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Noninvasive brain stimulation in the treatment of aphasia: Exploring interhemispheric relationships and their implications for neurorehabilitation

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Abstract. Aphasia is a common consequence of unilateral stroke, typically involving perisylvian regions of the left hemisphere. The course of recovery from aphasia after stroke is variable, and relies on the emergence of neuroplastic changes in language networks. Recent evidence suggests that rehabilitation interventions may facilitate these changes. Functional reorganization of language networks following left-hemisphere stroke and aphasia has been proposed to involve multiple mechanisms, including intrahemispheric recruitment of perilesional left-hemisphere regions and transcallosal interhemispheric interactions between lesioned left-hemisphere language areas and homologous regions in the right hemisphere. Moreover, it is debated whether interhemispheric interactions are beneficial or deleterious to recovering language networks. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two safe and noninvasive procedures that can be applied clinically to modulate cortical excitability during poststroke language recovery. Intervention with these noninvasive brain stimulation techniques also allows for inferences to be made regarding mechanisms of recovery, including the role of intrahemispheric and interhemispheric interactions. Here we review recent evidence that suggests that TMS and tDCS are promising tools for facilitating language recovery in aphasic patients, and examine evidence that indicates that both right and left hemisphere mechanisms of plasticity are instrumental in aphasia recovery.

Keywords: Aphasia, stroke, neuroplasticity, transcranial magnetic stimulation, transcranial direct current stimulation, neurorehabilitation, interhemispheric interactions

1. Introduction

Aphasia is one of the most common and devastating cognitive impairments associated with stroke, affecting 21–38% of acute stroke patients (Wade, Hewer, David & Enderby, 1989). It is marked by a significant loss or impairment of language functions and is associated with significant short- and long-term morbidity and increased care costs and caregiver burden (Laska, Hellblom, & Murray, 2001; Pedersen, Vinter, & Olsen, 1998). For the majority of patients (>80%), post-stroke aphasia is the result of ischemic injury to a network of left hemisphere cortical and subcortical

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regions perfused by the middle cerebral artery (Alexander, 1997; McNeil & Pratt, 2001).

While the majority of patients with aphasia due to stroke regain some language abilities during the acute and subacute phases following injury (Laska et al., 2001; Lendrem & Lincoln, 1985; Nicholas et al., 1993), post-stroke language recovery is highly variable (see Berthier, 2005; Lazar et al., 2008) and the persistence of chronic deficits is common. Converging evidence indicates that language recovery depends at least in part on the degree of plastic change that occurs in the brain of patients after injury (e.g., Cherney & Small, 2006; Musso, Weiller, Keibel et al., 1999; Thompson, 2000; Thompson, Shapiro, Ballard et al., 1997). Consistent with this notion, rehabilitation interventions that are associated with neuroplastic changes in the brains of recovering patients and are associated with more positive treatment outcomes (e.g., Horn, De Jong, Smout et al., 2005; Liepart, Bauder, Miltner et al., 2000; Kreisel, Bazner, & Hennerici, 2006; Nelles, 2004; Saur, Lange, Baumgaertner et al., 2006; Seitz, Bütefisch, Kleiser, & Hömberg, 2004).

Evidence from behavioral and neuroimaging studies point to two broad categories of functional reorganization that may affect language processing in patients with stroke and aphasia. A number of investigations have shown that increased activity in perilesional regions near damaged left hemisphere language areas is associated with better language performance. A second pattern of functional reorganization observed in patients with aphasia is increased activity of contralesional structures in the spared non-dominant right hemisphere. However, the role of the contralesional right hemisphere activity in language recovery is more controversial than that of the left, with some evidence suggesting that right hemisphere homologues of damaged left hemisphere language regions contribute beneficially to language networks while other evidence suggests that transcallosal inhibition of perilesional cortical activity by uninhibited regions of the non-dominant hemisphere may hinder language recovery (for reviews see Crinion & Leff, 2007; Crosson et al., 2007). Complicating this picture, additional factors such as premorbid laterality of language representation, chronicity of injury (i.e., acute, subacute, or chronic), and size of lesion are also important determinants of language reorganization in the recovery of patients with post-stroke aphasia (Knecht et al., 2002; Lazar, Speizer, Festa, Krakauer, & Marshal, 2008; Raymer et al., 2008).

Currently the most commonly used treatment for post-stroke aphasia is speech-language therapy. Although conventional speech-language therapy may promote recovery if the treatment is administered with high intensity during the acute period after stroke, for many patients these therapies are costly, time consuming, and difficult to implement (Bhogal, Teasell, Foley et al., 2003; Bhogal, Teasell, & Speechley, 2003). Such therapeutic approaches are typically associated with modest effects and their overall efficacy has been inconsistent (Basso & Marangolo, 2000; Nickels, 2002; Robey, 1994, 1995; Robey, Schultz, Crawford et al., 1999). Recent attempts to supplement speech-language therapies with pharmacological treatments (e.g., piracetam, bromocriptine, dexamfetamine, donepezil) have elicited some promising results associated with neuroplastic changes in temporal and frontal brain regions, however the long-term success of these approaches has not yet been verified with large randomized-control trials (for a review see Berthier, 2005).

A growing body of work now indicates that noninvasive brain stimulation techniques—specifically, transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)—can induce neuroplastic changes in cortical function with long-lasting salutary effects on behavior and cognition (e.g., Antal, Nitsche, & Paulus, 2001; Cotelli et al., 2006; Mottaghy, Sparing, & Töpper, 2006; Ziemann, 2004). These techniques are thus proving to be a promising approach to enhancing recovery of neurologic function after stroke. This article will review these two techniques and summarize existing data suggesting that they may contribute meaningfully to language recovery in patients with chronic aphasia following stroke. The impact that these data have on models of neural connectivity and plasticity after stroke will also be discussed, specifically focusing on the nature of interhemispheric cortical interactions after unilateral injury. Finally, practical advantages and limitations of each technique will be discussed in the context of stroke rehabilitation and aphasia recovery.

2. Noninvasive brain stimulation: TMS and tDCS

Transcranial magnetic stimulation (TMS) is a noninvasive technology that utilizes the principle of

electromagnetic induction to generate sufficient current in underlying neurons to cause them to depolarize (Bailey, Karhu, & Ilmoniemi, 2001; Walsh & Pascual-Leone, 2003). In order to accomplish this, the device discharges a very large current (peak current: approximately 5,000 amps) from a bank of capacitors, which rapidly flows through a simple circuit and then a copper-wire coil. This current induces a rapid time-varying magnetic field (rise time: approximately 0.1 ms, field strength: approximately 2T) in the coil. Held to the head of a subject, the magnetic field penetrates the scalp and skull and focally induces current in the cortex parallel to the plane of the coil. This causes neuronal membranes to depolarize and generates action potentials (Maeda & Pascual-Leone, 2003). Because the induced current flows parallel to the surface of the brain, interneuronal elements that are oriented horizontally to the cortical surface are preferentially depolarized (Day et al., 1989).

