Review

Is transcranial magnetic stimulation an effective therapy for aphasia?

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Practice Points

- Aphasia is a common deficit after ischemic stroke affecting about one-third of patients. Speech and language therapy in poststroke aphasia has limited efficacy.
- Functional neuroimaging by PET has demonstrated that a lesion of primary language areas activates perilesional and contralateral regions of the speech-specific functional networks.
- Long-term recovery of language function is related mainly to reactivation of primary or perilesional areas of the dominant hemisphere. Contralateral homolog areas have an inhibitory effect on the reintegration of perilesional ipsilateral regions into the functional network.
- Depending on the frequency, repetitive transcranial magnetic stimulation (rTMS) can exhibit inhibitory or excitatory effects on the cortex, which can be imaged by PET.
- Results from case reports, case series and small controlled trials suggest that inhibitory rTMS on contralateral homolog areas is able to improve language function in aphasics but a large controlled trial is necessary to prove the clinical efficacy of this therapeutic strategy.
- Alternative strategies of noninvasive stimulation techniques, such as excitatory rTMS, anodal and cathodal transcranial direct current stimulation and theta burst transcranial magnetic stimulation need to be investigated.

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SUMMARY Functional imaging studies suggest that recruitment of contralesional areas hinders optimal functional cortical reorganization in patients with post-stroke aphasia. In this review, imaging data of activation shifts in the course of poststroke aphasia are described and data on transcallosal disinhibition of right-hemispheric homolog speech areas are presented. The activated right-hemispheric regions are the target for inhibitory repetitive transcranial magnetic stimulation (rTMS) as a treatment option for aphasia. Several cases and one small controlled study have reported improved function after rTMS treatment in chronic aphasics. In one controlled feasibility study, rTMS over the right homolog of Broca's area was compared with sham stimulation over the vertex in the subacute stage and demonstrated a reduction of the activation shift to the right hemisphere in the treated group, which was related to a significantly improved outcome in the Aachen Aphasia Test. The clinical application of rTMS as a supportive treatment for poststroke aphasia requires further proof of efficacy in a large multicenter trial.

Aphasia, the inability to communicate by means of spoken or written language, is one of the most disabling consequences of ischemic stroke, which affects more than a third of all stroke victims [1,2]. Compared with nonaphasic stroke patients, patients with aphasia are more severely affected on admission, have more severe disability and are more frequently discharged to long-term care. The presence of aphasia is an independent predictor for longer hospital stays and increased use of rehabilitation services [3]. Early and intense speech and language therapy (SLT) seems to be the only effective treatment to date [4,5]. Emerging evidence from recent studies investigating the effectiveness of such treatments indicates that the intensity of treatment within the first weeks after stroke is an especially important predictor of stroke outcome, independent of initial stroke severity. The rehabilitation reality on stroke units, however, is far from the ideal of intensive early rehabilitation treatment. A study from Australia indicated that on acute stroke wards, patients spent 88.5% of their time in bed and only 5.2% of the day with a qualified therapist [6]. Therefore, additional treatment strategies are required to improve recovery of language functions, especially after stroke.

Cortical localization of language function

In the brain of healthy right-handers and the majority of left-handers, language function is a faculty of the left, dominant hemisphere. This asymmetry is established during language acquisition [7] and actively maintained in the adult brain by fiber bundles, connecting both hemispheres across the corpus callosum (so-called 'transcallosal pathways'). These fibers are glutamatergic and are connected to inhibitory interneurons in the nondominant hemisphere [8]. This means that language areas active in the dominant hemisphere (e.g., Broca's area) actively suppress activity in homologous areas of the nondominant hemisphere (transcallosal inhibition). A unilateral and focal brain lesion, such as a stroke, to language areas of the dominant hemisphere not only reduces activity in the affected hemisphere, thus causing aphasia, but also releases activity in the unaffected hemisphere via interruption of those transcallosal fibers (transcallosal disinhibition: reduction of excitatory activity in glutamatergic transcallosal fibers, which reduces the activity of inhibitory interneurons in the nondominant hemisphere; reviewed in [9,10]). This activity of brain regions in the nondominant hemisphere in the first days and weeks after a stroke has repeatedly been demonstrated in sequential brain imaging studies [10,11]. In the following weeks and months of recovery, brain activation shifts back to the dominant hemisphere. The extent of this backward shift to the dominant hemisphere varies from patient to patient and appears to be a major factor for successful recovery of language function [12] in the acute and subacute phase. Longitudinal studies of aphasia patients after stroke in the dominant hemisphere gave evidence for a hierarchical organization of recovery mechanisms [11,13,14]. Language restoration to a large extent is usually achieved by reintegration of the full language network within the dominant hemisphere. If primary functional centers are damaged, satisfactory function can be established by involving areas around the lesion; this intrahemispheric

