Novel Methods to Study Aphasia Recovery after Stroke

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Abstract

The neural mechanisms that support aphasia recovery are not yet fully understood. It has been argued that the functional reorganization of language networks after left-hemisphere stroke may engage perilesional left brain areas as well as homologous right-hemisphere regions. In this chapter, we summarize how noninvasive brain stimulation can be used to elucidate mechanisms of plasticity in language networks and enhance language recovery after stroke. We first outline some basic principles of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). We then present evidence from studies in healthy volunteers for a causal role of the right hemisphere in different language functions. Finally, we review recent studies that used TMS or tDCS to promote language recovery after stroke. Most of these studies applied noninvasive brain stimulation over contralateral right-hemisphere areas to suppress maladaptive plasticity. However, some studies also suggest that right-hemisphere regions may beneficially contribute to recovery in some patients. More recently, some investigators have targeted perilesional brain regions to promote neurorehabilitation. In sum, these studies indicate that language recovery after stroke may integrate left- as well as right-hemisphere brain regions to a different degree over the time course of recovery. Although the results of these preliminary studies provide some evidence that noninvasive brain stimulation may promote aphasia recovery, the reported effect sizes are not striking. Future studies on larger patient collectives are needed to explore whether noninvasive brain stimulation can enhance language functions at a level that is clinically relevant.

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Aphasia is a severely disabling consequence of stroke that typically results from injury to cortical and subcortical structures perfused by the left middle cerebral artery \([1]\). Estimations suggest that more than 20\% of patients suffering a stroke develop aphasia. While most patients show some degree of spontaneous recovery within the first months after stroke, the majority of patients with post-stroke aphasia are left with some degree of chronic deficit for which current rehabilitative treatments are marginally effective.
Recent studies suggest that noninvasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) may be of potential benefit in aphasia research in two ways. First, noninvasive brain stimulation may be used in evaluating the neural mechanisms of compensation following aphasia after stroke. Secondly, due to their potential to modulate cortical excitability and plasticity, these techniques may provide effective means in facilitating treatment by promoting adaptive processes when combined with language therapy.

**Shaping Language-Related Neural Processing with Transcranial Magnetic Stimulation**

TMS is a noninvasive tool for electrical stimulation of the human cortex (for reviews, see Barker et al. [3] and Siebner et al. [4]). TMS provides a means of transiently disrupting ongoing neuronal processing in the stimulated cortex and thus permits to draw causal conclusions regarding the contribution of the stimulated area to a specific brain function [5].

Repetitive TMS (rTMS) refers to the application of prolonged trains of stimuli which are either given continuously as long trains at a constant rate (continuous rTMS) or intermittently as repetitive bursts (i.e., intermittent or burst-like rTMS).

There are two different possibilities of applying (r)TMS to investigate cognitive functions: TMS can either be applied during the task (‘online’) or shortly before the task (‘offline’). Online TMS may consist of single pulses or short high-frequency trains given at distinct time points during a task to perturb intrinsic neuronal activity in the stimulated area (the ‘virtual lesion’ approach). An important advantage of TMS-induced lesions relative to studies of structural lesions is that there is insufficient time for functional reorganization to occur during online TMS and thus, the acute ‘lesion’ effect should not be confounded by chronic processes mediating functional recovery locally and at the systems level [5]. Of note, the term ‘virtual lesion’ implies that TMS always induces an impairment of brain functions. However, TMS-induced disruption of neuronal activity in one area may also lead to a paradoxical improvement or facilitation in task performance.

In contrast to online TMS, offline TMS involves longer rTMS protocols that are applied shortly before subjects perform an experimental task. Usually, the interventional rTMS protocol is ‘inhibitory’ [6]. This means that the rTMS intervention induces a lasting suppression of neuronal excitability in relevant areas. This conditioning approach bears some analogies to acute stroke, because inhibitory offline TMS gives rise to an acute adaptive reorganization within the nonstimulated functional loops of the networks to compensate for the TMS-induced suppression of neuronal activity in those components of the network that have been perturbed with TMS. It needs to be borne in mind that the local excitation induced in the stimulated cortical area can spread transsynaptically to remote brain regions via corticocortical and corticosubcortical projections. Hence, the behavioral changes induced by the TMS pulse...
may not only be caused by local neural excitation at the site of stimulation, but also by indirect excitation of connected cortical areas.

In sum, online and offline TMS represent complementary approaches: while online TMS acutely disrupts a specific function, offline TMS impairs cortical processing beyond the time of stimulation and thus can be used to induce and examine the capability of brain networks to undergo acute reorganization. Due to the possibility to change cortical excitability beyond the duration of stimulation, offline rTMS protocols are of particular relevance for the use in neurorehabilitation.