Different TMS paradigms employ various combinations of pulse frequencies, intensities, and stimulation locations to achieve specific diagnostic, therapeutic, and experimental objectives. Among them, repetitive TMS (rTMS)—which involves the application of a series of pulses that is presented at a predetermined frequency (typically >0.3 Hz)—is particularly relevant to neurorehabilitation because it can produce effects that outlast the application of the stimulation. For stimuli that are around the resting motor threshold (MT, defined as the minimum stimulus intensity that results in a motor evoked potential after stimulation of the motor cortex), rTMS delivered for a duration of minutes at a low frequency (0.5–2 Hz) tends to decrease resting corticospinal excitability, whereas higher frequencies (>5 Hz) tend to increase resting excitability (Chen et al., 1997; Maeda et al., 2000). High frequency TMS has thus been used to create excitatory effects on the underlying brain whereas low frequency rTMS is often presumed to have inhibitory effects on the underlying cortex. Due to its ability to modulate cortical activity, rTMS has been applied to a number of domains related to language function in healthy participants (see Devlin & Watkins, 2007, for a review), including improving performance in language production tasks such as picture naming (Mottaghy, Sparing, & Töpper, 2006) and examining the causal involvement of various cortical regions for specific linguistic functions (e.g., Cappa, Sandrini, Rossini, Sosta, & Miniussi, 2002; Gough, Nobre, & Devlin, 2005; Maneti et al., 2008; Matthews et al., 2003; Pobric, Jefferies, & Lambon Ralph, 2007; Pobric, Mashal, Faust, & Lavidor, 2008; Uddén et al., 2008).

Transcranial direct current stimulation (tDCS) involves the application of small currents (typically 1-2 mA) to the scalp for a few minutes through two surface electrodes (typically 35 cm^2; 5×7 cm), which modulates the excitability of cortical neurons without directly inducing neuronal action potentials (Baudewig, Nitsche, Paulus et al., 2001; Nitsche & Paulus, 2000; Priori, 2003). Cathodal stimulation is associated with decreased cortical excitability due to the incremental hyperpolarization of cortical neurons, whereas anodal stimulation is associated with increased cortical excitability due to incremental neuron depolarization; these effects may last for several minutes to an hour depending on the parameters of stimulation, which include duration, intensity, polarity, and electrode placement (Antal, Nitsche, & Paulus, 2001; see also Kuo, Paulus, & Nitsche, 2008).

Recently, there has been an upsurge of interest in the use of tDCS for both research and clinical purposes, particularly due to its ease of administration, versatility, and minimal side effects (Been et al., 2007; Nitsche, Liebetanz, Antal et al., 2003; Wagner, Valero-Cabré, & Pascual-Leone, 2007). Application of tDCS has been associated with experimental manipulation of performance in a variety of cognitive domains, including visual perception (Antal et al., 2001; Antal & Paulus, 2008), motor learning (Kuo et al., 2008; Nitsche, Schauenburg, Lang et al., 2003), decision-making (Fecteau et al., 2007a, 2007b), and social interaction (Knoch et al., 2008; Priori et al., 2007). Anodal tDCS has been used to elicit transient improvements in implicit probabilistic classification learning (Kincses et al., 2003), working memory (Ohn et al., 2008), and tactile spatial acuity (Ragert, Vandermeeren, Camus, & Cohen, 2008), while cathodal tDCS has been used experimentally to temporarily enhance motion perception and performance in visuomotor coordination tasks (Antal, Nitsche, Kruse et al., 2004). Clinically, tDCS has been shown to transiently improve cognitive functioning in Alzheimer's disease (Ferrucci et al., 2008), Parkinson's disease (Boggio et al., 2006; Fregni et al., 2006a), as well as major depression (Boggio et al., 2007; Fregni et al., 2006b). Finally, in recent years, tDCS has been investigated as a possible neurorehabilitation treatment for post-stroke deficits (e.g., Fregni et al., 2005; Hummel et al., 2005).

3. Interhemispheric interactions in stroke

It is well established that activity in one cerebral hemisphere affects activity in the other via a rich network of interhemispheric connections (Ferbert, Priori, & Rothwell, 1992; Ilmoniemi et al., 1997), and that these interactions represent a dynamic process that can be flexibly modulated based on task demands or by exogenous stimulation (e.g., Banich, 1998; Silvanto et al., 2009; Welcome & Chiarello, 2008). Even though the functional properties of interhemispheric connections are yet to be fully elucidated, converging evidence suggests that, in many instances, these connections appear to operate in a mutually inhibitory manner. This inhibitory interplay between homologous hemispheric regions likely contributes to normal performance on a variety of tasks, and can be manipulated with noninvasive brain stimulation. For example, several prior studies employing noninvasive brain stimulation on normal participants have shown that performance on motor and visuospatial tasks can be temporarily improved by downregulating cortical activity in the hemisphere ipsilateral to the side of the body on which the task is being performed (e.g., Bütefisch et al., 2004; Hilgetag et al., 2003; Jin & Hilgetag, 2008; Kim et al., 2005; Kobayashi et al., 2004).

The dynamics of interhemispheric interactions are especially germane to stroke and post-stroke recovery. Owing to the architecture of cerebral vascular anatomy, many cortical strokes are unilateral, affecting motor or cognitive functions that are localized predominantly in the affected hemisphere, such as aphasia after left-sided brain injury. One theory is that unilateral strokes give rise to maladaptive patterns of interhemispheric competition. According to this model, a stroke or other lesion in one hemisphere may give rise to unopposed inhibitory influence from homologous regions of the intact hemisphere, leading to further functional impairment of damaged brain areas. Studies in patients with stroke and hemiparesis seem to support this model, indicating that there is greater transcallosal inhibition emanating from the intact hemisphere to the lesioned hemisphere than in the reverse direction, and that this abnormal transcallosal inhibition manifests during attempted movement of paretic limbs (Kobayashi et al., 2003; Murase, Duque, Mazzocchio, & Cohen, 2004; Nair et al., 2007). Similarly, longitudinal observations of patients during poststroke recovery from paresis support the notion that increased activity of the intact motor cortex reflects an abnormal pattern of interhemispheric inhibition (Calautti & Baron, 2003; Rossini, Calautti, Pauri, & Baron, 2003; Ward, Brown, Thompson, & Frackowiak, 2003; Ward & Cohen, 2004).

