

Effects of Noninvasive Brain Stimulation on Language Networks and Recovery in Early Poststroke Aphasia

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Background and Purpose—Modulation of activity in language networks using repetitive transcranial magnetic stimulation (rTMS) may possibly support recovery from poststroke aphasia. Case series and feasibility studies seem to indicate a therapeutic effect; however, randomized sham-controlled, proof-of-principle studies relating clinical effects to activation patterns are missing.

Methods—Twenty-four patients with subacute poststroke aphasia were randomized to a 10-day protocol of 20-minute inhibitory 1 Hz rTMS over the right triangular part of the posterior inferior frontal gyrus or sham stimulation, followed by 45 minutes of speech and language therapy. Activity in language networks was measured with O-15-water positron emission tomography during verb generation before and after treatment. Language performance was assessed using the Aachen Aphasia Test battery.

Results—The primary outcome measure, global Aachen Aphasia Test score change, was significantly higher in the rTMS group (t test, $P=0.003$). Increases were largest for subtest naming ($P=0.002$) and tended to be higher for comprehension, token test, and writing ($P<0.1$). Patients in the rTMS group activated proportionally more voxels in the left hemisphere after treatment than before (difference in activation volume index) compared with sham-treated patients (t test, $P=0.002$). There was a moderate but significant linear relationship between activation volume index change and global Aachen Aphasia Test score change ($r^2=0.25$; $P=0.015$).

Conclusions—Ten sessions of inhibitory rTMS over the right posterior inferior frontal gyrus, in combination with speech and language therapy, significantly improve language recovery in subacute ischemic stroke and favor recruitment of left-hemispheric language networks. (*Stroke*. 2013;44:2240-2246.)

Key Words: plasticity ■ recovery ■ stroke ■ transcranial magnetic stimulation ■ treatment

Case studies and small controlled trials have indicated a beneficial effect of noninvasive brain stimulation (NBS) as supportive therapy, in addition to speech and language therapy (SLT), for the treatment of poststroke aphasia.¹⁻³

NBS methods, such as conventional repetitive transcranial magnetic stimulation (rTMS), theta burst TMS, or transcranial direct current stimulation, are capable of modulating cortical excitability within a brain region into inhibitory or excitatory direction using either magnetic or electric fields. These effects are foremost local insofar as they directly affect the cortex at the stimulation site,⁴ but if the stimulated region constitutes a node within a larger network (eg, human language networks), activity within the entire network might be affected indirectly.^{5,6}

The effects of NBS on disturbed language networks are not yet fully understood, and various mechanisms have been postulated to explain the compensation of focal disturbances within the functional networks by excitatory or inhibitory effects on different brain regions.^{5,7}

The complex interaction of various ipsi- and contralateral brain regions on language function after ischemic damage to the dominant hemisphere may be modulated by NBS in different ways: excitatory stimulation to perilesional areas of the ipsilateral hemisphere⁸ and inhibitory stimulation to contralateral homotopic speech areas seem to improve poststroke recovery.⁹⁻¹¹

After a feasibility study¹⁰ indicated the possibility to recruit appropriate patients with ischemic stroke and to combine a

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sham-controlled stimulation protocol with SLT, it was the aim of the present randomized, blinded, and sham-controlled proof-of-principle study to test an rTMS protocol that (1) could easily be integrated into a standard rehabilitation setting starting within the first weeks after the event, (2) could be tested under realistic clinical conditions on a typical population of poststroke aphasics, and (3) would measure activation-induced changes in language networks before and after therapy, although this neuroimaging component was not required to select patients or stimulation sites.

