Role of the Contralateral Inferior Frontal Gyrus in Recovery of Language Function in Poststroke Aphasia
A Combined Repetitive Transcranial Magnetic Stimulation and Positron Emission Tomography Study

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

Background and Purpose—Functional neuroimaging studies have demonstrated right inferior frontal gyrus (IFG) activation in poststroke aphasia. It remains unclear whether this activation is essential for language performance. We tested this hypothesis in a positron emission tomography (PET) activation study during a semantic task with repetitive transcranial magnetic stimulation (rTMS) on right-handed patients experiencing poststroke aphasia and examined whether rTMS stimulation over the right and left IFG would interfere with language performance.

Methods—Eleven patients with left-sided middle cerebral arterial infarction, 50 to 75 years of age, were tested with the Aachen Aphasia Test Battery and underwent 15O-H2O PET activation during a semantic task within 2 weeks after stroke. PET activation images were coregistered to T1-weighted MRIs. Stimulation sites were determined on renderings of head and brain over the maximum activation within left and right IFG. rTMS was performed with 20% maximum output (2.1 T), 10-s train duration, at 4Hz frequency. A positive rTMS effect was defined as an increased reaction time latency or error rate in the semantic task.

Results—PET activations of the IFG were observed on the left (3 patients) and bilaterally (8 patients). Right IFG stimulation was positive in 5 patients with right IFG activation, indicating essential language function. In a verbal fluency task, these patients had a lower performance than patients without right-sided TMS effect.

Conclusions—In some poststroke aphasics, right IFG activation is essential for residual language function. However, its compensatory potential seems to be less effective than in patients who recover left IFG function. These results suggest a hierarchy in recovery from poststroke aphasia and a (limited) compensatory potential of the nondominant hemisphere.

Key Words: aphasia □ recovery of function □ tomography, emission computed

More than 20% of patients with ischemic stroke experience aphasia, and 10% to 18% of survivors develop a persistent deficit. The extent of recovery ranges from complete restitution to severe aphasia without spontaneous speech production. The prognosis depends on the localization and extent of the ischemic lesion in the dominant hemisphere.

Functional neuroimaging (positron emission tomography [PET] or functional MRI) at rest and during activation tasks is used to visualize the brain areas involved in language processing and, in case of disturbance, the compensatory mechanisms within the functional network responsible for complete or partial recovery. Description and analysis of these mechanisms may help to understand the mechanisms of recovery and neuronal plasticity after ischemic stroke.

Recently, changes of activation patterns were investigated in their relationship with recovery from poststroke aphasia. From these studies, it has been hypothesized that patients with a favorable recovery predominantly activate structures in the ipsilateral hemisphere, but some activation of the right inferior frontal gyrus (IFG) has also been observed. One of the central questions is why right-handed, left-hemisphere language–dominant patients demonstrate activation in the contralateral hemisphere after left-hemispheric stroke and whether this activation is essential for recovery from aphasia.

Activated regions were observed in the superior temporal gyrus and in the IFG. There is little doubt that efficient restoration of language is usually achieved only if left temporal areas are preserved and can be reintegrated into the functional network. The activation of neighboring regions by collateral disinhibition results in a better residual function because homolateral original eloquent areas are involved. However, the question remains whether activation of the...
Clinical and Demographic Data of Patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Aphasia</th>
<th>Stroke Localization (All left-hemispheric)</th>
<th>Medication</th>
<th>HI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>53</td>
<td>Mild verbal amnesia, reduced verbal fluency</td>
<td>MT</td>
<td>ASA, HRI, PPI</td>
<td>100</td>
</tr>
<tr>
<td>P2</td>
<td>66</td>
<td>Moderate sensoric aphasia, reduced verbal fluency</td>
<td>AT, MT, PT</td>
<td>ASA, CPG, ACE-I</td>
<td>100</td>
</tr>
<tr>
<td>P3</td>
<td>59</td>
<td>Mild global aphasia</td>
<td>AT</td>
<td>ASA, ACE-I, DIU, BB, CaA</td>
<td>80</td>
</tr>
<tr>
<td>P4</td>
<td>50</td>
<td>Moderate sensoric aphasia, reduced verbal fluency</td>
<td>AT, MT, PT</td>
<td>ASA, GPT, DIU, BB</td>
<td>100</td>
</tr>
<tr>
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<td>ASA, CPG, ACE-I, DIU</td>
<td>100</td>
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<tr>
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<td>ASA, BB</td>
<td>100</td>
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<tr>
<td>P7</td>
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<td>MT, PT</td>
<td>HEP, AT2-A, BB</td>
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<td>ASA</td>
<td>100</td>
</tr>
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<td>P9</td>
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<td>AT</td>
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<td>P10</td>
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<tr>
<td>P11</td>
<td>69</td>
<td>Mild sensoric aphasia, severe expressive aphasia</td>
<td>AT, MT</td>
<td>ASA, HEP, ACE-I, BB, GLI</td>
<td>100</td>
</tr>
</tbody>
</table>