A number of investigations in patients with unilateral stroke suggest that abnormal interhemispheric interactions can be manipulated using TMS or tDCS (Hummel & Cohen, 2006). Because it is believed that TMS and tDCS can be used to either facilitate or inhibit cortical activity in a focal manner, two broad approaches have been adopted: 1) facilitation of activity in lesioned or perilesional areas or 2) inhibition of the intact hemisphere with the goal of diminishing abnormal transcallosal inhibition. High-frequency excitatory rTMS over the lesioned motor cortex has been shown to lead to significant temporary improvements in motor performance (e.g., Fregni, Boggio, Mansur et al., 2005; Hummel, Celnik, Giraux et al., 2005; Hummel & Cohen, 2005). In one study, high frequency rTMS of the lesioned hemisphere, combined with conventional rehabilitation therapy, elicited robust benefits that persisted for at least a week in patients with acute stroke (see Khedr et al., 2005). Stimulation of the intact contralesional hemisphere with low-frequency TMS has also been used to elicit beneficial effects on motor performance (Dafotakis et al., 2008; Mansur, Fregni, Boggio et al., 2005; Pal et al., 2005; Takeuchi et al., 2005; see also Nowak, Grefkes, Ameli, & Fink, 2009, for a review). Contralesional low-frequency stimulation of the intact hemisphere has also been shown to have beneficial effects in patients with unilateral right hemisphere strokes resulting in neglect (Brighina et al., 2003; Olivieri et al., 1999) and extinction (Marzi et al., 2000; Olivieri et al., 2000; Olivieri et al., 2002). Recent studies have explored interhemispheric interactions in post-stroke recovery using tDCS, with promising results. Both anodal stimulation applied over the lesioned hemisphere and cathodal stimulation applied over the contralesional hemisphere have been shown to temporarily improve motor function in patients with paresis (e.g., Hummel et al., 2005; Fregni et al., 2005; Hummel et al., 2006; Hesse et al., 2007), while repeated sessions of anodal and cathodal tDCS have been associated with sustained motor improvement lasting at least two weeks (Boggio et al., 2007). Cathodal tDCS of the intact hemisphere and anodal tDCS of the lesioned hemisphere have also been associated with reduction of visuospatial neglect symptoms (Ko et al., 2008; Sparing et al., 2009). Taken together, these results strongly suggest that

noninvasive brain stimulation may be used therapeutically to promote sensory and motor recovery from stroke by modulating maladaptive interhemispheric communication.

4. The right hemisphere in aphasia recovery: Beneficial or detrimental?

Although converging evidence suggests that abnormal activity in the intact hemisphere of patients with unilateral stroke may exacerbate lateralized deficits such as hemiparesis and neglect, the role of the non-dominant right hemisphere in language functions and in recovery from aphasia remains more controversial (Humphreys & Praamstra, 2002). Different lines of evidence support widely differing hypotheses, suggesting that the right hemisphere's role in aphasia recovery may be beneficial, deleterious, or either, depending on different factors.

The idea that the right hemisphere might play a compensatory role in language recovery after stroke dates back to the 19th century, when Barlow (1877) described the case of a 10-year old boy who suffered from aphasia after a left hemisphere stoke. The young patient initially recovered language abilities to a considerable degree, only to lose them again following a second stroke involving the right-hemisphere (see Finger, Buckner, & Buckingham, 2003, for a review). Consistent with Barlow's early finding, there have been more recent reports of patients with left-hemisphere strokes who lost residual language abilities after subsequent lesions to the right-hemisphere (e.g., Basso, Gardelli, Grassi, & Marioti, 1989; Gainotti, 1993). Furthermore, amobarbital studies have shown that for aphasic patients with extensive left-hemisphere strokes, residual speech may be disrupted by the administration of by right-side and not left-side carotid injections (Kinsbourne, 1971). Convincingly, it has also been reported that patients who have undergone surgical excision of the left hemisphere demonstrate substantial recovery of language ability, suggesting that the right hemisphere has played a compensatory role for these patients (Vargha-Khadem et al., 1997).

These results suggest a number of intriguing hypotheses regarding the role of the right hemisphere in language recovery after left-hemisphere stroke. One possibility is that the right hemisphere is equipotent for language compared to the left hemisphere, and it can support the recovery of language functions after left-hemisphere injury through a laterality shift. A related hypothesis is that language functions exist in homotopic right hemisphere regions, but are dormant due to transcallosal interhemispheric inhibition from the dominant left-hemisphere. According to this hypothesis, language recovery after left-hemisphere stroke is associated with a release of inhibition of the latent, right-hemisphere language functions. Cases such as that reported by Barlow, (1877), in which language recovery after left hemisphere injury is attributed to right hemisphere involvement, are consistent with this model. In addition, a number of recent neuroimaging studies involving language tasks have revealed that, after left-hemisphere stroke, there is unusually robust activation in right hemisphere regions that are homologous to the left-hemisphere language areas (e.g., Basso et al., 1989; Buckner et al., 1996; Gold & Kertesz, 2000; Ohyama et al., 1996; Rosen et al., 2000; Warburton, Price, Swinburn, & Wise, 1999; Weiller et al., 1995). For instance, Naeser and colleagues (2004) reported a significant increase in the right sensorimotor mouth and right supplementary motor area during overt propositional speech in four patients with non-fluent aphasia who were studied years following their strokes (see also Belin et al., 1996). Using an Activation Likelihood Estimation (ALE) meta-analysis of fMRI and PET studies of aphasic patients, we have also demonstrated that performance on language production tasks in aphasia is associated with activation of right inferior frontal gyrus, whereas performance on comprehension tasks is associated with reliable activation of the right middle temporal gyrus. Critically, among patients with left inferior frontal lesions, the patterns of activation in the right inferior frontal gyrus were often homotopic to left hemisphere regions in control participants (Turkeltaub, Messing, Norise, & Hamilton, 2011). Furthermore, recent studies employing diffusion tensor imaging (DTI) have revealed that the patterns of connectivity between inferior frontal and temporal language regions are similar between the two hemispheres (Kaplan et al., 2010). Finally, recent behavioral approaches to aphasia treatment that rely on the recruitment of right hemisphere structures have demonstrated increased post-treatment activation and extended functional connectivity of language-homologue regions in the right hemisphere, as a function of response to treatment (Crosson et al., 2009; Kaplan et al., 2010; Schlaug et al., 2009). These results suggest that the adaptive post-stroke reorganization of language abilities in the

right hemisphere may be beneficial for the recovery of language functions after stroke.

Another, not mutually exclusive, hypothesis is that language recovery in left-hemisphere stroke patients is related to pre-existing involvement of the right hemisphere in language functions. In fact, a recent study elegantly demonstrated that premorbid laterality for language determines the extent of impairment associated with subsequent left or right cortical lesions. Knecht and colleagues (2002) used functional transcranial Doppler sonography to determine the strength and orientation (left or right) of language lateralization in normal participants. They then employed bilateral TMS over language regions to induce transient aphasia in their participants. Relative to a control, non-language-specific stimulation site (occipital cortex), subjects with weak lateralization for language were less affected by TMS than strongly lateralized subjects, who were significantly impaired in language performance after TMS. Importantly, there was a significant double dissociation, such that participants with left-lateralized language were more impaired after left stimulation, whereas participants with right-lateralized language were more impaired after right stimulation. Hence, this study was the first to show that premorbid laterality for language may be a strong predictor of susceptibility to unilateral brain lesions and can complicate original interpretations of right-hemisphere involvement during poststroke recovery (see also, Andoh & Martinot, 2008; Humphreys & Praamstra, 2002).

