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Measuring and inducing brain plasticity in chronic aphasia

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Abstract

Brain plasticity associated with anomia recovery in aphasia is poorly understood. Here, I review four recent studies from my lab that focused on brain modulation associated with long-term anomia outcome, its behavioral treatment, and the use of transcranial brain stimulation to enhance anomia treatment success in individuals with chronic aphasia caused by left hemisphere stroke. In a study that included 15 participants with aphasia who were compared to a group of 10 normal control subjects, we found that improved naming ability was associated with increased left hemisphere activity. A separate study (N=26) revealed similar results in that improved anomia treatment outcome was associated with increased left hemisphere recruitment. Taken together, these two studies suggest that improved naming in chronic aphasia relies on the damaged left hemisphere. Based on these findings, we conducted two studies to appreciate the effect of using low current transcranial electrical stimulation as an adjuvant to behavioral anomia treatment. Both studies yielded positive findings in that anomia treatment outcome was improved when it was coupled with real brain stimulation as compared with a placebo (sham) condition. Overall, these four studies support the notion that the intact cortex in the lesioned left hemisphere supports anomia recovery in aphasia.

Learning outcomes: Readers will (a) be able to appreciate the possible influence of animal research upon the understanding of brain plasticity induced by aphasia treatment, (b) understand where functional changes associated with anomia treatment occur in the brain, (c) understand the basic principles of transcranial direct current stimulation, and (d) understand how brain stimulation coupled with aphasia treatment may potentially improve treatment outcome.

1. Introduction

Improved understanding of plasticity in the adult brain suggests that the human cortex is quite amenable to both functional and structural change (e.g., Butefisch, 2004; Heiss & Thiel, 2006; Meinzer et al., 2008; Nudo, 2003, 2007; Pascual-Leone, Amedi, Fregni, & Merabet, 2005; Saur et al., 2006; Thompson & den Ouden, 2008). Currently, there is no evidence suggesting that plasticity is absent or even reduced following brain damage. In fact, neural sprouting has been shown to be enhanced in the brain regions surrounding the frank cortical lesion (Nudo, 1999; Stroemer, Kent, & Hulsebosch, 1995). For the most part, aphasia treatment research has taken only limited advantage of the recently improved understanding of brain plasticity. Although several reasons may underlie this development, or lack thereof, it is undoubtedly important that much of the recent advances in

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understanding brain plasticity have been revealed in animal models of motor impairment. For example, utilizing a rat model, Jones and colleagues (as reviewed in the current issue) have shown how early training of the spared forelimb following induced motor cortex damage negatively affects later function of the affected forelimb. Related to language impairment and its rehabilitation, it is not clear how these findings by Jones' group can be applied. More generally, it is uncertain how improved understanding of brain plasticity in animal models of motor impairment may relate to aphasia. Nevertheless, it is crucial to emphasize that principles of brain plasticity in animal models probably relate to human recovery of communication abilities. At the very least, improved understanding between training in brain lesioned animals and outcome may fuel research questions that can be applied to recovery from aphasia. For example, is it possible that early treatment that targets relatively spared communication abilities may negatively affect later recovery of less spared language functions? Although the application of animal models to the understanding of brain plasticity associated with aphasia recovery is not so straightforward, neuroimaging studies in humans have so far provided some insight into brain plasticity associated with aphasia treatment (for a brief review see Crinion & Leff, 2007; Fridriksson, 2010). As importantly, studies have revealed, albeit indirectly, that external brain stimulation can enhance brain plasticity associated with aphasia treatment. In the following paragraphs, I will review recent studies conducted in my lab that have focused on functional brain changes associated with aphasia treatment as well as the use of transcranial low current brain stimulation to enhance aphasia treatment outcome. My aim is to demonstrate how studies of treatment-related brain plasticity (as measured with functional magnetic resonance imaging: fMRI) in persons with aphasia can motivate research that seeks to combine behavioral stimulation with transcranial brain stimulation to enhance treatment outcome and, presumably, brain plasticity.

