Curr Neurol Neurosci Rep (2015) 15: 72
DOI 10.1007/s11910-015-0593-6

BEHAVIOR (HS KIRSHNER, SECTION EDITOR)

Brain Stimulation and the Role of the Right Hemisphere in Aphasia Recovery

Peter E. Turkeltaub [1,2]

Published online: 22 September 2015

Abstract Aphasia is a common consequence of left hemisphere stroke and causes a disabling loss of language and communication ability. Current treatments for aphasia are inadequate, leaving a majority of aphasia sufferers with ongoing communication difficulties for the rest of their lives. In the past decade, two forms of noninvasive brain stimulation, repetitive transcranial magnetic stimulation and transcranial direct current stimulation, have emerged as promising new treatments for aphasia. The most common brain stimulation protocols attempt to inhibit the intact right hemisphere based on the hypothesis that maladaptive activity in the right hemisphere limits language recovery in the left. There is now sufficient evidence to demonstrate that this approach, at least for repetitive transcranial magnetic stimulation, improves specific language abilities in aphasia. However, the biological mechanisms that produce these behavioral improvements remain poorly understood. Taken in the context of the larger neurobiological literature on aphasia recovery, the role of the right hemisphere in aphasia recovery remains unclear. Additional research is needed to understand biological mechanisms of recovery, in order to optimize brain stimulation treatments for aphasia. This article summarizes the current evidence on noninvasive brain stimulation methods for aphasia and the neuroscientific considerations surrounding treatments using right hemisphere inhibition. Suggestions are provided for further investigation and for clinicians whose patients ask about brain stimulation treatments for aphasia.

Keywords Aphasia · Transcranial magnetic stimulation · Transcranial direct current stimulation · Stroke recovery · Neuromodulation · Noninvasive brain stimulation

This article is part of the Topical Collection on *Behavior*

✉ Peter E. Turkeltaub
turkeltp@georgetown.edu

[1] Neurology Department, Georgetown University Medical Center, 4000 Reservoir Road, NW; Building D, Suite 165, Washington, DC 20057, USA

[2] Research Division, MedStar National Rehabilitation Hospital, Washington, DC, USA

Introduction

Approximately one third of all people with acute stroke have aphasia, the vast majority due to left hemisphere (LH) lesions [1, 2]. Improvements in language are fastest in the first few months after stroke and gradually slow down over time [3]. Although recovery is highly variable, on average survivors achieve 70 % of the maximum possible recovery on common aphasia tests 90 days after stroke [4]. The only widely accepted treatment for post-stroke aphasia is speech-language therapy, which improves outcomes in some aspects of language and functional communication [5]. However, the effects of speech-language therapy on overall aphasia outcomes are relatively modest, and about two thirds of people with aphasia at stroke onset who survive to follow up continue to have chronic language deficits 18 months later [6]. Living with aphasia reduces participation in life activities, independence, and mood and increases the cost of care [7–10]. Clearly, new treatments are needed to improve outcomes for people living with aphasia.

Aphasia specialists have long sought biologically based interventions to augment recovery. A number of medications have been tested for aphasia, based on the theory that increasing neurotransmitter availability in partially disrupted pathways may mitigate deficits related to these disruptions. Correcting these neurotransmitter disruptions could enhance

language abilities on a day-to-day basis or potentially facilitate relearning of language skills during speech-language therapy, much as stimulants that improve attention in a child with attention deficit disorder might improve learning at school. The results for some medications have been encouraging [See 11 for review]. In general, these studies have been small, and larger, more definitive trials are needed.

A more ambitious and potentially more impactful goal of biologically based treatments is to alter the process of brain reorganization that underlies aphasia recovery. After the initial stabilization of blood flow and resolution of brain swelling in the first weeks after a stroke, recovery relies on reorganization of brain networks, which occurs both spontaneously and in response to behavioral training [12], such as speech-language therapy. As in animal models of sensorimotor stroke, the primary changes after a stroke causing aphasia include recruitment of perilesional tissue adjacent to the stroke in the LH and recruitment of homotopic (mirror image) right hemisphere (RH) sites (Fig. 1) [13•]. Engagement of preserved language areas of the LH and recruitment of nearby perilesional tissue is widely thought to support recovery of language functions [14–22]. The role of the RH in recovery is less clear [23••]. Optimizing brain reorganization to achieve a maximally efficient language network could theoretically yield significant

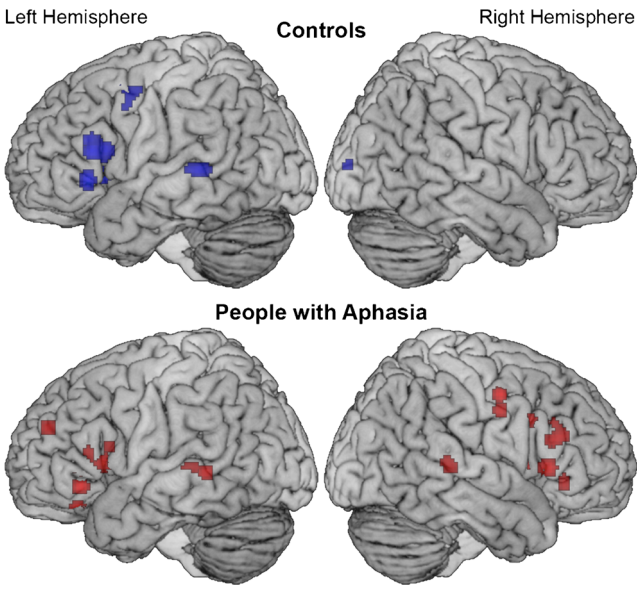

Fig. 1 Reorganization of language networks in post-stroke aphasia. Results are shown from a meta-analysis of functional neuroimaging studies of people with chronic post-stroke aphasia and matched control subjects (Adapted from [13•]). The *top row* shows normal brain activity in the left-lateralized language network in control subjects. The *bottom row* shows the reorganized brain activity during the same language tasks in people with aphasia. Results are rendered onto a template brain so the locations of stroke damage are not shown. Three patterns are notable: (1) preserved activity in native LH language areas when viable tissue remains in these areas, (2) shifts in activity within the LH to so called "perilesional" locations, and (3) activation of a "RH language network" that mirrors the native LH language network activated by controls

