every patient received 10 sessions of TMS due to patients’ indispositions unrelated to the study. During every session, subjects were stimulated for 20 minutes with a frequency of 1 Hz and a stimulation intensity of 90% of the daily defined individual motor threshold. The stimulation parameters were chosen according to current safety guidelines for rTMS.

Speech and Language Therapy Sessions

Each TMS session was immediately followed by speech and language therapy by clinically certified and blinded therapists. We refrained from concurrent magnetic stimulation and speech therapy due to the noise of the stimulator and the muscle contractions, which would have prevented effective therapy. All patients received model-oriented aphasia therapy focused on the individual specific linguistic problems. A duration of 45 minutes was chosen to fully use the assumed TMS effects on the cortical excitability (which are estimated to persist for at least 30 minutes) at the time of not overexerting the patients. The speech therapy plans had in common strongly stimulating techniques such as the melodic intonation therapy were foregone.

Data Analyses

Peak activations in the IFG, upper temporal lobes, and the supplementary motor areas were localized and quantified on the
z-transformed activation images merged with the coregistered MR images (Figure 2) as previously described. For data analysis, we used SPSS Statistics Version 17.0. We calculated laterality indices (LIs) as a measure of the hemispheric dominance in every region according to the formula LI=(\text{peak}_{\text{left}}−\text{peak}_{\text{right}})/(\text{peak}_{\text{left}}+\text{peak}_{\text{right}})∗100 with positive values representing left-hemispheric dominance. These indices as well as the standardized language test results (t-scores) at different time points were analyzed with 2-sample t tests for paired and unpaired groups taking into account the group allocation. The correlation between the extent of laterality shifts and the clinical improvement were calculated using Pearson. Gaussian distribution was confirmed with Shapiro-Wilk tests; 1-sided probability values were calculated to test the directed hypothesis that the treatment group would show greater improvement than the sham groups.

Results

Recruitment was undertaken from May 2008 until August 2009. Of 14 recruited right-handed patients with different aphasia syndromes such as Broca and Wernicke, as classified by the ALLOC classification procedure (Table 1), 3 were lost to follow-up due to temporary malfunction of the TMS device or claustrophobia in the PET or MR scanner. Furthermore, a patient with anomic aphasia was also excluded, because she exhibited near complete spontaneous remission even before intervention start. Six patients were allocated to the TMS group, whereas 4 patients were in the sham group. All subjects had left-hemispheric lesions due to first-time ischemic or hemorrhagic stroke that varied in size and location but without any significant group difference concerning the lesion size (Table 1). The mean age was 65 years with no significant group difference (TMS group 66.6, sham group 63.75 years). No patient withdrew his or her consent because of the TMS sessions and no serious adverse effect was reported. However, in 2 patients of the TMS group, the stimulation intensity had to be decreased because of patients’ discomfort on 2 of 10 and 7 of 10 stimulation days, respectively. The mean required intensity decreases were approximately 15% and 30% of the target intensity.

On average, baseline PET were conducted 50 days poststroke (TMS group 45 days, sham group 57 days, P=nonsignificant) with no significant between-group difference in LIs for all analyzed regions (Table 2). Comparison of LIs of the IFG pre- and postintervention across the entire sample, independent of the treatment groups, indicated an average increase in right-hemispheric activity (P=nonsignificant). Subjects of the sham group caused this overall increase having significantly lower LIs posttreatment (P=0.0165) indicating greater right-hemispheric activity. In contrast, a nonsignificant LI increase was observed in the TMS group. Direct comparison of this change in LIs (laterality shift) revealed a significant difference between groups (P=0.008; Figure 3). For the supplementary motor area and the upper temporal region, there was a nonsignificant tendency to lateralize to the left hemisphere without any significant group difference (Table 2).

Concerning the clinical improvement as determined by the increase of the total AAT score, exploratory analyses showed a significant group difference (P=0.047; Figure 4; Table 3). At baseline 49 days poststroke (TMS group 45 days, sham group 57 days), there had been no significant group difference concerning mean AAT scores (TMS group 239, sham group 249), but during the intervention period, patients of the TMS group improved significantly by 19.8 points in the AAT total score (P=0.002), whereas sham-stimulated subjects improved by 8.5 points (P=nonsignificant). However, there was no clear linear relationship between the extent of laterality shift and clinical improvement (r=0.193, P=nonsignificant). Exploratory Wilcoxon signed-rank tests revealed a significant improvement in the subtest naming of the AAT (P=0.03) only in the TMS group. There was however no significant group difference concerning the improvement in single subtests.

