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REVIEW

The Use of Non-invasive Brain Stimulation Techniques to Facilitate Recovery from Post-stroke Aphasia

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Abstract Aphasia is a common symptom after left hemispheric stroke. Neuroimaging techniques over the last 10–15 years have described two general trends: Patients with small left hemisphere strokes tend to recruit perilesional areas, while patients with large left hemisphere lesions recruit mainly homotopic regions in the right hemisphere. Non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have been employed to facilitate recovery by stimulating lesional and contralesional regions. The majority of these brain stimulation studies have attempted to block homotopic regions in the right posterior inferior frontal gyrus (IFG) to affect a presumed disinhibited right IFG (triangular portion). Other studies have used anodal or excitatory tDCS to stimulate the contralesional (right) fronto-temporal region or parts of the intact left IFG and perilesional regions to improve speech-motor output. It remains unclear whether the interhemispheric disinhibition model, which is the basis for motor cortex stimulation studies, also applies to the language system. Future studies could address a number of issues, including: the effect of lesion location on current density distribution, timing of the intervention with regard to stroke onset, whether brain stimulation should be combined with behavioral therapy, and whether multiple brain sites should be stimulated. A better understanding of the predictors of recovery from natural outcome studies would also help to inform study design, and the selection of clinically meaningful outcome measures in future studies.

Keywords Transcranial direct current stimulation · tDCS · Transcranial magnetic stimulation · TMS · Broca's aphasia · Language · Stroke · Neurorehabilitation

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Introduction and Statement of the Problems

Aphasia is a common symptom after left hemisphere stroke. Affected individuals often experience incomplete recovery despite intense speech therapy after the acute stroke phase (Kertesz and McCabe 1977; Pedersen et al. 1995, 2004; Wade et al. 1986). Most natural and speech-therapy facilitated recovery from aphasia occurs during the first 6 months following a stroke (Nicholas et al. 1993), but significant improvements in language functions have been described in case studies of patients even several years after stroke (Moss and Nicholas 2006; Schlaug et al. 2008a). These cases suggest that in contrast to stroke patients affected by a motor impairment, patients with aphasia may have a longer window for recovery, most likely because the unaffected hemisphere can compensate more for speech-motor impairments than for impaired distal limb-motor functions of the ipsilateral side. Factors that can determine a patient's recovery from aphasia include lesion size and lesion site (Lazar and Antoniello 2008; Marchina et al 2011), as well as the initial level of impairment (Lazar et al 2010). Other factors that are likely to play a role include: age, gender, degree of hemispheric language laterality, anatomical characteristics of the right auditory-motor white matter tracts (e.g., arcuate fasciculus), and the degree of inter-hemispheric connectivity of speech-motor regions (see

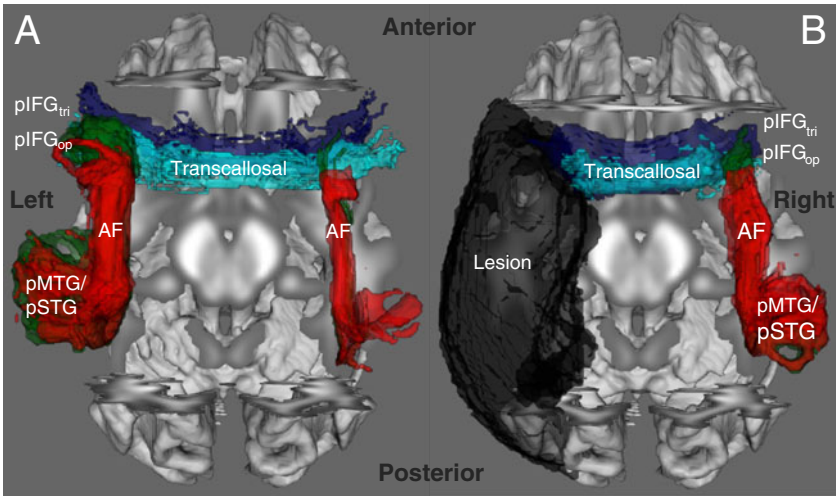

Fig. 1 Diffusion Tensor Imaging derived fiber tracts using probabilistic fiber tracking implemented in FSL (http://www.fmrib.ox.ac.uk/fsl). Tracts are superimposed onto an axial slice of a 3D-reconstructed brain. The left side of image shows left hemisphere (neurological view). **A** shows the two components of the arcuate fasciculus connecting the superior/middle posterior temporal gyrus (pSTG/pMTG) with the posterior inferior frontal gyrus (pIFG$_{op}$ and pIFG$_{tri}$). The two components of the AF are separated into those fibers that connect with the opercular portion (red, pIFG$_{op}$) and the triangular portion (green, pIFG$_{tri}$) of the posterior IFG. The opercular portion approximately corresponds to Brodmann area 44 and the triangular portion corresponds to Brodmann area 45 (Amunts et al 2010). The transcallosal connections between BA 44 (light blue) and BA 45 (dark blue) are shown as well. **B** shows the right hemisphere AF and the slightly reduced transcallosal fiber tracts in a chronic patient with a large left hemisphere stroke (lesion marked in black) and nonfluent aphasia

also Fig. 1), and small vessel ischemic lesion burden. However, their significance as predictors of recovery have not been examined in larger-scale studies.

Two important questions that researchers attempt to address in aphasia research are: (1) What are the neural mechanisms that support language recovery? (2) Can these mechanisms be modulated to improve outcomes? In this review, we will primarily focus on studies that have included patients with aphasia, who exhibit various degrees of dysfluency and problems with repetition and naming. In right-handed individuals, nonfluent aphasia generally results from lesions in the left frontal lobe, including the portion of the left frontal lobe known as Broca's region. Named after Paul Broca (1864), who first linked this area of the brain with nonfluent aphasia, this region is thought to consist of the posterior inferior frontal gyrus (IFG) encompassing Brodmann's areas 44 (approximately corresponding to the opercular portion of the posterior IFG) and 45 (approximately corresponding to the triangular portion of the posterior IFG). Subsequent reports after Broca's initial description have shown that a wider array of lesions in the frontal lobes and in subcortical brain structures are typically necessary to result in a clinical picture of a major motor aphasia (Kertesz et al. 1977; Mohr et al. 1978).

