The Right Inferior Frontal Gyrus and Poststroke Aphasia
A Follow-Up Investigation

Lutz Winhuisen, MD; Alexander Thiel, MD; Birgit Schumacher, MD; Josef Kessler, PhD; Jobst Rudolf, MD; Walter F. Haupt, MD; Wolf D. Heiss, MD

Background and Purpose—Recently, a combined repetitive transcranial magnetic stimulation (rTMS) and activation positron emission tomography (PET) study showed essential language function of the right inferior frontal gyrus (IFG) in some right-handed acute poststroke aphasics. We reexamined these patients in the chronic phase to test whether the right IFG remained essential for language performance.

Methods—We reexamined 9 male right-handed patients, age 41 to 75 years, with aphasia 8 weeks after left hemispheric stroke. rTMS was performed over the maximum activation within the left and right IFG as defined by $^{15}$O water PET to interfere with language function. A positive rTMS effect was defined as increased reaction time latency or error rate in the semantic task relative to no stimulation.

Results—PET activations of the IFG were observed on the left (2 patients) and bilaterally (7). During rTMS interference over the left IFG, all patients had positive TMS effects, indicating that the left IFG remained essential. Stimulation over the right IFG yielded positive rTMS effects in 2 patients with persisting right IFG activation. Two patients with positive rTMS effects over the right side in the initial study did not show these effects at follow-up. Language performance improved in all patients.

Conclusions—Successful regeneration from poststroke aphasia seems to depend more on the integration of available language-related brain regions than on recruiting new brain regions during the rehabilitation process. Restoration of the left hemisphere network seems to be more effective, although in some cases, right hemisphere areas are integrated successfully. (Stroke. 2007;38:1286-1292.)

Key Words: aphasia | positron emission tomography | recovery of function | stroke | transcranial magnetic stimulation

A previously published study$^1$ showed that activation of the right inferior frontal gyrus (IFG) is essential for residual language function in some right-handed patients experiencing aphasia early (10 days) after left hemispheric stroke. The compensatory potential, though, seemed to be less effective than in patients who recovered left IFG function in these early stages. A hierarchy in recovery from poststroke aphasia and a limited compensatory potential of the nondominant hemisphere were assumed.$^2$

Several prior studies investigated changes in activation patterns and their relation to recovery from poststroke aphasia$^3$–$^6$ over time. A favorable recovery was hypothesized when the patients predominantly activated structures in the ipsilateral hemisphere$^7$ during the recovery phase, eg, the left superior temporal gyrus$^8$ and IFG.$^9$–$^{11}$ Right IFG activation seemed to have some compensatory significance in the early recovery after poststroke aphasia. However, patients who activated the homologous contralateral regions in a semantic task showed poorer compensation of their deficits.$^1$

We thus reexamined the patients of the previous study,$^1$ again after 6 weeks of rehabilitation, including language therapy, to detect whether activation of the right IFG still persisted and whether it was still essential and had any influence on language performance. As in the previous study, we used individual positron emission tomography (PET) activation images coregistered to 3D-rendered MRI reconstructions of the patient’s brain and head to localize the stimulation sites for repetitive transcranial magnetic stimulation (rTMS) and to identify the activated areas in the left and right IFGs during a semantic task. The increase of latency and errors in verb generation during rTMS over the activated regions were measured and compared with the results of the initial examinations 10 days after stroke.$^1$ We estimated a correlation between regression of right IFG activation and recovery of language function.