2. Measuring brain plasticity in aphasia

Several studies have related language impairment to functional brain activity in persons with chronic stroke (Fridriksson, 2010; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Postman-Caucheteux et al., 2010; Rochon et al., 2010; van Oers et al., 2010). In one such recent study, our group examined if functional brain activation predicts the severity of anomia, an impairment in object naming that is commonly seen in aphasia (Fridriksson et al., 2010). This study involved 15 stroke survivors with chronic aphasia who underwent fMRI scanning while completing an overt picture naming task. Naming attempts were recorded with a non-ferrous microphone and stored electronically for later scoring by a certified speech-language pathologist. Then, brain activation associated with correct naming was analyzed for each participant and contrasted with naming related activation among a group of 10 control participants. To appreciate whether particularly high or low cortical activation, as compared to the normal controls, was related to naming ability, each participants' activation map was utilized as a predictor of correct naming in a group analysis. Overall, this analysis revealed that greater activation of both anterior and posterior regions in the left hemisphere was associated with successful picture naming. Specifically, participants who were able to name more pictures during the fMRI scanning had increased left hemisphere activation. Based on this finding, we suggested that improved long-term outcome of anomia among persons with aphasia is mediated via plastic changes (i.e., functional activation changes) in the left hemisphere.

In a related study, we examined functional brain changes associated with behavioral treatment of anomia in 26 persons with chronic aphasia caused by stroke (Fridriksson, 2010). The specific purpose of this study was to understand where functional brain changes that support treatment-assisted anomia recovery occur in the brain. As a secondary goal, this research also associated structural brain damage with treatment outcome to appreciate

whether damage to specific brain regions has a particularly negative effect on anomia treatment. Each participant underwent three hours of anomia treatment per day, five days a week, for two weeks. The anomia treatment protocol consisted of a cueing hierarchy where verbal cues of increasing cueing strength were administered to elicit correct naming of pictures depicting common objects. Participants underwent two fMRI sessions before and two fMRI sessions after the treatment period. As in the study discussed above, participants attempted to name pictures of common objects during the fMRI scanning. To understand treatment-related changes in functional activation, naming-related activity was compared between the first two and last two fMRI sessions for all participants. Then, the change in functional activation was utilized as a predictor of naming improvement (qualified as increase in correct naming). In short, the results revealed a strong association between anomia treatment success and increased cortical activation in the left hemisphere. That is, participants who fared well in treatment also experienced a significant increase in left hemisphere activation suggesting that recovery from anomia in chronic stroke is mediated by the left hemisphere. In addition to examining treatment-related changes in cortical activation, this study used voxel-wise lesion symptom mapping (VLSM) to examine the location and extent of structural brain damage as predictors of anomia treatment outcome. The results revealed that damage to the left posterior middle and inferior temporal lobes is especially detrimental for anomia treatment success. With regard to the number of participants with aphasia and extent of aphasia treatment, this group study is the largest of its kind in which changes in functional brain activation have been related to treatment success, providing strong evidence that treatment-assisted recovery from anomia among patients with chronic left hemisphere stroke is related to increased left hemisphere activation. Moreover, it demonstrates how damage to particular brain regions can not only cause the initial behavioral impairment but also affect the success of treatment targeting the same specific impairment.

3. Inducing brain plasticity in aphasia

Taken together, the two studies reviewed above suggest that long-term anomia status as well as its treatment rely on modulation of the left hemisphere. Based on these findings, we hypothesized that transcranial modulation of the left hemisphere in participants with aphasia could improve anomia treatment outcome (Baker, Rorden, & Fridriksson, 2010). Specifically, in a dissertation experiment (student: Julie Baker), the effect of anodal transcranial direct current stimulation (A-tDCS) was compared to the effect of sham tDCS (S-tDCS) as an adjuvant to anomia treatment in 10 persons with aphasia. tDCS utilizes a low current electrical stimulation (1–2 mA) that is induced between two saline soaked electrodes (an anode electrode that has a positive charge and a cathode electrode with a negative charge) placed on the scalp. A-tDCS is thought to have an excitatory effect on behavior while cathodal tDCS (C-tDCS) is thought to induce inhibition (Nitsche et al., 2005). This initial study utilized a crossover design in which 10 patients with chronic stroke-induced aphasia received five days of A-tDCS (1 mA; 20 min) and five days of S-tDCS (20 min, order randomized) while performing the computerized anomia treatment described in Fridriksson et al. (2009). Positioning of the anode electrode on the scalp was guided using *a priori* collected fMRI results on participant-by-participant basis during an overt naming task to ensure the active electrode was placed over a structurally intact cortex that showed naming-related functional activation. That is, the cortical area that showed the greatest naming related activation in the left frontal lobe was targeted with A-tDCS whereas the cathode electrode was placed on the right shoulder. This was a double-blinded study in that the order of treatment (A-tDCS vs. S-tDCS) was not revealed to the participants or the clinicians who scored the pre- and post-treatment naming tests (assessment sessions were audio-taped and scored offline). The results revealed significantly improved naming accuracy of treated items following A-tDCS as compared to S-tDCS, $F(1, 9) = 5.72, p <$