Discussion

Rationale

The rationale of using rTMS as a complementary therapy in neurorehabilitation is mainly to decrease the cortical excitability in regions that are presumed to hinder optimal recovery. In our pilot study, we assumed that right-hemispheric activation in aphasia patients represents an inferior adaptive strategy and hence we aimed to suppress activation in right the IFG with low-frequency rTMS.

Most adults exhibit lateralization of the language relevant areas to the left hemisphere. Functional imaging studies have suggested that this specialization is facilitated by the inhibition of adjacent, but also more remote cortical regions. A recent PET study directly demonstrated the discontinuation of this inhibition by suppressing the cortical excitability of the left IFG using repetitive rTMS.
In a similar way, the functional networks involved in language tasks are modified in patients recovering from aphasic stroke. The cortical excitability in perilesional, but also contralateral homologous, regions is increased.25,26 Several studies indicated the unfavorable influence of these abnormal right-hemispheric activation patterns for language recovery27–29; other neuroimaging studies confirm that patients with a favorable outcome predominantly functionally reintegrate left-hemispheric structures.26,27,30 Thus, recovery of poststroke aphasia seems to be most effective when perilesional cortical areas can be reactivated.5,22

### Table 1. Demographic and Language Data

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Group</th>
<th>Age, Years</th>
<th>Sex</th>
<th>Days Since Infarction</th>
<th>Type of Aphasia</th>
<th>Infarct Volume, mm³</th>
<th>Lesion Location</th>
<th>SLT Method</th>
<th>SLT Tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sham</td>
<td>59</td>
<td>M</td>
<td>37</td>
<td>Broca, nonfluent</td>
<td>6975</td>
<td>Frontal operculum, inferior precentral gyrus</td>
<td>PO</td>
<td>NP, R, MP, WN</td>
</tr>
<tr>
<td>6</td>
<td>Sham</td>
<td>68</td>
<td>M</td>
<td>97</td>
<td>Broca, nonfluent</td>
<td>687</td>
<td>Supramarginal gyrus, posterior superior temporal gyrus</td>
<td>PO</td>
<td>NP, R, WN</td>
</tr>
<tr>
<td>8</td>
<td>Sham</td>
<td>61</td>
<td>M</td>
<td>50</td>
<td>Global, nonfluent</td>
<td>17 978</td>
<td>Entire MCA territory</td>
<td>S</td>
<td>NS, WP, YN</td>
</tr>
<tr>
<td>12</td>
<td>Sham</td>
<td>67</td>
<td>M</td>
<td>46</td>
<td>Wernicke, fluent</td>
<td>88 882</td>
<td>Frontal operculum, posterior inferior frontal gyrus, anterior insula</td>
<td>SP</td>
<td>NS, SFA, R</td>
</tr>
</tbody>
</table>

Mean, 57.5* Mean, 28630.5*  

3 TMS 59 F 50 Wernicke, fluent 12 956 Posterior superior temporal gyrus P NP, R, MP  
4 TMS 66 F 78 Apraxic, fluent 1209 Putamen, external capsule, posterior insula P NP, R, MP  
7 TMS 59 F 44 Global, nonfluent 1114 Posterior superior temporal gyrus, angular gyrus SP NS, R  
10 TMS 83 M 21 Wernicke, fluent 61 238 Frontal operculum, posterior inferior frontal gyrus, anterior insula S, SP NS, WP, YN  
13 TMS 63 F 60 Wernicke, fluent 15 047 Putamen, external capsule, anterior insula P NP, R  
14 TMS 70 F 18 Wernicke, fluent 46 511 Posterior superior temporal gyrus, angular gyrus SP NS, WP, YN  

Mean, 45.2* Mean, 23012.5*  

The applied speech and language therapy methods and tasks are coded as follows: MP indicates minimal pairs; NP, naming with progressive phonemic cues; NS, naming with semantic cues; P, phonological therapy aiming at the phonological output lexicon; R, repetition; S, semantic therapy aiming at the semantic system; SFA, semantic feature analysis; SP, semantic therapy aiming at the connection between the semantic system and the phonological output lexicon; WN, written naming; WP, word–picture matching; YN, yes–no judgments for attributive information about the pictures.