compensation as a result of decreased collateral inhibition activates the ipsilateral network. If the functional network in the dominant hemisphere is severely damaged, contralateral homotropic areas are disinhibited and try to compensate for the defect; this interhemispheric compensation is the basis for some improvement of language function even in patients with severe destruction of the dominant speech network but, in most cases, is not as efficient as intrahemispheric compensation in the acute and subacute phase. Despite this compensatory and, to a limited extent, beneficial activity of the homotropic right hemisphere areas [14], re-establishing functional networks of the affected dominant hemisphere early in the course of recovery seems to be the superior strategy over recruiting homologous brain regions in the unaffected nondominant hemisphere in order to achieve good rehabilitation results [15,16]. This does not mean that right-hemisphere regions do not play a role in compensation of language function; in other words, patients with slowly evolving left-hemispheric lesions (low-grade gliomas) indeed manage to integrate right-hemisphere activity in a useful way but, with more rapid progressive lesions (high-grade gliomas) or lesions with sudden onset (stroke), good residual language function mainly depends on the extent of left-hemisphere activity [15,17]. In chronic aphasics, right-hemispheric regions can be compensatory [18,19] but this seems to only be the second-line long-term strategy if additional recruitment of left-hemisphere areas is no longer possible. It was also shown that a second stroke in the right hemisphere worsened aphasia due to an earlier left-sided lesion [18]. Based on this evidence, a reasonable strategy for improvement of language function would seek to actively suppress right-hemisphere and to enhance left-hemisphere activity in the early phase after stroke and possibly use techniques more targeted at the right hemisphere in the chronic stage.

Strategies for the treatment of aphasia

Most approaches to aphasia rehabilitation with SLT aim to activate residual functioning brain areas in the stroke-affected hemisphere. The theoretical foundation of such approaches to rehabilitation has been supported over the last decade by numerous functional imaging studies [16]. Independent of the affected modality (motor or language function), re-establishing functional networks of the affected hemispheres seems to be the superior strategy over recruiting homologous brain regions in the unaffected hemisphere in order to achieve good rehabilitation results. In the healthy brain the transcallosal pathway modulates interhemispheric inhibition meaning that areas active in one hemisphere (e.g., motor cortex) can suppress activity in homologous areas of the contralateral hemisphere. The existence of these mechanisms has been demonstrated in normal subjects using transcranial magnetic stimulation (TMS) in the motor system [20] and with imaging-guided TMS for the language system [21]. A unilateral and more focal brain lesion, such as a stroke, not only reduces activity in the affected hemisphere but also causes, via transcallosal fibers, a release of activity in the unaffected hemisphere (transcallosal disinhibition). The contribution of this activation in the nonlesioned hemisphere to functional recovery, however, seems to be limited [22]. It has thus been suggested that the lack of inhibition of the nonlesioned hemisphere is likely to interfere with the recovery of language function.

Based on results from chronic nonfluent aphasics [23,24], the overactivation of the right hemisphere was interpreted as a maladaptive strategy, which might be the result of decreased transcallosal inhibition due to damage of the left-hemispheric speech areas [25]. Thus, downregulating this increased activity in the unaffected hemisphere using noninvasive brain stimulation (NBS) should make language areas in the affected hemisphere more susceptible to the effects of SLT.

