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BRAIN STIMULATION

Left lateralizing transcranial direct current stimulation improves reading efficiency

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Background
Poor reading efficiency is the most persistent problem for adults with developmental dyslexia. Previous research has demonstrated a relationship between left posterior temporal cortex (pTC) function and reading ability, regardless of dyslexia status.

Objective/Hypothesis
In this study, we tested whether enhancing left lateralization of pTC using transcranial direct current stimulation (tDCS) improves reading efficiency in adults without dyslexia.

Method
Twenty-five right-handed adults with no history of learning disorder participated. Real and sham "Left lateralizing" tDCS were applied to the pTC in separate sessions. Standardized word and nonword reading tests were given immediately after stimulation.

Results
Modeling of the induced electrical field confirmed that tDCS was likely to increase left pTC excitability and reduce right pTC excitability as intended. Relative to sham, real tDCS induced improvements in word reading efficiency in below average readers.

Conclusions

Enhancing left lateralization of the pTC using tDCS improves word reading efficiency in below-average readers. This demonstrates that left lateralization of the pTC plays a role in reading ability, and provides stimulation parameters that could be used for a trial of tDCS in adults with developmental dyslexia. Such short-term gains could amplify the effect of appropriate reading interventions when performed in conjunction with them.

Keywords   dyslexia; alexia; language; reading fluency

Developmental dyslexia affects 5-17% of children.[1] Intense instructional programs are effective in improving reading accuracy in children with dyslexia, but in many cases reading efficiency (i.e., speed of accurate reading) lags behind, remaining impaired into adulthood.[2] New methods for improving reading efficiency could be useful to augment traditional remediation strategies in adults.

Left posterior temporal cortex (pTC), both inferior and superior, appears to be critical for reading competence. Non-dyslexic children show increasing left lateralization of inferior pTC activity as they learn to read, either through increases in left sided activity or decreases in the right.[3,4] Longitudinal increases in left inferior occipitotemporal sensitivity to text as measured by fMRI in non-dyslexic children correlate with increasing word reading efficiency.[5] Lesions to pTC cause acquired alexias,[6] and functional neuroimaging demonstrates reduced left pTC activity in individuals with developmental dyslexia.[7-9] Left lateralization of superior pTC activity increases in dyslexic children after successful reading remediation,[10] and a neuroimaging case report of a hyperlexic boy demonstrated that he activated the left superior pTC to a greater extent than controls during reading.[11] Based on these findings, we hypothesized that enhancing left lateralization of pTC function would improve reading efficiency, especially in slower readers.

Transcranial direct current stimulation (tDCS) provides a safe noninvasive method of inducing local changes in cortical excitability by applying low levels of direct electrical current through the scalp.[12] This subtle modulation of network properties has shown promising beneficial effects on naming in aphasic patients[13,14] and novel word learning in healthy controls.[15] TDCS is an ideal method of external neuromodulation for dyslexia because it is safe, portable, silent, and well tolerated, allowing it to be paired with traditional behavioral interventions to improve reading. Furthermore, electrical field modeling suggests that tDCS may affect a large area of the cortex,[16] which is disadvantageous for fine dissection of brain-behavior relationships, but has the potential to be clinically advantageous in dyslexia where hypoactivation occurs in both superior and inferior left pTC.[9]

In this study, we investigated the relationship between left lateralization of pTC function and reading efficiency in adults without a prior diagnosis of dyslexia with the use of tDCS. We used an electrode montage designed to enhance left lateralization of the pTC, based on electrical field modeling, and measured both reading efficiency and untimed reading accuracy after real or sham tDCS in a within-subjects design. Enhancement of left lateralization in the pTC might improve reading efficiency by easing access to lexical, semantic, or phonologic representations, but should not impact untimed reading accuracy, which would require explicit reading instruction for improvement. The effect should be greatest in individuals with poor reading efficiency, as they are expected to underengage the left pTC at baseline.