*No significant between-group difference.
SLT indicates speech and language therapy; M, male; F, female; MCA, middle cerebral artery.

In a similar way, the functional networks involved in language tasks are modified in patients recovering from aphasic stroke. The cortical excitability in perilesional, but also contralateral homologous, regions is increased.25,26 Several studies indicated the unfavorable influence of these abnormal right-hemispheric activation patterns for language recovery27–29; other neuroimaging studies confirm that patients with a favorable outcome predominantly functionally reintegrate left-hemispheric structures.26,27,30 Thus, recovery of poststroke aphasia seems to be most effective when perilesional cortical areas can be reactivated.5,22

### Table 2. LIs for the IFG, the Upper Temporal Region (Temporal), and the Supplementary Motor Area Before and After the Intervention Period (Pre/Post), No. of TMS Sessions, and Time Between Infarction and Baseline PET in Days

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Group</th>
<th>LI IFG Pre/Post</th>
<th>LI Temporal Pre/Post</th>
<th>LI SMA Pre/Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sham</td>
<td>12/−30</td>
<td>−34/−8</td>
<td>20/22</td>
</tr>
<tr>
<td>6</td>
<td>Sham</td>
<td>17/−12</td>
<td>−20/−12</td>
<td>18/24</td>
</tr>
<tr>
<td>8</td>
<td>Sham</td>
<td>22/3</td>
<td>−100/−100</td>
<td>−38/39</td>
</tr>
<tr>
<td>12</td>
<td>Sham</td>
<td>27/−41</td>
<td>−51/−49</td>
<td>−100/−100</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>17/54</td>
<td>38/−47</td>
<td>27/11</td>
</tr>
<tr>
<td>4</td>
<td>TMS</td>
<td>8/−12</td>
<td>−24/−6</td>
<td>40/24</td>
</tr>
<tr>
<td>7</td>
<td>TMS</td>
<td>−49/−17</td>
<td>1/0</td>
<td>−10/2</td>
</tr>
<tr>
<td>10</td>
<td>TMS</td>
<td>−100/−31</td>
<td>−15/24</td>
<td>−29/2</td>
</tr>
<tr>
<td>13</td>
<td>TMS</td>
<td>81/59</td>
<td>−7/20</td>
<td>−19/11</td>
</tr>
<tr>
<td>14</td>
<td>TMS</td>
<td>−8/35</td>
<td>−100/2</td>
<td>0/6</td>
</tr>
</tbody>
</table>

SMA indicates supplementary motor area.

**Figure 3.** Change of LIs in Broca area with positive values indicating a shift toward the left hemisphere and negative values indicating a shift to the right.
confirmed by studies aiming at facilitation of left-hemispheric activation in patients with chronic aphasia using transcranial direct-current stimulation, which suggested increased naming accuracy after anodal or cathodal stimulation of left-hemispheric areas, respectively.\textsuperscript{31,32} The role of a persistently increased contralateral activation however remains open to debate. According to some authors, it should be seen as a maladaptive, ineffective compensation channeled by the loss of left-hemispheric inhibition due to the lesion.\textsuperscript{19,30,33–35}

Uncontrolled case reports indicate persistent positive effects of repeatedly administered, inhibitory rTMS to the right-hemispheric Broca homolog in patients with chronic aphasia,\textsuperscript{6,7} although a recent open-protocol study by the same group suggests a good response for some patients only.\textsuperscript{5} Another uncontrolled case-series presented a clinical improvement in patients with chronic aphasia who were treated with low-frequency rTMS over the area that was homologous to the most activated one during word repetition, arguing that transcallosal inhibition of the compensating region should be suppressed irrespective of the hemisphere.\textsuperscript{36} However, the lack of a control group in all of these studies does not allow a final conclusion.