0.04. Crucially, this treatment effect persisted for at least one-week post-treatment. Moreover, a generalization of the treatment effect was demonstrated as A-tDCS also improved naming of untrained items beyond that seen with S-tDCS. Although this study did not definitively prove that using A-tDCS as an adjunctive to aphasia treatment improves outcome, it demonstrated that further study in the area is warranted.

In a follow-up study to Baker et al. (2010), we examined the effect of A-tDCS on reaction time (RT) during naming by persons with mild chronic aphasia caused by stroke (Fridriksson, Richardson, Baker, & Rorden, in press). In this study, we made the following methodological improvements:

1. Before, our study included a fairly heterogeneous sample of participants with different aphasia types and severity as well as lesion extent and location. The follow-up study employed eight participants with relatively mild fluent aphasia who had posterior brain damage.
2. In our previous study, we observed that those participants whose anode electrode was placed closest to the peri-lesional rim tended to improve the most with A-tDCS. Consistent with these findings, the follow-up study included fMRI and structural MRI to achieve anode electrode placement in peri-lesional regions.
3. As all of the participants included here suffered from relatively mild aphasia, the outcome measure was determined *a priori* as change in reaction time (RT).
4. This latter study also included blinding of the clinicians who administered the setup of the tDCS equipment and computerized treatment.

As before, we used a cross-over design where half of the participants first received a week (total of five treatment sessions) of A-tDCS administration along with a computerized treatment task that involved matching of pictures depicting low-frequency nouns with pre-recorded spoken words. Three weeks later, these participants were administered treatment for a week that included S-tDCS and the computerized treatment task. The other half of the participants received the opposite treatment order (S-tDCS first; A-tDCS three weeks later). The results revealed a clear advantage of coupling A-tDCS with behavioral language treatment to reduce RT during naming of trained items immediately post-treatment, $Z = 1.96$, $p = .025$, as well as at three-week follow up testing, $Z = 2.52$, $p = .006$ (Fig. 1). That is, participants were faster at naming after the completion of one week of computer training that was coupled with A-tDCS compared to the S-tDCS condition. As importantly, this effect was maintained at three weeks following the completion of each of the two treatment phases (A-tDCS vs. S-tDCS). So far, one other group has demonstrated positive effects of A-tDCS on treatment outcome in aphasia. Utilizing a crossover design in three persons with aphasia, Fiori et al (in press) compared the effects of A-tDCS to S-tDCS administered during an anomia treatment and found superior naming outcome following the A-tDCS phase. In fact, their findings are very much in line with our previous two studies with regard to design and overall results. Along with their results, we believe that our findings provide evidence that A-tDCS significantly enhances the effectiveness of anomia treatment in aphasia.

Several studies have examined the physiological and behavioral effects of A-tDCS. For example, utilizing a mouse model, Fritsch et al. (2010) examined the effect of low current electrical stimulation on secretion of neurotransmitters in M1 neurons. In a series of seven experiments, this research revealed strong evidence suggesting anodal low current electrical stimulation greatly boosts secretion of brain-derived neurotrophic factor (BDNF), a protein associated with brain plasticity (note: this study found no effect of cathodal stimulation upon neurotransmitter activity). Furthermore, numerous studies in normal human subjects have

demonstrated A-tDCS enhances motor learning, recall, and memory consolidation (e.g., Antal et al., 2004; de Vries et al., 2010; Fregni et al., 2005; Nitsche et al., 2003; Reis et al., 2009; Tecchio et al., 2010)