gains in aphasia recovery. This could potentially be accomplished in various ways, for instance enhancing plasticity in the months following stroke, coaxing the brain's language network into a more efficient organization, or by restoring plasticity long after stroke. Based on these goals, a number of small studies have recently examined whether noninvasive electrical or magnetic brain stimulation can improve aphasia recovery. These techniques are used to excite or inhibit particular areas of the brain and are being tested for use on a wide range of neurologic and psychiatric conditions [24]. There has been a great deal of excitement about these techniques amongst aphasia researchers, clinicians, patients, and families. Indeed, results from early studies have been encouraging, although certainly not definitive.

Most brain stimulation studies on aphasia to date have aimed either to enhance activity in brain areas thought to support good recovery from aphasia or, more commonly, to suppress activity in brain areas thought to interfere with recovery. These studies have proceeded, however, even as neuroscientists continue to debate basic questions about how language networks reorganize after stroke. There is a striking lack of consensus in the literature regarding key aspects of the neuroscientific theories guiding the use of brain stimulation for aphasia, particularly the role of the RH in recovery [23••]. In addition, the results of brain stimulation trials are often used as evidence supporting particular theories of aphasia recovery, despite a lack of neurobiological data to confirm the mechanisms of action of these methods. Without a better understanding of the brain basis of aphasia recovery and the mechanisms by which brain stimulation improves outcomes, the field risks developing suboptimal brain stimulation treatments based on erroneous assumptions and then reinforcing those assumptions based on weekly positive clinical results. A more thorough understanding of the brain basis of aphasia recovery and of the neurobiological effects of brain stimulation techniques will increase our chances of developing new interventions that have a meaningful clinical impact on outcomes for people with aphasia.

Below, I will describe the two main forms of noninvasive brain stimulation currently being investigated for use in post-stroke aphasia, and the current state of the evidence supporting their use. I will then describe the controversy surrounding the neurobiological theories guiding the most common approaches to treatment and suggest ways to improve the chances of turning these promising investigational techniques into meaningful clinical interventions.

Noninvasive Brain Stimulation Methods Used for Aphasia

The two most common noninvasive brain stimulation techniques are repetitive transcranial magnetic stimulation

(rTMS) and transcranial direct current stimulation (tDCS) (Table 1). rTMS involves passing a very brief high-current electrical pulse through an insulated coil of wire held over the scalp. The pulse produces a rapidly changing magnetic field that induces electrical current in underlying brain tissue, causing neuronal firing. rTMS, as commonly used for aphasia, is thought to affect a small area of brain tissue directly under the coil (approximately 1 cm^3), although downstream effects are expected in areas connected to the site of stimulation [25, 26]. Low-frequency rTMS (typically 1 Hz) reduces excitability of the stimulated cortical site, whereas high-frequency rTMS (>5 Hz) increases excitability. These effects persist minutes to hours after rTMS is stopped, and daily repeated sessions can induce more durable effects although the biological basis of these long-lasting effects is less clear. This "off-line" effect is the basis for therapeutic uses of TMS in a variety of neurological and psychiatric conditions [27].

In contrast to rTMS, which induces electrical currents in the brain using magnetic fields, tDCS directly applies a low level of constant electrical current to the scalp using electrodes [28]. In ex vivo studies, this direct electrical current slightly depolarizes or hyperpolarizes neurons, making them more or less likely to fire [29]. In aphasia treatment studies, the current is typically applied for 10–30 min, often in combination with speech-language therapy. Unlike the highly focal effect of TMS, tDCS has an anatomically broader effect. Electrical field modeling suggests that entire lobes of the brain may be impacted by typical tDCS methods, which use large saline-soaked sponges as electrodes [30]. Recently, "high definition tDCS" methods have been developed using multiple smaller electrodes to focus the electrical current [31•] although the effects are still thought to be less localized than typical rTMS methods. Like rTMS, tDCS can induce localized excitation or inhibition of neuronal populations that can last for minutes to hours after a short session [28, 32]. The polarity of the tDCS electrode is widely thought to determine whether the effect on the underlying brain tissue is excitatory or inhibitory. The anode is generally thought to induce excitation, whereas the cathode induces inhibition. This rubric, however, has been brought into question by electrical field modeling studies demonstrating large areas of current flow between the electrodes [31•] in sometimes unexpected distributions especially in people with brain lesions [33]. Further, effects of cathodal stimulation on cognitive tasks in healthy subjects have been inconsistent [34]. Despite these issues, most tDCS studies in clinical populations assume that activity in the brain area under the anode will be facilitated by stimulation, whereas the area under the cathode will be inhibited. Both rTMS and tDCS can enhance learning during motor or language training in healthy subjects [35–38]. These effects have generated a great deal of hope that rTMS or tDCS might improve language and communication outcomes for people with post-stroke aphasia.

