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 quadrantopia, 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 notice-ably 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 × 3 × 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 × 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
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
Supplementary data

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

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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

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

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Transcranial Direct Current Stimulation to Enhance Cognitive Remediation in Schizophrenia

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