Considerable evidence also suggests that significant reacquisition of language ability after stroke is often associated with recovery of injured left hemisphere regions or increased recruitment of residual perilesional left hemisphere sites. Indeed, patients who show better spontaneous recovery exhibit greater activation in the left-hemisphere (e.g., Karbe et al.; 1998a, 1998b; Miura et al., 1999; Warburton et al., 1999). Moreover, left hemisphere activation has been associated with better language improvement after aphasic patients have undergone speech therapy (e.g., Cornelissen et al., 2003; Leger et al., 2002; Musso et al., 1999). Some studies have suggested that both the right hemisphere and the injured left hemisphere contribute beneficially to aphasia recovery. For example, investigations involving patients with Wernicke's aphasia (a fluent aphasia) indicate that increased activation in the right posterior superior temporal gyrus in conjunction with residual left hemisphere regions is associated with language improvement (e.g., Musso et al., 1999; Weiller et al., 1995). Others have argued that the right hemisphere contributes to language recovery only when the damage to left hemisphere language regions is extensive (e.g., Cao et al., 1999; Heiss, Kessler, & Thiel, 1999).

Complicating the picture further, hemispheric involvement in language recovery may be a dynamic process that changes over the course of recovery and may be affected by factors such as time from aphasia onset, age, and task demands (Finger et al., 2003; Hillis, 2007). For example, Saur and colleagues (2006) demonstrated that in patients with acute stroke and nonfluent aphasia neither hemisphere was activated during attempted performance of an fMRI language task involving auditory comprehension. In the subacute phase the right hemisphere exhibited more robust activation during the language task, while in the chronic phase the left hemisphere was predominantly activated. 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 to the dominant hemisphere. 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 (see also Thiel et al., 2001).

An altogether different hypothesis regarding the role of the right hemisphere is that it is not beneficial, but rather that it is ineffective or deleterious with respect to language recovery (Belin et al., 1996). By this account, increased activity of right hemisphere structures may in fact interfere with the reacquisition of more efficient language processing by left-hemisphere cortical areas. Supporting this view, several studies have suggested that increased activation in the right hemisphere in aphasic patients is not always coupled with improved language performance (Naeser et al., 2002; Rosen et al., 2000; Saur et al., 2006). Moreover, in one recent fMRI study, Postman-Caucheteux (2010) demonstrated that increased right hemisphere activity was associated with worse performance on an overt naming task. It has been proposed that right hemisphere activity interferes with left hemisphere recovery of language function by means of inhibitory

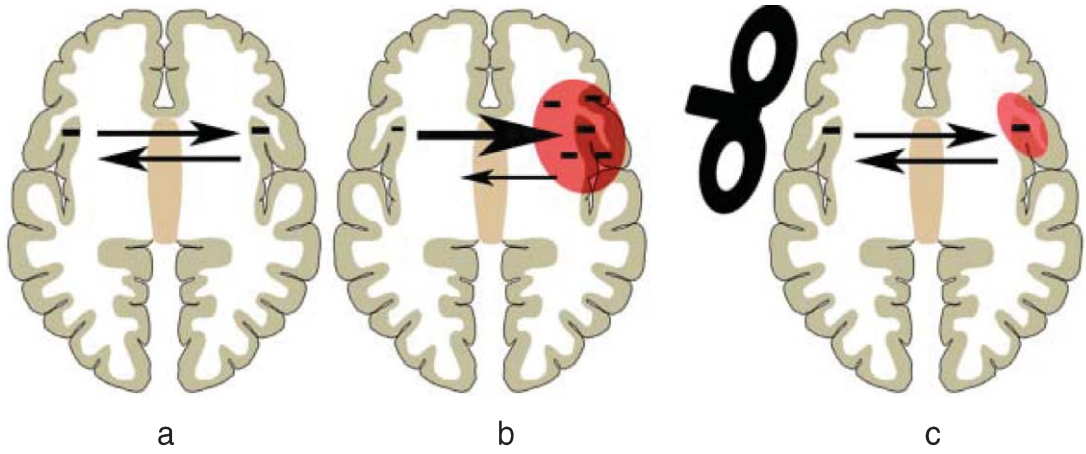

Fig. 1. The model of interhemispheric inhibition often used to explain the effect of contralesional transcranial magnetic stimulation (TMS) in patients with stroke. (1a). The cerebral hemispheres are richly interconnected. Many of these interhemispheric connections appear to be inhibitory in nature. (1b). Unilateral brain injury may result in decreased inhibition of the uninjured hemisphere, and subsequently to increased interhemispheric inhibition of the injured hemisphere. (1c). Contralesional transcranial magnetic stimulation of intact homologues of damaged brain areas may decrease interhemispheric inhibition, permitting more efficient use of previously injured or perilesional cortical areas.

interhemispheric interactions similar to those shown to exist in patients with hemiparesis or neglect (see above). According to this model, lesions of the left hemisphere may release the right hemisphere from the normal balance of transcallosal inhibitory inputs, leading to increased right hemisphere activation. Consequently, increased right hemisphere activation may result in abnormally increased transcallosal inhibition of left hemisphere perisylvian structures that are critical for language recovery (Belin et al., 1996; Martin et al., 2004; Rosen et al., 2000), which may in turn worsen language symptoms and impede recovery from aphasia (Fig. 1).

5. Treating nonfluent aphasia with rTMS

To date, most studies involving rTMS for stroke recovery have been predicated on the hypothesis that right hemisphere activation may be deleterious to language recovery and have therefore employed low frequency inhibitory stimulation to the right hemisphere with the goal of diminishing abnormal contralesional cortical activity. Here the work of Naeser and colleagues (2002, 2005a; Martin et al., 2004) has been seminal. These investigators (2002) first observed in six chronic nonfluent aphasic subjects that application of 1 Hz rTMS for 10 minutes to the anterior portion of the right Broca's area homologue (pars triangularis) resulted in significant albeit transient improvement in naming accuracy and reaction time, while similar stimulation of the posterior portion of the right-hemisphere homologue of Broca's area (pars opercularis) transiently worsened performance. This finding was followed up by a second study (Martin et al., 2004; Naeser et al., 2005a) in which the investigators applied 1 Hz stimulation to the right pars triangularis of four right-handed chronically aphasic patients daily (20 minutes per session) five days a week for two weeks. Two weeks after the final TMS treatment, there was a significant improvement relative to pre-treatment scores on the Animal Naming subtest of the Boston Diagnostic Aphasia Exam (BDAE, 3rd Ed.). Two months after treatment there was significant improvement on three tests of naming: The first 20 items of the Boston Naming Test (BNT), the Animal Naming subtest of the BDAE, and the Tools/Implements measure on the BDAE. Eight months after the end of treatment, scores on all three naming tests continued to improve relative to pre-treatment testing, although only the Tools/Implements measure on the BDAE reached statistical significance.