Evidence to Date for TMS and tDCS Treatments of Aphasia

Naeser and colleagues provided the first evidence that noninvasive brain stimulation might improve aphasia, applying low frequency rTMS to the pars triangularis of the right inferior frontal gyrus (IFG) in a small group of people with chronic nonfluent aphasia [39, 40]. These initial open-label studies suggested that this type of stimulation, aimed at suppressing the RH homolog to Broca's area, improved picture naming for

Table 1 Comparison of practical aspects of brain stimulation methods used in treatment studies of post-stroke aphasia

	rTMS	tDCS
Description of method	Uses electromagnetic induction in an insulated coil of wire on the scalp to induce neuronal firing, alter cortical excitability	Uses low levels of direct electrical current applied to electrodes on the scalp to modulate resting membrane potentials and alter likelihood of neuronal firing
Duration of session	Typically 10–30 min	Typically 10–30 min
Number of sessions	Typically 5/week × 2–3 weeks	Typically 5/week × 1–3 weeks
Pairing with speech therapy	Speech therapy can be given before or after treatment, but is difficult to conduct during treatment	Speech therapy can be given before, during, or after treatment
Portability	Not easily portable	Portable
Equipment cost	Approximately $50,000; up to $150,000 including neuronavigation equipment to precisely target specific brain areas	Approximately $1000 to $14,000 depending on features
Area of effect	More anatomically focal effect	Larger anatomical area of effect
Ability to target effect to selected brain area	Affected area is directly under the coil of wire	Area affected is not always directly under electrodes, may require individualized electrical field modeling, which is not yet widely available, to precisely target brain areas
Tolerability	Well tolerated; common side effects include transient headache, dizziness	Well tolerated; common side effects include transient tingling, itching, or burning sensation at stimulation site
Serious adverse events	Very rare instances of single seizure	None to date

up to 8 months after 10 daily sessions of treatment applied over 2 weeks.

Since the initial reports of Naeser and colleagues, over 20 other studies have tested rTMS treatments for post-stroke aphasia, with or without adjunct speech-language therapy. Collectively, these studies have included over 200 patients during either the subacute or chronic phases of recovery. Although a few have used other stimulation strategies (e.g., [41]), most rTMS studies on aphasia have used low frequency stimulation to the RH homolog of Broca's area, as in the original Naeser and colleagues' work. A recent meta-analysis of seven such trials including 160 patients found significant positive effects on naming, repetition, writing, comprehension, and global language impairment, with standardized mean differences of 0.32 to 0.70 on individual language domains, and 1.26 on global impairment [42••]. Studies that have examined durability of effects suggest that language improvements may last months after a single 2-week course of treatment in chronic patients [39, 43, 44].

tDCS studies on aphasia have emerged more recently and have been somewhat more varied in their design. Studies have targeted the LH [45], or the RH [46], or both [47]. Anodal and cathodal stimulation have variously been applied to each hemisphere in both fluent and nonfluent patients [48•]. Compared to rTMS, relatively fewer tDCS studies have been published to date, and the variability in the methods used makes it difficult to determine if effects on aphasia are reliable. A recent Cochrane review of six tDCS studies including a total of 66 patients concluded there were no reliable effects on picture naming [49•]. It is perhaps too early for this kind of quantitative review on tDCS, and future meta-analyses including more homogeneous groups of studies may yield different results. One recent meta-analysis combined six rTMS and three tDCS studies that aimed to suppress RH activity and found a significant positive effect of these methods on picture naming with a standardized mean difference of 0.52 [50•].

A common criticism of brain stimulation treatment studies for aphasia has been the focus on specific language tasks, particularly picture naming, as the outcome measures, rather than more ecologically valid measures of functional communication [49•]. Although it is hard to draw any firm conclusions regarding the importance of effects demonstrated to date on real-life communication ability, the primary aim of the small early phase studies conducted so far has been to establish safety and prove that particular stimulation protocols can modulate language abilities in aphasia. For these early stages of methods development, it is reasonable to focus on sensitive measures like picture naming. Larger phase II and phase III trials in the future should focus on more clinically relevant outcome measures after factors like location, duration, and type of stimulation are optimized.

Overall, the most consistently successful brain stimulation treatments for aphasia to date have utilized low frequency rTMS or cathodal tDCS aiming to inhibit the RH, most typically the right IFG [50]. This consistency may be somewhat misleading, however, as RH inhibition has been the most commonly used treatment strategy to date, based on the pioneering work of Naeser and colleagues. Indeed, some crossover studies have shown greater benefit for other modes of stimulation, including stimulation intended to inhibit the LH [51] or excite the right [46]. Despite these conflicting findings, many have taken the beneficial effects of low frequency rTMS and cathodal tDCS over the RH as evidence that involvement of the RH in aphasia recovery is maladaptive. However, these conclusions must be considered in the larger context of neuroscience research on aphasia recovery, in which there is still a great deal of debate about the role of the RH. It is thus worth considering the practical and scientific motivations for inhibiting the RH to facilitate aphasia recovery, along with supporting and contradictory neuroscientific evidence for this treatment strategy.

Why Inhibit the RH?

Targeting the intact RH provides distinct practical advantages for brain stimulation treatments of LH stroke survivors with aphasia. Since stroke locations differ within the LH between patients, stimulating the LH requires individualized targeting to ensure that TMS or tDCS is administered to intact brain tissue rather than an area of encephalomalacia. In addition, because reorganization of LH language circuits likely differs depending on stroke location, extra techniques like fMRI may be needed to ensure that spared areas of the LH are involved in language processing [52]. There are also theoretical safety concerns for stimulating tissue around the lesion, including current shunting through cerebrospinal fluid cavities and seizure induction from excitation of epileptogenic tissue, although the risk of significant adverse events with either TMS or tDCS is extremely low regardless of the brain area stimulated [53, 54]. Targeting the intact RH allows for the possibility of identifying a single target that can be used across groups of people with aphasia, without these complications [13]. The simplicity of this approach could be key to making brain stimulation treatments for aphasia accessible for widespread clinical use in the future, just as the simplicity of the TMS protocol used for depression has led to FDA clearance and more widespread use than would be possible with a more complicated approach [55].

