Review

Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation

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ABSTRACT

One of the most frequent symptoms of unilateral stroke is aphasia, the impairment or loss of language functions. Over the past few years, behavioral and neuroimaging studies have shown that rehabilitation interventions can promote neuroplastic changes in aphasic patients that may be associated with the improvement of language functions. Following left hemisphere strokes, the functional reorganization of language in aphasic patients has been proposed to involve both intrahemispheric interactions between damaged left hemisphere and perilesional sites and transcallosal interhemispheric interactions between the lesioned left hemisphere language areas and homotopic regions in the right hemisphere. A growing body of evidence for such reorganization comes from studies using transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), two safe and noninvasive procedures that can be applied clinically to modulate cortical excitability during post-stroke language recovery. We discuss a hierarchical model for the plastic changes in language representation that occur in the setting of dominant hemisphere stroke and aphasia. We further argue that TMS and tDCS are potentially promising tools for enhancing functional recovery of language and for further elucidating mechanisms of plasticity in patients with aphasia.

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1. Introduction

Aphasia is a common consequence of stroke that typically results from injury to an extended network of cortical and subcortical structures perfused by the middle cerebral artery in the left hemisphere (Alexander, 1997; McNeil & Pratt, 2001). Most patients who experience aphasia in the setting of acute stroke show some degree of spontaneous recovery, most notably during the first 2–3 months following stroke onset (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Lendrem & Lincoln, 1985; Nicholas, Helm-Estabrooks, Ward-Lonergan, & Morgan, 1993). However, the majority of patients with post-stroke aphasia are left with some degree of chronic deficit for which current rehabilitative treatments are marginally effective (Basso & Marangolo, 2000; Nickels, 2002; Robey, 1994; Robey, 1995; Robey, Schultz, Crawford, & Sinner, 1999).

A number of factors have been shown to influence aphasia recovery, including lesion site and size, and the existence of prior strokes (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). Recent neuroimaging and behavioral data indicate that considerable changes in the cortical representation of language processing can occur in the days, weeks, and months following stroke in the left hemisphere (Horn et al., 2005), and that language recovery after stroke depends significantly on the degree of plastic change observed in the brains of patients after injury (Cherney & Small, 2006; Musso et al., 1999; Thompson, 2000; Thompson et al., 1997). TMS and tDCS are safe noninvasive methods that can be used to induce or enhance neuroplastic changes in brain activity (Antal, Nitsche, & Paulus, 2001): a small but growing body of evidence indicates that noninvasive brain stimulation can have beneficial effects in the treatment of aphasia after stroke. These studies also inform our understanding of potential mechanisms of language recovery following injury to language networks.

Current evidence suggests that three kinds of changes in neural activity after stroke may be most relevant for aphasia recovery: (1) Recruitment of lesioned and perilesional left hemisphere regions for language-related tasks, (2) acquisition, unmasking or refinement of language processing ability in the nondominant right hemisphere, and (3) dysfunctional activation of the nondominant hemisphere that may interfere with language recovery. We will examine the evidence for each of these kinds of plasticity in language recovery after stroke. Importantly, we will emphasize that these mechanisms are not mutually exclusive, but rather may comprise a hierarchical framework of interacting language

recovery mechanisms. Finally, we will consider how evidence from studies that employ TMS and tDCS contributes to the understanding of language recovery mechanisms.

2. Recruitment of the left hemisphere in aphasia recovery

There is considerable evidence that perilesional areas of the left hemisphere acquire or reacquire language ability in the weeks and months following injury. It has long been accepted that the size of left hemisphere infarction in perisylvian language areas correlates with initial aphasia severity and inversely with aphasia recovery (Kertesz, Harlock, & Coates, 1979). A number of functional imaging studies of nonfluent aphasic patients have also demonstrated that better spontaneous language recovery is associated with greater activation of left-hemisphere structures (Karbe, Thiel, & Weber-Luxenburger, 1998; Karbe, Thiel, Weber-Luxenburger, Herholz, et al., 1998; Miura et al., 1999; Warburton, Price, Swinburn, & Wise, 1999). Left hemisphere activation has been associated with better language improvement among nonfluent aphasic patients who undergo speech therapy (Cornelissen et al., 2003). In patients with fluent aphasia it has been observed that efficient restoration of language is more frequently achieved if left temporal language networks are relatively well-preserved (Gainotti, 1993).

While the mechanisms underlying increased perilesional activation in language recovery have not been fully elucidated, one important contributor may be the release of inhibitory input from the lesioned cortex, leading to increased activity in nearby cortical areas. Evidence indicates that unilateral injury—such as left-hemisphere lesions that give rise to aphasia—can lead to cortical disinhibition in at least two regions: (1) neighboring ipsilesional cortical areas and (2) contralesional homotopic areas connected via the corpus callosum (Bütefisch, Kleiser, & Seitz, 2006; Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004; Shimizu et al., 2002). In the case of the ipsilesional left hemisphere, release from cortical inhibition in the setting of focal injury may facilitate activation of these areas during language tasks. Animal studies of cortical plasticity suggest that persistent recruitment of cortical areas during specific tasks may result in functional modifications that allow perilesional networks to engage more efficiently in the service of those tasks (Nudo & Friel, 1999). Activity-dependant plasticity, facilitated by ipsilesional disinhibition, may thus promote the recruitment and functional reorganization of perilesional regions of the left hemisphere to subserve language processing.

3. The beneficial role of the right hemisphere in aphasia recovery

While most evidence suggests that ipsilateral perilesional activation in chronic aphasic patients is associated with better language recovery, the role of right hemisphere recruitment during language tasks is more controversial. By some accounts, the right hemisphere plays a beneficial role in language recovery by assuming functions previously represented in the left hemisphere, while other evidence suggests that activation of the right hemisphere during language tasks in patients with chronic aphasia is a reflection of inefficient mechanisms of language processing and may be detrimental to aphasia recovery. Others have argued that functional activation of right hemisphere areas in aphasic patients during language tasks is epiphenomenal, and neither facilitates nor hinders language recovery (Thiel et al., 2001).