Methods

A total of 30 patients with first ischemic infarct within the left middle cerebral artery territory were recruited at the rehabilitation hospital RehaNova in Cologne, Germany. Based on variance estimates from our feasibility study,¹⁰ this sample size has a power of 0.91 to detect a 5% change in global Aphasia score at $P=0.05$. All patients were right handed,¹² with German as the first language. Exclusion criteria were symptomatic prior cerebrovascular accidents, neurodegenerative or psychiatric disease, epilepsy, renal or liver failure, life-threatening diseases, and auditory or visual deficits that might impair testing and metallic implants. All patients were assessed with the Aachen Aphasia Test (AAT)¹³ by a certified speech and language therapist blinded to randomization. The study protocol was approved by the Ethics Committee of the Cologne University and the Federal Office for Radiation Protection. From the total of 30 patients, 15 were consented and randomized to the sham group and 15 to the treatment group. Four patients discontinued the study because they did not tolerate MRI or PET scans, and 2 patients were unable to complete the protocol within the time window because the TMS device was defective and required repair. Of these, 4 were randomized to the sham group and 2 to the TMS group, thus yielding a total of 24 patients with 11 subjects assigned to the sham and 13 to the TMS group (Table 1).

PET imaging was performed after a previously published protocol.¹⁰ Briefly, 8 consecutive measurements of relative cerebral blood flow with O-15-water (370 MBq per injection) were performed on a CTI/Siemens ECAT EXACT HR scanner in 3-dimensional (3D) mode. During the activation condition, high-frequency German nouns were presented over headphones at a fixed rate of 1 noun every 6 seconds, and patients were instructed to generate out loud 1 semantically matching verb to each noun. A low-level baseline task with eyes closed and no auditory input was used as control condition. Patients were familiarized with the task in a training session before the scan. 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 3D filtered back projection. All patients also underwent MRI scanning comprising T1-weighted, diffusion-weighted, and FLAIR images.

After randomization, patients either received 20 minutes of inhibitory 1 Hz rTMS with an intensity of 90% of the daily-defined individual resting motor threshold over the triangular part of the right posterior inferior frontal gyrus (treatment group)¹⁴ or over the midline at the vertex (sham group) using a Magstim Rapid² stimulator with a double 70-mm coil. The magnetic field for the sham procedure was maximal over the sagittal sinus, with the somatosensory cortex of the lower extremity being the closest cortical regions. Coil positions were determined based on individual MR images following a recently published protocol.^{10,15} SLT sessions were started immediately after the stimulation procedure.

Patients in both groups received 45 minutes of deficit-specific aphasia therapy focused on the individual linguistic symptoms by a blinded certified therapist. Therapeutic tasks were chosen to preferentially activate left hemisphere networks.¹⁶ Although the stimulation procedure itself could only be done single blinded, the subsequent SLT sessions, as well as the pretreatment and posttreatment assessments and PET activation studies, were double blinded. Statistical analysis of clinical and imaging data was done by the Montreal group

(C.A. and A.T.) who were not involved in patient recruitment and treatment, and unblinding was done in the last step of the analysis.

Raw scores from all AAT subtests (language comprehension, token test, picture naming, writing, and repetition) were transformed to T-scores based on a standardization sample.¹³ The global AAT score was calculated as the sum of subtest scores, and the absolute difference between posttreatment and initial global score was the primary clinical outcome, variable global AAT change. Changes in test scores of the 5 subtests were secondary outcome variables (Table 1).

The 8 PET images of each patient were spatially normalized to MNI space using SPM8 (Wellcome Trust Center for Neuroimaging).¹⁷ Individual images of task-associated relative cerebral blood flow changes were generated for each patient and transformed to Z-score images as previously described. Z-score images were thresholded at $Z>2$, and activation volumes (AV) of all suprathreshold voxels were calculated for each hemisphere using the 3D tool.¹⁸ AV indices (AVI) were calculated following the formula $[(AV_{\text{left}} - AV_{\text{right}}) / (AV_{\text{left}} + AV_{\text{right}})] \times 100$, thus yielding AVIs between -100 (voxels in right hemisphere only) and $+100$ (voxels only in left hemisphere). For visualization purposes, spatially normalized AVs of all patients were summed up and the percentage of subjects activating at a certain voxel was calculated, thus yielding a volume of activation map with voxel values representing the percentage of subjects with above-threshold activation (Figure 3).