**Shaping Language-Related Neural Processing with Transcranial Direct Current Stimulation**

tDCS modulates cortical excitability by application of weak direct electrical currents (1–2 mA) between two electrodes applied to the scalp over a relatively extended period of time (e.g. 5–20 min). Depending on the orientation of the stimulation electrodes and the direct current polarity, tDCS has been shown to elicit polarity-dependent changes in cortical excitability, presumably due to direct current-induced changes in the resting membrane potentials. In the motor cortex, anodal tDCS may increase motor-cortical excitability while cathodal tDCS may decrease excitability [7]. Emerging evidence suggests that the effects of tDCS can persist beyond the period of stimulation, and changes in task performance were reported for up to 6–12 months after intervention [8].

An attractive feature of tDCS is the apparent lack of any significant side effects when using standard protocols. For instance, tDCS has not been reported to provoke seizures in nonacute neurological deficits since intervention protocols are well below the threshold of tissue damage [9]. In contrast to TMS, it is relatively easy to blind the patient and examiner to the type of tDCS which enables a double-blind study design. Therefore, compared with TMS, tDCS may be a viable option for stimulation of the perilesional cortex where the threshold to induce seizures is lower. This makes tDCS an appealing form of neurostimulation in chronic stroke populations. Like TMS, tDCS may be applied before a certain task (offline) or during task processing (online). We also wish to mention that additional transcranial stimulation techniques such as alternative direct current stimulation or transcranial random noise stimulation have been introduced in recent years which may also be suited as interventional tools to modulate the impaired language system after stroke.

**Right-Hemisphere Contributions to Language Processing in the Healthy Brain**

There is consensus about a dominant role of the left hemisphere in language processing and most of the studies investigating language functions in the healthy brain with noninvasive brain stimulation techniques were restricted to left-hemisphere
brain regions. However, recent TMS studies provided some evidence that the right hemisphere is causally involved in different aspects of language processing, including phonological decisions, reading, and the processing of paralinguistic features such as (emotional) prosody or metaphor processing (for a review, see Hartwigsen and Siebner [10]).

Adopting a novel dual-site approach in which TMS was applied either unilaterally over homologous areas in the left or right hemisphere or simultaneously to both hemispheres, we recently tested the functional relevance of the previously reported activation of the left and right supramarginal gyrus (SMG) for phonological judgments [11]. We thus applied 10 Hz online rTMS over either the left, right or bilateral SMG while subjects performed phonological judgments (does a word have 2 or 3 syllables?) or semantic judgments (does a word represent a natural or man-made item?).

We hypothesized that if right supramarginal activation is redundant to phonological processing, then task performance should only be impaired when online TMS was applied over the left SMG but not the right SMG. In contrast, if the right SMG also contributes to phonological decisions, then task performance should also be disrupted with TMS of right SMG. The simultaneous application of TMS over the left and right SMG enabled us to test whether both areas can compensate a virtual lesion to the respective other area. We expected that if phonological decisions are possible with either the left or right SMG, the lesion effect should be greater when TMS was applied over both the left and right SMG. In contrast, if the left and right SMG are equally necessary for efficient phonological decisions, the effect of TMS should be the same irrespective of whether it was applied unilaterally or bilaterally.

TMS relative to an ineffective sham procedure significantly impaired task performance for phonological decisions, but not for the semantic task independent of the stimulated hemisphere. Additionally, we found that both hemispheres were equally sensitive to the disruptive effect of TMS. Together, these findings indicate that both hemispheres are equally necessary for intact phonological processing. Furthermore, the results suggest that efficient phonological judgments require both the left and the right SMG in healthy subjects without any evidence that both areas can compensate a lesion to the respective other area.

In sum, these results indicate that the involvement of right-hemisphere language areas is not limited to aphasia recovery after stroke but is also essential for phonological processing in healthy subjects.

Other studies reported increased task-related neuronal activity in right-hemisphere areas during language processing after the contralateral homologous area had been suppressed with offline rTMS [12]. These studies show how offline TMS can be used to investigate short-term plasticity in language networks in the healthy brain which might ultimately contribute to the understanding how such networks reorganize after long-term disruption such as occurring after stroke.