**PET Imaging and Data Analysis**

Our data analysis focused on the change of the laterality index in the IFG, calculated by subtraction of the laterality indices pre- and post-TMS, with additional exploration of clinical outcome parameters. LIs were based on peak values within the regions of interest. In patients in whom the IFG is completely destroyed, left frontal activations can occur in cortex adjacent to the lesion.\textsuperscript{20} We thus evaluated peak activations in the immediate surrounding target area in those cases. Because the absolute level of activation can vary between patients, we used LIs as outcome variables to test our primary hypothesis that inhibitory stimulation of the contralateral homologous region would shift task-induced brain activity back to the left hemisphere. As hypothesized, we observed an activation shift toward the right hemisphere in the control group, which was suppressed in the therapy group.

The observed between-group differences in both network reorganization and clinical improvement were relatively large so that they were significant despite our limited sample size and the use of a placebo group, which typically decreases observed effects.\textsuperscript{37} We did not control for factors such as gender, infarction size, or time since stroke, which may have caused significant bias into any direction. However, infarction size and time since stroke did not differ significantly between the groups.

**Transcranial Magnetic Stimulation**

In contrast to former studies, we included a control group that received speech and language therapy and TMS with the same intensity and duration as the therapy group, but that was stimulated over the vertex instead of the right-hemispheric IFG. Because TMS elicits sensations such as muscle twitches, this sham-stimulation procedure as well as the high level of blinding increased the specific contrast between the groups. Stimulating the vertex very probably has no negative effect on speech and language, as it has none in healthy subjects.\textsuperscript{38} To establish a therapy protocol that could easily be used in large multicenter trials of stroke rehabilitation, we chose a navigation method that is based on individual neuroanatomy but does not require devices for stereotaxic tracking.

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**Table 3. Subtest and Total Scores in the AAT Before and After the Intervention Period (Pre/Post) TT Token Test**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>TT (Error) Pre/Post Maximum</th>
<th>Repetition Pre/Post Maximum</th>
<th>Written Pre/Post Maximum</th>
<th>Naming Pre/Post Maximum</th>
<th>Comprehension Pre/Post Maximum</th>
<th>Total Pre/Post Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>0/0</td>
<td>73/73</td>
<td>99/110</td>
<td>48/50</td>
<td>53/68</td>
<td>78/73</td>
</tr>
<tr>
<td>02</td>
<td>0/5</td>
<td>73/65</td>
<td>83/92</td>
<td>45/46</td>
<td>50/57</td>
<td>52/57</td>
</tr>
<tr>
<td>03</td>
<td>45/40</td>
<td>40/44</td>
<td>0/15</td>
<td>36/37</td>
<td>0/0</td>
<td>34/34</td>
</tr>
<tr>
<td>04</td>
<td>36/33</td>
<td>46/48</td>
<td>127/132</td>
<td>55/57</td>
<td>47/63</td>
<td>50/54</td>
</tr>
<tr>
<td>05</td>
<td>40/26</td>
<td>44/50</td>
<td>70/88</td>
<td>43/46</td>
<td>37/65</td>
<td>48/54</td>
</tr>
<tr>
<td>06</td>
<td>4/3</td>
<td>66/67</td>
<td>146/147</td>
<td>66/68</td>
<td>86/85</td>
<td>68/67</td>
</tr>
<tr>
<td>07</td>
<td>35/35</td>
<td>47/47</td>
<td>71/54</td>
<td>43/42</td>
<td>15/20</td>
<td>44/45</td>
</tr>
<tr>
<td>08</td>
<td>32/32</td>
<td>48/48</td>
<td>146/146</td>
<td>66/66</td>
<td>65/82</td>
<td>54/64</td>
</tr>
<tr>
<td>09</td>
<td>33/27</td>
<td>48/50</td>
<td>97/130</td>
<td>47/56</td>
<td>15/23</td>
<td>44/45</td>
</tr>
<tr>
<td>10</td>
<td>41/44</td>
<td>43/41</td>
<td>0/59</td>
<td>29/42</td>
<td>10/32</td>
<td>42/47</td>
</tr>
</tbody>
</table>

*All scores are raw scores.*
pared with state-of-the-art frameless stereotaxy systems, this method for localization of Broca area is sufficiently precise. Surface distance measurements were calculated in the imaging laboratory and could then easily be communicated to the rehabilitation facility. In the same manner, this could be done in multicenter trials, which increases the applicability of our approach in future studies.