Repetitive transcranial magnetic stimulation

TMS, a noninvasive tool for the electrical stimulation of neural tissue, produces a magnetic field and due to the rapid changes in magnetic field strength induces electrical currents through the intact skull in the brain area beneath the coil. The induced current pulse lasts approximately 200 µs, and activates the axons of neurons in the cortex and subcortical white matter [26] if the induced current exceeds the threshold for generating an action potential (suprathreshold stimulation). This current threshold is usually determined by recording compound muscle action potentials from a relaxed muscle after application of single TMS pulses over primary motor cortex. The stimulator output (in percent of maximum output) corresponding to this threshold current is referred

to as resting motor threshold (RMT). Since this electrical current activates different types of neurons – excitatory or inhibitory – the result of this stimulation is complex and depends on different thresholds of neurons and on the intensity and pattern of the pulse. Whereas single-pulse TMS was originally applied to studies of the human motor cortex and evokes activity in muscles on the opposite side of the body [27], repetitive TMS (rTMS) has been introduced as a therapeutic alternative in a large number of diseases of the CNS (reviewed in [28,29]). rTMS uses a train of pulses of the same intensity at a given frequency from one to 20 stimuli per second. Depending on the frequency and intensity of the repetitive stimuli, rTMS can modulate or disrupt cortical function; the resulting inhibition or facilitation depends particularly on the frequency of pulses, with rates below 4 Hz suppressing, and above 5 Hz increasing cortical excitability [30]. As a consequence of these effects, suppressed or increased regional cerebral blood flow and regional metabolism were detected by combining rTMS and functional neuroimaging techniques [31], which also demonstrated functional connectivity between regions in the brain [32]. Other TMS modalities using patterns of high-frequency pulses (so-called 'theta bursts') are thought to modulate cortical excitability by long-term potentiation and depression of cortical synapses. These, and related neuronal mechanisms, have been suggested to induce changes in neurotransmitter–receptor interaction and gene induction and may explain long-lasting modulatory effects by rTMS. These modulatory effects of rTMS may correct an imbalance in function due to disease and even cause reorganization in brain circuitry, helping the brain to restore itself. This mechanism of action might be especially effective in functional deficits observed after stroke, in which reorganization in remaining undamaged pathways may compensate for loss of function [33]. This approach might be especially useful in situations where overactivity in areas in the nonstroke hemisphere interferes with the recruitment and functional integration of perilesional regions in the affected hemisphere and thereby impairs recovery [34]. In this interaction model, rTMS facilitates the recruitment of perilesional regions into the functional network by diminishing activity in contralateral brain regions that was released by transcallosal inhibition and thereby increasing the compensatory ability to re-establish function [29].

Imaging of effects of rTMS

Low-frequency, inhibitory rTMS – the so-called 'lesion mode' – interferes with normal brain function and can be used to identify cortical areas involved in selective language functions. rTMS at 4 Hz applied for 10–30 s interferes consistently with language function and, at the same time, minimizes the risk of inducing seizures [35].

Collateral ipsilateral as well as transcallosal contralateral inhibition were shown by applying rTMS during PET activation studies [21]: rTMS of 4 Hz at RMT for 30 s interfered with the function of Broca's area, which was identified as the left inferior frontal gyrus by maximal flow activation during verb generation. The positive TMS effect (interference with normal function) is classified into three levels:

- No response to stimulus (e.g., no verb generated to a presented noun);
- Wrong response to the stimulus (e.g., a verb is generated that is not semantically related to the presented noun);
- The latency of the reaction time to the stimulus is changed (e.g., faster response indicates facilitation and slower response indicates inhibition).

During the resting state, inhibitory rTMS decreased ipsilateral and contralateral regional cerebral blood flow **(Figure 1)**. During the task (e.g., verb generation), rTMS caused a decrease in regional cerebral blood flow under the coil and often an increase in the surrounding ipsilateral regions outside the coil as well as in the contralateral homologous area **(Figure 2)**. Despite this activation of the Broca's area homolog in the right hemisphere, rTMS prolonged the latencies of the responses to verbal stimuli. This result indicates that right-sided activity can be increased in normal subjects by TMS as a result of decreased transcallosal inhibition, but disinhibition cannot compensate for the interference with the left Broca's area.