The notion that the right hemisphere may play a facilitative role in language recovery after left hemisphere stroke dates as far back as the late 19th century. Barlow (1877) described the case of a 10-year old boy who lost but then recovered the capacity for speech after a left hemisphere stroke, only to lose it again after acquiring a second, right-hemisphere lesion (Finger, Buckner, & Buckingham, 2003). Other reported cases have shown that new right-hemisphere lesions acquired after functional recovery in aphasia can cause deterioration of language (Basso, Gardelli, Grassi, & Mariotti, 1989; Gainotti, 1993; Gowers, 1887). Amobarbital studies have demonstrated that for healthy right-handed adults, language functions are suspended after left-sided carotid injections; however, for aphasic patients with extensive left hemisphere strokes, residual speech may be suspended by right- and not left-sided carotid injections (Kinsbourne, 1971). Furthermore, some patients who have undergone surgical left hemispherectomy have shown substantial language recovery (Vargha-Khadem et al., 1997) indicating that the right hemisphere possesses the capacity to process language information in the absence of a functioning left hemisphere.

It has been proposed that the capacity for language processing exists in right hemisphere regions that are homotopic to left hemisphere perisylvian structures, but is usually masked by transcallosal interhemispheric inhibition from the dominant left-hemisphere (Karbe, Thiel, Weber-Luxenburger, Herholz, et al., 1998). According to this hypothesis, language recovery after left hemisphere stroke is associated with a release from inhibition of latent, right-hemisphere language functions. A number of neuroimaging studies involving language tasks have revealed that there is, in addition to activation of left hemisphere language regions, robust activation in homotopic right hemisphere regions after left hemisphere stroke (Basso et al., 1989; Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Gold & Kertesz, 2000; Ohyama et al., 1996; Rosen et al., 2000; Warburton et al., 1999; Weiller et al., 1995). We recently pursued an investigation of fMRI and PET studies in patients with aphasia using Activation Likelihood Estimation (ALE) meta-analysis in which we analyzed 240 activation foci from 104 aphasics, and 197 foci from 129 controls (see Fig. 1). We found that performance on language production tasks in aphasic patients is reliably associated with activation of regions in the right inferior frontal gyrus, whereas comprehension tasks are associated with activation of the right middle temporal gyrus (Turkeltaub, Messing, Norise, & Hamilton, submitted for publication). In addition to determining the degree to which the location of right hemisphere activation in aphasic patients mirrors that in the left hemisphere, we also examined the degree to which these right hemisphere areas were functionally homologous, that is, the degree to which they activated during the same tasks as left hemisphere areas in normal subjects. We found that among patients with chronic left inferior frontal lesions, patterns of activation in the right inferior frontal gyrus (specifically in the pars opercularis and pars orbitalis) were both homotopic to left inferior frontal gyrus sites in control patients and functionally homologous with respect to the tasks that activated them. Further evidence of functional homology is provided by recent diffusion tensor imaging (DTI) data that indicate that connections between inferior frontal and temporal language regions seen in the left hemisphere are mirrored in homotopic regions of the right hemisphere (Kaplan et al., 2010). These similarities in activation patterns and connectivity support the notion that the right hemisphere possesses and utilizes the functional architecture needed to assume language operations after left hemisphere injury.

The potential for the right hemisphere to acquire or unmask language abilities is the central principle behind at least two behavioral approaches to aphasia treatment. Crosson and colleagues (2009) have described a naming task designed to stimulate reorganization of word production to the right lateral frontal lobe. This task involves subjects making a complex left-hand movement to initiate picture naming attempts, with the rationale that the hand movement activates intention mechanisms in the right medial frontal lobe (Coslett, 1999; Picard & Strick, 1996) that subsequently engage right lateral frontal structures that participate in
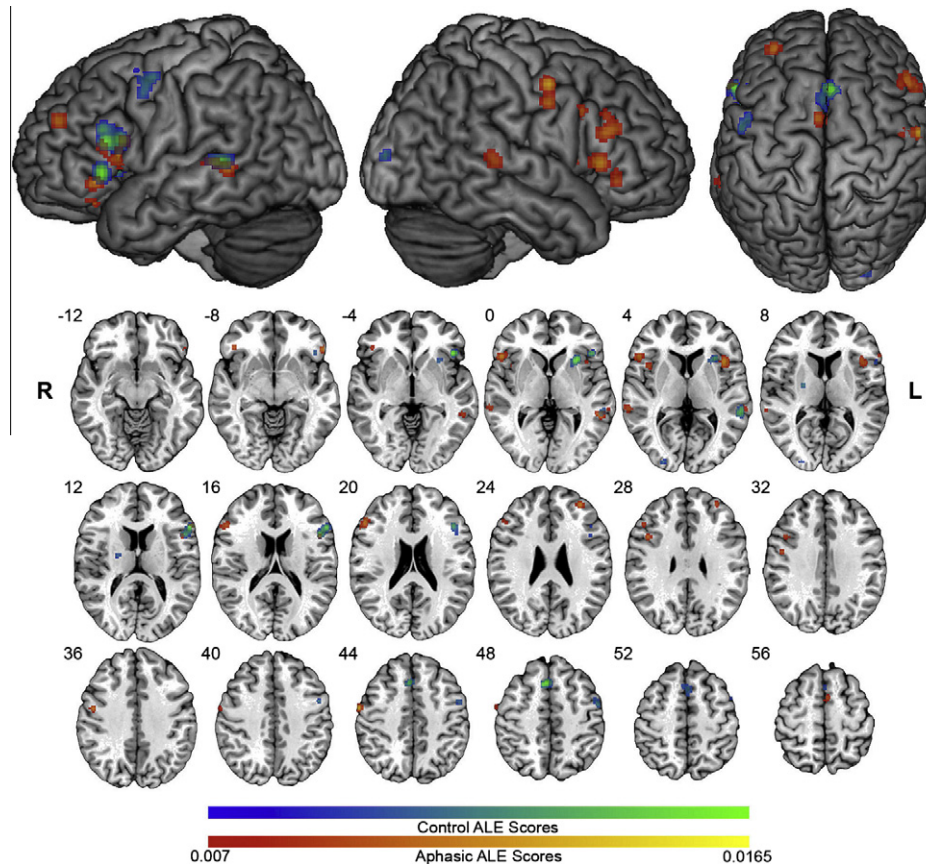
Fig. 1. We submitted activation foci from fMRI and PET studies using the same language tasks on both aphasic patients and control subjects to Activation Likelihood Estimation (ALE) analysis. Control ALE clusters are in blue–green scale, and show left hemisphere language and motor activity. Aphasic ALE clusters are in red–yellow scale, and show bilateral activations with right hemisphere areas that are homotopic to control ALE clusters. ALE maps are overlaid on the standard Colin brain in MNI space, using an FDR $q = .01$ critical threshold, and minimum cluster size of 100 mm^3. (Reproduced with permission from Turkeltaub et al., submitted for publication.)