For all outcome measures, the null hypothesis of normality and independence could not be rejected at the $P=0.05$ level. Thus, between-group differences in global AAT change and AVI change were assessed using *t* tests for independent samples. A 2-factor repeated measures ANOVA was performed to test for differential treatment effects on AAT subtests and linear regression to model the relationship between global AAT and AVI changes. Statistical analysis was performed using SPSS Statistics 20, IBM.

Results

Aphasia types, infarct location, and volumes, as well as initial test scores and other relevant demographic information, are listed in Table 1. The T1-weighted MRI scans are provided for each case as Figure I in the online-only Data Supplement. Average treatment onset time was 5.4 weeks (TMS group) and 7.2 weeks (sham group), with 50% of subjects in each group starting between 24 and 59 days (interquartile range). All aphasia types were represented in both groups, with Wernicke aphasia being the most frequent. There was no significant between-group difference for these variables; patient groups were very closely matched regarding initial test performance. Only 3 patients achieved the highest possible raw test scores in 1 subtest each at posttreatment (2 patients in token test and 1 patient in repetition), thus introducing only minimal bias in terms of ceiling effects. No serious adverse events (eg, seizures) were observed during or after the therapy. Patients were debriefed after the last therapy session with respect to possible side effects of the stimulation, but none was reported. None of the patients in the TMS group showed a decline of language function in any subtest.

Aphasia recovery measured as absolute change in global AAT score was significantly higher in the TMS group (mean $23.6 \pm SD 12.15$) than in the sham group (mean $7.55 \pm SD 11.00$; $P=0.003$; Figure 1A; Table 2).

A highly significant overall treatment effect ($P=0.003$) was also found in the subtest analysis. There was no significant interaction between treatment and subtest. The mean increase in subtest scores was higher for the TMS group in all subtests. It was highest for subtest naming ($P=0.002$) and showed a

Table 1. Demographic Data

	Sham	TMS	<i>P</i> Value
Total n	11	13	
By aphasia type			
Broca	3 (27%)	1 (8%)	
Wernicke	5 (45%)	7 (54%)	
Global	2 (18%)	2 (15%)	
Amnesic	1 (9%)	3 (23%)	
By infarct location			
Anterior MCA	3 (27%)	2 (15%)	
Posterior MCA	2 (18%)	4 (31%)	
Anterior and posterior MCA	1 (9%)	1 (8%)	
Subcortical	5 (45%)	6 (46%)	
Age, y	71.2 (7.78)	69.8 (7.96)	0.67
Infarct volume, ccm	244 (242.9)	233 (197.0)	0.89
Activation volume index	−14.2 (40.93)	−17.2 (32.54)	0.84
Initial Aphasia Test T-Scores			
Global (sum)	251.1 (39.51)	251.5 (32.44)	0.98
Comprehension	48.3 (5.68)	48.5 (12.82)	0.97
Token test	53.3 (11.93)	51.5 (7.66)	0.66
Naming	48.6 (10.38)	47.2 (6.33)	0.69
Writing	47.1 (7.29)	51.5 (7.29)	0.19
Repetition	53.6 (8.39)	53.4 (10.87)	0.95
Time after stroke, d	50.6 (22.63)	37.5 (18.52)	0.13
Time between assessments, d	16.1 (1.97)	18.5 (5.55)	0.18

Values represent mean and SD in parenthesis (if not otherwise specified). The *P* value refers to a *t* test for independent samples. MCA indicates middle cerebral artery; and TMS, transcranial magnetic stimulation.

significant trend for subtest comprehension, writing, and token test ($P < 0.1$; Figure 1B; Table 2). No differential treatment effect was found for different aphasia types (2-factor ANOVA with factors treatment group and aphasia type, summary Table 2).

Changes in AVI were significantly larger in the treatment group (TMS 40.9 ± 29.91) compared with the sham group (sham -9.8 ± 39.71), indicating a shift toward the left hemisphere in the TMS and a consolidation of the right-hemispheric network in the sham group ($P = 0.002$; Figure 2A; Table 2). Figure 3 illustrates the differential response.