With respect to potential beneficial effects of right-hemisphere noninvasive brain stimulation on language functions, Ross et al. [13] recently demonstrated that anodal
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Reorganization of Language Networks after Stroke – Evidence from Repetitive Transcranial Magnetic Stimulation Studies

The majority of rTMS studies in post-stroke aphasia used low-frequency rTMS to inhibit contralateral homologous areas (for an overview, see Chrysikou and Hamilton [14]). These studies were based on the assumption that following left-hemisphere stroke, the right hemisphere is released from transcallosal inhibition and thus exerts an increased transcallosal inhibitory effect on perilesional regions of the left hemisphere, thereby suppressing language-related left-hemisphere activity. According to this interhemispheric inhibition model, improvements in language function after a left-hemisphere lesion can be achieved either by inhibition of right-hemisphere activity or via facilitation of left-hemisphere activity [15] (fig. 1a, c). For instance, in 4 patients with chronic aphasia after stroke, Naeser et al. [16] showed that repeated daily application of 1 Hz rTMS over the right anterior inferior frontal gyrus significantly improved picture naming abilities for up to 2 months after treatment. More recent studies suggest that the reported benefits in naming after 1 Hz rTMS of the contralesional right anterior inferior frontal gyrus in patients with non-

Fig. 1. Different accounts of plasticity in language systems in chronic aphasia. a After unilateral left-hemisphere stroke (in gray), some language functions may be subserved by perilesional areas (in white). b Right perisylvian areas (in white) may be recruited to subserve some language functions, a process facilitated by decreased transcallosal inhibition of the right hemisphere by the damaged left hemisphere. c By contrast, right-hemisphere activity may be deleterious. Released from interhemispheric inhibition, right-hemisphere structures (in black) may exert an increased inhibitory influence on left perisylvian areas, impeding functional recovery of lesional and perilesional areas in the left hemisphere (in black). Modified and reprinted from Hamilton et al. [2], copyright (2011), with permission from Elsevier.

tDCS over the right anterior temporal lobe improved naming possibilities in 15 healthy subjects. These results suggest that anodal tDCS may have some potential to promote language recovery in patients with post-stroke aphasia.
fluent aphasia generalize to other language abilities like spontaneous speech and auditory comprehension [17].

Of note, not all aphasic patients benefit from suppression of right-hemisphere activation and lesion location might be a critical determinant of recovery success. It was further suggested that aphasia recovery might depend on the extent to which some areas are affected or spared by stroke [18].

While many studies demonstrated that suppression of right-hemisphere activity after left-hemisphere stroke may promote recovery, evidence from other TMS studies suggests that the right hemisphere might also be critically contributing to language performance in some patients [19, 20] (fig. 1b). This may indicate that although recovery from post-stroke aphasia seems to depend more on an effective integration of available perilesional left-hemisphere regions, right-hemisphere areas may be successfully integrated in some cases [19]. While the role of the contralesional right hemisphere in language recovery is more controversial than that of the left hemisphere, a beneficial contribution of right-hemisphere areas to the successful reorganization of language networks after stroke is compatible with the results from previous neuroimaging studies (for a review, see Saur and Hartwigsen [21]). It has been argued that additional factors such as premorbid laterality of language representation, the time course of recovery, and the lesion size are important determinants that might influence the successful integration of right-hemisphere activity during post-stroke reorganization of language networks [14].

A recent study explored the possibility of facilitating cortical activity in the left hemisphere to improve language recovery. Szaflarski et al. [22] applied intermittent theta burst stimulation over Broca’s area in 8 chronic stroke patients with aphasia. In 6 of the 8 patients, semantic fluency was improved after intermittent theta burst stimulation, and subsequent functional magnetic resonance imaging data demonstrated a leftward shift in language-related activation. These preliminary results suggest that the application of facilitatory protocols over left-hemisphere perilesional areas may enhance language recovery.

In sum, the potential of TMS to promote aphasia recovery after stroke remains to be determined as the results of the above-cited studies are heterogeneous and limited by the small number of patients included. Moreover, it is unclear whether TMS should target perilesional left-hemisphere areas or contralateral right-hemisphere areas to enhance neurorehabilitation. The use of TMS in clinical settings is further limited by the fact that stimulation can be unpleasant, especially if frontal regions like Broca’s area are targeted at high intensities. While the high focality of figure-of-eight-shaped TMS coils allows for the functional segregation of subareas, it requires anatomical specific hypotheses with respect to the precise desired stimulation site (e.g. anterior vs. posterior part of Broca’s area). Since accurate placement of the TMS coil over the cortical area of interest and continuous monitoring of the coil throughout the TMS experiment is crucial to assure high spatial accuracy, TMS may not be used simultaneously with language therapy.
Reorganization of Language Networks after Stroke – Evidence from Transcranial Direct Current Stimulation Studies

To date, only a few studies have applied tDCS in post-stroke aphasic patients to facilitate treatment in language recovery (see table 1 for details). The majority of these studies investigated the effects of cathodal tDCS over perilesionel left-hemispheric regions to facilitate picture naming. For instance, Monti et al. [23] showed that cath-
odal tDCS significantly improved picture naming in 8 ischemic stroke patients with aphasia. It was concluded that the effect of cathodal stimulation may be a downregulation of overactive inhibitory cortical interneurons in the lesioned hemisphere that ultimately give rise to increased activity and function in the damaged left hemisphere. In contrast, several other investigators have reported improved language performance after either anodal stimulation of the left hemisphere or cathodal stimulation of the right hemisphere [24–26]. Recently, two studies found significant language improvement after anodal tDCS over the right hemisphere [27, 28]. These preliminary results suggest that an upregulation of right-hemisphere activity may be beneficial for language recovery in some patients.