To date, functional imaging studies have been used to increase our understanding of the neural mechanisms underlying post-stroke recovery. Some of these reports have emphasized the role of preserved language function in the left hemisphere (Cappa and Vallar 1992; Heiss et al. 1999), while others have proposed that language function is restored when right hemisphere regions compensate for the loss (Basso et al. 1989; Blasi et al. 2002; Cappa and Vallar 1992; Cappa et al. 1997; Kinsbourne 1998; Selnes 1999; Weiller et al. 1995). Still other studies provide evidence for a bi-hemispheric role or even a right hemisphere only role in language recovery following an insult, particularly if the insult involves large parts of the left hemisphere (Heiss and Thiel 2006; Mimura et al. 1998; Rosen et al. 2000; Saur et al. 2006; Winhuisen et al. 2005). Interestingly, few studies have examined the neural correlates of an aphasia treatment by contrasting pre- and post-therapy assessments (Cornelissen et al. 2003; Musso et al. 1999; Saur et al. 2006; Schlaug et al 2008a, 2009a; Small et al. 1998; Thompson and Shapiro 2005).

The current consensus is that there are two paths to recovery. First, in patients with small lesions in the left hemisphere, there tends to be recruitment of left perilesional areas with variable involvement of right-hemispheric structures (Heiss et al. 1999; Heiss and Thiel 2006; Hillis 2007; Rosen et al. 2000). These regions are often mirror structures of the lesioned left hemisphere (i.e., homotopic regions), although they may become functional equivalents over time if these regions on the right, non-dominant hemisphere are going to subserve language functions during recovery (i.e., homologous regions). In patients with relatively large lesions in the left hemisphere involving language-related areas of the fronto-temporal lobes, the

only path to recovery may be through the recruitment of homologous language and speech-motor regions in the right hemisphere (Heiss and Thiel 2006; Hillis 2007; Rosen et al. 2000; Schlaug et al. 2008a, 2010). The mechanisms underlying right hemisphere involvement in these patients are not fully understood, but one plausible hypothesis is that the right hemisphere assumes speech-motor output functions through a rudimentary arcuate fasciculus. This rudimentary arcuate fasciculus consists of the homologous right posterior IFG as well as the adjacent premotor and motor regions, which are of critical importance in the feedforward and feedback control of speech output. In addition to enabling speech output through right sensorimotor regions, recovery of language functions may depend on posterior perisylvian language comprehension regions, which are often preserved in a typical middle cerebral artery stroke. The recruitment of right hemisphere regions during speech production not only occurs in patients with Broca's aphasia, but also in healthy individuals, especially if the rate of production is reduced (Ozdemir et al. 2006). This suggests that both hemispheres could play a role in initiating and controlling speech output.

Can the right hemisphere of patients with relatively large left hemispheric lesions actually substitute for the left hemisphere? Some researchers have suggested that recovery via the right hemisphere may be less efficient than recovery via perilesional left hemispheric regions (Heiss et al. 1999; Heiss and Thiel 2006), possibly because patients with relatively large left hemispheric lesions are generally more impaired than patients with smaller lesions. Nevertheless, activation of right hemispheric regions during speech and language fMRI tasks has been reported in patients with aphasia, regardless of lesion size (Rosen et al. 2000).

While functional imaging studies are useful in revealing brain regions that remain active in patients during language tasks, they do not provide information about causality. Accordingly, areas that are active during task performance may not be functionally significant but merely a neural correlate or an epiphenomenon. To address this possibility, non-invasive brain stimulation studies offer important insights into the causality of neural connectivity. For example, to examine whether right hemisphere activation in aphasia is a sign of disinhibition and interferes with the recovery process, researchers have focused on the right IFG, particularly the triangular portion, and have attempted to modulate the activity of this region to test whether short-term improvements can be observed (Baker et al. 2010; Floel et al. 2011; Fridriksson et al. 2011; Hamilton et al. 2011; Monti et al. 2008; Naeser et al. 2005a, b; Vines et al. 2011; Weiduschat et al. 2011). In addition, several reports have described therapies that specifically engage or stimulate the homologous right hemisphere regions, which might have the potential to facilitate the language recovery process beyond the limitations of natural recovery (Schlaug et al. 2008a, 2009b; Vines et al. 2009, 2011). A recent proof-of-concept study showed that a combination of an intonation-based therapy and simultaneous anodal tDCS over the right IFG led to an improvement in speech fluency compared to a condition in which sham tDCS was applied to patients receiving intonation-based therapy (Vines et al. 2011).

Most post-stroke language interventions are administered by speech therapists who evaluate patients' individual needs, and then use a combination of techniques tailored to the individual patient's impairment profile. At present, there are no universally accepted methods or "gold standards" for the treatment of severe, nonfluent aphasia against which new or experimental interventions could be compared. Nevertheless, a general effect of post-stroke aphasia therapy has been established, and studies using new approaches have had positive outcomes if therapy was applied in an intense and long-term manner (Bhogal et al. 2003; Robey 1994). Criteria for efficacy and clinically meaningful outcome measures to assess treatment efficacy have not been established and generally agreed upon. Yet, most therapists, clinicians, and researchers in the aphasia field would probably agree that a treatment should be considered effective if patients show improvement in speech output that generalizes to untrained language structures and contexts (Thompson and Shapiro 2007). This is an important concept to keep in mind when we are discussing the various brain stimulation studies that have been conducted so far.