P1 through P11 indicates patients 1 through 11; ACE-I, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid; AT, anterior territory of the middle cerebral artery; AT2-A, angiotensin II type 2 antagonist; BB, β-blocker; CPG, clopidogrel; DIG, digoxin; DIU, diuretic; CaA, calcium antagonist; GLI, glibenclamide; GPT, gabapentin; HEP, heparin; HRI, 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor; MT, middle territory of the middle cerebral artery; PPI, proton pump inhibitor; PT, posterior territory of the middle cerebral artery; THY, thyroxin; TOL, tolterodine; verbs/min, verb generation per minute; fluency, verbal fluency test; HI, handness index; LI, lateralization index; NR, no response; LAT, latency increase.

PET and MRI

PET scans were performed on a CTI/Siemens ECAT EXACT HR scanner in 3D mode. Data acquisition started with intravenous bolus injection of 370 MBq of $^{15}$O-H$_2$O and lasted for 45 s. Eight subsequent scans were obtained on each patient. After corrections for random coincidences, scatter, and measured attenuation, each scan was reconstructed to 47 slices (3.125-mm thickness, and 2.16-mm pixel size within a 128×128 matrix), yielding images of relative cerebral blood flow (CBF). For localization of infarcts and PET-measured CBF changes, MRI scanning was performed with a 1.5-T Philips Gyroscan using a spin echo sequence (repetition time 700 ms; echo time 8 ms), producing 256 transaxial T1-weighted slices of 1-mm thickness.

Semantic Task Paradigm

During the PET scans, patients had to perform a semantic matching task with 4 replications. They had to decide whether a given verb read aloud matched semantically with an object presented as a line drawing a computer monitor. As a resting condition, subjects looked silently at nonsense characters. The presentation of stimuli began with tracer injection and ended 45 s after scan start. Because a wide range of aphasia symptoms were included in the study, the presentation rate was adapted to the patients’ ability to perform the task. Frequency effects in PET have been reported as changes in the activation intensity, which do not interfere with our study because we used PET only to localize the IFG. Tasks were presented in a balanced sequence. Because the same regions are activated in semantic decision tasks as in verb generation tasks, we chose the semantic task because it was less exhausting for the partly critically ill patients.

Image Analysis

The PET scans of each patient were coregistered to the MRI and were normalized by dividing each intracerebral voxel by the average of all intracerebral voxels, thus yielding normalized relative CBF values. Normalized PET images were smoothed applying a spherical Gaussian filter with 12-mm full width at half maximum. Activation images were generated as z-score images. Activation foci were localized on a fusion of the z-transformed activation image with the coregistered MRI. The maximum z-scores within the left and right IFG (Table) were used to determine the optimum stimulation point for rTMS.

Patients and Methods

We examined 11 male right-handed patients aged 50 to 75 years with aphasia after left-hemispheric stroke within 2 weeks after stroke (Table). All examinations were done within 24 hours to ensure minimal time lag between the PET and rTMS examinations. Patients with a wide range of aphasia symptoms were formally tested using the Aachen Aphasia Test Battery. The documented deficits ranged from mild to severe aphasia. No patients 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.

Contralateral IFG is essential for the observed level of residual language production. Functional imaging studies alone can only demonstrate that regions are involved in a certain task but not whether they are essential for it. In recent years, studies with repetitive transcranial magnetic stimulation (rTMS) concentrated on inhibiting speech production by inducing a transient “lesion” over the assayed areas, and rTMS-induced inhibition was used to investigate the distinct contributions of the frontal inferior and medial frontal gyrus in verbal working memory.

