Brain Stimulation 8 (2015) 305–309

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: www.brainstimjrnl.com

Letters to the Editor

Transcranial Direct Current Stimulation for Pure Alexia: Effects on Brain and Behavior

Dear Editor,

In this case report, we investigate whether transcranial direct current stimulation (tDCS) coupled with MOR (multiple oral re-reading) therapy can improve reading in a person with mild pure alexia (PA) due to chronic brain injury. We also investigate neural changes using fMRI to further determine the potential of this combination of therapies. Practice-related improvements in text reading speed have been found after MOR for alexia [1] and studies of rehabilitation in aphasia have found promising results with the addition of tDCS to naming therapy [2]. However, tDCS has not been studied in alexia to date.

PA is associated with lesions to word-sensitive areas of left ventral occipitotemporal cortex [3] or disconnection of this tissue from visual input [4], resulting in impaired whole word visual access with relatively preserved spelling. Patients employ a letter-by-letter reading strategy wherein reading times correlate with word length [5]. Text reading, if possible at all, is therefore slow and laborious.

Methods

Case

NHL, a 70-year-old, right-handed, retired executive, suffered a coup contrecoup injury when he was hit by a car 8 years before the study (Fig. 1A). His chief complaint is reading difficulty. He has a right upper quadrantanopia, and mild anomia (Boston Naming Test: 47/60), but scored 90–100% on all other cognitive tests, including reading, writing, spelling, memory, and visuospatial tests (Supplemental Table). His oral reading is accurate but noticeably slow. On single words, he showed a length effect in reaction time, prompting the diagnosis of mild PA.

Treatment

NHL practiced oral re-reading of 4 passages, 1 h per day during 5 consecutive days of tDCS. Ten days later, he practiced reading 4 matched passages for 5 consecutive days while receiving sham tDCS. He was blind to treatment condition. tDCS was applied at 2 mA for the first 20 min of each treatment session. During sham, the current was ramped up and down over 30 s at the beginning and end, to mimic tDCS sensations. For real and sham tDCS, two HD-tDCS anodes were placed at T7 and TP7 and two cathodes at T8 and TP8. Finite element electrical field modeling [6] using NHL's T1-weighted MRI demonstrated an expected area of greatest neuronal enhancement in the left perilesional occipitotemporal cortex (Fig. 1C).

Passage reading speed was measured at the beginning of each treatment session. NHL also read a list of 90 single words of 3–9 letters in length, matched for frequency, before and after real tDCS. Pain was rated after real and sham tDCS using the Wong–Baker scale. Unfortunately, NHL became unavailable for personal reasons after sham tDCS, so some follow-up testing and imaging could not be obtained after the course of sham tDCS. However, the effect of tDCS vs. sham could still be assessed by treatment paragraph reading times.

Imaging

FMRI data were obtained before and after 5 days of tDCS. The task was silent reading of 3–8 letter words with a button-press to indicate that he had finished reading. Blocks of words alternated with control blocks in which strings of plus signs with one minus sign were presented (matched for length with the words). NHL pressed the button when he found the minus sign (1 trial per block included no minus sign). Stimuli were presented for 3000 ms with an inter-stimulus interval of 1000 ms. Three runs of BOLD fMRI data were acquired on a 3T scanner pre- and post-tDCS and images were preprocessed for analysis using SPM8. Functional connectivity during the reading task was assessed from seed regions using a $3 \times 3 \times 3$ voxel cubic search-light [7].

The Georgetown University IRB approved this study and NHL gave written consent.

Results

There were no differences between NHL's pain ratings for tDCS vs. sham. Reading times (normalized as a percentage of pre-tDCS/sham reading times) were shorter during the week of tDCS treatment compared to sham (main effect of tDCS $F(1,6) = 10.74$, $P = .017$). Reading times improved earlier in the 5-day course of treatment with tDCS, reaching a significant difference after day 3 ($T = 5.21$, Bonferroni corrected $P = .03$), but total improvement was similar for both conditions after the final day of treatment (Supplemental Figure S1). NHL's length effect decreased after tDCS (Length $\times$ Time $F(2,172) = 4.942$, $P = .008$).