naming (Crosson et al., 2007). Limited fMRI evidence suggests that improvement in naming in patients who utilize this technique is accompanied by increased right frontal lobe activity (in particular the motor and premotor cortex, and pars opercularis). Melodic intonation therapy (MIT)—a therapeutic approach that relies on the exaggeration of the musical qualities of speech—is another treatment technique that is predicated on recruitment of the right hemisphere for language (Albert, Sparks, & Helm, 1973; Sparks, Helm, & Albert, 1974). Recently, Schlaug and colleagues (2009) have shown using DTI that intense treatment with MIT results in an increase in white matter fibers and volume in the right arcuate fasciculus correlating with subjects' degree of improvement. This finding further supports the notion that the functional architecture of right hemisphere language areas may mirror that of the left hemisphere perisylvian network (Kaplan et al., 2010), and suggests that these right hemisphere networks may be modified beneficially with training.

A number of additional factors may be important determinants of the degree to which right hemisphere networks are engaged in language recovery. Two of the most important determinants of right hemisphere involvement are lesion size and location. In patients with chronic aphasia, larger lesions involving eloquent cortex of the left hemisphere are associated with greater recruitment of the right hemisphere during language tasks (Heiss & Thiel, 2006; Kertesz et al., 1979). Evidence also suggests that premorbid differences in language lateralization may be a strong predictor of susceptibility to unilateral brain lesions, and may complicate interpretations of left- and right-hemisphere plasticity during post-stroke recovery (Andoh & Martinot, 2008; Humphreys & Praamstra, 2002; Knecht et al., 2002). Additionally, it has been

argued that hemispheric involvement may be a dynamic process that changes during the course of recovery as a function of time from aphasia onset, patient age, and specific task demands (Finger et al., 2003; Hillis, 2007). In one longitudinal imaging study it was shown that in patients with acute stroke and nonfluent aphasia neither hemisphere is activated during attempted performance of a language task. In the subacute phase, the right hemisphere exhibited stronger involvement in language functions, whereas in the chronic phase, the left hemisphere appeared to regain dominance (Saur et al., 2006). These findings are supported by two studies by Winhuisen and colleagues (2005, 2007), who employed PET and rTMS in the same cohort of aphasic stroke patients within two weeks and again 8 weeks following acute stroke. These authors found that the majority of patients showed bilateral activation of the inferior frontal gyrus during a verbal semantic task, but that over time the proportion of patients in whom inhibitory rTMS of the right inferior frontal lobe disrupted performance decreased. Taken together, these findings indicate both the potential of the right hemisphere to engage in language-related tasks after left hemisphere stroke as well as its likely evolving role over time (Winhuisen et al., 2005; Winhuisen et al., 2007).

The extent to which the right hemisphere may be able to compensate efficiently after left-hemisphere damage can also depend on the timecourse of injury. For example, Thiel and colleagues (2006) used functional neuroimaging and TMS to elucidate the transferred representation of language functions to the right hemisphere in patients with left-hemisphere tumors. Due to the insidious progression of left hemisphere injury in these patients, gradual neuroplastic changes may have allowed for adaptive reorganization of language ability in the right hemisphere to an extent that

does not occur after acute stroke (Thiel et al., 2006). Cerebral reorganization of language may also depend in part on the age of left hemisphere stroke onset. Elkana and colleagues (2011) reported that pediatric patients who had previously acquired language but then suffered from left hemisphere strokes exhibited right hemisphere activation during language tasks, but that greater proficiency with these language tasks was associated with greater left hemisphere activation. Moreover a shift toward left hemisphere activation during language tasks was observed in a single young patient who they followed over the course of years, suggesting that language reorganization, at least as seen in younger individuals, is a dynamic process that may last for years after stroke onset (Elkana et al., 2011).

4. The detrimental role of the right hemisphere in aphasia recovery

Increased right hemisphere activity seen after stroke in patients with aphasia may not represent an entirely beneficial change. One alternative account is that right hemisphere involvement after left hemisphere stroke and aphasia reflects inefficient or maladaptive plastic changes in neural activity that have emerged during language reorganization (Belin et al., 1996). According to this model, ineffective changes in language representation may interfere with the reacquisition of more efficient language processing by recovering left-hemisphere cortical networks. Consistent with this argument, it has been shown that increased activation in the right hemisphere in aphasic patients is not always coupled with improved language performance (Naeser, Theoret, & Kobayashi, 2002; Rosen et al., 2000; Saur et al., 2006). In at least one recent fMRI study, increased right hemisphere activity was associated with worse performance on an overt naming task (Postman-Caucheteux et al., 2010).