In the remaining sections, we will examine the theoretical and practical issues relating to the use of non-invasive brain stimulation, and examine the causal roles of particular brain regions in the recovery process. Ultimately, we hope to further our understanding of the mechanisms that might underlie the facilitatory treatment effects of brain stimulation.

Non-invasive Brain Stimulation Methods

Two non-invasive brain stimulation methods have been used and tested in stroke patients. So far, most studies have examined patients with ischemic lesions affecting the motor system leading to variable degrees of hemiparesis. Transcranial magnetic stimulation (TMS), applied in a repetitive manner, can have inhibitory or excitatory effects on cortical tissue depending on the stimulation frequency (1 Hz has more of an inhibitory effect while 5–10 Hz has more of an excitatory effect). When applied over the injured hemisphere, however, TMS may have some safety issues (e.g., possibility of provoking seizures) that has limited its

applicability in research studies. Transcranial direct current stimulation (tDCS) is a relatively safe, portable, non-invasive brain polarization technique capable of modulating cortical excitability in a polarity-specific manner using weak direct currents (Nitsche and Paulus 2000; Priori et al. 1998, 2003). Nitsche and Paulus demonstrated modulatory effects of anodal (increasing cortical excitability) and cathodal (decreasing cortical excitability) tDCS on brain tissue, and these effects surprisingly outlasted the duration of stimulation (Nitsche and Paulus 2000, 2001), with residual electrophysiological effects detectable up to 90 minutes after a 20 minute stimulation period (Nitsche and Paulus 2000).

The goals of non-invasive brain stimulation protocols can be to increase excitation in ipsilesional cortical regions (Khedr et al. 2005; Kim et al. 2006; Malcolm et al. 2007; Yozbatiran et al. 2009) or decrease excitation in contralesional cortical regions. The potential beneficial effects of decreasing excitation in contralesional, healthy cortical regions are based on neurophysiological studies in chronic stroke patients. These studies have demonstrated that *disinhibition* of *contralesional* motor regions coexists with *increased inhibition* of *ipsilesional* motor regions, resulting in an imbalance of inter-hemispheric interactions (Duque et al. 2005; Murase et al. 2004; Shimizu et al. 2002). This imbalance in inhibition appears to interfere with the recovery process under some circumstances, as supported by imaging studies in patients showing an activation of the contralesional motor regions when the affected arm/hand performs a motor task (Calautti and Baron 2003; Cramer et al. 2002; Johansen-Berg et al. 2002; Lotze et al. 2006; Loubinoux et al. 2003; Nair et al. 2007). Although this model of inter-hemispheric imbalance in inhibition may appear to be a simplified representation of the many underlying pathophysiological processes involved in stroke recovery, it provides a framework for hypotheses focused on three facets: 1) downregulating activity in the contralesional motor region to offset its unbalanced influence on the lesional motor region; 2) facilitating activity in the ipsilesional motor region (Fregni et al. 2005; Hesse et al. 2007; Hummel et al. 2005; Hummel and Cohen 2005; Mansur et al. 2005; Ward and Cohen 2004); and 3) a combination of both approaches (Lindenberg et al. 2010; Vines et al. 2008). Support for these approaches can be found in pilot and proof-of-concept studies that have shown temporary beneficial effects in motor outcome measures, primarily in single session experiments using either transcranial magnetic stimulation (TMS), or more recently, transcranial direct current stimulation (tDCS) (Fregni et al. 2005; Hesse et al. 2007; Hummel et al. 2005; Lindenberg et al. 2010).

Several studies have examined high frequency (≥ 3 to 20 Hz) rTMS applied to the ipsilesional hemisphere in stroke patients. Khedr and colleagues (Khedr et al. 2005) found that 10 sessions of 3 Hz rTMS to the motor cortex during the subacute stroke period led to reduced disability and improved overall neurological status when compared with sham rTMS. This advantage was observed immediately after the 10 sessions as well as at 3 months follow-up after stroke. All patients had received standard physiotherapy. No effect was seen in patients with very large strokes affecting the entire middle cerebral artery territory. Furthermore, no correlation was found between behavioral gains and changes in cortical excitability, suggesting that electrostimulation effects on behavior are not mediated by simply changing motor cortex excitability. In a cohort of patients with chronic hemiparetic stroke, Kim and colleagues (Kim et al. 2006) found that a single session of 10 Hz rTMS applied to ipsilesional motor cortex, while subjects practiced a complex finger sequencing motor task, improved motor learning more than sham rTMS. Application of rTMS induced a significantly larger increase in the MEP amplitude than did sham rTMS. In this study, a change in motor cortex excitability was associated with greater motor behavioral gains. In a small sample of patients, Talelli and colleagues (Talelli et al. 2007) found that a single session of excitatory theta burst stimulation, consisting of three pulses at 50 Hz repeated 5 times/sec, increased amplitude from the affected hemisphere and also improved reaction time. Yozbatiran and colleagues (Yozbatiran et al. 2009), in a study of patients with chronic hemiparetic stroke, found small increases in blood pressure when applying a single session of 20 Hz rTMS to the premotor region on the affected side, but no clear improvement in any of the motor outcome measures. The authors concluded, however, that high frequency rTMS applied to intact parts of the lesional hemisphere might be safe.

Application of low frequency rTMS to the contralesional hemisphere is intended to reduce its excitability and activity, which can minimize its unbalanced inhibitory effects on the ipsilesional hemisphere, resulting in improvements in motor control of the ipsilesional motor cortex of the affected hand (Butefisch et al. 2008; Murase et al. 2004; Nowak et al. 2008; Webster et al. 2006). This suppressive approach can be effective in modifying cortical silent periods (Takeuchi et al. 2005) and in increasing excitability of the ipsilesional motor cortex (Fregni et al. 2006). A single session of low frequency (1 Hz) rTMS to the affected hemisphere in subacute stroke patients, followed by motor training, can increase cortical excitability, without affecting motor behavior (Pomeroy et al. 2007).