A linear regression analysis was performed to test the hypothesis whether the extent of left or right language network recruitment as measured with the change in AVI would correlate with clinical recovery (Table 2). The regression analysis showed a moderate but significant linear correlation between both variables (linear regression, $P = 0.015$; $r^2 = 0.25$; Figure 2B).

Discussion

Aphasia affects more than a third of all stroke victims, and early and intensive SLT is the only effective treatment to date¹⁹ but usually is limited in duration and intensity. Thus, new treatment strategies are required, which render conventional SLT more effective. With this sham-controlled, blinded, and randomized study, we present first evidence that inhibitory rTMS over the right posterior inferior frontal gyrus can

easily be applied in a clinical rehabilitation setting, is safe, and improves the effectiveness of conventional SLT by fostering the reconstitution of left-hemispheric language networks.

Severity of aphasia and recovery potential depend on the extent of damage to the bihemispheric functional network (reviews).^{20,21} Restoration of the original activation pattern within the language network seems to be the most effective strategy toward complete recovery but is usually only possible after transient ischemic attacks or small ischemic lesions outside the primary language centers and their connections. A satisfactory recovery can be obtained if lesion effects can be compensated by activation of perilesional areas within the ipsilateral hemisphere, a strategy called intrahemispheric compensation. The importance of this mechanism has been demonstrated in imaging and combined imaging and TMS studies.²² Lesions affecting crucial nodes of the ipsilateral network release activity in homotopic areas of the contralateral hemisphere as a result of reduction in transcallosal inhibition.⁶ This interhemispheric compensation is usually less efficient, especially when language dominance is more or less shifted to the right hemisphere. Reversal of this dominance shift with SLT may improve recovery of speech performance^{21,23} by reestablishing functional networks of the affected hemisphere.²⁴ This can be achieved by excitatory stimulation of speech-relevant perilesional areas in the dominant hemisphere. Another possible approach is to reduce overactivation of homotopic regions in the nondominant hemisphere, which

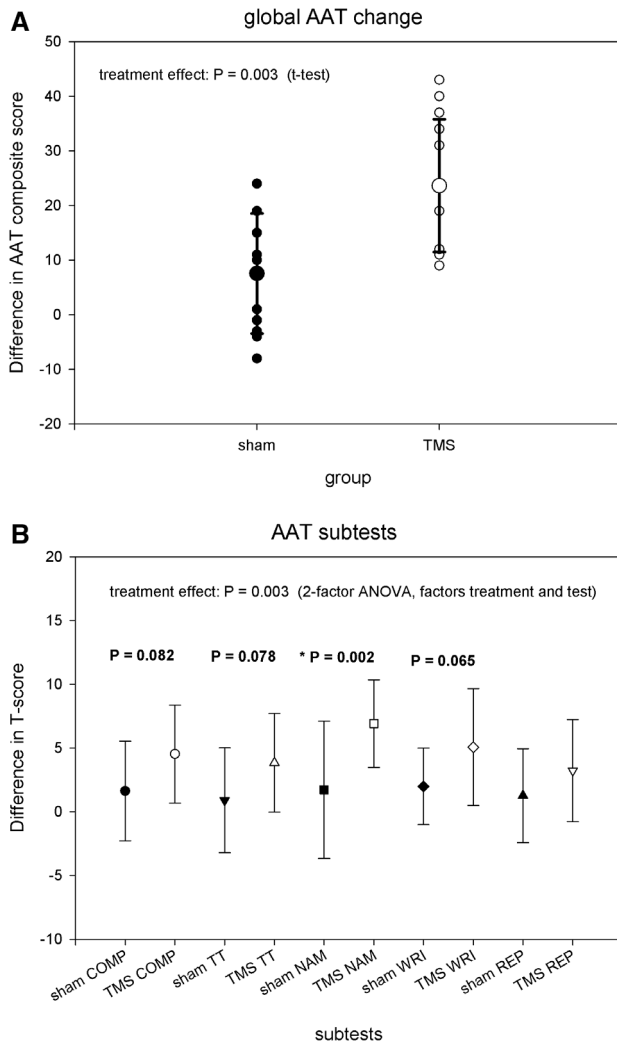


Figure 1. Change in global Aachen Aphasia Test (AAT) score is significantly greater in the transcranial magnetic stimulation (TMS) group than in the sham-treated group (**A**). The TMS effect is largest for naming (NAM) performance, but a trend toward better performance of the treatment group was also observed for comprehension (COMP), token test (TT), and writing (WRI) performance. No effect was seen on word repetition (REP).