Materials and methods

Participants

Twenty-five right-handed native English-speakers (15 female, ages 20-50, mean = 26.7) participated. Subjects had at least 12 years of education, no history of neurologic disorder, psychiatric disorder, significant head trauma, hearing loss, or personal or family history of learning disorder (including dyslexia). Subjects denied the presence of metal in the head, implanted electrical devices, or history of seizure. The University of Pennsylvania Medical Center Institutional Review Board approved all procedures. Written informed consent was obtained.

Procedures

Subjects participated in two sessions on different days in which real or sham tDCS was administered using a Magstim Eldith device via two 5 × 5-cm saline-soaked pads. In both sessions, the anode was centered over the left pTC (midway between T7 and TP7) and the cathode was centered over the right pTC (between T8 and TP8). Because the anode facilitates neuronal activity and the cathode inhibits it, this montage is expected to drive processing to the left hemisphere, enhancing left lateralization. During real tDCS sessions, 1.5 mA of current was applied for 20 minutes, with 10 seconds ramp up and down. During sham sessions, current was ramped up to provide initial sensations (e.g., tingling) associated with tDCS and then extinguished over 10 seconds. These parameters are within safety limits established in prior studies on humans and animals.[17-20]

Induced electrical fields were modeled in a single individual to assess the likely area of effect (Figure 1). The goal
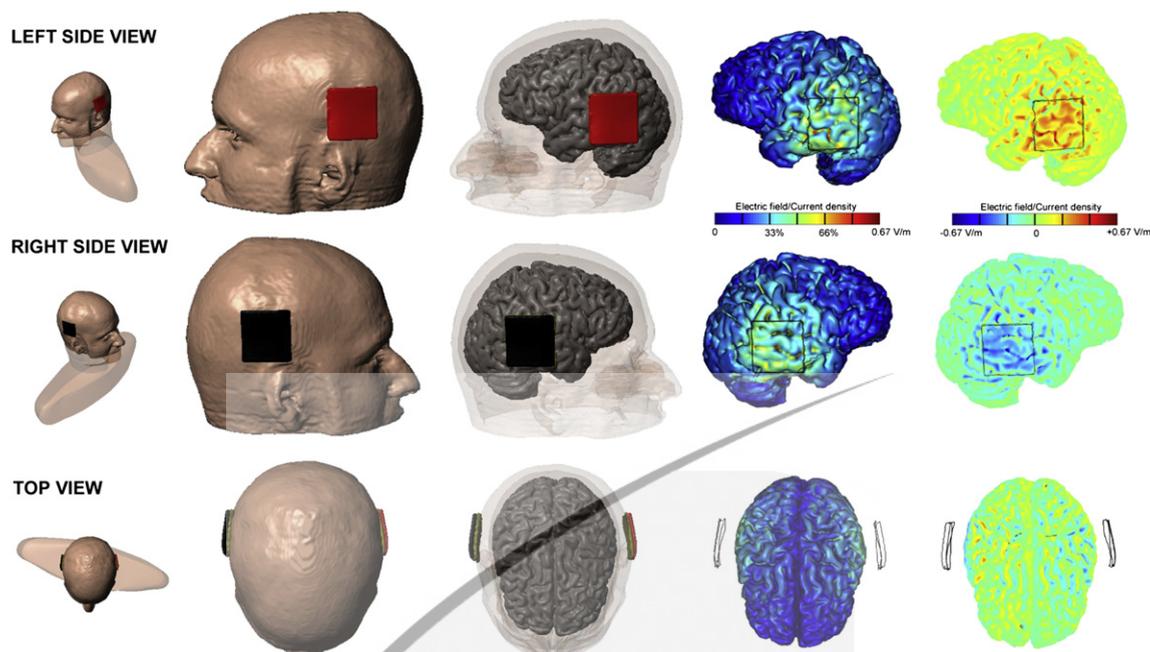
Figure 1 Modeling of electrical fields induced by tDCS. Placement of the electrode pads are shown in the first three columns. The anode is shown in red, and the cathode in black. The fourth column shows the magnitude of the induced electrical field, which is maximal directly under the electrodes. The rightmost column shows the directional fields normal to the cortical surface, demonstrating mainly inward current in left pTC, and outward in right pTC. This pattern of directional current is expected to increase left pTC excitability, and decrease right pTC excitability, thus enhancing left lateralization of the pTC. Individual variation in gyral anatomy may result in differences in the precise location of the effect across subjects, but the model serves to confirm the expected lateralizing effect of this montage on the pTC in general. (Color version of figure is available online.)