The role of activation in the right hemisphere for residual language performance can be investigated by combining rTMS with functional imaging, for example, PET [36]. Such an approach was used in 11 patients with predominantly nonfluent aphasia 2 weeks after left-sided middle cerebral artery infarction [37]. The rTMS coil was positioned over areas within the left and right inferior

frontal gyrus (IFG) with maximal flow activation during speech stimulation. During word generation three patients activated only the left IFG while eight activated both IFGs. Inhibitory stimulation by rTMS (4 Hz) increased reaction time latency or error rate in the task in five patients with right IFG activation, indicating an essential language function in this contralateral area. These patients performed worse in a verbal fluency task than patients with rTMS effects only on the left IFG; this finding suggests that right-sided areas of the language network have a less effective compensatory potential. Similar results have been obtained in tumor patients [10,17].

Noninvasive brain stimulation & aphasia recovery

Most approaches to aphasia rehabilitation aim to generally activate all available networks, paying little attention to the fact that activation of brain regions in the nondominant hemisphere may actually be counterproductive [14,38,39]. It has thus been suggested that the lack of inhibition of the intact hemisphere is likely to interfere with early aphasia recovery because SLT may facilitate establishing networks in the right hemisphere rather than train residual left-hemisphere networks [40]. Thus, downregulating this increased activity in the nondominant hemisphere using NBS should render language areas in the affected hemisphere more susceptible to conventional SLT [12,41,42]. In order to achieve this modulation of brain activity, two methods have been used: rTMS, which uses rapidly changing magnetic fields at low frequency (usually 1 Hz at RMT for 20 min) to induce currents in the cortex [14]; and transcranial direct current stimulation (tDCS), which applies cathodal or anodal low-intensity direct currents [43,44]. Whereas most studies used inhibitory low-frequency rTMS to right-hemisphere homotropic areas for improving aphasia or supporting SLT (reviewed in [14,45–48]), only a few investigated the effect of excitatory high-frequency rTMS to left-hemispheric regions and also reported an improved language function in chronic post-stroke aphasics [49–51]. Most publications report on single cases or small case series and it is sometimes difficult to decide if cases included in a paper were reported previously. These uncontrolled case reports indicate positive effects of repeatedly administered inhibitory rTMS to the right-hemispheric Broca homolog in patients with chronic aphasia [52,53], although