Another hypothesis that further extends the notion of the maladaptive right hemisphere is that increased right hemisphere activation after left hemisphere stroke results in abnormally increased and deleterious transcallosal inhibition of the already damaged left hemisphere. As has been observed with unilateral lesions leading to other deficits such as hemiparesis and neglect, increased contralesional activity after left hemisphere injury may reflect loss of interhemispheric inhibitory influence from damaged language areas in the left hemisphere to right-sided homologues (Martin et al., 2004; Rosen et al., 2000; Shimizu et al., 2002). This release of inhibition and resulting upsurge in right hemisphere activity may thus result in increased interhemispheric inhibitory influences from the right hemisphere on left hemisphere perisylvian areas, which may exacerbate language symptoms and impede recovery from aphasia (Fig. 2).

5. Noninvasive brain stimulation techniques: TMS and tDCS

Transcranial magnetic stimulation (TMS) is a technology that can be used to manipulate cortical activity focally, creating either transient or enduring changes in patterns of brain activity (Bailey, Karhu, & Ilmoniemi, 2001; Walsh & Pascual-Leone, 2003). TMS employs the principle of electromagnetic induction and involves the generation of a rapid time-varying magnetic field in a coil of wire. When this coil is held to the head of a subject, the magnetic field penetrates the scalp and skull and induces a small current parallel to the plane of the coil in the brain that is sufficient to depolarize neuronal membranes and generate action potentials. Different TMS paradigms employ various combinations of pulse frequencies, intensities, and stimulation locations. Repetitive TMS (rTMS) involves the application of a series of pulses at a predetermined frequency and can produce effects that outlast the application of the stimulation. Evidence suggests that rTMS delivered at a low frequency (0.5–2 Hz) tends to focally decrease cortical excitability, whereas higher frequencies (faster than 5 Hz) tend to increase excitability (Maeda & Pascual-Leone, 2003). Repetitive TMS has been employed in numerous experiments examining the role of specific cortical areas in the execution of specific linguistic functions (Devlin & Watkins, 2007),

Transcranial direct current stimulation (tDCS) involves the application of small electrical currents (typically 1–2 mA) to the scalp through a pair of surface electrodes. Current flows from the anode, through the cortex, and out through the cathode. Unlike TMS, which induces currents of sufficient magnitude to stimulate action potentials, the weak electrical currents employed in tDCS are thought to modulate the resting membrane potentials of neurons (Nitsche & Paulus, 2000, 2001). The effect of tDCS depends on which electrode is applied to the scalp: cathodal stimulation is associated with decreased cortical excitability due to hyperpolarization of cortical neurons, while anodal stimulation is associated with increased cortical excitability due to subthreshold depolarization. These effects may last for minutes to hours depending on the intensity, polarity, and duration of stimulation (Antal et al., 2001). A growing number of studies have employed of tDCS as an experimental means for manipulating performance in a variety of cognitive domains, and investigators have started to explore the use of tDCS as a possible neurorehabilitation tool for patients with post-stroke deficits (Fregni et al., 2005; Hummel et al., 2005).

6. Noninvasive brain stimulation informs models of aphasia recovery

A small but growing body of evidence suggests that noninvasive brain stimulation techniques may provide a supplementary
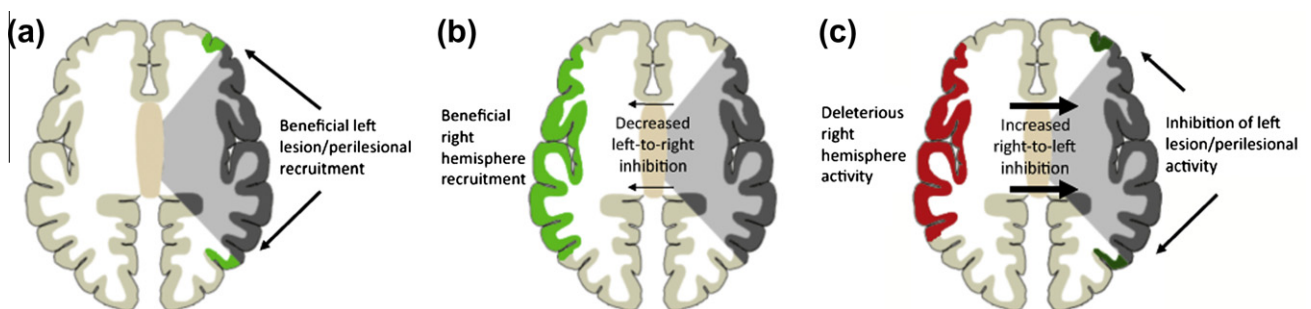

Fig. 2. Differing accounts of plasticity in language systems in chronic aphasia. (a) After unilateral left hemisphere stroke (grey), some language functions may be subserved by recovered lesional areas or recruited perilesional areas (light green). (b) Right perisylvian areas (light green) may be recruited 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 (red) may exert increased inhibitory influence on left perisylvian areas, impeding functional recovery of lesional and perilesional areas in the left hemisphere (dark green).

treatment approach for certain language deficits in patients with chronic stroke-induced aphasia (See Table 1). Several TMS studies have employed low frequency inhibitory stimulation of the right hemisphere with the goal of focally diminishing neural activity in the intact contralesional hemisphere. Here the work of Naeser and colleagues (Martin et al., 2004; Naeser et al., 2005a; Naeser et al., 2002) has been central. In an initial investigation, 1 Hz inhibitory rTMS was applied to four different points on right-hemisphere perisylvian regions of six chronic nonfluent aphasia patients at 90% of motor threshold for 10 min. Following stimulation of the anterior portion of the right-hemisphere homologue of Broca's area (pars triangularis) they observed significant but transient improvement in accuracy and reduction in reaction time with respect to picture naming (Naeser et al., 2002). Conversely, application of 1 Hz rTMS to the posterior portion of the right-hemisphere homologue of Broca's area (pars opercularis) was associated with a transient decrease in picture naming accuracy and an increase in reaction time. Extending these findings, the same investigators stimulated the right pars triangularis for 20 min 5 days a week for two weeks in four right-handed chronically aphasic patients. Significant improvements in naming were observed, which persisted for at least 8 months following completion of stimulation (Martin et al., 2004; Naeser et al., 2005a). We have replicated these results and demonstrated that stimulation of the right pars triangularis also results in persistent improvements in spontaneous elicited speech (Hamilton et al., 2010). Naeser and colleagues have also recently reported on the case of a patient with chronic nonfluent aphasia and sleep apnea who experienced substantial gains in language ability when 1 Hz rTMS of the right pars triangularis was paired with continuous positive airway pressure (CPAP) (Naeser, Martin, Lundgren, et al., 2010).