of the model was to verify the lateralized (bipolar) dominant mode of polarization under each respective electrode, namely, dominantly inward current under the anode leading to somatic depolarization/increased excitability, and dominantly outward current under the cathode leading to somatic hyperpolarization/decreased excitability.[21-23] A head model was created from a high resolution magnetic resonance imaging (MRI) of an adult male, and segmented into gray matter, white matter, cerebrospinal fluid (CSF), skull, scalp, eye region, muscle, and air compartments (Custom Segmentation, Soterix Medical, New York, NY). The finite element mesh generated from the segmentation masks was exported to COMSOL Multiphysics 3.5a (Burlington, MA) for computation of electric fields (EF).[16] To complete the model, a synthetic region was added to replace tissue clipped by the MRI acquisition volume. The following isotropic electrical conductivities (in S/m) were assigned: gray matter: 0.276; white matter: 0.126; CSF: 1.65; skull: 0.01; scalp: 0.465; eye region: 0.4; muscle: 0.334; air: 1e-15; synthetic region: 0.17; sponge: 1.4; electrode: 5.8e7. The Laplace equation was solved and induced cortical EF maps were determined.[16]

Tasks

During each session, subjects performed either a phoneme perception task (n = 15) or a color perception task (n = 10) for the last 15 minutes of tDCS to maintain attention and

arousal. After tDCS, they performed a computerized version of the Woodcock Reading Mastery Test-Revised-Normative Update (WRMT)[24] Word ID and Word Attack subtests (untimed tests of word and nonword reading accuracy respectively), followed by the primary outcome measure, the Test of Word Reading Efficiency (TOWRE),[25] in which subjects read aloud a list of either real words (Sight Reading Efficiency subtest) or nonwords (Phonetic Decoding Efficiency subtest) as quickly as possible. Two equivalent forms of the WRMT and TOWRE were given, one at each session. Psychometric data establishing equivalency of forms are available in the manuals of the tests.[24,25] Three subjects were excluded because they scored at ceiling on the TOWRE at both sessions. The remaining 22 subjects (13 female; Mean Edinburgh Handedness = 91.4, range = 60-100) were counterbalanced for order of sessions, order of TOWRE and WRMT subtests, and TOWRE form administered at real versus sham sessions. Subjects completed a questionnaire at the end of each session asking them to rate the severity of a variety of symptoms during and after tDCS (1-5 scale, 26 questions total, data available for 21/22 subjects).

Statistical analysis

All statistical tests were performed in SPSS 16 for Mac, with a two-tailed alpha of .05. Dependent variables were

standardized scores on each reading measure (mean = 100, SD = 15). The effect of tDCS on each reading measure was assessed using paired t tests comparing performance after real tDCS to sham. Significant effects were further evaluated using repeated-measures analysis of variance (ANOVA) with tDCS as a within-subject factor (real versus sham) and task (phoneme versus color perception), ability (above average versus below average score at sham session, that is, greater or less than 100), and session order (real versus sham first) as between-subject factors. Differences in cumulative symptom ratings between sessions were entered as a covariate.