To investigate the role of the right IFG in poststroke aphasia after left-hemispheric stroke, we identified the activated areas in the left and right IFG in H$_2$O-PET during a semantic task in right-handed patients experiencing poststroke aphasia after left-hemispheric stroke. We examined whether rTMS over the activated right IFG can induce increased latencies or verb generation errors as it does over the left IFG in normal controls. Taking into consideration the variability in the functional and cytoarchitectonic anatomy of the IFG, we individually coregistered PET activation images to 3D-rendered MRI reconstructions of the patient’s brain and head to localize the stimulation sites for rTMS over both hemispheres. We hypothesized a distinct role of the right IFG for language recovery in poststroke aphasia.
Repetitive Transcranial Magnetic Stimulation

The stimulation sites were determined by surface 3D magnetic resonance imaging of the skull and the brain. The lateral end of the eyelid (A) and the tragus (B) were identified. Then a point on the skin over the maximum of the activation of the IFG in PET was marked (C). The software calculated a baseline on the surface of the skin connecting A and B and constructed a perpendicular line from C onto the baseline, thus yielding the intersection (I). The distances of AB, AI, BI, and CI were calculated and used to determine the stimulation point C on each individual patient’s head. In case of right inferior frontal activation, the same procedure was applied to define the optimum position over the right side. In case of no right inferior frontal activation, the triangular part of the IFG was used as the target. The precision of this approach is 6 mm.22 rTMS was performed using a Magstim 200 rapid stimulator with an intensity of 20% maximum output (2.1 T) at a frequency of 4 Hz. A 76-mm figure-8 coil was positioned over the defined stimulation sites over the right and the left IFG. For each trial, a list of nouns was used for the generation task, with 2 minutes of rest in between trials and stimulation sites. Over each stimulation site, rTMS stimulation was started after 10 words. After the end of the 10-s pulse train, the generation task was continued for another 5 nouns. The stimulation sites were determined by surface 3D magnetic resonance imaging. Over each stimulation site, rTMS stimulation was performed using a Magstim 200 rapid stimulator with an intensity of 20% maximum output (2.1 T) at a frequency of 4 Hz. A 76-mm figure-8 coil was positioned over the defined stimulation sites over the right and the left IFG. For each trial, a list of nouns was used for the generation task, with 2 minutes of rest in between trials and stimulation sites. Over each stimulation site, rTMS stimulation was started after 10 words. After the end of the 10-s pulse train, the generation task was continued for another 5 nouns. The stimulation parameters were chosen according to current safety guidelines for rTMS.23–25 We used subthreshold intensity because we assumed increased sensitivity to stimuli in poststroke patients. In a previous study, it was shown that subthreshold rTMS led to an increase of CBF in H$_2$O-PET.30

After the TMS session, all patients were admitted to ward for ≥12 hours after the procedure. No epileptic seizures were observed during the session or within the 12-hour observation period. During each trial, the voices of investigator and patient were recorded digitally, and reaction time latencies between the end of the word pronounced by the investigator and the onset of phonation by the subject were measured using a freely available software package (Quartz AudioMaster). Three types of TMS effects were observed: (1) the patient did not respond to the word (no response), (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 [VGD]).

The differences in verb generation latencies between periods before and after onset of stimulation were assessed for each individual using a nonparametric version of the Stewart chart method for single case statistics.31 The median, twenty-fifth, and seventy-fifth percentile of the reaction time latencies without TMS were calculated. A latency increase during TMS was significant if ≥3 latencies were above the seventy-fifth percentile of the trial without stimulation, corresponding to a P<0.016. According to the presence or absence of TMS effects over the right IFG, patients were divided into 2 groups and tested for verbal fluency performance using a signed rank test.

**Results**

As a group, patients had significantly longer latencies during stimulation over the left IFG compared with no stimulation (signed rank test; P<0.05) but not over the right IFG. Eight patients showed a TMS effect with significant increase of reaction time during stimulation over the left IFG. Two patients immediately ceased to respond after the beginning of the stimulation and resumed response only after the end of the stimulation train (Table). Stimulation over the right IFG led to an increase of response latencies in 4 patients, and 1 patient additionally demonstrated a VGD that he had not shown without stimulation. One patient stopped responding to the nouns during stimulation over the right IFG. The individual results in PET and in the verb generation task with and without rTMS are shown in the Table. From the Table, it can be seen that all patients with rTMS right positive showed significant activation in the right IFG in PET.

The patients with TMS effect only over the left IFG demonstrated a significantly better performance in the verb generation task than those with TMS effect over the right IFG. (P<0.05; signed rank test; Figure).