A case report of one of these four patients (Naeser et al., 2005a) provided additional evidence of continued spontaneous language recovery as well as increased responsiveness to speech therapy after brain stimulation (Naeser et al., 2005b). The patient was a 57-year old right-handed woman who had suffered an

intracerebral hemorrhage of the basal ganglia at age 51, resulting in severe right-sided hemiplegia and severe nonfluent/global aphasia. Imaging (obtained a number of years following the injury) demonstrated extensive lesions of the basal ganglia and of the subcortical white matter underlying perisylvian language-related cortical areas. At 21 months poststroke, the patient was considered too severe to be tested with the BNT or BDAE. Her speech output was limited to infrequent one-word utterances and she was classified as having severe global aphasia. She was tested on multiple occasions prior to receiving TMS, and her poor language performance was stable. Approximately 6.5 years after her stroke, the patient underwent treatment with 1 Hz rTMS to the right pars triangularis, as described above (Naeser et al., 2005a). The treatment resulted in improved naming on the BNT and the Animals and Tools/Implements subsets of the BDAE at 2 and 8 months following 10 rTMS treatments, relative to pre-TMS testing. At one-year following rTMS, she had improved sufficiently to be referred for speech therapy, where she continued to show measurable progress in her language skills. Although her overall improvement has been modest, her results are encouraging: Patients with comparably severe language impairments are among the most difficult to treat (Goodglass, Kaplan, & Barresi, 2001; Naeser et al., 2005b) and the onset of improvement 6.5 years poststroke speaks to the therapeutic potential of brain stimulation for the treatment of chronic aphasia. Naeser and colleagues have also reported on the case of a patient with chronic nonfluent aphasia and sleep apnea who experienced substantial recovery of language ability after 1 Hz rTMS of the pars triangularis was administered concurrently with continuous positive airway pressure (CPAP) (Naeser, Martin, Lundgren et al., 2010).

An important question regarding the application of contralesional rTMS in patients with nonfluent aphasia is whether the benefits in naming seen in these patients generalize to other language abilities. Addressing this issue, we recently reported a patient who showed stable deficits of elicited propositional speech over the course of five years, and received 1200 pulses of 1 Hz rTMS daily for 10 days at a site in the right pars triangularis identified as being optimally responsive to rTMS. Consistent with prior studies, the patient experienced improvement in object naming, with a statistically significant improvement in action naming. Importantly, improvement was also demonstrated in picture description at 2, 6, and 10 months after rTMS with respect to the number of narrative words and nouns used, sentence length, and use of closed class words. Compared to his baseline performance, the patient showed significant improvement on the Western Aphasia Battery subscale for spontaneous speech. These findings suggest that manipulation of the intact contralesional cortex in patients with nonfluent aphasia may result in language benefits that generalize beyond naming to include other aspects of language production (Hamilton et al., 2010).

Recently, additional investigations have replicated and extended our results and those of Naeser and colleagues. Barwood and colleagues (2010) studied 12 subjects with chronic aphasia (six real stimulation; six sham) and used stimulation parameters identical to those employed by Naeser and colleagues. They reported in significant improvements in picture naming, spontaneous elicited speech, and auditory comprehension following real rTMS that persisted 2 months following discontinuation of stimulation (Barwood et al., 2011a). Stimulated subjects also showed a treatment-related modulation of N400, an event-related potential (ERP) component that has been associated with lexical and semantic processing (Barwood et al., 2011b). In another recent study, Weiduschat and colleagues (2011) extended earlier findings by applying the same rTMS parameters (1 Hz stimulation to the right pars triangularis for 20 minutes; 10 sessions over two weeks) in six patients with subacute stroke (mean period after stroke = 50 days) and aphasia. Compared to four subjects who received sham stimulation, stimulated subjects improved significantly on the Aachen Aphasia test.

Not all aphasic patients appear to benefit from suppression of the right-hemisphere with rTMS. Martin and colleagues (2009) explored anatomic and functional differences between two nonfluent aphasic patients receiving rTMS, one of whom was found to be a 'good responder' whereas the other was a 'poor responder'. During pre-stimulation functional imaging, the 'good responder' showed significant activation in bilateral sensorimotor cortex, right inferior frontal gyrus, and bilateral SMA during overt naming. At 3 months post-rTMS the patient continued to show activation in these regions. This pattern was replicated at 16 months post-treatment, except that there was greater activation of the left SMA compared to the right SMA and compared to activation in the left SMA at earlier points in the study. This increased left-sided activity in the left hemisphere persisted 46 months

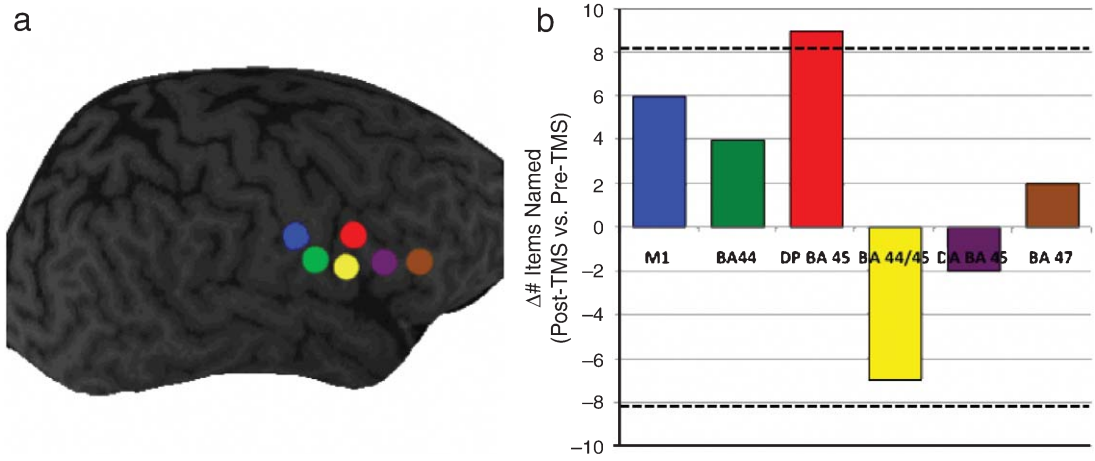

Fig. 2. Topographic specificity of contralesional TMS in patients with stroke and aphasia. Our approach, modeled after that employed by Naeser and colleagues, entails exploratory delivery of TMS to multiple sites in the right inferior frontal gyrus, in order to identify a region of maximal responsiveness prior to initiation of treatment. (2a). Results are shown for an illustrative patient who received TMS to M1 corresponding to the mouth (blue), Brodmann area 44 (BA 44; green), dorsal posterior BA 45 (red), anterior BA 44/ventral posterior BA 45 (yellow), anterior BA 45 (purple), and BA 47 (brown). The difference in performance on a naming task before and after rTMS was assessed at each site. (2b). Hatched lines indicate statistically significant differences. Our findings indicate that small changes in stimulation location result in dramatic shifts in TMS-induced performance, arguing against the interhemispheric inhibition model.

post-treatment. By contrast, pre-rTMS imaging for the 'poor responder' revealed significant activation in the right inferior frontal gyrus and bilateral SMA. Subsequent scans also showed significant activation in the right sensorimotor cortex. On all scans this patient had significant activation in both the left and right SMA, without significant left-sided asymmetry or left perilesional activation. This latter patient's performance on the naming task remained very poor after the treatment. These results are important in elucidating the individual variability observed in response to therapeutic stimulation interventions, and also suggest that lesion location might be a critical determinant of recovery success. The patient who responded poorly to rTMS had widespread left frontal lesions that extended dorsally into the motor and premotor cortex, as well as lesions neighboring regions inferior and posterior to Wernicke's area, which were absent in the patient who responded well to rTMS treatment. The authors suggest that recovery from nonfluent aphasia might depend on the extent to which some of these areas are affected or spared by stroke (see Martin et al., 2009).