is because of reduced transcallosal inhibition after damage of primary language areas of the dominant hemisphere. This overactivation of the right hemisphere was interpreted as a maladaptive process^{25,26} and actually may interfere with reactivation of the residual functional networks in the dominant hemisphere. Therefore, the reduction of the increased activity in the unaffected hemisphere by inhibitory NBS might be an alternative strategy to increase the susceptibility of language areas to SLT in the affected hemisphere.

Based on these pathophysiological concepts, most evidence for the effectiveness of rTMS in the literature comes from case reports, case series, and small pilot studies applying inhibitory low-frequency rTMS to right-hemispheric homotopic areas^{27–29} (and from reviews,^{2,3,7,30}) specifically to the right pars triangularis.^{14,31} In all these reported patients, a positive effect on the tested deficit was observed with the exception of one.³² We have thus chosen this inhibitory contralateral paradigm for our study.

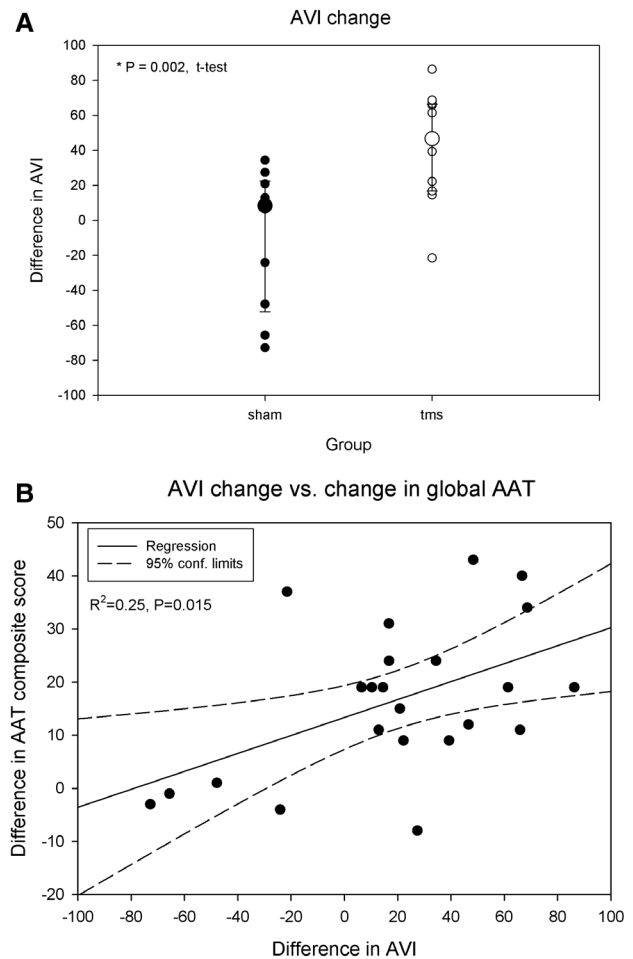


Figure 2. Changes in activation volume indices (AVI) after treatment of sham and transcranial magnetic stimulation (TMS) groups (**A**). Negative values indicate a larger volume shift toward the right hemisphere, and positive values indicate a larger volume shift toward the left hemisphere. Changes were significantly larger in the TMS group, indicating a relative increase in left-hemispheric activation volumes after treatment. Patients with relatively larger shifts (positive AVI change) showed larger changes in global Aachen Aphasia Test (AAT) scores after treatment (**B**).