Figure 1B shows overall fMRI reading-related activity. Figure 1D shows that, post-tDCS, reading-related activity decreased in right angular gyrus, bilateral dorsal premotor, and middle frontal gyri (right more than left), and increased in right primary visual cortex and perilesional left ventral occipitotemporal cortex. Functional connectivity to this area increased after tDCS in left frontal areas, and decreased in right occipitotemporal and parietal areas (Fig. 1E). Although Broca's area was highly engaged by reading, its level of activity did not change after tDCS. However, its network properties did, with increased functional connectivity to left

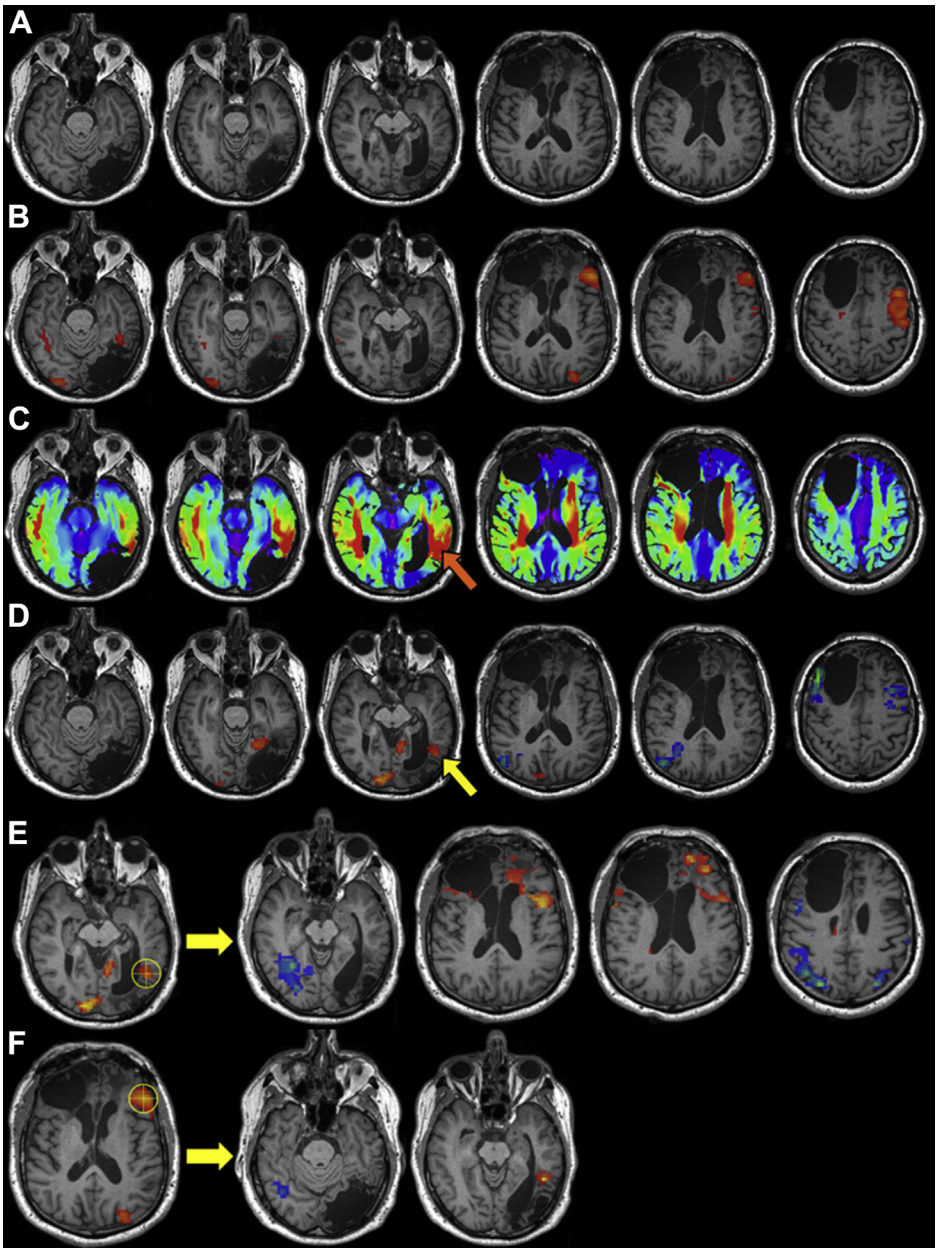

Figure 1. Imaging results. (A) High resolution T1-weighted imaging demonstrates coup contrecoup injury; (B) Overall reading-related brain activity for the word vs. control contrast including both pre- and post-tDCS scans (voxelwise $P < .00001$, cluster-level family-wise error correction at $P < .05$). (C) Finite element model of the expected electrical field magnitude induced by tDCS. Red indicates areas of high field intensity at which the effect of tDCS is expected to be greatest (orange arrow). Neuronal excitation is expected in LH structures and inhibition in RH structures due to the left-to-right direction of the current flow (not shown); (D) Changes in reading-related activity after tDCS treatment (voxelwise $P < .005$, cluster-level family-wise error correction at $P < .05$). Red-yellow = increased activity after treatment. Blue-green = decreased activity after treatment. Yellow arrow shows area of increased activity in left perilesional occipitotemporal cortex that was exposed to maximal electrical field. Changes in functional connectivity from pre- to post-tDCS are shown with seed regions in (E) perilesional occipitotemporal cortex and (F) Broca's area defined based on the overall word vs. control activity (pre- and post-tDCS). Red-yellow = increased connectivity, blue-green = decreased connectivity after tDCS (voxelwise $P < .001$, clusters > 20 voxels). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perilesional occipitotemporal cortex and decreased connectivity to right occipitotemporal cortex (Fig. 1F).

Discussion

This case, the first use of tDCS for alexia to our knowledge, suggests that tDCS may accelerate training effects in alexia therapy such that fewer sessions are needed to train the same amount of material. The reduction of the length effect and changes in fMRI activity may indicate that tDCS has a general effect on the reading network aside from the effects on trained material.