One major limitation in prior studies employing rTMS in chronic aphasia has been the small number of subjects reported. Encouragingly, our results and those of Naeser and colleagues were recently further replicated by Barwood and colleagues (2010), who studied a cohort of 12 subjects with chronic aphasia (six real stimulation; six sham) and found that 1 Hz rTMS (20 min; 10 sessions over 10 days) administered to the right pars triangularis resulted in significant improvements in picture naming, spontaneous elicited speech, and auditory comprehension in the real rTMS group compared to the sham group. These benefits were observed 2 months following discontinuation of stimulation. In another recent study, Weiduschat and colleagues (2011) extended earlier findings by applying 1 Hz rTMS (20 min; 10 sessions over two weeks) to the right pars triangularis of six patients with subacute aphasia (mean period after stroke = 50 days). Four similar patients received only sham stimulation. Stimulated subjects improved significantly on the Aachen Aphasia test, while patients receiving sham did not. While such studies lend further support to the notion that low-frequency rTMS of the right pars triangularis can facilitate recovery in patients with aphasia, additional investigations that replicate and extend these results in even larger cohorts of patients will be crucial in order to convincingly demonstrate the reliability of this technique.

Not all patients with chronic nonfluent aphasia appear to benefit from low-frequency rTMS of the pars triangularis. In a recent small case series, Martin and colleagues (2009) contrasted findings in two aphasic subjects, one of whom showed improvement after receiving rTMS and one of whom did not. The authors emphasized differences in the distribution of the subjects' lesions. The subject who responded poorly to rTMS had a lesion that extended beyond the inferior frontal gyrus to encompass dorsal regions of the left motor and premotor cortex, deep white matter near the left supplementary motor area, and the posterior portion of the middle frontal gyrus, a region previously implicated as having an important role in naming ability (Duffau et al., 2005). These structures

were spared in the subject who responded well. The subject who responded to rTMS of the right pars triangularis also showed increased fMRI activity in left supplementary motor area (SMA) during a naming task 16 months after receiving rTMS compared to his earlier neuroimaging studies. This change in activation was not seen in the patient who responded poorly to stimulation. These data suggest that differences in lesion anatomy may strongly modulate the functional and behavioral consequences of intervention with rTMS.

Not all investigations using TMS in chronic aphasia have solely targeted the right hemisphere. Hypothesizing that inhibitory interhemispheric connections may have deleterious effects on recovering language networks in either hemisphere, Kakuda, Abo, Kaito, Watanabe, and Senoo (2010) recently applied 1 Hz rTMS (20 min; 10 sessions over 6 days) to sites that were contralateral to those found to be most activated by fMRI during a repetition task. Stimulating the right frontal lobe in two patients and the left frontal lobe in two others, they observed modest benefits in measures of spontaneous speech, repetition, writing, and naming that lasted at least 4 weeks (Kakuda, Abo, Kaito, et al., 2010). In another recent study, Kakuda, Abo, Uruma, Kaito, and Watanabe (2010) found that 1 Hz TMS (20 min; 10 sessions over 6 days followed by weekly sessions for 3 months) administered to Wernicke's area in the left hemisphere resulted in improvement on a Token Test and several subtests of the Standard Language Test of Aphasia (SLTA; a Japanese language instrument) in two patients with chronic fluent aphasia (Kakuda, Abo, Uruma, et al., 2010). Unfortunately, both studies reported by Kakuda and colleagues were limited in that neither demonstrated that the gains in performance made by subjects were statistically significant and neither employed a control condition to ensure that patients' behavioral changes were specifically attributable to TMS.

Data from tDCS studies are limited but encouraging (See Table 2). Monti and colleagues (2008) explored the immediate effects tDCS in patients with chronic aphasia by applying anodal, cathodal and sham stimulation (2 mA, 10 min) over the left frontotemporal cortex of eight aphasic patients who had suffered ischemic strokes. In their first experiment, four subjects underwent a single session of cathodal tDCS and a single sham tDCS session separated by at least one week; the four other subjects underwent anodal tDCS and sham sessions. Subjects performed a 20-item list picture-naming task immediately prior to and after completion of stimulation with no additional behavioral or language training prior to or during the task. Reaction time and accuracy on a picture-naming task was observed before and immediately after stimulation (Monti et al., 2008). Cathodal tDCS improved accuracy on the naming task by 34%, whereas anodal and sham stimulation had no effect. In a second experiment, stimulation over an occipital control site elicited no effects, supporting the conclusion that the influence of cathodal tDCS was site- and polarity-specific. These results suggest that a single 10-min tDCS application is able to induce an immediate improvement in naming, although the duration of this benefit was not explored. The authors argue that cathodal stimulation may down-regulate overactive inhibitory cortical interneurons in the lesioned hemisphere, ultimately giving rise to increased activity and function in the damaged left hemisphere. In a more recent study, Baker, Rorden, and Fridriksson (2010) found that anodal tDCS (1 mA, 20 min for 5 days) to the left frontal lobe resulted in improvements in naming accuracy among 10 patients with left hemisphere strokes and chronic aphasia (Baker et al., 2010). In this study, administration of tDCS was paired with a concurrent anomia treatment consisting of a picture-naming task and the benefit observed persisted for at least one week following administration of stimulation. In another recent study by Fiori and colleagues (2010), five daily sessions of anodal stimulation (20 min, 1 mA) over Wernicke's area in the left hemisphere paired with intensive

Table 1
rTMS studies in aphasia.