4. tDCS related considerations

Although tDCS may seem a promising method to improve aphasia treatment outcome, much work is needed to better examine factors such as optimal dosage, the exact nature of tDCS-induced brain plasticity, and optimal electrode positioning. With regard to the last factor, electrode positioning, most previous studies that have utilized tDCS in humans assumed that the greatest stimulation intensity occurred directly under the electrodes. However, Bikson and colleagues have demonstrated that this is not necessarily the case (Datta et al., 2009; Datta, Elwassif, Battaglia, & Bikson, 2008). In relation to brain size, the size of the electrodes traditionally used in tDCS is fairly large, typically ranging in size from 5 cm² to 7 cm². Therefore, the spatial extent of stimulation using such large electrodes may span, for example, the whole temporal lobe. With regard to rehabilitation, this may not necessarily be a disadvantage as A-tDCS does not polarize neurons but, rather, increases the concentration of BDNF (Fritsch et al., 2010) and, perhaps, decreases GABA (gamma aminobutyric acid: an inhibitory neurotransmitter) under the anode electrode (Stagg et al., 2009). Therefore, greater dispersion of the current concentration over a larger cortical area could potentially improve outcome compared to more focal stimulation. Nevertheless, it is crucial that electrode placement achieves stimulation of the targeted brain region (for an extensive discussion of this topic, see Datta et al., 2009).

If tDCS is to be used to target peri-lesional areas in stroke to improve behavioral treatment outcome, it is imperative that the electrode placement take into account the location and extent of the brain lesion. When electrical current is induced between two electrodes, the current will pass across a path of least resistance. Given that the lesion is filled with cerebral spinal fluid (CSF), it may disperse the current and prevent maximal electrical stimulation from occurring in the targeted peri-lesional cortex. In a retrospective case study, we modeled the passage of the electric current in one participant from Baker et al. (2010) who responded more favorably to A-tDCS compared to S-tDCS (Datta, Baker, Bikson, & Fridriksson, in press). To model the current flow, a finite element model (FEM) was built based on density values assigned to different tissue types in the human head (e.g., scalp, bone, CSF, gray matter, white matter). The FEM model is constructed consistent with a whole head T1-weighted MRI scan where the different tissue types are segmented. Currently, much of the tissue segmentation relies on manual parcellation of different tissues to adjudicate between, for example, CSF and bone. To be brief, the FEM model takes into account the electrode placement on the scalp and how different tissue shapes and densities that lie between the electrodes shape the direction of the current. Our case study revealed that much of the current concentration under the anodal electrode occurred in the peri-lesional rim in the left hemisphere. However, it is also worth noting that some of the current appeared to be “funneled” through the lesion, causing it to concentrate in the middle of the lesion rather than targeting the peri-lesional cortex. In addition to modeling the electrode placement used in Baker et al. (2010), we also examined current concentration using other electrode constellations. For example, the cathode electrode was “placed” on the contralateral orbitofrontal scalp (an electrode setup frequently used in tDCS studies in humans), resulting in somewhat less peri-lesional current concentration compared to when the cathode electrode was placed on the contralateral shoulder. Although our study only included one subject, it demonstrates that future studies that use tDCS in stroke may need to model the electrical current flow to optimize electrode placement so as not to disperse the current in the CSF-filled lesion but, rather, to target cortical areas thought to be recruited for recovery.

5. Focal brain stimulation

Rather than rely on large sponge electrodes for tDCS application, Datta et al. (2009) have demonstrated how the use of an electrode array with relatively small ring electrodes (4mm radius) can achieve relatively focal stimulation of the cortex. This is accomplished by placing a single electrode on the scalp that is surrounded by an array of four electrodes with the opposite polarity. Using such a setup, it is potentially possible to specifically target regions such as the posterior middle temporal lobe or, perhaps, the posterior portion of Broca's area, while having minimal effect on the surrounding cortex.