In addition to data indicating that some aphasic patients fail to respond to inhibition of right hemisphere structures, evidence from other TMS studies suggests that for some patients the right hemisphere is contributing to language performance, such that inhibiting its function might prove deleterious to language recovery. Winhuisen and colleagues (2005) conducted an investigation in which positron emission tomography (PET) was employed to identify left and right-hemisphere involvement in a semantic task in 11 aphasic patients within 2 weeks of stroke onset; these activation patterns were subsequently used to target those regions with rTMS in each patient. Three of the patients showed left laterality for the semantic task; however, eight of the patients showed bilateral activation following stroke, and of those, 5 were impaired after right-hemisphere rTMS stimulation on semantic and verbal fluency tasks. In a follow-up study employing similar procedures, Winhuisen and colleagues (2007) reexamined 9 of the original 11 patients to investigate whether the right hemisphere remained critical for language performance in the chronic stroke phase (8 weeks poststroke). Importantly, task performance improved for all patients between the acute and chronic phase. Left IFG activation was observed for 2 patients, whereas bilateral IFG activation was observed for 7 patients. Administration of rTMS over the left IFG impaired task performance for all of these patients; by contrast, rTMS over the right IFG was associated with increased latencies in two patients with persistent right IFG activation. Two of the patients who had exhibited right-sided interference effects during the acute phase

were not influenced by rTMS over the right hemisphere during the chronic phase. These results suggest that for some poststroke aphasic patients the right IFG may play an essential role in residual language function—at least during the acute and postacute phases (see Saur et al., 2006). The findings also support the conclusion that in some aphasic patients the rehabilitative contribution of the right hemisphere may diminish over time, whereas in other aphasic patients, effective recovery depends largely on the restoration of the left hemisphere language networks (Winhuisen et al., 2007).

Consistent with the notion that the role of the right hemisphere in language recovery varies among patients, Kakuda and colleagues (2010) recently employed fMRI during a repetition task and found that two out of four nonfluent aphasic poststroke patients showed an area of maximal activation in the right hemisphere, whereas the remaining two showed maximal activation in the left hemisphere. The authors subsequently administered 10 sessions of 1200 pulses of low frequency rTMS to the homologous region contralateral to the site of maximal activation (i.e., right-sided rTMS was administered in patients with maximal left-sided activation and left-sided rTMS was administered in patients with maximal right-sided activation). They found that all four subjects experienced improvement in performance on the Western Aphasia Battery, Standard Language Test of Aphasia (SLTA), and the supplementary test of SLTA (SLTA-ST) following rTMS, and that these benefits persisted for at least four weeks. While these data support the hypothesis that rTMS can facilitate language recovery by mitigating the inhibitory effects of interhemispheric interactions, they also suggest that for some patients recovering from aphasia right hemisphere structures may function beneficially, whereas for other patients recovering from aphasia the persistent activity of perilesional left hemisphere homologues may actually be deleterious.

Evidence suggests that even within individual patients the right hemisphere may play multiple roles. We recently reported (Turkeltaub et al., *in press*) the case of a 72-year-old patient with chronic nonfluent aphasia who received inhibitory TMS to the right pars triangularis (1 Hz stimulation for 20 minutes; 10 sessions over two weeks). Stimulation induced immediate improvement in naming, which persisted 2 months later, and fMRI data confirmed a local reduction in activity at the TMS target without evidence of increased activity in corresponding left hemisphere areas. Three months after TMS, the patient suffered a right hemisphere ischemic stroke, resulting in worsening of aphasia without other clinical deficits. Behavioral testing 3 months later confirmed that language function was impacted more than other cognitive domains. While the patient's response to inhibitory TMS of the right hemisphere suggests that suppression of activity of a specific right hemisphere site may improve language function, the patient's worsened language deficits following a second stroke of the right hemisphere strongly suggests that, much like the case reported by Barlow (1977), other areas of the right hemisphere had been playing a compensatory role in language recovery. Importantly these finding do not appear to support the notion of interhemispheric inhibition, since that model would have predicted that the presence of a new right hemisphere lesion would facilitate language recovery.

While the majority of studies employing rTMS to treat aphasia have focused on the low frequency stimulation of the contralesional hemisphere, investigators have begun to explore the possibility of facilitating cortical activity in the left hemisphere as a means of improving language recovery. Szaflarski and colleagues (2011) recently administered excitatory rTMS using intermittent theta burst stimulation (subjects received bursts of three pulses at 50 Hz given every 200 milliseconds in two second trains, repeated every 10 seconds over 200 seconds for a total of 600 pulses) to 8 patients with moderate to severe chronic aphasia. Stimulation was applied to Broca's area as identified by fMRI activity observed during a semantic decision and tone decision task. Out of 8 subjects, 6 demonstrated significant improvements in semantic fluency, and subsequent fMRI data demonstrated a leftward shift in language-related activation. While this study was small and lacked both subject blinding and a control group, the results suggest that future studies should continue to investigate rTMS therapies aimed at directly increasing activity in left hemisphere language areas.

6. Treating aphasia with tDCS

In the domain of language, tDCS has been used experimentally to enhance language performance in normal participants (Sparing et al., 2008). Fifteen healthy volunteers performed a visual picture-naming task before, during, and after administration of tDCS (57 $\mu A/cm^2$) over the left posterior perisylvian region

(PPR), including Wernicke's area (BA 22), and its homologous region in the right hemisphere. After anodal stimulation to the left PPR there was a significant reduction in latencies during picture naming. This finding indicates that tDCS can be used to focally manipulate cortical function in ways that can affect and potentially improve language ability, and implies that this technique could potentially be employed to enhance language recovery in patients with aphasia.