In order to select potential target sites for non-invasive brain stimulation, one needs to develop an understanding of the mechanisms underlying spontaneous functional recov-

ery after stroke. These mechanisms are likely to differ from patient to patient depending on such factors as initial syndrome severity, lesion site and size, affected hemisphere and hemispheric dominance among others. Similarly, the optimal approach to pairing with behavioral experience (Stefan et al. 2008), the role that adjuvant cellular or pharmacological therapy might play (Kirschner et al. 2003; Lang et al. 2008), the proper dose of rTMS (Hiscock et al. 2007) or tDCS, and the preferred stimulation site(s) require further clarification,

Although the efficacy of tDCS has not been formally compared against TMS, there are advantages for using tDCS to induce polarity-specific excitability changes in stroke patients. First, tDCS does not directly lead to neuronal discharges and may be safer than TMS, with a lower incidence of adverse effects (Poreisz et al. 2007). Second, the current is usually transmitted through large electrodes, possibly modulating a larger neural network (Lang et al. 2005) that might include multiple brain regions that play a role in the recovery process (e.g., premotor, somatosensory, primary motor cortex). Conversely, the presumed advantage could have a negative effect if a more focal stimulation is required or needed. Third, tDCS has a sham mode that cannot be easily detected by participants, making it possible to be used in controlled experiments and randomized controlled clinical trials (Gandiga et al. 2006; Lindenberg et al. 2010). Fourth, a key advantage of tDCS over TMS is that tDCS can be combined in real-time with other behavioral or peripheral training protocols (e.g. simultaneous occupational therapy or speech therapy), thus optimizing the brain's plasticity by inducing Hebbian or long-term potentiation-like mechanisms (Schlaug et al 2008b; Vines et al. 2011). Finally, tDCS can be used in a dual mode applying anodal stimulation to one hemisphere and cathodal stimulation to a homolog region on the other hemisphere. This dual hemispheric stimulation has been shown to lead to stronger behavioral effects in normal subjects and in stroke patients than a uni-hemispheric montage (Lindenberg et al. 2010; Vines et al. 2008).

The prolonged sensory, motor, and cognitive effects of tDCS have been attributed to a persistent bidirectional modification of post-synaptic connections similar to long-term potentiation (LTP) and long-term depression (LTD) effects (Hattori et al. 1990; Islam et al. 1995; Moriwaki 1991). Dextromethorphan, an N-methyl-D-aspartate (NMDA) antagonist, suppressed both anodal and cathodal tDCS effects, strongly suggesting the involvement of NMDA receptors in both types of stimulation-induced neuroplasticity. In contrast, carbamazepine selectively eliminated anodal effects. Because carbamazepine stabilizes the membrane potential through voltage-gated sodium channels (stabilizing the inactivated state of sodium channels), the results were interpreted as indicative that after-effects of anodal tDCS require a depolarization of membrane potentials (Liebetanz et al. 2003). Recent studies on brain modeling and current density distribution have suggested that in spite of a large fraction of the direct current being shunted through the scalp, tDCS carries adequate currents to the underlying cortex to be able to modulate neuronal excitability (Miranda et al. 2006; Wagner et al. 2007), and corresponding regional blood flow changes have been seen using non-invasive arterial spin labeling technique (Zheng et al. 2011).

Recruitment of Peri-lesional Brain Regions in Facilitating Aphasia Recovery

A number of functional imaging studies on nonfluent aphasia have demonstrated that better spontaneous language recovery is associated with greater activation of left-hemisphere structures (Karbe et al. 1998; Warburton et al. 1999). Furthermore, the size of left hemisphere infarction and the degree of overlap of the lesion with a language-related white matter tract correlate with aphasia severity after stroke and recovery potential (Kertesz et al. 1979; Marchina et al. 2011). To date, the mechanisms underlying increased perilesional activation in language recovery have not been fully elucidated. One explanation is that perilesional activation is related to the diminished effects of inhibitory influence from the lesion onto its surrounding intact brain regions, leading to increased perilesional activation. The same explanation suggests that the decrease in transcallosal inhibitory influence can lead to a disinhibition of contralesional homotopic regions (Murase et al. 2004; Shimizu et al. 2002). Thus, it is possible that reduced inhibition of the perilesional region facilitates its recruitment, even though the same area might not have been activated during language processing before the stroke. An unbalanced transcallosal inhibitory influence from the intact hemisphere onto the perilesional cortex of the affected hemisphere could potentially interfere with the perilesional recruitment. If this phenomenon really exists, then it could support the use of inhibitory brain stimulation to suppress unwanted inhibitory influences from the intact hemisphere onto the perilesional cortex of the affected hemisphere. However, the lesion would have to be small on the affected hemisphere, such that parts of the perilesional language region are preserved. Animal studies support the notion that the perilesional cortex can remodel itself, with increased recruitment of perilesional regions during task performance (Nudo 2006; Nudo and Friel 1999). Whilst most non-invasive brain stimulation studies in aphasia have not directly targeted perilesional areas, electrodes for

tDCS are typically so large that both the lesion and its surrounding regions are stimulated (Baker et al. 2010). Another methodological consideration for stimulating the affected hemisphere is that it is often difficult to predict the distribution of the currents around the lesion.