For the purpose of the present discussion, it should be possible to use the electrode array setup to focally target the peri-lesional rim in stroke – an area that we have suggested to be recruited for aphasia recovery (Fridriksson, 2010). Moreover, it is possible that the electrode arrays could be designed on a patient-by-patient basis to attain maximum electrical stimulation in areas that may contribute to recovery. For example, Fig. 2 illustrates electrical current concentration using a 4×2 electrode array in the participant discussed above (Datta et al., in press). Based on the FEM model, using this electrode pattern allows for specific stimulation of the cortical region immediately posterior to the lesion location. At this time, we cannot suggest that this electrode placement would have yielded superior results compared to the use of more diffuse stimulation achieved using the large sponge electrodes. However, using a focal array setup, it should be possible to test specific hypotheses regarding the contribution of particular areas in stroke recovery by comparing different electrode constellations that have been modeled as showing maximal electrical current stimulation in different cortical areas.

6. Conclusion

Our studies of functional brain changes associated with improved naming in aphasia suggest that, in general, the left hemisphere is recruited for better outcome. Importantly, this does not necessarily mean that the right hemisphere does not contribute to anomia recovery in some patients. Rather, those individuals that benefit the most from treatment primarily recruit the left hemisphere to support naming improvement. Our studies also suggest that A-tDCS targeting the left hemisphere can improve anomia treatment outcome. In a series of elegant studies, Naeser and colleagues have found that low frequency transcranial magnetic stimulation (TMS) over the right hemisphere homologue of Broca's area may decrease activity in this region and, as a result, improve naming by persons with nonfluent aphasia (Naeser et al., 2010; Martin et al., 2009; Naeser, Martin, Nicholas, Baker, Seekins, Helm-Estabrooks et al., 2005; Naeser, Martin, Nicholas, Baker, Seekins, Kobayashi et al., 2005). It is possible that the use of cathodal tDCS (C-tDCS), a method that has been suggested to decrease cortical excitability, to target the right hemisphere homologue of Broca's treatment during anomia treatment can yield similar effects as that demonstrated by Neaser's group. Perhaps future studies can examine the combined effects of targeting maladaptive brain activation with C-tDCS while using A-tDCS to increase activity in cortical regions whose increased activation is thought to improve treatment outcome. Currently, no studies of this nature have been presented.

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Appendix A. Continuing education

1. Long-term recovery from anomia in chronic aphasia primarily relies brain plasticity in the:
 - a. The bilateral frontal lobes
 - b. The left hemisphere

- c. The right hemisphere
 - d. The right temporal lobe
- 2. Improved anomia treatment outcome using a verbal cueing hierarchy primarily relies on recruitment of the:
 - a. The bilateral frontal lobes
 - b. The left hemisphere
 - c. The right hemisphere
 - d. The right temporal lobe
- 3. Anodal tDCS:
 - a. Increases localized BDNF concentration in the cortex (correct answer)
 - b. Decreases localized BDNF concentration in the cortex
 - c. Decreases cortical excitability
 - d. Enhances learning
- 4. Focal tDCS stimulation:
 - a. Yields diffuse stimulation of the peri-lesional cortex
 - b. Has been used extensively to study its effect on aphasia recovery as well as on learning in normal subjects
 - c. Is accomplished by using two large sponge electrodes
 - d. Can potentially be used to test specific hypotheses regarding the location of treatment related brain plasticity
- 5. Low frequency TMS targeting the right hemisphere homologue of Broca's area:
 - a. Decreases cortical excitability in Broca's area
 - b. Has been shown to improve naming in non-fluent aphasia
 - c. Has been shown to improve naming in fluent aphasia
 - d. None of the above

Answer key: 1, b; 2, b; 3, a; 4, d; 5, b

Fig. 1.

A box-plot showing treatment related change in RT associated with A-tDCS (light gray) and S-tDCS (dark gray). The error bars show the data range, the median is shown as the dark line in the middle of each box, and the inter-quartile range is represented as the top to bottom of each box. Printed by permission from *Stroke*.

Fig. 2.

A 4×2 electrode array setup: (A) The electrode array shown on the scalp of the subject with four cathodal electrodes (cyan) around two anode electrodes (red). (B) The same electrode array shown in relation to the underlying cortex. Notice the cortical lesion lying anterior to the anode electrodes. (C) The FEM model showing the greatest AC concentration (in red) directly under the anode electrodes on the posterior peri-lesional cortex. (D) An enhanced view of the peri-lesional regions seen in panel C showing a more detailed representation of the current concentration in relation to the cortical lesion.