The contralateral inhibitory paradigm also seems to have greater potential with respect to actual clinical implementation because only structural MR images are required to localize the posterior inferior frontal gyrus¹⁵ and stimulation is given only to the unaffected hemisphere, thus minimizing the risk of inducing seizures by stimulation of peri-infarct tissue. Excitatory stimulation to the affected hemisphere will likely require functional imaging for stimulation site selection because intrahemispheric compensational activations are more variable.

Our study, based on these pathophysiological considerations, demonstrated a highly significant treatment effect: the intervention group experienced a significantly larger improvement in the global AAT score than the sham group (Figure 1A). We did not find a significant interaction between treatment group and subtest, suggesting that the TMS effect may lead to similar improvements in all subtests. Consistent with previous studies,^{28,33} the strongest increase was observed on naming performance. However, we also observed a trend

Table 2. Summary of Statistical Tests

Test and Variables	Parameters	95% Confidence Interval	P Value
<i>t</i> test: global AAT change			
Treatment effect			
TMS vs Sham	16.2	6.18 to 25.96	0.003**
2-Factor RM ANOVA: subtest change			
Treatment effect			
TMS vs Sham	3.2	1.23 to 5.19	0.003**
Treatment×subtest interaction			NS
Subtests (TMS vs sham)			
Comprehension	2.9	−0.34 to 6.20	0.082*
Token test	2.9	−0.45 to 6.32	0.078*
Naming	5.2	1.44 to 8.96	0.002**
Writing	3.1	−0.23 to 6.43	0.065*
Repetition	2.0	−1.33 to 5.24	NS
2-Factor ANOVA: global AAT change			
Treatment effect			
TMS vs sham	16.2	6.18 to 25.96	0.012**
Aphasia types			NS
Treatment×aphasia interaction			NS
<i>t</i> test: AVI change			
Treatment effect			
TMS vs sham	50.7	20.57 to 80.85	0.002**
Linear regression: global AAT change			
AVI change	$b=0.17\pm0.063$		0.015**
	$a=13.3\pm2.89$		<0.001**
	$r^2=0.25$		

Parameters in column 2 are the differences between group means for *t* test and ANOVAs, as well as slope (*b*) and intercept (*a*) with respective SEs for linear regressions. AAT indicates Aphasia Test battery; AVI, activation volume index; NS, not significant; and TMS, transcranial magnetic stimulation.

*A trend at $P<0.1$.

**Significance at $P<0.05$.

toward a higher average change in comprehension, writing, and token test (Figure 1B), thus explaining the absence of a significant interaction. This observation may indicate that the TMS effect is perhaps less specific than initially assumed and that the application of TMS pulses to a very specific but crucial network node (like the pars triangularis)¹⁴ might indeed modulate activity in a wider network and thus also contribute to recovery of different linguistic functions. It remains to be tested whether, for example, inhibitory modulation of other crucial network nodes (like the right posterior superior temporal gyrus) may yield different results in terms of recovery of specific language functions. A small pilot study with inhibitory transcranial direct current stimulation of the right posterior superior temporal gyrus¹¹ in global aphasics also reported a global improvement that, however, was strongest in auditory comprehension, thus suggesting a possible weighting of the desired therapeutic effect by the choice of stimulation side.

In our study, different aphasia types were balanced between treatment groups, with Wernicke aphasia being the most frequent type. A formal statistical analysis did not indicate an influence of aphasia type on recovery; however, the study was underpowered to detect a specific aphasia type and treatment interaction, so larger studies are needed to specifically address

this question. The same limitation holds for possible differential effects of infarct size and location. In the present study, both groups were matched with respect to average infarct size; however, infarct location probably is the more relevant indicator because small strategic lesions can have severe clinical effects.²⁷