To date, only two studies have applied tDCS to the affected hemisphere of patients with aphasia. Monti and colleagues (Monti et al. 2008) applied either anodal, cathodal, or sham stimulation with 2 mA (for 10 min) over left fronto-temporal regions with an occipital reference region for 10 min in eight patients with aphasia. Reaction time and accuracy on a picture-naming task were measured before and immediately after stimulation. Only cathodal tDCS was found to improve accuracy on the naming task, whereas anodal and sham stimulation had no effect. They argued that the effect of cathodal stimulation might have been to downregulate the overactive, inhibitory cortical interneurons in the injured hemisphere. In another study, Baker and colleagues (Baker et al. 2010) found that anodal tDCS (1 mA, 20 min/day for 5 days) to the left inferior frontal lobe compared to sham tDCS while practicing a picture naming task in a cross-over design resulted in improved naming accuracy on trained items that persisted for at least one week among 10 chronic aphasic patients (6 fluent and 4 nonfluent aphasic patients). A follow-up study with only fluent patients combined anodal tDCS with fMRI reported activity in the perilesional region of the left hemisphere in comparison to a sham stimulation (5 days) coupled with picture-naming training (Fridriksson et al. 2011). In this fluent group, effects of reaction time for the trained items were seen with anodal stimulation only, but not with sham stimulation, and these effects lasted for 3 weeks. Fiori et al (Fiori et al. 2011) found an overall improvement in accuracy in a picture naming paradigm with anodal stimulation and sham stimulation to the left CP5 region (1 mA for 20 min/day for 5 days) but no clear difference in accuracy between the two stimulation conditions, although there was a difference in the reaction time after anodal stimulation compared with sham stimulation. Given these inconsistent findings with regard to whether anodal or cathodal stimulation applied to the affected hemisphere can lead to an accuracy or just reaction time effect, more carefully designed studies, preferably without using cross-over designs because carry-over effects are difficult to control statistically, are needed to examine the precise effects of anodal and cathodal tDCS on the affected hemisphere in patients with aphasia; such studies also need to take into account the effects of lesion size and site (see (Marchina et al. 2011 for details). The following sections will describe studies that have used non-invasive brain stimulation to target mainly the unaffected hemisphere. We will also focus on studies that have combined non-invasive brain stimulation with forms of speech therapy (see Table 1 for an overview of these studies)

The Role of the Contralesional Right Hemisphere in Facilitating Recovery from Aphasia

Although some researchers have postulated that right hemisphere activation may not be useful or be an epiphenomenon in patients with aphasia (Heiss et al. 1999; Heiss and Thiel 2006), there is increasing evidence that suggests a potentially beneficial role of the right hemisphere in facilitating language recovery. In particular, for patients with large lesions that cover language-relevant regions on the left, therapies that specifically engage or stimulate the homologous right hemisphere regions have the potential to facilitate the language recovery process beyond the limitations of natural recovery (Schlaug et al. 2008a, 2009b; Vines et al. 2009, 2011). Consistent with this idea, imaging studies have suggested that language function can be restored when right hemisphere regions compensate for the loss (Basso et al. 1989; Blasi et al. 2002; Cappa and Vallar 1992; Cappa et al. 1997; Kinsbourne 1998; Selnes 1999; Weiller et al. 1995). Moreover, there is evidence for a bi-hemispheric role or even a right hemisphere only role in language recovery following an insult, particularly if the insult involves large parts of the left hemisphere (Heiss and Thiel 2006; Mimura et al. 1998; Rosen et al. 2000; Saur et al. 2006; Winhuisen et al. 2005). Saur and colleagues (Saur et al. 2006) and Hillis (Hillis 2007) have also suggested that right hemisphere involvement could be due to a dynamic process that changes during the course of recovery. Further support for the notion that the right hemisphere can play an important role in language recovery comes from several reports of children with large left hemisphere lesions or left hemispherectomies showing a remarkable recovery of language function which can only be attributed to the right hemisphere (Vargha-Khadem et al. 1997). In a large meta-analysis using Activation Likelihood Estimation, Turkeltaub and colleagues (Turkeltaub et al. 2011) found that activations in the right IFG were reliably observed in language production tasks in patients with aphasia and that the location of these activations corresponded with activation sites on the left hemisphere in healthy individuals (Turkeltaub et al. 2011).

The involvement of the right hemisphere may also be dependent on the premorbid characteristics of right hemisphere systems for speech-motor output (Humphreys and Praamstra 2002; Knecht et al. 2002). It is conceivable that preexisting (naturally endowed) variability in brain anatomy (e.g., larger than typical right arcuate fasciculus or reduced left-right asymmetry) may explain why some

Table 1 Summary presentation of TMS and tDCS studies in subacute and chronic aphasic patients as discussed in this review

Author	Year	#Pt	A-Type	Design	Stimulation	Loc	Outcome
Naeser	2005	4	Broca(3), Global(1)	Open label	1 Hz rTMS, 20 mins/day, 10 days over 2 wks	R IFG_{tri}	Increased Accuracy+Decreased RT in Snodgrass (after 10 sessions), BNT (sig. at 2 months post TMS,), BDAE (sig. at 2 wks and 2 months post TMS)
Winhuisen	2005	11	Wernicke(6), Global (4), Anomic(1); Subacute	rTMS over PET spot	4 Hz rTMS, 10s pulse train	L+R IFG	Decreased accuracy with L IFG TMS in 10/11 pts; 6/11 had significant L IFG activation. Decreased Accuracy with R IFG TMS in 5/11 pts, 5/5 of them had right IFG activation
Monti	2008	8	Nonfluent	Rand. anodal (4) cathodal (4) tDCS, sham-controlled; anodal+cathodal tDCS(2)	2 mA of anodal vs cathodal vs sham tDCS, 10 min; 1 sess	L FT (Broca)	Increased Accuracy with cathodal tDCS
Martin	2009	2	Nonfluent	Open label	1 Hz rTMS, 20 min, 10 sessions over 2 wks	R IFG_{tri}	Increased Accuracy in pt1; No change in pt2
Fiori	2010	3	Nonfluent	Crossover, sham-controlled, double-blind	1 mA anodal vs sham tDCS, 20 min/day, 5 days, with picture naming training	L Wernicke (CP5)	Increased Accuracy with anodal tDCS on trained items, lasting for 3 weeks in 2/3 pts
Baker	2010	10	Fluent(4), Nonfluent(5)	Crossover, randomized, sham-controlled, double-blind	1 mA anodal vs sham tDCS, 20 min/day, 5 days with picture naming training	L Front, Perilesional (fMRI spot)	Increased Accuracy on trained and strong trend for untrained items with anodal tDCS, lasting for 1 week
Hamilton	2010	1	Nonfluent	Open label	1 Hz TMS	R IFG_{op}	Increased Accuracy over several sites (R M1, R IFGop, R IFGtri), most pronounced over R IFG_{tri}
Fridriksson	2011	8	Fluent	Crossover, randomized, sham-controlled, double-blind	1 mA anodal vs sham tDCS, 20 min/day, 5 days, with picture naming training	L Frontal, Perilesional (fMRI spot)	Decreased RT on trained items; Effects lasts for 3 weeks
Weidushat	2011	10 (6TMS,4S)	Broca's, Wernicke's; Subacute	Randomized, sham-controlled, single-blind	1 Hz TMS over R IFG vs active control site; followed by Speech-therapy	R IFG	Increased Accuracy in AAT in R IFG group over control group
Floel	2011	12	Anomic	Crossover, randomized, sham-controlled, double-blind	1 mA anodal vs cathodal vs sham tDCS with picture naming training	R TPJ	Increased Accuracy on trained items with anodal more than cathodal tDCS; Effects lasted for 2 weeks
Vines	2011	6	Broca's	Crossover, randomized, sham-controlled, double-blind	1.2 mA anodal vs sham tDCS, 20 min/day, 3 days, combined with 20 min of Melodic Intonation Therapy	R IFG	Increased fluency with anodal tDCS, but not sham