From a neurobiological perspective, the hypothesis that inhibiting the intact RH might improve aphasia outcomes is derived primarily from the motor literature, based on the so called "theory of interhemispheric inhibition." In the motor system, transcallosal inhibitory connections between the primary motor cortices of the two hemispheres may help to coordinate bimanual movement [56]. After a stroke involving the motor cortex, the interhemispheric inhibitory balance is

disrupted and the intact motor cortex in the hemisphere opposite the stroke inhibits the injured side [57, 58], contributing to deficits [59, 60]. Inhibition of the intact motor cortex using rTMS or tDCS can increase cortical excitability on the lesioned side and improve clinical motor function [61–64], suggesting that this transcallosal inhibitory imbalance is clinically important and modifiable. The theory of interhemispheric inhibition thus is well supported in the human motor system.

The design of Naeser and colleagues' original rTMS study was based on the hypothesis that the principles of interhemispheric inhibition apply to language systems as well. The specific hypothesis was that LH damage releases transcallosal inhibition on the RH homolog to Broca's area, allowing it to suppress surviving tissue around Broca's area in the LH and hence impede aphasia recovery. A logical treatment intervention to remedy this right-to-left suppression would be to inhibit the RH homolog to Broca's area, restoring proper interhemispheric balance and allowing Broca's area and surrounding tissue to play a larger role in language. Since the success of the original rTMS protocol for aphasia, the theory of interhemispheric inhibition has served as the framework guiding many similar protocols using rTMS and tDCS to inhibit the RH in aphasia [65–67]. The success of these protocols has been taken as evidence that interhemispheric inhibition plays a key role in language reorganization in aphasia [66, 42].

Transcallosal fiber pathways between language areas do exist, providing the anatomical basis for interhemispheric inhibition [68] although it remains unclear whether or not these connections are predominantly inhibitory. Two rTMS studies in the subacute phase of stroke recovery have included PET activity during a verb generation task as an outcome measure in order to assess the biological effects of treatment [67, 69]. In these cases, laterality indices of activity demonstrated a leftward shift after rTMS that did not occur with sham rTMS. These findings could support the theory of interhemispheric inhibition, but a number of caveats limit their interpretation. For example, PET scans restrict the ability to control for task difficulty (see below for more discussion on this issue). Further, the use of laterality indices of activity precludes localization of activation changes, making it difficult to know whether changes occurred primarily in the RH, LH, or both, as would be predicted by the theory of interhemispheric inhibition. As such, it remains unclear whether the findings of these studies truly support the theory of interhemispheric inhibition. Moreover, studies have not assessed neurobiological outcome measures in the chronic phase of aphasia recovery, from which most clinical evidence for efficacy of rTMS and tDCS derives. Thus, despite the success of rTMS and tDCS studies aiming to inhibit the RH to improve aphasia, the existence and importance of interhemispheric inhibitory interactions in language networks still remains largely theoretical, based mainly on extrapolation from the motor system.

Apart from rTMS and tDCS studies, several recent functional imaging studies do provide some support for the notion that RH activity in aphasia is maladaptive, although not for interhemispheric inhibition specifically. These studies have noted increased RH activity during incorrect naming responses or inverse relationships between activity and performance across groups, suggesting that some RH areas recruited in aphasia might be ineffective, inefficient, or maladaptive [70–74]. In some longitudinal functional imaging studies, RH recruitment has peaked early in recovery or immediately after training and has diminished over time in association with clinical improvements, suggesting that "turning off" the RH might improve long-term recovery [15, 75–77].

Contradictory Evidence Regarding the Role of the RH in Aphasia Recovery

In contrast to the results of rTMS and tDCS studies and the recent functional imaging studies above, multiple older lines of evidence suggest instead that the RH compensates for LH damage and supports recovery from aphasia. This evidence begins with Barlow's 1877 case of a boy who became aphasic after a small stroke to the left posterior IFG, then recovered, but worsened again after a small symmetrical stroke in the RH [78]. More recently, similar adult cases have been reported in which a first LH stroke caused aphasia and after partial recovery a second RH stroke worsened language performance [79, 80]. Several other lines of evidence have also suggested RH compensation in aphasia: a relationship between poor aphasia outcomes from LH stroke and "clinically silent" RH strokes [81], worsening of language performance in aphasic patients after right carotid anesthesia [82], and left visual field and left ear advantages in people with aphasia [83–85]. These sources lack the spatial resolution to implicate particular parts of the RH in aphasia recovery but suggest that overall the RH contributes to language ability after damage to the native LH language network.

More recently, some functional imaging and electrophysiological studies of aphasia have reported activity in RH areas that mirror typical LH language areas, corresponding to a clinical response to treatment [86, 87]. Based on evidence for RH compensation in aphasia, some successful forms of speech-language therapy have been designed to engage the RH in language processes, for example Melodic Intonation Therapy. These methods have been shown to induce remodeling of the RH as predicted [88, 89], and in a pilot study, applying anodal tDCS to enhance right IFG activity during treatment improved fluency of speech output compared to sham tDCS [90].

Understanding the apparent contradictions in the literature on the role of the RH in aphasia recovery will be critical to

optimizing brain stimulation treatments for aphasia. Multiple factors may contribute to the conflict in the field: methodological limitations in brain stimulation and neuroimaging studies, differences in the RH role in recovery of specific language functions and between the roles of specific RH brain areas, and individual differences in the brain basis of aphasia recovery. In terms of methodological limitations, the first concerns the poor understanding of the long-term neurobiological effects of RH inhibitory brain stimulation protocols. As noted above, it remains unclear that brain stimulation protocols known to induce short-term inhibition at the site of stimulation induce long-term inhibition lasting weeks to months in association with the behavioral benefits on language. The theory of interhemispheric inhibition specifically suggests that such long-term RH inhibition at the site of stimulation should be accompanied by enhanced LH engagement in brain areas directly opposite the stimulation site; this too remains unproven. In a case study on a chronic nonfluent aphasic patient who received a 2-week course of low frequency rTMS to the right pars triangularis and then unfortunately suffered a second stroke, this time affecting the RH, we found no evidence to support the theory of interhemispheric inhibition in either the fMRI activity or the behavioral effects of the second stroke [79]. It thus remains possible that a different unpredicted neurobiological effect accounts for the long-term effects of brain stimulation, at least in chronic aphasia. For instance, altering the inhibitory-excitatory balance within a reorganized bihemispheric language network might induce a renewed period of plasticity in the chronic phase, allowing for further optimization of network efficiency in both hemispheres [91]. Alternatively, multiple sessions of RH inhibition might induce a longer-term excitatory overshoot after treatment ends, such that enhanced RH compensation accounts for behavioral improvements seen after RH inhibitory brain stimulation.