Methods

Patients
We re-examined 9 male right-handed patients, age 41 to 75 years, with aphasia after a left hemispheric stroke within 8 weeks after stroke (the Table). Eight of the patients had already been examined...
Clinical and Demographic Data of Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, y</th>
<th>Aphasia</th>
<th>Stroke Location (All Left Hemisphere)</th>
<th>HI</th>
<th>Verbal Fluency</th>
<th>rTMS Left, 10 Days</th>
<th>rTMS Right, 10 Days</th>
<th>Maximum z-Scores Within IFG at 10 Days (Used for Coil Positioning) Left [z]</th>
<th>Maximum z-Scores Within IFG at 8 Weeks (Used for Coil Positioning) Left [z]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Mild verbal amnesia, reduced verbal fluency</td>
<td>MT</td>
<td>100</td>
<td>26 32</td>
<td>+ (LAT)</td>
<td>...</td>
<td>+ (LAT)</td>
<td>5.16 3.05 3.9 0.5</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>Moderate sensory aphasia, reduced verbal fluency</td>
<td>MT, PT</td>
<td>100</td>
<td>14 15</td>
<td>+ (LAT)</td>
<td>...</td>
<td>+ (LAT)</td>
<td>2.23 1.47 2.2 1.3</td>
</tr>
<tr>
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<td>50</td>
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<td>MT, PT</td>
<td>100</td>
<td>13 19</td>
<td>+ (LAT)</td>
<td>...</td>
<td>+ (LAT)</td>
<td>1.85 1.29 6.1 2.7</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>Mild global aphasia, reduced verbal fluency</td>
<td>AT</td>
<td>100</td>
<td>11 24</td>
<td>+ (NR)</td>
<td>...</td>
<td>+ (NR)</td>
<td>2.8 2.78 2.9 2.5</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>Moderate global aphasia</td>
<td>MT, PT</td>
<td>100</td>
<td>12 20</td>
<td>+ (LAT)</td>
<td>...</td>
<td>+ (LAT)</td>
<td>1.8 3.46 3.4 2.5</td>
</tr>
<tr>
<td>6</td>
<td>63</td>
<td>Mild global aphasia, reduced verbal fluency</td>
<td>AT</td>
<td>100</td>
<td>9 24</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>1.81 4 2.8 3.7</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>Mild sensory aphasia, severe expressive aphasia</td>
<td>AT, MT</td>
<td>100</td>
<td>8 24</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>1.96 5.35 3.2 2.3</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
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<td>AT</td>
<td>80</td>
<td>8 22</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>1.8 1.8 4.1</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>Mild sensory and moderate expressive aphasia</td>
<td>AT</td>
<td>100</td>
<td>10 25</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>+ (LAT)</td>
<td>2.7 3.2 1.8 3.2</td>
</tr>
</tbody>
</table>

AT indicates anterior territory of the middle cerebral artery; MT, middle territory of the middle cerebral artery; PT, posterior territory of the middle cerebral artery; fluency, verbal fluency test; HI, handedness index; NR, no response; VGD, verb generation disturbance; LAT, latency increase; +, positive rTMS effect. Other abbreviations are as defined in text.

in the previous study,1 and 1 additional patient was included. In 3 patients included in the first study, the follow-up examination after 8 weeks could not be performed because they refused further participation in the study. The follow-up PET and rTMS examinations were performed on the same day. The patients with a wide range of aphasia symptoms were formally tested with the Aachen Aphasia Test Battery.12 The documented deficits ranged from mild to severe aphasia. No patient experienced epileptic seizures before or after stroke. Written, informed consent was obtained from all patients or their next of kin. The study protocol was approved by the ethics committee of the University of Cologne. A detailed description of the PET and rTMS methods has already been published in our previous study,1 and here we present only a summary of the rTMS and PET paradigms.

PET/Semantic Task Paradigm

We used PET to localize and measure language-associated activity within the IFG. The patients had to perform a semantic matching task and had to decide whether a given verb read aloud matched semantically with an object presented on a computer monitor. The PET scans of each patient were normalized and coregistered to the MR image. Activation images were generated as z-score images; the activation foci were localized on a fusion of the z-transformed activation image with the coregistered MR image. The maximum z-scores within the left and right IFGs (see the Table) were used to determine the optimum stimulation point for rTMS.

Repetitive Transcranial Magnetic Stimulation

The stimulation sites were determined by surface 3D MR images of the skull and brain and marked on the skin over the maximum of activation of the left IFG on PET. The same procedure was applied to the right side. In cases of no right IFG activation, the triangular part of the IFG was used as the target. The precision of this approach is 6 mm.11 rTMS was performed with a Magstim 200 rapid stimulator with a 76-mm figure-of-eight coil and an intensity of 20% maximum output (2.1 T) at a frequency of 4 Hz.

A list of nouns was used for the generation task, with 2 minutes of rest between trials and stimulation sites. The nouns had been selected for high association content from a list of high-frequency German nouns.14 rTMS stimulation was started after 10 words and continued for high association content from a list of high-frequency German nouns.14 rTMS stimulation was started after 10 words and continued for another 5 nouns after the end of the 10-second pulse train. The stimulation parameters were chosen according to current safety guidelines for rTMS.15,16

The voices of investigator and patient were recorded digitally, and the reaction time latencies were measured with use of a freely available software package (Quartz AudioMaster). Three types of TMS effects were observed: (1) the patient did not respond to the word, (2) the reaction time for the response increased during stimulation, or (3) the produced verbs were not semantically related to the noun (verb generation disturbance).