**Discussion**

In our study, 53% of the patients had a persisting significant left IFG activation (z=2) despite left hemispheric infarction. The right IFG was activated in 73% of subjects. This reproduces the findings of previous studies,8,10 which reported activation of the right IFG in patients with poststroke aphasia. In normal subjects, right hemispheric dominance was found only in 7.5%32 and no significant right-hemispheric activation.22 Thus, it may be concluded that this increased proportion was caused by the infarction and not by physiological variation of hemisphere dominance. These results coincide with those of Thiel et al.12,33 who found a proportion of 60% right IFG activation in patients with aphasia caused by brain tumors.
rTMS was applied over the left and right IFG to determine the functional role of these brain areas for language performance. Language production comprises different processes such as semantic retrieval, semantic processing, phonological encoding, articulatory planning, and vocalization. Depending on the site of TMS interference, different types of effects on verbal output are observed. Early rTMS studies, which were performed without guidance by neuroimaging, mainly produced anarthria, and the correlation of TMS effects with WADA test results was poor. Stimulation sites associated with these effects were localized posterior to the IFG over the premotor, motor, and insular cortex. Using neuroimage guidance and more sophisticated systems for coil placement, more distinguished types of TMS interference could be evoked. Of special interest is the interference of semantic processing over the anterior part of the IFG (as in the present and a previous study with normal subjects), which clearly is an impairment of language function and not a simple motor speech disruption because the main effect was a latency increase. This indicates an interference with semantic processing but not phonological encoding (no anarthria) even in the hyperactive state. There has been extended discussion whether the IFG serves for decision function or semantic processing, which goes beyond the scope of the present article. Because we found longer answering latencies with rTMS over the right IFG than we did over the left in normal subjects and no anarthria, a semantic or memory function can also be assumed for the right IFG in aphasics and be distinguished from simple speech function (articulation and vocalization).

In accordance with the PET results, 10 of 11 patients showed a disturbance of verb generation during TMS stimulation over the left IFG, indicating that the latter is still essential for language production in the majority of left hemisphere stroke patients. Right-handed controls also show left-hemispheric activation with a positive rTMS effect.

In 5 patients, language production could also be inhibited during TMS over the right IFG, demonstrating its additional role for language performance in these subjects. Thus, the patients can be distinguished with regard to their reaction to TMS interference: 1 group with an effect during TMS over the right IFG (and thus essential language function, further referred to as right positive) and the other group with a TMS effect exclusively over the left IFG (right negative). The 2 groups differed with respect to language performance. The right negative group performed significantly better than the right positive group in a verbal fluency test (Figure).

One patient stands out who demonstrated inhibition over the right IFG but not over the left. An explanation for this result might be that localization of the stimulation site was inaccurate on the left. On the other hand, the possibility remains that this subject had a premorbid bilateral language representation, and the rTMS result indicates a loss of function of the left IFG and a functional transfer to the right IFG.

Our findings indicate that the increased activation of right IFG in PET concurs with TMS vulnerability and thus with essential language function. However, the level of performance achieved by this interhemispheric compensation is lower than in patients without essential language function of the right IFG. Only the reactivation of ipsilateral eloquent areas results in satisfactory recovery of language function; the contralateral areas only have a limited compensatory capacity. The left IFG is still essential for language function in nearly all patients, irrespective of the right IFG activation. The fact that patients without right-sided TMS effect showed a better verbal fluency than right positive ones underlines the role of left hemisphere language areas and intrahemispheric compensation for the quality of residual language function.

The question remains whether the observed shift of language dominance is attributable to some kind of brain plasticity or whether it is only a limited compensatory mechanism of the preexisting language network.

The surprising finding that the bilateral participation in speech production is less efficient for residual language function than the contribution restricted to left-hemispheric areas might justify a speculation: the destruction of left eloquent areas reduces the effect of transcallosal inhibition and thereby affects the left dominant specialization for language. This modified network after loss of the leading role of specialized left hemispheric centers represents a deficient network for speech production and explains the observed deficits in performance. For this speculation, it must be kept in mind that this study was performed in the subacute phase (within 2 weeks) after the stroke to show the mechanisms in acute aphasia. Previous studies indicate that the right IFG activation is temporary and decreases within 8 weeks after onset of stroke (ie, as soon as long term reorganization processes turn out to be more effective and speech performance improves).

Further studies are necessary to prove the hypothesis that a blockade of the potentially irritating effect of the right hemispheric activation can improve disturbed speech production and could play a role as an adjuvant treatment strategy for rehabilitation of poststroke aphasia.

**Conclusions**

This combined PET and rTMS study shows that the activation of the right IFG is essential for language function in some
right-handed, acute poststroke aphasics after left-hemispheric stroke. These patients have less favorable language performance than patients in whom the right IFG is not contributing to task performance. Thus, the compensatory potential of right IFG activation seems to be less effective for residual language function than that of the left IFG. These data support the hypothesis of a hierarchy in recovery mechanisms from poststroke aphasia with a restricted compensatory potential of the nondominant hemisphere.

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References
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