Study	N	Lesion location	Time since stroke	Aphasia type(s)	Location(s) stimulated	Stimulation parameters	Outcome measures	Results
Naeser et al. (2005a)	4	Large left frontotemporal cortical/subcortical lesions (n = 3); frontotemporal subcortical lesion with cortical sparing (n = 1)	5–11 years	Broca's (n = 2); anomic/ conduction (n = 1); global (n = 1)	Right pars triangularis	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks	Boston Naming Test (BNT), Boston Diagnostic Aphasia Examination (BDAE); Snodgrass and Vanderwart (S&V) picture naming	Improved accuracy and speeded reaction time for S&V items after 10 TMS sessions; improvement on BNT and Animal and Tool/ Implement subtests of BDAE 2 and 8 months after stimulation
Naeser et al. (2005b)[a]	1	Left frontotemporal subcortical lesion with cortical sparing	6.5 years	Global	Best cortical region of interest (ROI) determined by stimulation of multiple left hemisphere targets; Right pars triangularis selected	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks	BNT, BDAE, Cognitive Linguistic Quick Test (CLQT)	Improvements in BNT and Animal and Tool/ Implement subtests of BDAE as above; further improvement on BDAE and CLQT in speech therapy 1 year following stimulation
Martin et al. (2009)	2	Subjects 1 & 2: Large left frontotemporal cortical/ subcortical lesions; Subject 2: Additional involvement of fibers under SMA, Wernicke's area, and posterior middle frontal gyrus	1.5 and 10 years	Nonfluent	ROI determined by stimulation of multiple targets; Right pars triangularis selected	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks	BNT, BDAE, Cookie Theft Picture Description, fMRI during overt naming task	Subject 1: Improvement on BNT, BDAE, and Cookie Theft; new perilesional left frontal activation on fMRI 16 months post-TMS; Subject 2: No significant language improvement or fMRI changes
Naeser et al. (2010)	1	Left temporal cortical/ subcortical lesion; minor involvement of left inferior frontal gyrus	2 years	Nonfluent	ROI determined by stimulation of multiple targets; Right pars triangularis selected	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks; patient started on CPAP	BDAE, BNT	Increased phrase length, auditory comprehension, and naming persisting 3 months, 6 months, and 2.4 years after stimulation
Hamilton et al., 2010	1	Large left frontotemporal cortical/subcortical lesion	7 years	Broca's	ROI determined by stimulation of multiple targets; Right pars triangularis selected	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks	Western Aphasia Battery (WAB), BDAE, Cookie Theft Picture Description.	Improved object and action naming and Cookie Theft. Persistent benefits at 2,6, and 10 months
Kakuda et al. (2010a)	4	Left frontotemporal cortical lesion (n = 2); frontal cortical lesion (n = 1); left putamen (n = 1)	5–28 years	Motor-dominant (impaired speech).	Site determined by fMRI activation during naming task: left frontal (n = 2) and right frontal (n = 2).	1 Hz rTMS; 90% MT; 10 sessions over 6 days	Japanese versions of WAB, Standard Language Test of Aphasia (SLTA), and Supplementary tests of SLTA (SLTA-ST)	Presumed improvement in WAB, SLTA, and SLTA-ST (no statistical analyses)
Kakuda et al. (2010b)	2	Left MCA territory lesions	7 months and 8 months	Sensory-dominant (impaired comprehension)	Wernicke's area	1 Hz rTMS; 90% MT; 10 sessions over 6 days; daily language therapy	Token test, Japanese SLTA	Presumed improvement in scores on Token test and some subtests of SLTA that persisted at 3 months (no statistical analyses).
Barwood et al. (2010)	12	Left MCA territory cortical/subcortical lesions	2–6 years	Nonfluent	Right pars triangularis; subjects received real (n = 6) or sham (n = 6) stimulation	1 Hz rTMS; 90% MT; 10 daily sessions over 10 days	BDAE, Cookie Theft, BNT, S&V.	Improved naming and picture description among subjects receiving real TMS but not sham; persistent effects 2 months after real stimulation.
Weiduschat et al. (2011)	10	Left posterior temporoparietal lesions (n = 4); frontal cortical/ subcortical lesions (n = 3); subcortical lesions (n = 2); entire left MCA territory (n = 1)	16 weeks	Wernicke's (n = 5); Broca's (n = 2); global (n = 1); amnestic (n = 1)	Right pars triangularis (study group, n = 5), vertex (control control group, n = 5)	1 Hz rTMS; 90% MT; 10 daily sessions over two weeks; Speech and language therapy after each TMS session	Aachen Aphasia Test (AAT), PET activation during verb generation task	Improved AAT scores 2 weeks after stimulation in study patients but not control group; PET activation toward right hemisphere in control but not in treatment group 2 weeks after stimulation compared to baseline; no relationship between laterality shift and clinical improvement.

[a] Naeser et al. (2005b) describes in further detail a patient previously reported in Naeser et al. (2005a).

Table 2
tDCS studies in aphasia.