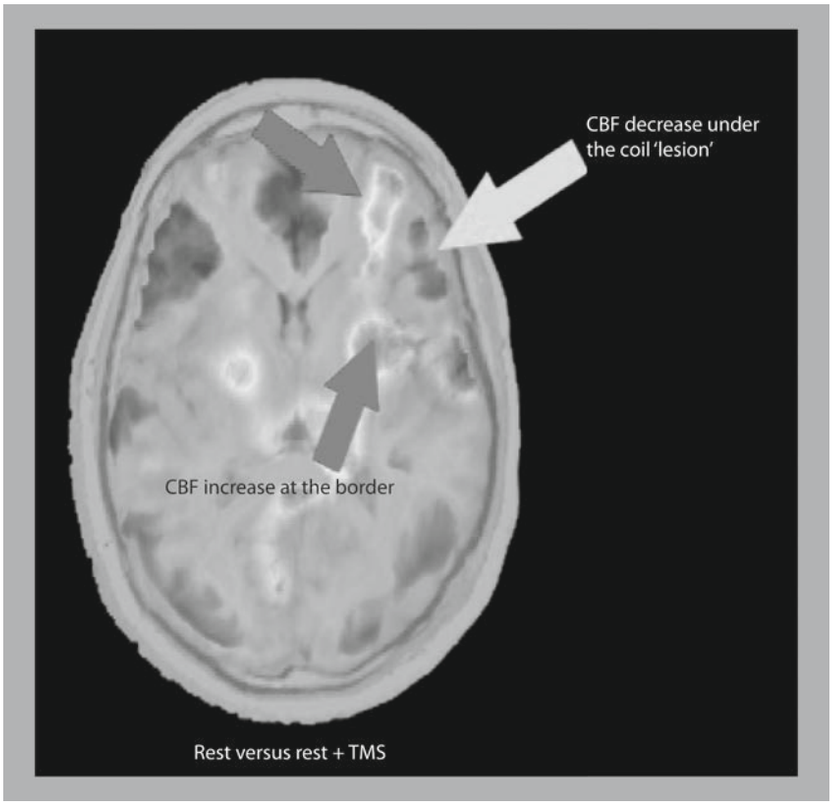

Figure 1. Effect of repetitive transcranial magnetic stimulation on regional cerebral blood flow measured by H215O-PET. Depression of activity-related blood flow under the coil leads to decreased inhibition in the surrounding areas and causes increased blood flow in the adjacent brain areas.
CBF: Cerebral blood flow; TMS: Transcranial magnetic stimulation.

a more recent open-protocol study by the same group suggests a good response for only some patients **(Table 1)** [40]. Another uncontrolled case series presented a clinical improvement in four 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 (two right and two left frontal lobe), arguing that transcallosal inhibition of the compensation region should be suppressed irrespective of the hemisphere [54]. The same group reported improvements in four patients after right frontal lobe stimulation [55]. Additional case reports support the positive effect of inhibitory rTMS to right frontal regions [18,56]; in the case of the report by Turkeltaub *et al.* [18], a subsequent stroke to the right hemisphere resulted in worsening of aphasia, indicating that some parts of the right hemisphere supported improvement of aphasia in this patient. In the 18 patients included in these case studies and case series **(Table 1)**, improved function was

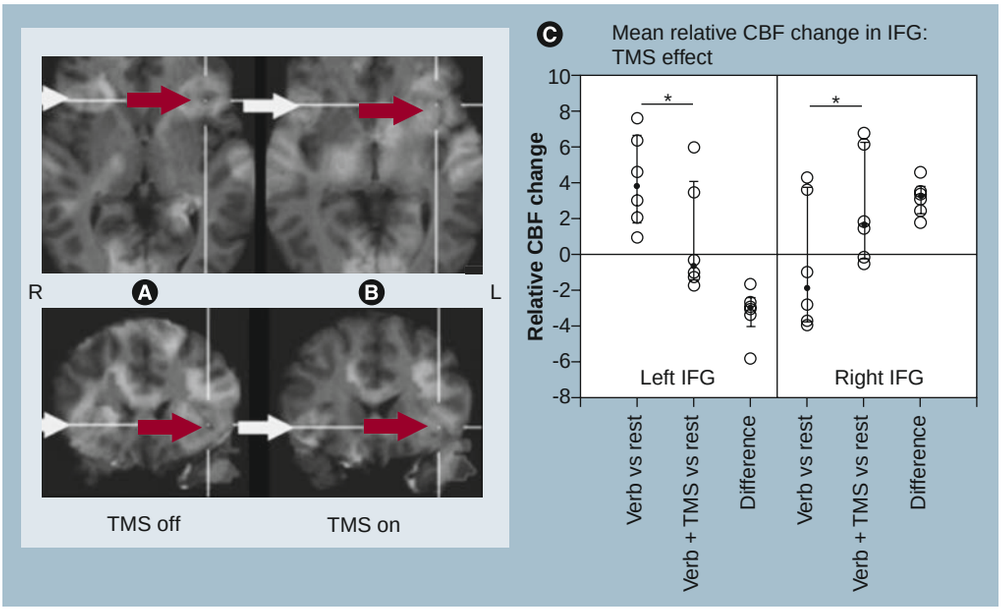

Figure 2. Effect of repetitive transcranial magnetic stimulation on activation pattern by verb generation.

*Significant: p = 0.03, signed rank test.

(A) TMS off: shows activation of the left IFG during verb generation (dark arrows). **(B)** TMS on: clearly shows the decreased activation on the left (dark arrows) and the increased activity on the right side (light arrows) during repetitive TMS. **(C)** Shows relative CBF changes during verb generation in the left and right IFG at rest, during repetitive TMS and the differences. The decrease in the left frontal gyrus during reptitive TMS is accompanied by the increase in the right frontal gyrus [21].