Activation patterns before treatment showed the expected rightward shift of network activity, which has been reported in multiple imaging studies.^{21,22,34} The spatial extent of the right-hemispheric network involvement was comparable between both treatment groups in terms of quantitative indices (Figure 2) and AV maps (Figure 3). The treatment effect was going along with a change in the network activity mainly in the treatment group: whereas the right accentuated activation pattern persisted in the control group, a shift in the extent of network activity to the left hemisphere was observed in the TMS group. This means that TMS treatment seems to modulate network activity in a direction that is known to be associated with a favorable recovery²³ and gives first evidence that language recovery can be achieved by reactivating the dominant left-hemispheric functional network. Results of the linear regression analysis suggest that this change in interhemispheric balance as measured with the AVI explains

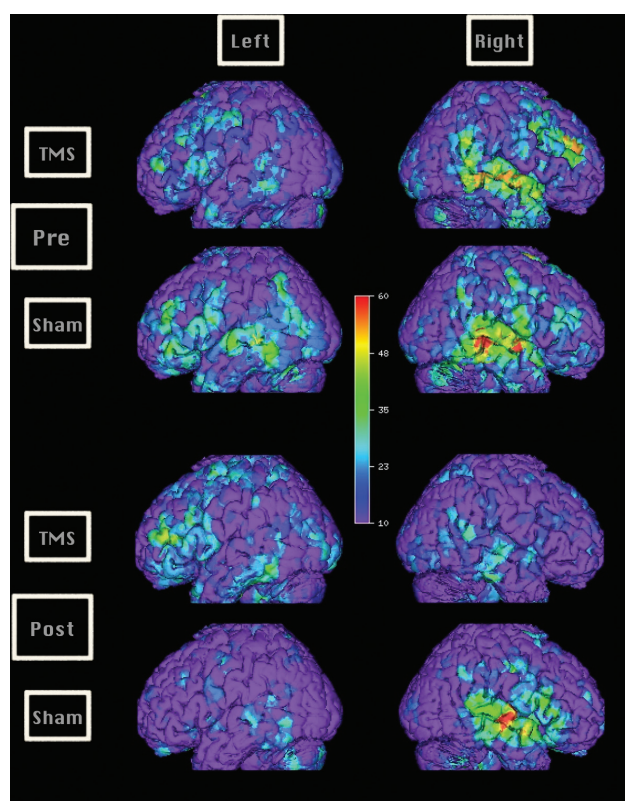


Figure 3. Maps of activated volumes in different patient groups. Voxel values represent the number of patients activating at each voxel before and after treatment. TMS indicates transcranial magnetic stimulation.

≈25% of the observed variability of our primary outcome variable. Larger multicenter clinical trials are now required to identify further factors that impact aphasia recovery.

Our study is the first to apply rTMS to patients with aphasia in the subacute stage after stroke. Although the advantage of studying chronic patients (>6 months) is obvious with respect to a stable baseline condition, aphasia rehabilitation usually takes place in the subacute phase. Within the German rehabilitation system, patients are usually referred to rehabilitation clinics within 4 to 6 weeks after stroke, and daily SLT sessions as standard of care are started during that period. Supportive therapies thus need to fit into these procedures should they become a viable treatment option in the future. Evidence from motor recovery studies in humans³⁵ also lends support to the concept of early treatment within the first days and weeks after ischemia when upregulation of neurotrophic factors peaks and synaptic plasticity is increased. Indeed, our patients on average exhibited relatively larger right-hemispheric AV before the treatment, and only the rTMS group had a positive average AVI posttreatment, indicating larger left-hemispheric AV, whereas in the right hemisphere preponderance seemed to consolidate in the sham group, thus pointing to a window of opportunity for modulation of activation patterns within the first couple of weeks.

Conclusion

The results of this study indicate that inhibitory 1 Hz rTMS over the right posterior inferior frontal gyrus, in combination

with SLT, improves recovery from poststroke aphasia and favors recruitment of left-hemispheric language networks. The proposed protocol sets the stage for larger multicenter trials to further confirm the effectiveness of NBS and to specifically address the influence of lesion location, stimulation site, activation pattern, and possibly timing of NBS therapies.³⁶ Finally, studies directly comparing different NBS modalities are required to determine the most effective and economic treatment strategy under clinical conditions.

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Disclosures

None.

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