Study	N	Lesion location	Time since stroke	Aphasia type(s)	Location(s) stimulated	Stimulation parameters	Outcome measure	Results
Monti et al. (2008)	8	Left frontal cortical/subcortical lesions (n = 3); frontoparietal cortical/subcortical lesions (n = 2); frontotemporoparietal cortical/subcortical lesions (n = 2); frontoparietal subcortical lesion (n = 1)	2–8 years	Broca's aphasia (n = 4); global aphasia (n = 4)	Broca's area; occipital lobe control site	Single session of anodal, cathodal, and sham tDCS over Broca's area at 1 mA for 20 min; cathodal and sham tDCS applied to occipital lobe in separate experiment	Picture naming	Improved picture naming accuracy immediately after cathodal tDCS of Broca's area but not anodal, sham, or occipital tDCS
Fiori et al. (2010)	3	Left frontoparietal subcortical lesion (n = 1); frontoparietal cortical/subcortical lesion (n = 1); large frontotemporoparietal cortical/subcortical lesion (n = 1)	∼2–6 years	Mild (n = 1), moderate (n = 1), and severe (n = 1) nonfluent aphasia	Wernicke's area	5 consecutive daily sessions of anodal (1 mA for 20 min) or sham tDCS paired with language therapy	Picture naming	Improved naming accuracy and reaction time after 5 days of anodal but not sham tDCS. In 2 subjects, improvements persisted at 1 and 3 weeks after stimulation
Baker et al. (2010)	10	Left temporoparietal lesions (n = 4); frontotemporal lesions (n = 3); frontotemporoparietal lesion (n = 1); temporoparietooccipital lesion (n = 1); Lesion of entire MCA territory, medial frontal lobe, and basal ganglia (n = 1)	∼1–20 years	Anomic aphasia (n = 6), Broca's aphasia (n = 4)	tDCS localization guided to left hemisphere targets by fMRI activation during an overt naming task: premotor cortex (n = 5), dorsolateral prefrontal cortex (n = 2), anterior prefrontal cortex (n = 1), pars triangularis (n = 1), pars opercularis (n = 1)	5 consecutive daily sessions of anodal (1 mA for 20 min) or sham tDCS paired with anomia therapy	Picture naming	Improved picture naming after anodal tDCS compared to sham stimulation; persistent benefits 1 week after treatment

language training resulted in improved accuracy on a picture-naming task in three patients with chronic nonfluent aphasia (Fiori et al., 2010). In two of these patients, benefits were shown to persist for at least three weeks. One notable difference between the study by Monti and colleagues (2008) and later investigations is the polarity of the electrode (anode or cathode) associated with behavioral benefits. Other differences in the execution of these studies, including the number of sessions employed and the presence or absence of concurrent behavioral treatment may have contributed to different results. Nonetheless, these reported differences in the polarity-specific effects of tDCS complicates our understanding of the neurophysiologic and behavioral effects of tDCS in aphasia, and indicates the need for additional investigations.

To date, findings from the use of TMS and tDCS to treat chronic aphasia have largely been interpreted as supporting the model of interhemispheric inhibition, on the presumption that either facilitating activity in lesioned or perilesional areas or decreasing activity in inhibitory contralesional areas allows for improved language function (Fregni & Pascual-Leone, 2007). However, this model cannot easily account for all TMS and tDCS findings in patients with chronic aphasia. One important issue in this regard is the possible topographic specificity of rTMS. Almost all prior studies that have demonstrated a beneficial effect of right hemisphere stimulation have involved the administration of TMS specifically to the pars triangularis (Barwood et al., 2010; Hamilton et al., 2010; Martin et al., 2009; Naeser et al., 2005b,a; Naeser, Martin, Treglia, et al., 2010; Weiduschat et al., 2011). Naeser and colleagues and we have employed an approach that involves stimulating various sites in the right inferior frontal gyrus as well as the right motor cortex, in order to determine whether there is a specific site that responds best to TMS. Both our preliminary data and that of Naeser and colleagues suggest that TMS-induced improvements in naming are often associated with stimulation of the pars triangularis, but not with stimulation of other nearby right hemisphere sites (Hamilton et al., 2010; Naeser, Martin, Treglia, et al., 2010). Although more data are needed to support this finding conclusively, we believe it is unlikely in the setting of large left-hemisphere lesions, that the inhibitory transcallosal connections between left and right hemisphere regions would be so specific as to account for differences in performance that are linked to a single site in the right hemisphere.

An alternative explanation for these findings is that the right hemisphere may contribute to language function in chronic aphasic patients, but not always efficiently. By this account, TMS applied to different right perisylvian regions in patients may differentially affect specific components of a remodeled language network. In some cases, inhibitory stimulation of a right-hemisphere target might increase the overall function of the language network by decreasing the contribution of a dysfunctional element in that network. Our own ALE meta-analysis findings suggest that the pars triangularis is activated in a homotopic manner but is not homologous in its function compared to sites in the left hemisphere language network in normal individuals (Turkeltaub et al., submitted for publication). In other words, activity in this site is unlikely to contribute efficiently to the operation of reorganized language networks in the right or left hemisphere. Extending this reasoning further, inefficient neural activity in the right pars triangularis may contribute deleterious noise to the operation of reorganized language circuits. Thus inhibition of this site may result in beneficial suppression of a cortical region that would otherwise have an adverse effect on performance.

The notion that noninvasive brain stimulation improves the functionality of an inefficiently reorganized language network fits one aspect of the data that is not readily explained by other hypotheses, namely the finding that language function improves over the course of months following stimulation (Martin et al., 2004; Naeser et al., 2005a; Naeser, Martin, Treglia, et al., 2010). This improvement may reflect further enhancement of connection strengths in improved networks over time as they are reinforced by their continued use in the service of language processing (Bi & Poo, 2001; Spatz, 1996).

7. Limitations and challenges of noninvasive brain stimulation in aphasia

While mounting evidence suggests that noninvasive brain stimulation may be a useful adjunctive treatment for patients with aphasia after stroke, both TMS and tDCS have limitations that must be considered. One important caveat regarding noninvasive brain stimulation techniques is their limited spatial resolution and the difficulty of knowing precisely which region or regions of the brain are being affected. These concerns are especially applicable to tDCS, which employs relatively large electrodes (typically 5×7 or 5×5 cm) for stimulation. Evidence from computer modeling studies also suggests that the distribution of current in the brain associated with tDCS can be quite diffuse, and that regions of maximal stimulation can be unpredictable, varying with factors like reference electrode size and position (Bikson, Datta, & Elwassif, 2009). While the spatial resolution of TMS is understood to be considerably higher than that of tDCS, evidence suggests that the degree of spatial resolution required to target specific cortical sites such as the pars triangularis is achieved more readily when rTMS is used in conjunction with image-guided navigation techniques (Julkunen et al., 2009), which are not employed by many investigators currently using TMS. Moreover, predictions about neurophysiologic effects of brain stimulation are further complicated in stroke patients by the presence of lesions of varying size and distribution (Wagner et al., 2006).