CBF: Cerebral blood flow; IFG: Inferior frontal gyrus; L: Left; R: Right; TMS: Transcranial magnetic stimulation.

reported in 17 with long-term improvement in seven patients. An analysis of the effect of 1-Hz rTMS on picture naming and response time in eight aphasia patients showed improvement of both functions with suppression of the right pars triangularis, but an increase in response time and no change in number of pictures with suppression of right pars opercularis. These results indicate different functional roles for those regions [57]. However, the lack of a control group in all of these studies does not allow a final conclusion.

In a controlled study, Barwood *et al.* compared the effect of 1-Hz rTMS over the apical portion of right BA45 in six verum patients with sham stimulation (audible click without production of magnetic field) in six controls [58,59]. In these chronic aphasics (2–6 years after a stroke), significant differences were found between the stimulation and the sham group 1 week [59] and 2 months [58] after the stimulation in several language subtests (naming performance as well as aspects of expressive language and auditory comprehension); however, the authors postulated that further longitudinal studies were needed to establish rTMS as a treatment tool in aphasia. In the same patients, long-term modulation of the lexical–semantic event-related potential (ERP) component N400 was observed after rTMS treatment [60]. This group now offers their rTMS protocol in an open-protocol case series [61].

However, stroke is an acute event and the question arises of whether better treatment effects can be achieved in the acute or subacute stage, while most neuroplastic processes are active. Indeed, gene transcription of several neurotrophic factors, as well as proteins regulating synaptic plasticity, is highest within 2 weeks after a stroke and returns to normal levels at approximately 4 weeks [62,63]. Therefore, the feasibility of rTMS as supportive therapy was tested in a randomized controlled study in subacute post-stroke aphasia [64]. In addition to conventional SLT, patients received multiple sessions of 1-Hz rTMS either over the right-hemispheric inferior frontal gyrus (intervention group; n = 6) or over the vertex (control group; n = 4). PET revealed an

Table 1. Inhibitory repetitive transcranial magnetic stimulation studies in poststroke aphasia.

Author	Study type	Method	Patients	n/(c)	Stimulation site	Ref.
Naeser *et al.* (2005)	Case study	1 Hz rTMS	Chronic	1	Right Broca	[53]
Naeser *et al.* (2005)	Case series	1 Hz rTMS	Chronic	4	Right Broca	[52]
Martin *et al.* (2009)	Case series	1 Hz rTMS	Chronic	2	Right Broca	[40]
Kakuda *et al.* (2010)	Case series	1 Hz rTMS	Chronic	2 2	Right frontal lobe Left frontal lobe	[54]
Kakuda *et al.* (2011)	Case series	1 Hz rTMS	Chronic	4	Right frontal lobe	[55]
Turkeltaub *et al.* (2011)	Case study	1 Hz rTMS	Chronic	1	Right pars triangularis	[18]
Hamilton *et al.* (2010)	Case study	1 Hz rTMS	Chronic	1	Right inferior frontal gyrus	[56]
Naeser *et al.* (2011)	Case series	1 Hz rTMS	Chronic	8	Right pars triangularis Right pars opercularis	[57]
Barwood *et al.* (2011)	RCT	1 Hz rTMS	Chronic	6(6)	Contralesional hemisphere	[59]
Weiduschat *et al.* (2011)	RCT	1 Hz rTMS	Subacute	6(4)	Right Broca	[64]

n/(c): Number of patients/(controls); RCT: Randomized controlled trial; rTMS: Repetitive transcranial magnetic stimulation.

activation shift towards the right hemisphere in the control group, which was absent in the intervention group (Figure 3). The intervention group improved significantly by a mean of 19.8 points in the Aachen Aphasia Test, whereas the control group did not. These promising results were supported in a recent interim analysis of the ongoing study, by which an even bigger difference in pre- and post-treatment global AAT scores between treated and control patients was found (TMS group: n = 14, 22.8 ± 12.36; sham group: n = 7, 9.4 ± 12.79; p = 0.032). A repeated measures analysis of variance demonstrated a highly significant treatment effect over all subtests (p = 0.002); the most significant effect for the picture naming subtest. After completion of this proof-of-principle study, which may establish the relationship between reverse of activation pattern (demonstrated by PET) and clinical improvement, a large-scale multicenter controlled trial is planned to prove the clinical benefit of rTMS in post-stroke aphasia.