Recovery of specific areas of the left hemisphere is crucial to reading recovery [8], and here, tDCS designed to left-lateralize posterior temporal activity was associated with enhanced left ventral occipitotemporal activity and improved performance. Changes in functional connectivity suggest that the treatment also enhanced communication between the left ventral occipitotemporal cortex and Broca's area, while disengaging right occipitotemporal regions during reading.

Although fMRI data could not be obtained after sham stimulation, the leftward shift in activity for untreated words after only 5 days of behavioral treatment with tDCS is compelling. A previous

fMRI study of behavioral reading treatment [9] found increased right hemisphere recruitment after short-term treatment, with shifts to left hemisphere perilesional areas occurring only after an additional 8 weeks of reinforcing the learned material. Similarly, in a study using audio-visual reading training of single words for 9 people with PA, 6 weeks of training resulted in improved reading speed and reduction of the length effect, similar to the current study. Also similar were the MEG results, showing increased connection strength in the left hemisphere and reduced connection strengths in the right hemisphere [10]. Here, we found functional connectivity to perilesional ventral occipitotemporal cortex increased from left frontal areas and decreased from right occipitotemporal and parietal areas after only 5 days of treatment using tDCS.

This case demonstrates that tDCS may enhance behavioral treatment for alexia, allowing successful results in fewer sessions, and accelerating changes in brain activity and connectivity associated with improvement. Though behavioral treatment certainly has the power to reorganize the brain, tDCS might offer a way to accelerate that reorganization and enhance recovery of reading after brain injury. Based on the positive, albeit preliminary findings in this case, demonstrating both accelerated learning and rapid changes in brain activity and connectivity associated with good treatment outcome, we believe that further studies are warranted to examine the use of tDCS for alexia.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.10.019.