mA miliampere; *RT* reaction time; *BNT* Boston Naming Test; *BDAE* Boston Diagnostic Aphasic Evaluation; *IFG* inferior frontal gyrus (*op* pars opercularis; *tri* parts triangularis); *TPJ* temporo-parietal junction; *AAT* Aachen Aphasia Test; *pts* patients

patients recover better than others when they sustain left hemisphere damage.

Additional support for the involvement of the right hemisphere in language functions comes from cases of relatively slow growing tumors involving the left IFG, a condition not dissimilar to patients with aphasia after stroke. In the instance of a tumor, the adaptive reorganization and plasticity occur slowly as the tumor develops. In the case of stroke, however, the injury occurs quickly while plasticity and reorganization of potential right hemisphere language regions may occur over a much longer time-window, to allow successful integration of the right hemisphere into the language network (Thiel et al. 2006).

A number of behavioral interventions have been used to facilitate the recovery process by engaging the intact right hemispheres of patients with aphasia. Crosson and colleagues (Crosson et al. 2009) described a method of using gesturing and other complex motor tasks with the intact left hand when a patient with aphasia was asked to perform a picture naming task. The hypothesis here was that the right sensorimotor system controlling hand actions would become active and that this activity would then engage the shared structures for articulatory and auditory-motor mapping in the right inferior frontal gyrus. Another behavioral intervention for aphasia that has been used is Melodic Intonation Therapy (MIT). This intervention is an intonation-based method for nonfluent or dysfluent patients that was developed in response to the observation that severely nonfluent patients can often produce well-articulated, linguistically accurate words while singing, but not during speech (Gerstman 1964; Geschwind 1971; Hebert et al. 2003; Keith and Aronson 1975; Kinsella et al. 1988; Yamadori et al. 1977).

The original interpretation of MIT's path to successful recovery was that it engaged homotopic anatomical areas for articulation and speech output in the right hemisphere (Albert et al. 1973; Sparks et al. 1974), although to date, this has not been proven. An alternative explanation has been that MIT may exert its effect by either unmasking existing music and language connections in both hemispheres, or by engaging preserved language-capable regions in either or both hemispheres. Since MIT incorporates both the melodic and rhythmic aspects of music (Albert et al. 1973; Boucher et al. 2001; Cohen and Masse, 1993; Helm-Estabrooks et al. 1989; Norton et al. 2009; Sparks et al. 1974; Sparks and Holland 1976), it may be unique in its potential for engaging not only the right, but both hemispheres. In the first imaging study on MIT, Belin and colleagues (Belin et al. 1996) suggested that MIT-facilitated recovery could be associated with the reactivation of left hemisphere regions, most notably the left prefrontal cortex, anterior to Broca's region. At first glance, the findings may appear inconsistent with the hypotheses put forth by the original developers of MIT and also with subsequent imaging studies (Albert et al. 1973; Bonakdarpour et al. 2000; Schlaug et al 2008a, 2009b, 2010; Sparks et al. 1974). However, whilst their primary finding was an activation of left prefrontal regions when participants were asked to repeat intoned words, Belin and colleagues also reported blood flow changes in the right hemisphere (including the right temporal lobe and the right central operculum) when comparing the repetition of spoken words with the hearing of those words. Thus, it appears that their results also point to the involvement of right hemisphere structures during language processing in patients with aphasia who had been treated with MIT.

Non-invasive brain stimulation has been shown to enhance speech and language functions in healthy individuals as well as in patients with aphasia. In healthy individuals, studies have found that applying anodal tDCS to regions in the left IFG and left posterior perisylvian region significantly improved fluency (Cattaneo et al. 2011; Iyer et al. 2005). In patients with aphasia, applying PET and rTMS to the right IFG resulted in bilateral activation of the inferior frontal gyrus during a verbal semantic task in most patients, but that over time, there was a decrease in the proportion of patients in whom inhibitory rTMS of the right IFG disrupted performance (Winhuisen et al. 2005, 2007). This suggests that the potential of the right hemisphere to engage in language-related tasks after left-hemispheric stroke might change over time.