Another important limitation of noninvasive brain stimulation techniques in aphasia is that current understanding of their neurophysiologic effects and their impact on behavior remains incomplete. For example, while low-frequency rTMS is often presumed to have inhibitory effects and high frequency rTMS to have excitatory effects on cortical activity and related behaviors, considerable interindividual variability in these effects has been observed (Gangitano et al., 2002). Perplexingly, some studies that have employed TMS and tDCS in patients with aphasia have reported results contrary to what would have been predicted based on the findings of other investigators. For instance, recent tDCS studies have reported improvement on language performance measures in aphasic patients receiving stimulation of opposite polarities—either cathodal (Monti et al., 2008) or anodal (Baker et al., 2010)—to the left frontal lobe. Thus, while a growing body of evidence suggests that noninvasive brain stimulation techniques may be useful for facilitating aphasia recovery, specific inferences about the anatomic or functional mechanisms of TMS and tDCS in patients with aphasia must still be viewed with some caution until more data has been reported.

8. A hierarchical model of aphasia recovery

Varying accounts of post-stroke language recovery are not mutually exclusive. Given the weight of evidence supporting both left- and right-hemisphere models of aphasia recovery, it is most likely the case that the recovery process is a dynamic one that involves a variety of plastic changes in both hemispheres. To that end, it has been argued (Heiss & Thiel, 2006) that a hierarchical combination of changes is likely to occur in patients recovering language function after stroke.

According to this hierarchical model, when lesions of the left hemisphere are very small or do not affect critical left hemisphere language centers, complete or near-complete language recovery can often be achieved by restoration of normal patterns of activation in left hemisphere language networks. When lesions of the left-hemisphere damage important language centers, perilesional regions of the left hemisphere may be recruited to subserve language function, often leading to good recovery (Karbe, Thiel, Weber-Luxenburger, Herholz, et al., 1998; Karbe, Thiel, & Weber-Luxenburger, 1998; Miura et al., 1999; Warburton et al., 1999). However, when left hemisphere networks are more severely impaired, the right hemisphere appears to be capable of assuming some language functions, by employing homotopic regions in ways that may mirror some aspects of language processing in the left hemisphere (Basso et al., 1989; Buckner et al., 1996; Gold & Kertesz, 2000; Ohyama et al., 1996; Rosen et al., 2000; Warburton et al., 1999; Weiller et al., 1995). This right hemisphere recruitment for language may be facilitated by the release of interhemispheric inhibition from the damaged left hemisphere. 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 to premorbid intact left hemisphere perisylvian regions. This is in part because networks in the nondominant right hemisphere may be intrinsically less adept at language processing compared to their dominant left hemisphere counterparts due to genetic predisposition, developmental factors, neuroplastic changes that occur during language learning, or any combination thereof. However, increased recruitment of right hemisphere networks may also be inefficient because they may prevent activation of more efficient left hemisphere language networks via transcallosal inhibition (Belin et al., 1996; Martin et al., 2004; Rosen et al., 2000; Shimizu et al., 2002). In short, the hierarchical model of effective aphasia recovery can be summarized as follows: (1) Best recovery is achieved when left hemisphere language networks recover normal function, (2) good recovery is achieved when perilesional left hemisphere areas compensate for damaged left hemisphere language regions, and (3) limited recovery is achieved when the right hemisphere is inefficiently recruited for language tasks.

As discussed above there also appears to be a temporal component to the distribution of right- and left-sided language function after stroke (Saur et al., 2006). In the context of acute and subacute lesions of the left hemisphere language network there appears to be greater tendency for reallocation of language function to right-hemisphere perisylvian circuits, particularly among patients with extensive left hemisphere injury. Over time there is, for a number of patients at least, diminished recruitment of right hemisphere structures for language tasks. Eventually, for some patients with chronic aphasia, significant language recovery is associated with redistribution of language processing back to left hemisphere perisylvian areas.

Intervention with noninvasive brain stimulation may work in several different ways. To date, most therapeutic stimulation studies have employed inhibitory stimulation of right hemisphere structures. This approach may modulate both right and left hemisphere components of chronically reorganized language networks in ways that allow them to function more efficiently. The effect of stimulation in the right hemisphere may be to down-regulate local inhibition of right hemisphere regions engaged in language-related tasks. Concurrently, inhibitory stimulation of intact contralesional cortical areas may facilitate increased recruitment of perilesional regions of the left hemisphere into reorganized language networks by diminishing the impact of transcallosal inhibitory inputs to those areas. Finally, although it has been proposed that the effects of noninvasive brain stimulation are specific with respect to their effect on reorganized language networks, it may be the case that the changes in language performance observed after brain stimulation may relate to alterations in cerebral function that are less focal and that may affect a variety of neural functions in ways that have not yet been described. Further investigations will be critical to further clarifying the impact of noninvasive brain stimulation on different mechanisms of aphasia recovery.

9. Future directions

Noninvasive brain stimulation provides a potentially promising set of tools for understanding and enhancing aphasia recovery. Future investigations involving noninvasive brain stimulation may be able to further characterize the roles of the left and right hemispheres in aphasia recovery by employing a variety of experimental manipulations. For example, noninvasive brain stimulation techniques could be paired with behavioral techniques that are believed to facilitate right hemisphere involvement in language tasks (Crosson et al., 2007; Schlaug, Marchina, & Norton, 2009). Other investigations may explore the degree to which reorganized language networks in the right hemisphere share functional homology with perisylvian language circuits in the left hemisphere. Administration of therapeutic rTMS to different regions in the right hemisphere could result in manipulation of specific linguistic processes, further elucidating structure–function relationships in reorganized language networks. Additional noninvasive stimulation studies could further characterize temporal aspects of language recovery by stimulating the right and left hemispheres at different timepoints relative to stroke onset. Finally, one important caveat to the current body of data on brain stimulation, as used to enhance language recovery, is that studies to date have largely focused on patients with frontal lobe lesions and nonfluent aphasia. Future studies will need to explore the effects of brain stimulation across a range of aphasia types and in a variety of lesion locations.

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