Results

Tolerability and blinding of tDCS

All subjects completed the protocol and no significant adverse events were reported. On the post-tDCS symptom questionnaire, median ratings were 1 (none or very mild) for both sessions on all items assessing symptoms occurring after tDCS. Ratings for symptoms during tDCS were 1 on all questions, except difficulty concentrating, itching, and tingling, which were 2 at both sessions. Subjects were not directly asked to guess the session at which they received real stimulation, so we assessed the likelihood of unblinding based on cumulative symptom ratings (the sum of all 26 ratings). Eleven subjects rated severity of symptoms as higher during real tDCS, nine subjects rated severity as higher during sham stimulation, and one subject rated the symptoms equally at both sessions. There was no significant difference in the cumulative symptom scores between sessions (median real tDCS cumulative score = 33 (standard deviation [SD] = 6.65), sham = 31 (SD = 5.17); Wilcoxon signed rank Z = 1.41; P = 0.16).

Effect of tDCS on reading

Only word reading efficiency demonstrated a significant effect of tDCS (TOWRE Sight Word Efficiency subtest T(21) = 2.26, P = 0.034; Figure 2, Table 1). Sixteen of 22 subjects scored higher after real tDCS than sham (binomial P = 0.026). The main effect of tDCS on word reading efficiency was no longer significant in the repeated-measures ANOVA including task, ability, session order, and symptoms as between-subjects factors (F(1,18) = 1.29, P = 0.27). There were no interactions between tDCS and task (F(1,15) = 1.61, P = 0.22), session order (F(1,15) = 0.087, P = 0.77), or symptoms (F(1,15) = 0.072, P = 0.79). However, there was a significant interaction of tDCS with reading ability (F(1,15) = 9.82, P = 0.007). There were no second-order interactions between reading ability and task (F(1,18) = 1.65, P = 0.22) or session order (F(1,18) = 1.00, P = 0.33).
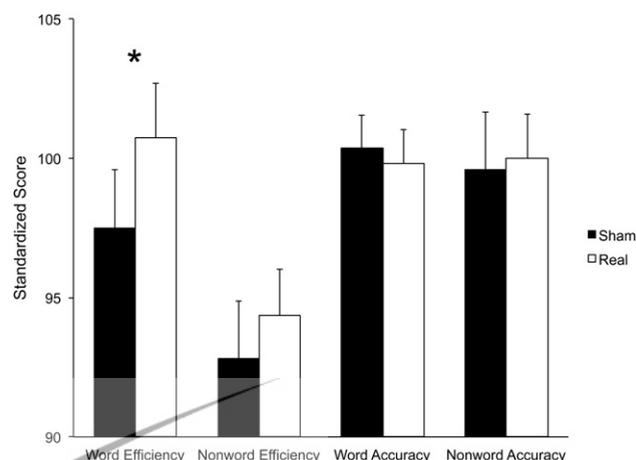

Figure 2 Effect of tDCS on standardized reading scores. Standardized scores have a population mean of 100 and SD of 15. Word Efficiency = TOWRE Sight Efficiency Test. Nonword Efficiency = TOWRE Phonetic Decoding Efficiency Test. Word Accuracy = WJRMT Word ID. Nonword Accuracy = WJRMT Word Attack. *P = 0.034.

All 12 below-average subjects scored higher on the TOWRE Sight Word Efficiency subtest after real tDCS than sham (mean difference = 6.58 points, T(11) = 4.24, P = 0.001; binomial $P_{(12/12)}$ = 0.0002, Figure 3). This group was unbalanced on session order (eight received tDCS in the second session) and TOWRE form assignment (eight received form A during the real tDCS session). To ensure that these imbalances did not impact the results, we removed every combination of subjects that rebalanced the group for these factors and rechecked the paired t test for each rebalanced group (n = 8 for each). The effect of tDCS was significant in every case (range of P = 0.0019 to 0.04; binomial $P(8/8)$ = 0.0038). There was no effect of tDCS in above-average subjects (mean difference = −0.8, T(9) = 0.42, P = 0.68).