Non-invasive brain stimulation has been used to test the hypotheses that right hemisphere activation could either (1) hinder language recovery in chronic patients with aphasia (Martin et al. 2004; Naeser et al. 2005b) or (2) be used as a target site to facilitate language recovery (Vines et al. 2011). "Blocking" the right hemisphere comes from the disinhibition model of the motor system (Murase et al. 2004; Shimizu et al. 2002). Specifically, the loss of transcallosal inhibition onto the right hemisphere may result in increased, uninhibited activity of the right hemisphere, which in turn leads to increased inhibitory effects on left perilesional cortex, thereby interfering with the recovery process. Naeser and colleagues (Naeser et al. 2005b) showed that 1 Hz inhibitory rTMS applied to the triangular portion of the right IFG for 20 min/day for 10 days over two weeks resulted in an improvement in naming. Their effects were somewhat mixed immediately after cessation of treatment, but were significant at the two and eight months follow-up assessments (Martin et al. 2004; Naeser et al. 2005a). Hamilton and colleagues (Hamilton et al. 2010) replicated this finding in one patient and found evidence for improvement in propositional speech. Immediate effects in phase 1 of this experiments were also found in motor cortex and BA 44 (opercular) as well as dorsal

BA45, but not inferior BA45 region. Kakuda and colleagues (Kakuda et al. 2010) pursued a different approach and applied 1 Hz inhibitory TMS (20 min/day for 10 sessions over 6 days) to sites that were contralateral to those found to be most activated during fMRI with a repetition task. They had two patients with left hemisphere lesions in which the right frontal lobe was targeted and two patients with right hemisphere lesions in which the left frontal lobe was targeted. They observed slight improvements in spontaneous speech and repetition that lasted at least four weeks.

Naeser et al (Naeser et al. 2010) and Hamilton (Hamilton et al. 2010) both emphasize that the application of 1 Hz TMS (inhibitory) to the right pars opercularis would lead to a decrement in performance but that the same stimulation (1 Hz inhibitory TMS) of the right pars triangularis may have facilitatory effects. One possible explanation is that the interhemispheric connectivity of the pars triangularis and that of the pars opercularis (see Fig. 1 for these regions and their connectivity) are different (Hamilton et al. 2010; Turkeltaub et al. 2011). An alternative explanation is that blocking the right pars triangularis exerts its effect by disinhibiting the adjacent parts opercularis. Nevertheless, these effects are based on the assumption that TMS is highly localized, and that moving the stimulation coil by just a few millimeters may lead to completely different results. A third possibility is that any "blocking" effect from 1 Hz stimulation of the right pars triangularis may actually depend on the size and location of the left hemisphere lesion, as well as the connections between the pars triangularis on the right and the perilesional region on the left. This may help explain why only certain patients respond to TMS that targets the right pars triangularis (Martin et al. 2009). Future studies could incorporate structural imaging (such as diffusion tensor imaging), to determine whether or not the right IFG (pars opercularis or pars triangularis) has fiber connections to any language-related perilesional regions in the affected hemisphere (see Fig. 1).

tDCS has also been applied to the affected hemisphere, although the two studies published so far have used anodal stimulation. Floel and colleagues (Flöel et al. 2011) recently applied anodal stimulation to the right temporo-parietal junction in chronic aphasic patients with a predominant anomia in a cross-over design with sham stimulation, the patients simultaneously underwent computerized picture-naming training. They found an effect that outlasted the stimulation period by at least 2 weeks. Vines et al (Vines et al. 2011) also applied anodal stimulation to the right posterior IFG in combination with melodic intonation therapy, details of this study will be discussed below (see Table 1 for an overview of all studies).

Combining Non-invasive Brain Stimulation with Peripheral Sensorimotor Activities and Neuromodulatory Agents

To enhance the facilitating effects of non-invasive brain stimulation on recovery outcomes, a number of recent studies (Hesse et al. 2007; Nair et al. 2007) have combined tDCS with rehabilitative interventions. Most of the research to date has been within the motor domain. The idea behind this simultaneous approach is that combined peripheral sensorimotor activities (which also provide increased sensory feedback) and central brain stimulation (which has the ability to modulate regional excitability) can enhance synaptic plasticity and motor skill learning by modulating afferent inputs to the cortex. Cortical stimulation studies in animal stroke models have shown stronger effects when peripheral sensorimotor activities were combined with central stimulation than stimulation alone (Adkins-Muir and Jones 2003). It has been shown that compared to cortical stimulation only conditions, the associative pairing of brain stimulation and repetitive median nerve stimulation raised motor cortical excitability to a much higher level (Stefan et al. 2000). This increase was not observed when the same procedure was performed under the influence of dextromethorphan, which is known to block LTP (Stefan et al. 2002). Motor skill learning has shown to produce LTP and LTD changes in the primary motor cortex in animal studies (Rioult-Pedotti et al. 2000). It appears possible that a combination of repetitive peripheral stimulation or rehabilitative therapy with non-invasive brain stimulation can potentiate relearning and consolidation of motor skills to a level unattainable by any of these interventions alone in subacute or chronic stroke patients (Celnik et al. 2009). One of the first pilot studies to test the efficacy of this approach used multiple sessions of anodal tDCS (1.5 mA for 7 min), which combined brain stimulation with a robot-assisted arm training protocol in severely-affected, sub-acute stroke patients (Hesse et al. 2007). This study used an open-label protocol without a sham stimulation condition. Although no significant improvements in motor function were observed at a group level, some of the patients did show a pronounced facilitatory effect. A more recent study compared the effects of bihemispheric stimulation (anodal tDCS to the affected motor cortex and cathodal tDCS to the unaffected motor cortex) with those of sham stimulation, while patients underwent concurrent physical therapy. Following five consecutive days of treatment, significant improvement in motor outcomes were observed in the real stimulation group compared to the sham group (Lindenberg et al. 2010).