**Clinical Variables**

Analyses of the change in total AAT score revealed a significant clinical improvement in the therapy group, whereas the patients of the sham group did not improve significantly. The fact that all patients showed some clinical improvement is not contrary to our hypothesis that right-hemispheric recruitment impedes optimal functional recovery. At baseline, there had been no significant group difference concerning mean AAT scores. The significant clinical group difference concerning the AAT improvement in addition to the PET results supports the assumption of a regional hierarchy in regeneration of poststroke aphasia. Looking at the AAT subtests, we found a significant improvement in the naming subtest in the TMS group ($P = 0.03$) in line with previous studies.6,7

The patients in our study had different aphasia types with Wernicke aphasia being the most common followed by Broca and global aphasia and 1 patient with amnic aphasia. These figures differ slightly from previous studies with more global and anomic aphasia cases,39–41 but this can be explained by our selection of moderately affected subjects. Random allocation to the groups resulted in both Broca aphasia cases being treated in the sham group and the only subject with anomic aphasia being treated in the TMS group. Due to the pilot nature of the present study, the significance of this can only be speculated. Generally it can be said that Broca is more severe than anomic aphasia,39 but also might have a larger potential for clinical improvement.42

Furthermore, given the rationale behind inhibitory stimulation of the right IFG, we would expect the therapy to be especially effective in Broca aphasia. The fact that all patients with Broca aphasia were assigned to the sham group thus indicates that right frontal stimulation is effective, although the lesion does not necessarily affect the Broca area per se. This is in accordance with a previous study in patients with brain tumor, in which we have shown that for a right frontal activation to occur, the lesion needs to affect the perisylvian cortex.20 Such similar remote effects of lesions in different locations may also explain why there is no clear 1-to-1 relationship among lesion location, aphasia type, and extent of improvement of language function.41

Especially the contribution of subcortical structures in language is not clear.43 A recent study found more severe aphasias in patients with cortical than in subcortical damage,29 but this might be partly due to lesion size rather than specific location alone. In the present study, 2 patients in the TMS group presented with subcortical lesions and had clear, but not higher-than-average, increases in total AAT scores. Interestingly, these 2 patients did not show a shift back to the left hemisphere in response to stimulation.

The inclusion of subjects with heterogeneous aphasia forms and different lesion locations might complicate the interpretation of our preliminary results because these variables affect the activation patterns and mechanisms of cortical reorganization.22,44,45 However, as discussed, both frontal and temporal lesions lead to activation of right-hemispheric Broca homolog and thus might benefit from complementary rTMS.20 Furthermore, effectiveness in only selected aphasia syndromes or lesion locations would severely limit the clinical significance of this new approach. It remains however to be tested in future studies if the outcome can further be improved by stimulating syndrome- or lesion-specific sites.

We took several measures to provide for best possible blinding. Subjects in both groups were treated and examined following a protocol that differed only by the magnetic stimulation location. Everyone except those applying the rTMS was blinded. Unblinded analysis was performed only at the level of statistical group comparisons. In retrospect, it might have been advantageous to let an outsider perform a group allocation aimed at balancing for selected patient factors such as the patient gender (minimization) instead of the restricted block randomization (fixed block size of 10 patients without stratification) we used. Randomization strategies are however mostly favored because minimization does not account for elimination of bias on unknown factors.46

**Summary**

We examined patients with aphasia in the subacute phase after first-time stroke. Our results suggest that inhibitory magnetic stimulation of the right-hemispheric Broca homolog together with subsequent speech therapy prevents establishing right-hemispheric lateralization and, furthermore, that this normalization of the activation pattern might be accompanied by better clinical improvement. These results should encourage the next step toward larger multicenter clinical trials. To explore the long-term effectiveness, applicability, and safety of rTMS as a complementary aphasia therapy, large clinical trials including the systematic assessment of adverse effects and the comparison to other methods of noninvasive brain stimulation are necessary. Furthermore, they will examine the value of different rTMS protocols and the effects of rTMS in different lesion locations, thus defining indications and contraindications for specific patients with aphasia.

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**Disclosures**

None.

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