Monti and colleagues first reported the use of tDCS as an adjuvant neurorehabilitation treatment for chronic aphasia after stroke (Cappa, 2008; Monti et al., 2008). These investigators applied anodal, cathodal and sham tDCS (2 mA, 10 minutes) over the left frontotemporal region and a control occipital region of eight aphasic patients who had suffered ischemic strokes. Reaction time and accuracy on a picture-naming task was observed before and immediately after stimulation. Cathodal tDCS improved accuracy on the naming task by 34%, whereas anodal and sham stimulation had no effect. Stimulation over the 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-minute tDCS application was able to induce improvements similar to those obtained by Naeser et al. (2002, 2005a) through rTMS. The authors argue that the effect of cathodal stimulation may be downregulation of overactive inhibitory cortical interneurons in the lesioned hemisphere, ultimately giving rise to increased activity and function in the damaged left hemisphere. However, these results could potentially be viewed as contradictory to those reported by Naeser and others, insofar as they might be interpreted as indicating that downregulation of neural activity in the lesioned hemisphere of aphasic patients leads to improved naming.

Contrary to the findings of Monti et al. (2008), several other investigators have recently reported improved language performance after either anodal stimulation of the left hemisphere or cathodal stimulation of the right hemisphere. For example, Baker and colleagues (2010) noted improved naming performance in 10 aphasic patients with left-hemisphere strokes and various aphasias after treatment with anodal tDCS (1 mA, 20 minutes for 5 days) over the left frontal lobe. The same investigators futher examined the effect of anodal tDCS on reaction time during picture naming in a cohort of 8 chronic stroke patients with fluent aphasia. Targeting the anode to the perilesional site shown to be most active on an fMRI scan during a pretreatment naming task, subjects received stimulation (1 mA, 20 minutes for five days) or sham stimulation (also for five days) in a crossover design while receiving a computerized anomia treatment. Pairing anodal tDCS with language treatment significantly reduced naming reaction time compared to sham both immediately after treatment and three weeks later.

To date, two studies have explored the use of contralesional inhibitory tDCS as a treatment for aphasia. Kang and colleagues recently conducted a double-blind sham-controlled crossover study in which 10 patients with aphasia received cathodal tDCS (2 mA for 20 minutes) and sham stimulation (2 mA for 1 minute) daily for five days. The authors found that subjects showed significant improvement in picture naming on the Korean version of the Boston Naming Test one hour following discontinuation of the last stimulation session compared to the sham condition. Similarly, You and colleagues (2011) recently reported that in patients with subacute stroke and global aphasia cathodal stimulation (2 mA for 30 minutes, 5 days per week for two weeks) of the right hemisphere region homotopic to Wernicke's area resulted in significantly improved verbal comprehension on the Korean version of the Western Aphasia Battery compared to anodal tDCS of the left Wernicke's area and sham tDCS (7 patients in each arm).

7. Noninvasive brain stimulation informs models of interhemispheric interaction

To date, many investigators exploring the use of TMS or tDCS as a treatment for aphasia have used the model of interhemispheric inhibition as the conceptual framework for the design of their experiments. Not surprisingly, the results of these studies have been interpreted as supporting this model. According to the model, following left hemisphere stroke the right hemisphere, released from transcallosal inhibition by the lesioned left hemisphere, exerts an increased transcallosal inhibitory effect on perilesional regions of the left hemisphere, thereby suppressing language-related left hemisphere activity. Similar to what is seen in paresis and neglect (see above) the model predicts two possible approaches to improving language function after a left hemisphere lesion: 1) facilitation of left

hemisphere activity or 2) inhibition of right hemisphere activity (Fregni & Pascual-Leone, 2007). Many of the results discussed above seem broadly consistent with these predictions. However, the notion of interhemispheric inhibition appears inadequate to account other important observations in studies of noninvasive brain stimulation and aphasia.

One such observation is the topographic specificity of rTMS effects in the right hemisphere. The majority of studies that have shown a benefit of rTMS in the right hemisphere have specifically involved stimulation of the pars triangularis (e.g., Naeser et al., 2002; Naeser et al., 2005a; Naeser et al., 2005b; Martin et al., 2009; Hamilton et al., 2010; Barwood et al., 2010; Weiduchat et al., 2011). In fact, evidence suggests that stimulation of nearby right hemisphere sites is either ineffective or potentially deleterious to language performance (Naeser et al., 2002; Hamilton et al., 2010). It is unlikely in the setting of large hemispheric strokes seen in patients with aphasia that critical inhibitory transcallosal connections would be so topographically specific in the right hemisphere. On the contrary, if the interhemispheric inhibition model was the sole explanation for the beneficial effects of inhibitory right hemisphere brain stimulation on language recovery, one would predict that additional suppression of right hemisphere activity would further enhance left hemisphere activity and hence language recovery. However, our recently reported case study of a patient who experienced a right hemisphere stroke after receiving TMS clearly demonstrates that this is not the case (Turkeltaub et al., *in press*). A second finding in this study which speaks against the interhemispheric inhibition model is that inhibitory rTMS of the right pars triangularis was associated with improved language ability and with decreased fMRI activity at the stimulation site, but not with increased activation of left hemisphere centers.

An alternative hypothesis to the interhemipsheric inhibition model is that both spared left hemisphere regions and contralesional right hemisphere sites play a beneficial role in language recovery, but that right hemisphere centers that become part of a reorganized language network may be less efficient at language-related processing. According to this model, some right hemisphere sites in the reorganized language network may contribute to language processing in a dysfunctional or noisy manner, such that suppressing the activity of these specific nodes may increase the overall efficiency of the language network. Our recent ALE analysis demonstrated that across several fMRI studies of right hemisphere activity in aphasia, the right pars triangularis emerged as the single site that was active during many language tasks but did not appear to contribute meaningfully to performance of those tasks (Turkeltaub et al., 2011). Because inefficient neural activity in the right pars triangularis may add deleterious noise to the operation of the reorganized language network, inhibiting this specific site may increase the overall efficiency of the network and result in improved performance.

While TMS studies of the right hemisphere in aphasia are remarkably topographically specific, tDCS studies of the right hemisphere seem to indicate that cathodal inhibitory stimulation over a broad area of the right hemisphere can improve language function (Kang et al., 2011; You et al., 2011). The effects of right cathodal tDCS may initially appear difficult to reconcile with the notion that the right hemisphere contributes beneficially to language recovery. However, an important point to consider is that tDCS is thought to have its effects via subtle subthreshold modulation of the activity of large numbers of neurons rather than the suprathreshold depolarization of neurons induced by TMS. Extending the notion that right hemisphere sites may be relatively inefficient contributors to the reorganized language network, one plausible explanation for the beneficial effects of cathodal right hemisphere stimulation is that subthreshold inhibition of right hemisphere sites incrementally decreases the noise of right hemisphere targets, leading to increased efficiency and improved performance. Additional experiments will be important to further explore this model of right hemisphere inefficiency.

The notion that both hemispheres contribute to remodeled language networks after stroke but that the right does so inefficiently is consistent with a previously proposed hierarchical scheme of language recovery mechanisms (Heiss & Theil, 2006). According to this hierarchical framework, the reacquisition of language functions in previously injured left hemisphere areas, particularly following smaller focal lesions, is associated with normal or near normal recovery. If these areas cannot recover their function, the activation of residual perilesional left-hemisphere sites is also associated with good recovery. Finally, when left hemisphere language networks are more severely impaired, homologous sites in the non-dominant right hemisphere may be engaged, albeit inefficiently, leading to more limited recovery of function.