Similar positive effects in aphasia were obtained with inhibition of right homolog language areas by cathodal tDCS [65,66]. This method employs small direct currents to modulate the resting membrane potential of neurons: negative, cathodal currents are thought to decrease excitability while positive, anodal currents are thought to increase it, thus allowing for modulation of task-induced brain activation [67]. Accordingly, anodal tDCS, as an excitatory stimulus of cortical activity, improved various language functions if applied over selected left areas [68–74]. For this treatment approach,

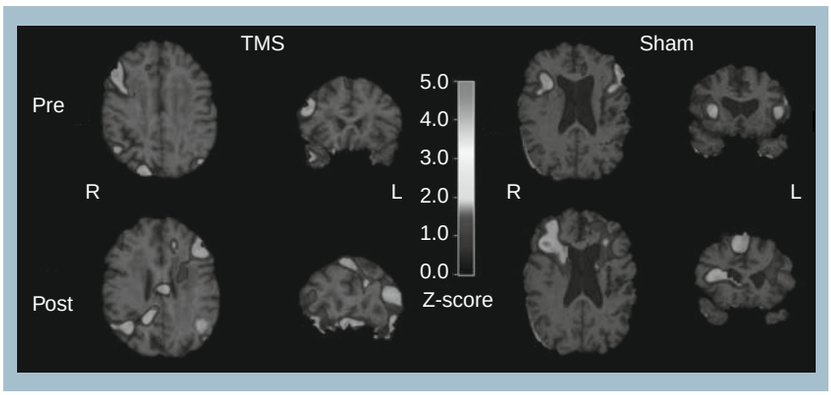

Figure 3. Illustrative single-subject activation during verb generation in one subject of the transcranial magnetic stimulation group (patient 7) and the sham group (patient 6), respectively, before and after the 2-week rehabilitation period. Although there is a reactivation of left-hemispheric structures in the patient from the intervention group, the patient from the sham group presents with increasing right-hemispheric activity.
L: Left; R: Right; TMS: Transcranial magnetic stimulation.
Reproduced from [64].

which is simpler and less expensive than rTMS, a large controlled clinical trial in subacute stroke is missing. Such a study should also include a group with rTMS in order to decide which method produces better long-term outcome.

Conclusion

Several preliminary studies indicate that rTMS might be an effective, safe and feasible complementary therapy enhancing the effect of SLT in post-stroke aphasia. A problem with any stimulation procedure is the selection of the cortical area to be suppressed or excited and PET or functional MRI scanning might be too complicated and too expensive for an informed decision in every patient. Additionally, the variability in the response and in the sensitive location for stimulation might conceal a positive effect. Inhibitory stimulation protocols therefore may have an advantage over excitatory protocols; they do not necessarily require functional imaging for localization, because the homologous area can usually be determined with a morphological scan only, and even the use of neuronavigation devices may not be required [75]. Before this treatment can be recommended for routine clinical use, the optimal combination and sequence with SLT, and the duration of the combined efforts must be elucidated [29]. Finally, the clinical efficacy of this treatment strategy must be proved in a blind, randomized, sham-controlled trial, in which the effect of inhibitory rTMS, and also the effect of tDCS as add-on therapy for the recovery of language function in the subacute phase after stroke, in a larger patient sample, representative of a typical clinical post-stroke aphasia population, is compared with stimulation over nonlanguage-related areas.

Future perspective

Before NBS can be applied in clinical routine, the best technique – inhibitory or excitatory rTMS, anodal or cathodal tDCS, or even theta burst TMS [76] – needs to be identified and the most effective stimulus parameters and sequences must be defined. It will also be important to establish the best mode of combining stimulation techniques with other rehabilitative measures, for example, SLT. NBS can only enter broad clinical application after large-scale controlled clinical trials have proven its efficacy, and these trials are especially required in the acute/postacute stage after stroke, in which each therapeutic intervention has the best chance to improve final outcome.

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