Limitations of task-related brain activity, the primary metric used to quantify RH involvement in language, may also account for some inconsistent findings in the literature on aphasia recovery. In particular, the impact of performance and effort on task-related activity complicates the interpretation of many functional imaging results. Increasing effort on language tasks produces more activity in both hemispheres in both controls and people with aphasia [92, 93]. Thus, while inverse correlations between activity and performance may suggest maladaptive activity, an alternate interpretation is that individuals with large strokes and more severe aphasia must exert more effort to perform the task and thus engage the RH to a greater degree. In this context, when in-scanner performance is not controlled in longitudinal imaging studies, a decrease in RH activity may be a consequence of improved aphasia, not a cause.

Aside from methodological limitations, some of the inconsistencies between previous studies on the RH's role in aphasia recovery may derive from a complicated relationship between the RH and recovery. For instance, different specific parts of the RH may play different roles in aphasia recovery, such that some areas of the RH compensate for damage to the LH language networks, while others are too inefficient to be effective, and others may indeed interfere with optimal recovery [13•, 79]. Likewise, the RH may be able to compensate more effectively for some specific language functions compared to others [94]. Finally, the specific pattern of language system reorganization likely differs somewhat between individuals, based on personal characteristics and features of the stroke [95, 96], and also may change substantially over time after stroke [97•].

Conclusions

Overall, we are still early in the development of noninvasive brain stimulation treatments for aphasia, but it appears that protocols aimed at suppressing the RH, particularly the pars triangularis of the right IFG, do improve specific language abilities. However, many questions remain unanswered. Too few studies have directly compared different brain stimulation protocols to determine whether alternate approaches might produce larger effects or whether personalizing stimulation protocols based on individual differences will maximize benefits. There is also inadequate evidence to determine the long-term biological changes caused by rTMS and tDCS treatments for aphasia, and so the mechanism of effect is poorly understood. For this reason, it seems inappropriate to use behavioral effects occurring days, weeks, or months after brain stimulation treatments to support particular neurobiological theories of aphasia recovery, most notably the theory of interhemispheric inhibition. Going forward, including neurobiological outcome measures in brain stimulation studies will produce a great deal more progress toward understanding the biological basis of aphasia recovery and optimizing brain stimulation treatments. In particular, because of the thorny dependence of task-related functional activity on effort and task performance, it will be particularly useful to examine more stable brain measures that do not depend on effort, such as gray and white matter morphology and resting functional connectivity. Finally, although some clinicians are now providing brain stimulation treatments for aphasia on an out-of-pocket fee-for-service basis, this is not yet clearly justified by the available data. Patients or families interested in brain stimulation treatments should instead be referred to clinicaltrials.gov or other resources to identify ongoing studies, and encouraged to participate, given the safety of these techniques and the promise of future benefits for people with aphasia.