This study was supported by The Doris Duke Charitable Foundation (Grant 2012062), NIH/NCATS via the Georgetown–Howard Universities Center for Clinical and Translational Sciences (KL2TR000102), and The Vernon Family Fund.

E.H. Lacey*
Department of Neurology, Georgetown University, 4000 Reservoir Road, NW Building D, 165, Washington, DC 20057, USA

MedStar National Rehabilitation Hospital, USA

X. Jiang
Department of Neuroscience, Georgetown University, USA

R.B. Friedman
S.F. Snider
Department of Neurology, Georgetown University, USA

L.C. Parra
Y. Huang
Department of Biomedical Engineering, City College of New York, USA

P.E. Turkeltaub
Department of Neurology, Georgetown University, USA

MedStar National Rehabilitation Hospital, USA

* Corresponding author. Department of Neurology, Georgetown University, 4000 Reservoir Road NW Building D, 165, Washington, DC 20057, USA. Tel.: +1 202 877 1124; fax: +1 202 726 7521.
E-mail address: EHL4@georgetown.edu

Received 9 October 2014
Available online 12 December 2014
http://dx.doi.org/10.1016/j.brs.2014.10.019

References

[1] Lacey EH, Lott SN, Snider SF, Sperling A, Friedman RB. Multiple oral re-reading treatment for alexia: the parts may be greater than the whole. Neuropsychol Rehabil 2010;20:601–23.
[2] 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 2011;42(3):819–21.
[3] Turkeltaub PE, Goldberg EM, Postman-Caucheteux WA, et al. Alexia due to ischemic stroke of the visual word form area. Neurocase 2014;20:230–5.
[4] Damasio AR, Damasio H. The anatomic basis of pure alexia. Neurology 1983; 33:1573–83.
[5] Coslett HB. Acquired dyslexia. Semin Neurol 2000;20:419–26.
[6] 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;2:201–7.
[7] Dosenbach NU, Nardos B, Cohen AL, et al. Prediction of individual brain maturity using fMRI. Science 2010;329:1358–61.
[8] Philipose LE, Gottesman RF, Newhart M, et al. Neural regions essential for reading and spelling of words and pseudowords. Ann Neurol 2007;62: 481–92.
[9] Kurland J, Cortes CR, Wilke M, et al. Neural Mechanisms underlying learning following semantic mediation treatment in a case of phonologic alexia. Brain Imaging Behav 2008;2:147–72.
[10] Woodhead ZVJ, Penny W, Barnes GR, et al. Reading therapy strengthens top–down connectivity in patients with pure alexia. Brain 2013;136: 2579–91.

Transcranial Direct Current Stimulation to Enhance Cognitive Remediation in Schizophrenia

Dear Editors,

The global cognitive deficit in schizophrenia is identifiable by the first episode of psychosis, endures over time, and is large, averaging between 1 and 2 standard deviations below that of healthy control subjects [2]. Patients' neurocognitive functioning has further been identified to be strongly related to functional capacities, including psychosocial functioning, independent living and vocational outcomes. Pharmacological interventions so far have demonstrated limited efficacy to enhance cognitive processes or circumvent cognitive impairments [6]. Over the last three decades research attention has therefore largely focused on non-pharmacological interventions, the most studied being cognitive remediation.

Cognitive remediation interventions lead to improvements in cognition and day-to-day functioning in patients, however, overall effect sizes have been small-to-moderate [10]. On the basis of these modest findings, adjunctive therapies have been proposed to further 'boost' treatment effects. One hypothesized adjunctive strategy, which we showed in a proof of concept study to enhance effects of cognitive training in healthy adults [7]; is the combination of non-invasive brain stimulation with cognitive training (CT).

Here, we report two cases where transcranial direct current stimulation (tDCS) was used in combination with CT specifically developed to target dysfunctional pre-attentive auditory processing in schizophrenia. Following 40–50 h of training [3,4]; or when augmented with weekly meta-cognitive bridging groups [5] this computerized CT program has been associated with moderate-to-large sized improvements in auditory working memory and verbal learning skills. However, the intensity and duration of these