Besides combining behavioral therapy or peripheral nerve stimulation with tDCS, combining tDCS with neuro-

modulatory substances may also produce a stronger effect than stimulation alone. For example, administering L-dopa to healthy individuals prolonged the cathodal tDCS-induced reduction in excitability, as well as the behavioral after-effects typically observed following a 20–30 minute stimulation session by a factor of about 20 (Kuo et al. 2008). One explanation for this effect could be that dopamine exerts an influence on synaptic plasticity in cortical networks affected by the regional brain cathodal stimulation.

Given the positive neuroplastic influence of combining tDCS with rehabilitative interventions on the motor system (Celnik et al. 2009; Fritsch et al. 2010; Lindenberg et al. 2010), a promising avenue for aphasia rehabilitation may lie in the combination of behavioral therapy and non-invasive brain stimulation methods to further engage brain regions that are important for language recovery (Baker et al. 2010; Floel et al. 2011; Fridriksson et al. 2011; Monti et al. 2008; Vines et al. 2011). To directly examine the role of right hemisphere in language recovery, a recent study examined the effects of either anodal or sham tDCS applied over the right IFG during MIT sessions (Vines et al. 2011). It was hypothesized that compared to sham, applying anodal tDCS in combination with MIT would enhance neural activity and synaptic plasticity in the right-hemispheric brain regions, thereby driving the positive effects of MIT on language production and promoting further recovery.

In contrast to previous studies that applied tDCS to the left perilesional hemisphere in combination with a computerized picture-naming training to facilitate recovery from non-fluent aphasia (Baker et al. 2010; Fridriksson et al. 2011; Monti et al. 2008), Vines and colleagues (Vines et al. 2011) combined anodal right IFG stimulation with MIT. The decision to stimulate the right hemisphere and not the left was made for three main reasons. First, the patients in that study had minimal or no surviving tissue in their primary language centers of the left hemisphere. For these patients, the best or only path of recovery may be through brain regions in the right hemisphere to compensate for damaged language areas in the left hemisphere. Second, imaging research has provided evidence that improvements in speech output due to MIT correlated with increased activity in the right IFG (Schlaug et al. 2008a). The selection of right IFG as a stimulation site was aimed at complementing the effects of MIT on brain activity. Finally, stimulating over the injured hemisphere may lead to unpredictable current distributions and corresponding effects on brain activity. This may explain variability in results obtained from studies that stimulated the left hemisphere to enhance recovery from aphasia. For example, some studies reported that anodal stimulation led to speech output improvements (Baker et al. 2010; Fridriksson et al. 2011), whereas others found improvements following cathodal stimulation (Monti et al. 2008). Floel and colleagues (Floel et al. 2011) recently combined anodal stimulation of the right temporo-parietal junction in combination with a picture-naming training therapy and also found significant effects.

The question of whether tDCS should be applied before, during, or after a behavioral therapy remains to be investigated. If the desired effect of tDCS is on enhancing task performance, then it may be ideal to stimulate before or during therapy, in order to prime particular brain areas. However, if the desired effect of tDCS is on consolidation, then it may be best to apply the stimulation either during or after therapy. Vines and colleagues chose to apply tDCS during MIT for the following reasons: 1) a number of tDCS studies have reported positive effects on task performance during stimulation (Celnik et al. 2009; Fritsch et al. 2010; Hesse et al. 2007; Iyer et al. 2005; Lindenberg et al. 2010); 2) in the context of neuro-rehabilitation, applying stimulation during the behavioral therapy saves time for both the patient and the therapist; 3) stimulation during the therapy has the potential to influence both the performance and the consolidation phases of learning; and 4) animal studies have shown that the combination of peripheral and central stimulation enhances synaptic plasticity more than central stimulation alone (Fritsch et al. 2010).

Interpreting the Literature and Directions for Future Research

How can one make sense of the inconsistent findings in the neuroimaging and non-invasive brain stimulation literature, especially those concerning the type of tDCS (anodal or cathodal) or TMS (inhibitory versus excitatory) that could be applied to the lesional or contralesional hemisphere in patients with aphasia? One explanation is that language recovery is a dynamic process that involves both hemispheres at different times during recovery to different degrees (Saur et al. 2006). Furthermore, variability in lesion site and size can predict language recovery in chronic patients (Marchina et al. 2011). Heiss and Thiel as well as our group (Heiss and Thiel 2006; Schlaug et al. 2010) have suggested that recovery from aphasia and hemispheric involvement in the recovery process depends on lesion size. When lesions in the left hemisphere are small, persilesional regions of the left hemisphere contribute most to the recovery process, while additional right hemisphere activation may be transient or an epiphenomenon. When lesions are large and left hemisphere networks are severely damaged, then the right hemisphere assumes a greater functional role and recovery is likely to occur by engaging homologous regions on the right for language

tasks. This right hemisphere recruitment for language may be facilitated by the absence of interhemispheric inhibition from the injured left hemisphere. Nevertheless, although right hemisphere recruitment for language tasks may contribute to the overall language recovery in severely affected patents, the remodeled language network in these patients is likely to be less efficient compared to that of the intact left hemisphere of healthy individuals. For example, the arcuate fasciculus in the right hemisphere is usually not as well-developed as the one in the left (Nucifora et al. 2005; Vernooij et al. 2007), suggesting that it may potentially be less efficient if it assumed linguistic functions that are typically left-lateralized.

Finally, recent research on the temporal dynamics of language recovery after stroke has shed light on the differential involvement of both hemispheres over time (Hillis 2007; Saur et al. 2006). Initially after a stroke, there may be a reallocation of language function to the right hemisphere, particularly in patients with extensive left hemisphere injury. Over time this recruitment diminishes, followed by a redistribution of language processing back to the left hemisphere, although this process is more likely to occur in patients with relatively small lesions. Future neuroimaging and non-invasive brain stimulation studies should further explore the temporal dynamics of stroke recovery. Findings from such studies will help guide the interpretation of current data. Furthermore, combining non-invasive brain stimulation studies with behavioral interventions may be a promising new approach in facilitating language recovery in patients with aphasia.

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