Compliance with Ethics Guidelines

Conflict of Interest Peter E. Turkeltaub declares that this work was supported by the National Center for Advancing Translational Sciences via the Georgetown-Howard Universities Center for Clinical and Translational Science (KL2TR000102), the Doris Duke Charitable Foundation (Grant 2012062), and the Vernon Family Trust.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Aphasia in acute stroke: incidence, determinants, and recovery. Ann Neurol. 1995;38(4):659–66.
2. Dickey L, Kagan A, Lindsay MP, Fang J, Rowland A, Black S. Incidence and profile of inpatient stroke-induced aphasia in Ontario. Canada Arch Phys Med Rehabil. 2010;91(2):196–202.
3. Lendrem W, Lincoln NB. Spontaneous recovery of language in patients with aphasia between 4 and 34 weeks after stroke. J Neurol Neurosurg Psychiatry. 1985;48:743–8.
4. Lazar RM, Minzer B, Antoniello D, Festa JR, Krakauer JW, Marshall RS. Improvement in aphasia scores after stroke is well predicted by initial severity. Stroke J Cereb Circ. 2010;41(7):1485–8.
5. Brady MC, Kelly H, Godwin J, Enderby P. Speech and language therapy for aphasia following stroke. Cochrane Database Syst Rev. 2012;5:CD000425.
6. Laska AC, Hellblom A, Murray V, Kahan T, Von Arbin M. Aphasia in acute stroke and relation to outcome. J Intern Med. 2001;249(5):413–22.
7. Lyon JG. Communication use and participation in life for adults with aphasia in natural settings the scope of the problem. Am J Speech-Lang Pathol. 1992;1(3):7–14.
8. Cruice M, Worrall L, Hickson L. Reporting on psychological well-being of older adults with chronic aphasia in the context of unaffected peers. Disabil Rehabil. 2011;33:219–28.
9. Gialanella B, Bertolinelli M, Lissi M, Prometti P. Predicting outcome after stroke: the role of aphasia. Disabil Rehabil. 2011;33(2):122–9.
10. Ellis C, Simpson AN, Bonilha H, Mauldin PD, Simpson KN. The one-year attributable cost of poststroke aphasia. Stroke J Cereb Circ. 2012;43(5):1429–31.
11. Berthier ML, Pulvermuller F, Davila G, Casares NG, Gutierrez A. Drug therapy of post-stroke aphasia: a review of current evidence. Neuropsychol Rev. 2011;21(3):302–17.
12. Kerr AL, Cheng SY, Jones TA. Experience-dependent neural plasticity in the adult damaged brain. J Commun Disord. 2011;44(5):538–48.
13.• Turkeltaub PE, Messing S, Norise C, Hamilton RH. Are networks for residual language function and recovery consistent across aphasic patients? Neurology. 2011;76(20):1726–34. **This meta-analysis of functional neuroimaging studies on post-stroke aphasia demonstrates the patterns of reorganization of language networks after stroke, including recruitment of a mirror image "right hemisphere language network," and suggests that different mechanisms of plasticity account for recruitment of different brain regions.**
14. Karbe H, Kessler J, Herholz K, Fink GR, Heiss WD. Long-term prognosis of poststroke aphasia studied with positron emission tomography. Arch Neurol. 1995;52(2):186–90.
15. Saur D, Lange R, Baumgaertner A, Schraknepper V, Willmes K, Rijntjes M, et al. Dynamics of language reorganization after stroke. Brain. 2006;129(Pt 6):1371–84.
16. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, et al. The right IFG and poststroke aphasia: a follow-up investigation. Stroke. 2007;38(4):1286–92.
17. Heiss WD, Kessler J, Thiel A, Ghaemi M, Karbe H. Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. Ann Neurol. 1999;45(4):430–8.
18. Heiss WD, Thiel A, Kessler J, Herholz K. Disturbance and recovery of language function: correlates in PET activation studies. NeuroImage. 2003;20 Suppl 1:S42–9.
19. Fridriksson J, Bonilha L, Baker JM, Moser D, Rorden C. Activity in preserved left hemisphere regions predicts anomia severity in aphasia. Cereb Cortex. 2010;20(5):1013–9.
20. Miura K, Nakamura Y, Miura F, Yamada I, Takahashi M, Yoshikawa A, et al. Functional magnetic resonance imaging to word generation task in a patient with Broca's aphasia. J Neurol. 1999;246(10):939–42.
21. Meinzer M, Flaisch T, Breitenstein C, Wienbruch C, Elbert T, Rockstroh B. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. NeuroImage. 2008;39(4):2038–46.
22. Fridriksson J, Richardson JD, Fillmore P, Cai B. Left hemisphere plasticity and aphasia recovery. Neuroimage. 2012;60(2):854–63.
23.•• Gainotti G. Contrasting opinions on the role of the right hemisphere in the recovery of language. A critical survey. Aphasiology. 2015;1–18. This review paper provides an excellent summary of the ongoing debate regarding the role of the RH in aphasia recovery.
24. Fregni FF, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. Nat Clin Pract Neurol. 2007;3:383–93.
25. Paus T, Jech R, Thompson CJ, Comeau R, Peters T, Evans AC. Transcranial magnetic stimulation during positron emission tomography: a new method for studying connectivity of the human cerebral cortex. J Neurosci. 1997;17(9):3178–84.
26. Wang JX, Rogers LM, Gross EZ, Ryals AJ, Dokucu ME, Brandstatt KL, et al. Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science. 2014;345(6200):1054–7.
27. Hallett M. Transcranial magnetic stimulation and the human brain. Nature. 2000;406(6792):147–50.
28. Zaghi S, Acar M, Hultgren B, Boggio PS, Fregni F. Noninvasive brain stimulation with low-intensity electrical currents: putative mechanisms of action for direct and alternating current stimulation. Neuroscientist. 2010;16(3):285–307.
29. Reato D, Rahman A, Bikson M, Parra LC. Low-intensity electrical stimulation affects network dynamics by modulating population rate and spike timing. J Neurosci. 2010;30(45):15067–79.
30. Parazzini M, Fiocchi S, Rossi E, Paglialonga A, Ravazzani P. Transcranial direct current stimulation: estimation of the electric field and of the current density in an anatomical human head model. IEEE Trans Biomed Eng. 2011;58(6):1773–80.
31.• Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial DC stimulation: improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul. 2009;2(4):201–7. **This paper uses electrical field modeling to demonstrate that the expected inhibitory and excitatory effects of tDCS may not be as simple as most studies propose. It also introduces "high definition tDCS" which uses**

smaller electrodes to provide a more anatomically localized effect.

32. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527(Pt 3):633–9.
33. Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimul. 2011;4(3):169–74.
34. Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res. 2012;216(1):1–10.
35. de Vries MH, Barth ACR, Maiworm S, Knecht S, Zwitserlood P, Floel A, et al. Electrical stimulation of Broca's area enhances implicit learning of an artificial grammar. J Cogn Neurosci. 2009;22: 2427–36.
36. Floel A, Rosser N, Michka O, Knecht S, Breitenstein C, Flöel A, et al. Noninvasive brain stimulation improves language learning. J Cogn Neurosci. 2008;20:1415–22.
37. Meinzer M, Jahnigen S, Copland DA, Darkow R, Grittner U, Avirame K, et al. Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary. Cortex. 2014;50:137–47.
38. Reis J, Robertson E, Krakauer JW, Rothwell J, Marshall L, Gerloff C, et al. Consensus: "Can tDCS and TMS enhance motor learning and memory formation?". Brain Stimul. 2008;1(4):363–9.
39. Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Kobayashi M, et al. Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. Brain Lang. 2005;93(1):95–105.
40. Martin PI, Naeser MA, Theoret H, Tormos JM, Nicholas M, Kurland J, et al. Transcranial magnetic stimulation as a complementary treatment for aphasia. Semin Speech Lang. 2004;25(2):181–91.
41. Szaflarski JP, Vannest J, Wu SW, DiFrancesco MW, Banks C, Gilbert DL. Excitatory repetitive transcranial magnetic stimulation induces improvements in chronic post-stroke aphasia. Med Sci Monit. 2011;17(3):CR132–9.
42.•• Ren CL, Zhang GF, Xia N, Jin CH, Zhang XH, Hao JF, et al. Effect of low-frequency rTMS on aphasia in stroke patients: a meta-analysis of randomized controlled trials. PLoS One. 2014;9(7): e102557. **This meta-analysis of rTMS studies aiming to inhibit the RH demonstrates that this treatment method improves scores on tests of multiple different language functions as well as overall aphasia severity.**
43. Hamilton RH, Sanders L, Benson J, Faseyitan O, Norise C, Naeser M, et al. Stimulating conversation: enhancement of elicited propositional speech in a patient with chronic non-fluent aphasia following transcranial magnetic stimulation. Brain Lang. 2010;113(1):45–50.
44. Barwood CH, Murdoch BE, Whelan BM, Lloyd D, Riek S, O'Sullivan JD, et al. Improved receptive and expressive language abilities in nonfluent aphasic stroke patients after application of rTMS: an open protocol case series. Brain Stimul. 2012;5(3): 274–86.
45. Fridriksson J, Richardson JD, Baker JM, Rorden C. Transcranial direct current stimulation improves naming reaction time in fluent aphasia: a double-blind, sham-controlled study. Stroke J Cereb Circ. 2011;42(3):819–21.
46. Floel A, Meinzer M, Kirstein R, Nijhof S, Deppe M, Knecht S, et al. Short-term anomia training and electrical brain stimulation. Stroke. 2011;42(7):2065–7.
47. Marangolo P, Fiori V, Gelfo F, Shofany J, Razzano C, Caltagirone C, et al. Bihemispheric tDCS enhances language recovery but does not alter BDNF levels in chronic aphasic patients. Restor Neurol Neurosci. 2014;32(2):367–79.
48.• de Aguiar V, Paolazzi C, Miceli G. tDCS in post-stroke aphasia: the role of stimulation parameters, behavioral treatment and patient characteristics. Cortex. 2015;63:296–316. **This review article provides a thorough accounting of tDCS studies for aphasia and the differences between these studies. It attempts to identify patterns relating particular treatment parameters with results to provide recommendations for future tDCS studies.**
49.• Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke. Cochrane Database Syst Rev. 2013;6:CD009760. **This meta-analysis suggests that the evidence to date suggests that tDCS does not improve aphasia, and recommends inclusion of functional communication measures in future studies. Although the tDCS literature is perhaps too small and diverse for this type of analysis, it serves as a useful note of caution when considering the state of the current evidence on tDCS for aphasia.**
50.• Otal B, Olma MC, Floel A, Wellwood I. Inhibitory non-invasive brain stimulation to homologous language regions as an adjunct to speech and language therapy in post-stroke aphasia: a meta-analysis. Front Hum Neurosci. 2015;9:236. **This paper presents a meta-analysis combining six low frequency rTMS and three cathodal tDCS studies all intended to inhibit the RH in aphasia. The results indicate a positive effect of these treatments on naming.**
51. Monti A, Ferrucci R, Fumagalli M, Mameli F, Cogiamanian F, Ardolino G, et al. Transcranial direct current stimulation (tDCS) and language. J Neurol Neurosurg Psychiatry. 2013;84(8):832–42.
52. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke. 2010;41(6):1229–36.
53. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol. 2009;120(12):2008–39.
54. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. Brain Res Bull. 2007;72(4-6):208–14.
55. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry. 2007;62(11):1208–16.
56. Daffertshofer A, Peper CL, Beek PJ. Stabilization of bimanual coordination due to active interhemispheric inhibition: a dynamical account. Biol Cybern. 2005;92(2):101–9.
57. Takeuchi N, Izumi S. Maladaptive plasticity for motor recovery after stroke: mechanisms and approaches. Neural Plast. 2012;2012:359728.
58. Rehme AK, Eickhoff SB, Wang LE, Fink GR, Grefkes C. Dynamic causal modeling of cortical activity from the acute to the chronic stage after stroke. Neuroimage. 2011;55(3):1147–58.
59. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. Ann Neurol. 2004;55(3):400–9.
60. Duque J, Hummel F, Celnik P, Murase N, Mazzocchio R, Cohen LG. Transcallosal inhibition in chronic subcortical stroke. Neuroimage. 2005;28(4):940–6.
61. Pal PK, Hanajima R, Gunraj CA, Li JY, Wagle-Shukla A, Morgante F, et al. Effect of low-frequency repetitive transcranial magnetic stimulation on interhemispheric inhibition. J Neurophysiol. 2005;94(3):1668–75.
62. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. Restor Neurol Neurosci. 2007;25(2):123–9.
63. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor

cortex improves hand function after stroke. Stroke. 2005;36(12): 2681–6.
64. Fregni F, Boggio PS, Valle AC, Rocha RR, Duarte J, Ferreira MJ, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. Stroke J Cereb Circ. 2006;37(8):2115–22.
65. Martin PI, Naeser MA, Ho M, Treglia E, Kaplan E, Baker EH, et al. Research with transcranial magnetic stimulation in the treatment of aphasia. Curr Neurol Neurosci Rep. 2009;9(6):451–8.
66. Barwood CH, Murdoch BE, Whelan BM, Lloyd D, Riek S, O Sullivan JD, et al. Improved language performance subsequent to low-frequency rTMS in patients with chronic non-fluent aphasia post-stroke. Eur J Neurol. 2011;18(7):935–43.
67. Weiduschat N, Thiel A, Rubi-Fessen I, Hartmann A, Kessler J, Merl P, et al. Effects of repetitive transcranial magnetic stimulation in aphasic stroke: a randomized controlled pilot study. Stroke. 2011;42(2):409–15.
68. Schlaug G, Marchina S, Wan CY. The use of non-invasive brain stimulation techniques to facilitate recovery from post-stroke aphasia. Neuropsychol Rev. 2011;21(3):288–301.
69. Thiel A, Hartmann A, Rubi-Fessen I, Anglade C, Kracht L, Weiduschat N, et al. Effects of noninvasive brain stimulation on language networks and recovery in early poststroke aphasia. Stroke. 2013;44(8):2240–6.
70. Winhuisen L, Thiel A, Schumacher B, Kessler J, Rudolf J, Haupt WF, et al. Role of the contralateral IFG in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. Stroke. 2005;36(8):1759–63.
71. Postman-Caucheteux WA, Birn RM, Pursley RH, Butman JA, Solomon JM, Picchioni D, et al. Single-trial fMRI shows contralesional activity linked to overt naming errors in chronic aphasic patients. J Cogn Neurosci. 2010;22(6):1299–318.
72. Belin P, Van Eeckhout P, Zilbovicius M, Remy P, Francois C, Guillaume S, et al. Recovery from nonfluent aphasia after melodic intonation therapy: a PET study. Neurology. 1996;47(6):1504–11.
73. Cao Y, Vikingstad EM, George KP, Johnson AF, Welch KM. Cortical language activation in stroke patients recovering from aphasia with functional MRI. Stroke. 1999;30(11):2331–40.
74. Allendorfer JB, Kissela BM, Holland SK, Szaflarski JP. Different patterns of language activation in post-stroke aphasia are detected by overt and covert versions of the verb generation fMRI task. Med Sci Monit. 2012;18(3):CR135–CR47.
75. Fernandez B, Cardebat D, Demonet JF, Joseph PA, Mazaux JM, Barat M, et al. Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. Stroke. 2004;35(9):2171–6.
76. Breier JI, Juranek J, Maher LM, Schmadeke S, Men D, Papanicolaou AC. Behavioral and neurophysiologic response to therapy for chronic aphasia. Arch Phys Med Rehabil. 2009;90(12):2026–33.
77. Kurland J, Cortes CR, Wilke M, Sperling AJ, Lott SN, Tagamets MA, et al. Neural mechanisms underlying learning following semantic mediation treatment in a case of phonologic alexia. Brain Imaging Behav. 2008;2(3):147.
78. Barlow T. On a case of double cerebral hemiplegia, with cerebral symmetrical lesions. Br Med J. 1877;2:103–4.
79. Turkeltaub PE, Coslett HB, Thomas AL, Faseyitan O, Benson J, Norise C, et al. The right hemisphere is not unitary in its role in aphasia recovery. Cortex. 2012;48(9):1179–86.
80. Basso A, Gardelli M, Grassi MP, Mariotti M. The role of the right hemisphere in recovery from aphasia. Two case studies. Cortex. 1989;25(4):555–66.
81. Yarnell P, Monroe P, Sobel L. Aphasia outcome in stroke: a clinical neuroradiological correlation. Stroke. 1976;7(5):516–22.
82. Kinsbourne M. The minor cerebral hemisphere as a source of aphasic speech. Arch Neurol. 1971;25(4):302–6.
83. Moore Jr W, Weidner WE. Dichotic word-perception of aphasic and normal subjects. Percept Mot Skills. 1975;40(2):379–86.
84. Moore Jr W, Weidner WE. Bilateral tachistoscopic word perception in aphasic and normal subjects. Percept Mot Skills. 1974;39(2): 1003–11.
85. Johnson JP, Sommers RK, Weidner WE. Dichotic ear preference in aphasia. J Speech Lang Hear Res. 1977;20(1):116–29.
86. Pulvermuller F, Hauk O, Zohsel K, Neininger B, Mohr B. Therapy-related reorganization of language in both hemispheres of patients with chronic aphasia. Neuroimage. 2005;28(2):481–9.
87. Harnish SM, Neils-Strunjas J, Lamy M, Eliassen JC. Use of fMRI in the study of chronic aphasia recovery after therapy: a case study. Top Stroke Rehabil. 2008;15(5):468–83.
88. Crosson B, Moore AB, Gopinath K, White KD, Wierenga CE, Gaiefsky ME, et al. Role of the right and left hemispheres in recovery of function during treatment of intention in aphasia. J Cogn Neurosci. 2005;17(3):392–406.
89. Schlaug G, Marchina S, Norton A. Evidence for plasticity in white-matter tracts of patients with chronic Broca's aphasia undergoing intense intonation-based speech therapy. Ann N Y Acad Sci. 2009;1169:385–94.
90. Vines BW, Norton AC, Schlaug G. Non-invasive brain stimulation enhances the effects of melodic intonation therapy. Front Psychol. 2011;2:230.
91. Torres J, Drebing D, Hamilton R. TMS and tDCS in post-stroke aphasia: Integrating novel treatment approaches with mechanisms of plasticity. Restor Neurol Neurosci. 2013;31(4):501–15.
92. Just AM, Carpenter PA, Keller TA, Eddy WF, Thulborn KR. Brain activation modulated by sentence comprehension. Science. 1996;274:114–6.
93. Fridriksson J, Morrow L. Cortical activation and language task difficulty in aphasia. Aphasiology. 2005;19(3-5):239–50.
94. Gazzaniga MS. Cerebral specialization and interhemispheric communication. Brain. 2000;123(7):1293–326.
95. Heiss WD, Thiel A. A proposed regional hierarchy in recovery of post-stroke aphasia. Brain Lang. 2006;98(1):118–23.
96. Shah-Basak PP, Norise C, Garcia G, Torres J, Faseyitan O, Hamilton RH. Individualized treatment with transcranial direct current stimulation in patients with chronic non-fluent aphasia due to stroke. Front Hum Neurosci. 2015;9:201.
97.• Anglade C, Thiel A, Ansaldo AI. The complementary role of the cerebral hemispheres in recovery from aphasia after stroke: a critical review of literature. Brain Inj. 2014;28(2):138–45. **This article reviews the literature on the differing roles of the two hemispheres in aphasia recovery, concluding that their roles differ based primarily on the severity of the damage to the language system and the time since the stroke.**