8. Comparing rTMS and tDCS as tools for neurorehabilitation

Based on the growing body of literature supporting the therapeutic potential of TMS and tDCS, it would be valuable to examine how these two techniques compare on a number of practical areas that can affect their clinical use (see also George & Aston-Jones, 2010). Some of these areas are listed in Table 1. TMS is a better-established procedure that has high spatial and temporal resolution, but it is more difficult to administer, more expensive, and entails some safety concerns (namely, a small risk of seizure induction). By contrast, tDCS stimulates the cortex with considerably less spatial and temporal resolution than TMS, but is a well-tolerated, inexpensive, safe, portable, and versatile stimulation alternative that can be administered easily in a variety of settings.

The topographic specificity of right hemisphere stimulation with rTMS suggests the potential of this technique for targeting specific language functions. Research employing rTMS in the left IFG of normal individuals has implicated different sites within this region in different aspects of language processing, such as phonology, syntax, or semantics (e.g., Gough et al., 2005). Moreover, it has been suggested that semantic networks might be strongly lateralized to the left in healthy individuals, whereas phonological networks might show a more bilateral organization (Hickok & Poeppel, 2007; Hickok et al., 2008). If right hemisphere sites recruited to subserve language are both anatomically homotopic and functionally homologous to injured left hemisphere language areas, it may be the case that targeting specific right hemisphere regions with rTMS my lead to changes in processing of aspects of language. By contrast, tDCS is unlikely to allow for such selectivity in targeting particular language functions, due to its lower spatial resolution.

With respect to combined treatment approaches, tDCS can be readily paired with language therapy due to its ease of administration and minimal patient discomfort. Although rTMS could also be part of such a combined treatment regimen, the more involved administration parameters and potential side effects would make the application of such approaches more challenging. It is possible that pairing noninvasive brain stimulation with appropriate cognitive tasks and behavioral therapies may increase the "behavioral resolution" of the stimulation procedures. That is, combining the stimulation of a given region with a behavioral task designed to elicit activity in that region may facilitate plastic changes in the specific circuits of neurons invoked by the task via Hebbian-like processes.

Table 1
Comparison between rTMS and tDCS

	TMS	tDCS
Temporal resolution	Milliseconds	Minutes
Spatial resolution	Millimeters	Centimeters
Duration of effects	Weeks to months after repeated sessions, possibly longer	Not yet fully characterized
Ease of localization	High spatial precision requires an MRI-guided stereotactic system. Less precise localization possible using the 10–20 system or other scalp measurements	Large area of effect allows for localization using 10–20 system or other scalp measurements
Safety	Safe when applied within established safety guidelines. The additional risk is conferred by prior stroke is not fully known	No lasting adverse effects reported within currently used stimulation parameters. Additional risk conferred by prior stroke is not fully known
Patient discomfort	Mild muscle twitches during stimulation uncomfortable to some subjects. Transient mild headaches reported. Rare cases of dental pain reported	Itchiness and occasional mild burning sensation has been reported under scalp electrodes. Usually well tolerated
Ability to use Sham control condition	Sham often readily distinguished from real stimulation. Newer sham coils may simulate stimulation more realistically	Realistic sham stimulation is easily administered by briefly delivering current
Portability	Typical setup includes TMS unit, stimulation coils, devices for securing the subject and coil position, and hardware for MRI-guided localization	Highly portable. Can be used in any traditional experimental or clinical setting
Cost	Relatively expensive: Approximately $100,000 - $150,000 for TMS unit, coils, and MRI-guided localization system	Very cost-effective: Approximately $10,000 for tDCS unit

Finally the difference in safety concerns between rTMS and tDCS may prove relevant to future investigations. It remains to be seen whether facilitation of activity in damaged cortical areas of the dominant hemisphere, inhibition of contralesional homologous areas in the non-dominant hemisphere, or another approach to stimulation will prove most effective in promoting language recovery (Andoh et al., 2008; Devlin et al., 2003; Dräger et al., 2004; Naeser et al., 2005a). Even though there have been no reports of seizures or other serious adverse events resulting from rTMS in patients being treated for chronic stroke and aphasia, the theoretical risk may make investigators wary of pursing treatment approaches that involve administration of facilitative TMS to the lesioned or perilesional cortex. By comparison, the reassuring safety profile of tDCS makes it likely that future investigations will employ this technique in both hemispheres.

9. Further considerations and future directions

As growing evidence indicates that TMS and tDCS can have therapeutic benefit in aphasia recovery, a number of additional factors must be considered that may ultimately impact the efficacy of therapeutic brain stimulation. The marked variability in language recovery among patients suggests that successful treatment approaches may need to take into account a variety of patient-specific factors such as a premorbid laterality for language, the location and extent of injury, age, gender, handedness, education, premorbid cognitive ability, prior strokes, other comorbid neurologic conditions, and concurrent use of pharmacological agents (e.g., Hillis, 2007; Knecht et al., 2002; Martin et al., 2009; Rosen et al., 2000). Future work should also focus on characterizing the duration of the beneficial effects of stimulation and examine which TMS and tDCS stimulation parameters are most effective at different stages following stroke (e.g., acute, subacute, and chronic; c.f. Khedr et al., 2005). The existence of various accounts on the possible mechanisms underlying the recovery of language function after left-hemisphere stroke suggests that the recovery process is dynamic and involves a number of plastic changes that can take place in both hemispheres. Evaluating the extent to which each of these mechanisms plays a role in the recovery of a given patient may allow to selection of therapeutic approach (e.g., left hemisphere excitation vs. right hemisphere suppression) that will maximize the success of therapeutic interventions with TMS and tDCS.

Considerably more work is needed to establish the generalizability and efficacy of TMS and tDCS for the treatment of aphasia (George & Aston-Jones, 2010; Ridding & Rothwell, 2007). Future work combining noninvasive brain stimulation with functional neuroimaging has the potential to elucidate the mechanisms underlying both ipsilesional and interhemispheric interactions during recovery (e.g., Martin et al., 2009). Additional protocols involving stimulation in conjunction with speech therapy (e.g., Naeser et al., 2005b), behavioral (e.g., Crosson et al., 2007, 2009; Schlaug et al., 2009), or pharmacological interventions (see Berthier, 2005) may further promote neural plasticity and functional reorganization after brain injury (e.g., Mottaghy et al., 2006; see also Devlin & Watkins, 2007). Finally, future studies should address specific structure-function relationships that mediate different aspects of language (e.g., phonology, semantics; Gough et al., 2005; Zatorre et al., 1992) in both normal and aphasic individuals. Better characterization of these anatomical and functional distinctions may soon allow for patient-focused interventions that target specific language deficits.

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