The differences in verb generation latencies were assessed for each individual with use of a nonparametric version of the Stewart chart method for single-case statistics.17 The median, 25th, and 75th percentiles of reaction time latencies without TMS were calculated. A latency increase during TMS was significant if at least 3 latencies were >75th percentile of the trial without stimulation, corresponding to P<0.016. According to the presence or absence of TMS effects over the right IFG, patients were divided in 2 groups and tested for verbal fluency performance with a signed-rank test.

Results

Ten days after stroke,1 PET activations of the IFG were observed on the left (3 patients) and bilaterally (8). The
patients as a group had significantly longer latencies during stimulation over the left IFG, compared with no stimulation, but not over the right IFG (signed-rank test, P<0.05), thus indicating essential language function of the left hemisphere. In an individual analysis, 8 patients showed a TMS effect with a significant increase in reaction time during stimulation over the left IFG. Two patients immediately ceased to respond during stimulation. Thus, each of the 10 patients exhibited a TMS effect during stimulation over the left hemisphere. Right IFG stimulation was positive in 5 patients with right IFG activation, indicating essential language function. The individual results on PET and in the verb generation task with and without rTMS are shown in the Table.

In the follow-up examination 8 weeks after stroke, PET activations of the IFG were observed on the left (2 patients) and bilaterally (7). The patients as a group showed longer latencies during stimulation over the left IFG compared with no stimulation (signed-rank test, P<0.05) but not over the right IFG. These findings were similar to those of the first study. In individual results (Figure 1 and the Table), 8 patients showed a TMS effect with a significant increase in reaction time during stimulation over the left IFG, and 1 patient did not respond after stimulation onset but started responding again after the TMS stimulation ceased, indicating complete inhibition of language production. Our interpretation is that the damaged left hemispheric network in this case reacted in a very sensitive way to the rTMS pulse. The patient himself reported that he understood the words and wanted to speak, but immediately after the TMS train started, he could not imagine any words related to the nouns.

These findings indicate a persisting essential language function of the left IFG in all patients. Stimulation over the right IFG led to an increase in response latency in 2 patients, and 1 patient again additionally demonstrated a verb generation disturbance during stimulation. Both patients with a right positive rTMS effect showed significant activation in the right IFG in the PET study at 8 weeks. On the behavioral level, patients with a TMS effect over the left IFG only showed better performance in the verb generation task than did those with TMS effects over the right IFG (P<0.05, signed-rank test; Figure 2) 10 days after stroke. After 8 weeks, there was no significant difference between the groups (Figure 2).

Right IFG language function as determined by TMS was observed in 4 of 11 patients at day 10 and in 2 of 9 patients 8 weeks after stroke. Thus, as shown in the Table, in 2 patients the TMS effect of the right IFG persisted, and in 2 patients the effect vanished at follow-up. These changes in TMS were associated with a shift of language dominance back to the left hemisphere. However, new right IFG function did not occur after 8 weeks, and both persistence and disappearance of right IFG language function were associated with an increase of verbal fluency at follow-up.

**Discussion**

The activation of contralateral right hemispheric regions in right-handed poststroke aphasics has been reported repeatedly, but its contribution to the recovery of language function seems subsidiary. An efficient restoration of language networks depends on reintegration of homolateral predominant areas or their neighboring regions. The right hemispheric activation may be a result of insufficient recovery attempts or reduced transcallosal inhibition.

To investigate the functional impact of these activated areas, rTMS can be combined with functional neuroimaging methods, eg, PET, and applied to chronic or acute aphasic patients. Because PET activation alone does not give information about functional relevance, it was the aim of our study to show whether these activation patterns are essential for language function. We conclude that if rTMS over the right IFG is negative, despite right IFG activation in PET, the PET activation only reflects reduced inhibition of the disturbed left hemispheric network onto the right hemisphere but has no functional relevance.