The above-cited studies show that tDCS might be of potential benefit in promoting aphasia recovery after stroke. However, the results are heterogeneous and it is currently impossible to judge the value of tDCS as a means to enhance neurorehabilitation of language. For instance, it remains to be determined whether anodal or cathodal tDCS should be applied to perilesional left-hemisphere regions or contralateral right-hemisphere areas.

With respect to the usability of tDCS in clinical settings, an important advantage of tDCS compared with TMS is the relatively easy application and the absence of any severe side effects if tDCS is applied within the published safety guidelines. Finally, tDCS can be administered concurrently with language therapy and may be easily applied in double-blind settings.

**A Hierarchical Model of Aphasia Recovery after Stroke**

While many of the studies discussed above were based on the assumption that suppression of activity in the 'overactive' right hemisphere after left-hemisphere stroke may promote language recovery, others provided some evidence that the right hemisphere might play a beneficial role in aphasia recovery. Consequently, it was argued that language recovery is a dynamic process that may involve a variety of plastic changes in both hemispheres [2]. In their hierarchical model of language recovery, Heiss and Thiel [29] assumed that with small left-hemisphere lesions, complete or near-complete language recovery may be achieved by restoration of normal patterns of activation in left-hemisphere language networks. If lesions of the left hemisphere damage important language centers, perilesional regions may be recruited to subserve language functions. However, when left-hemisphere networks are more severely impaired, the right hemisphere appears to be capable of assuming some functions. While right-hemisphere recruitment for language tasks may contribute to overall language recovery in severely affected patients, the remodeled language network in these patients is likely inefficient compared with premorbid intact left-hemisphere perisylvian regions. The hierarchical model of effective aphasia recovery is based on the assumption that best recovery is achieved when left-hemisphere language networks recover.
normal function. According to this model, good recovery is achieved when perilesional left-hemisphere areas compensate for damaged left-hemisphere language regions. In contrast, a preferential recruitment of the right hemisphere during language tasks is associated with limited recovery from aphasia because of limited right-hemispheric processing capacities with respect to language.

Conclusions and Future Directions

Recent studies provide some first evidence that noninvasive brain stimulation techniques might be beneficial in promoting aphasia recovery after stroke. However, although these preliminary results are interesting, they should be interpreted with caution and the therapeutic potential of the various transcranial cortex stimulation protocols still remains to be determined. The reported findings are inconsistent and partly contradictory. For instance, there is strong variation across studies with respect to the outcome of different stimulation protocols (e.g., anodal vs. cathodal tDCS) and the optimal stimulation site (i.e., perilesional left-hemisphere regions vs. right hemisphere homologues). Further, previous studies only included a small number of patients (usually less than 10 patients per group) and the reported effect sizes were moderate. Some studies lacked control groups and subject blinding. The literature on noninvasive brain stimulation in aphasia recovery is further limited by the fact that there are no long-term investigations on the duration of the reported effects. Future studies should investigate larger patient collectives to explore whether noninvasive brain stimulation can enhance language functions at a level that is clinically relevant beyond the time of stimulation. Here, the combination of brain stimulation and language therapy seems promising. These studies should also address the optimal time point of intervention (i.e., before, during or after language therapy). Finally, it might also be promising to use multifocal approaches allowing for the simultaneous application of TMS over multiple brain sites within specific language networks.

One possible explanation for the partly inconsistent findings across different studies is that language recovery is a dynamic process that involves both hemispheres at different times to different degrees [30]. Future studies should systematically investigate the use of different protocols over the time course of recovery to advance the current knowledge about critical areas for specific language functions during language reorganization. For instance, it might be worthwhile to apply facilitatory protocols over right-hemisphere homologue regions in the subacute phase after stroke while an enhancement of left-hemisphere functions may be more beneficial in the chronic phase after stroke.

A possible way forward is to use multimodal approaches combining different methods, such as functional and structural imaging with transcranial stimulation techniques in both healthy volunteers and stroke patients with aphasia to identify critical networks for different language functions across the time course of recovery [21].
References


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