A previous study showed that rTMS over the left IFG in right-handed normal volunteers interferes with semantic processing and repetition priming. TMS studies in patients with focal brain lesions (stroke or tumor) have shown that patients with such lesions are more susceptible to TMS interference than are normal subjects. Thus, qualitative TMS effects, like cessation of language production or semantic paraphasias, are observed almost exclusively in patients in whom the language network is already damaged. It has been demonstrated in studies with normal subjects that the relevant lateralized activation of the left IFG during semantic tasks (like the one used in this study) is located in the triangular part, which mainly corresponds to BA45. TMS interference in this area produces an increase in reaction time latencies only during semantic processing tasks but not during phonological tasks. In healthy volunteers, phonetic paraphasias and anarthria do not occur, nor does disturbance of articulation (no anarthria).

In our first study, we showed that right IFG activation can be essential for language function in some right-handed, acute poststroke aphasics patients after left hemispheric stroke, but that these patients have less favorable language performance (only initially, not at follow-up). A central question was whether this activation occurs in a long-term process of language rehabilitation or whether it is only a sign of a preliminary mismatch. Even if interhemispheric compensation seems to improve results in verbal comprehension, at least in some patients with Wernicke’s aphasia, it must be kept in mind that a recent study showed an improvement in naming pictures by suppressing the right Broca’s homolog with slow-rated rTMS treatment. This result is in line with findings that demonstrated improvements in finger movement tasks owing to rTMS-induced suppression of the contralateral premotor areas in healthy volunteers and premotor and primary motor areas of the unaffected hemisphere in stroke patients, which are probably explained by the interruption of contralateral inhibition. It would therefore be helpful to analyze the dimension of the interhemispheric inhibition and to identify the differences between patients with or without a positive rTMS effect over the right IFG by using an rTMS-adapted paired-pulse paradigm. This is difficult, however, because no quantifiable electrophysiological measures (like the amplitude of evoked motor potentials for the motor system) exist for the language system, and all rTMS effects...
can be observed only on the behavioral level. To circumvent these problems, rTMS has been used over the left IFG while task-associated changes in regional cerebral blood flow were measured simultaneously with PET in normal subjects. With this experimental design, a regional cerebral blood flow increase in the right IFG could be demonstrated. One may thus speculate that analogous regional cerebral blood flow changes could be shown in patients.

Our study is the first combined longitudinal rTMS and PET trial on poststroke aphasics and demonstrates the different

Figure 1. Individual results for the patients. The differences in verb generation latencies were assessed for each individual by using a nonparametric version of the Stewart chart method for single-case statistics. We show the median and the 25th and 75th percentiles (error bars) of reaction time latencies with and without TMS. A latency increase during TMS was significant when at least 3 latencies were >75th percentile of the trial without stimulation, corresponding to \( P<0.016 \). Patient 4 did not respond to the word (no response, NR) at 10 days and after 8 weeks during stimulation over the left IFG. Patient 8 additionally showed verb generation disturbance (VGD) during stimulation over the right IFG that he had not shown without stimulation.
Figure 1. continued
compensation strategies after left hemispheric stroke. We conclude from our data that the initially remaining language performance 10 days after stroke is mainly determined by the left hemisphere. During recovery, restoration of left hemisphere dominance seems to be a general principle. In only 2 patients, persistence of right IFG language function 8 weeks after stroke was observed, which also was associated with good recovery. However, restoration of transcallosal inhibition after recovery of the left hemispheric areas seems more likely. An important fact is that the right IFG activity seen after 8 weeks already occurred after 10 days. No patient showed right IFG activity for the first time after 8 weeks; thus, integration of the existing right IFG activation into the language network seems to play a greater role in recovery from poststroke aphasia than recruiting regions that were not activated initially. Other studies failed to show a late right hemispheric activation after stroke, which gives evidence for the hypothesis that the brain has to recruit preexisting language-competent areas in acute poststroke aphasia. Pre-morbid and perhaps bilateral language dominance and development might be an explanation for the successful integration of right hemispheric areas. Nevertheless, all patients were right handed and showed handedness indices ≥80. On the other hand, persisting right IFG activation may implicate a different compensation strategy. At least the abrupt occurrence of language disturbance in poststroke aphasics seems to limit the successful integration of contralateral speech areas, a compensation strategy that seems to be more effective in patients who experience language impairment that has developed over a longer period, eg, due to slowly growing left hemispheric brain tumors.

Conclusions
The set of brain regions available for language recovery is defined within the first days after stroke. Successful recovery from poststroke aphasia is probably more a question of integrating the available regions in a meaningful way than of recruiting new brain regions during the recovery phase. This integration process seems to be facilitated if the left hemisphere network can be restored. In some cases, however, right hemisphere areas can be successfully integrated.

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Disclosures
None.

References
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