Discussion

These results demonstrate that enhancing left lateralization of pTC using tDCS can induce short-term improvement in word reading efficiency in below-average readers. This confirms the relationship between pTC lateralization and reading ability, and provides a possible avenue for development of the first neuromodulatory intervention for dyslexia based on decades of evidence for the biologic basis of the disorder.[1] Because this study was designed as a clinical proof of principle, rather than a fine-grained cognitive neuroscience experiment, we focus below on avenues of research that might help to optimize the potential applications of tDCS for dyslexia.

The specificity of the effect on below average readers observed here confirms previous correlational imaging evidence linking reduced pTC activity with lower reading

Table 1   Effect of tDCS on standardized reading scores

Test	Mean score after sham tDCS (SD)	Mean score after real tDCS (SD)	P value
TOWRE-sight reading	97.5 (9.8)	100.7 (9.2)	0.034
TOWRE-phonetic decoding	92.8 (9.6)	94.4 (7.8)	0.327
WRMT-word ID	100.4 (5.6)	99.8 (5.6)	0.533
WRMT-word attack	99.6 (9.7)	100 (7.5)	0.825

Scores have a population mean of 100 and SD of 15.

performance, and provides a possible avenue for development of the first neuromodulatory intervention for dyslexia based on decades of evidence for the biological basis of the disorder.[1] This protocol provides stimulation parameters that could be used for a double-blind trial of tDCS in adults with persistent reading difficulties because of developmental dyslexia. The beneficial effect of tDCS observed specifically in below average readers suggests a high likelihood of success for this intervention in dyslexia. Still, several factors should be considered in designing clinical investigations of tDCS for dyslexia. Subject blinding was not directly assessed here, and unblinding of subjects could have biased the outcome, although the results of the symptom questionnaire mitigate this concern considerably. Testing the electrode montage used in this study against other active stimulation configurations that induce identical sensations would be useful to limit unblinding to the degree possible. Clinical investigations should also determine whether improvement in reading efficiency is sustained after repeated sessions, as has been demonstrated previously in a variety of conditions (e.g., aphasia,[13,14] hemiparesis,[26,27] and depression[28,29]). Even short-term enhancement of reading efficiency may be valuable though. When administered concurrently with appropriate reading instruction programs, short-term changes induced by tDCS could amplify the effectiveness of these programs, as been shown previously for novel word learning.[15] Ultimately, tDCS may be useful in primary remediation of children with dyslexia who are predicted to fail standard educational approaches,[30] but substantially more evidence of its safety in children is needed before this strategy is pursued.

To optimize the effect of stimulation on successful remediation, the specific anatomic source of the effect should be delineated. The "lateralizing" electrode montage used in this study is specialized in that the EF model predicts a focal directional effect under the electrodes, whereas other standard montages may have anatomically broader and less directional effects.[16] However, we cannot determine whether reading efficiency improved in this study because of alteration of the balance between left and right pTC processing, or strictly because of facilitation of the left or inhibition of the right. A recent longitudinal fMRI study found that improvement in word (but not nonword) reading efficiency as measured by the TOWRE in school age children over a four year period correlated with changes in the left (but not right) ventral occipitotemporal cortex's sensitivity to text.[5] This suggests the left ventral pTC as the main locus of the tDCS effect observed here, but confirming this will require further investigation. This is an important issue to address because the right hemisphere cathodal stimulation might negatively impact cognitive processes not examined in this experiment. If the right pTC cathode is not essential to the efficacy of the technique, unilateral stimulation would be preferable to reduce this concern. Extending the behavioral battery used, and investigating electrode montages that impact only one hemisphere will address these questions. Because individual variation in gyral anatomy may result in differences in the precise location of maximal current flow across subjects, targeting enhancement or inhibition more precisely using MRI-guided TMS will help to further delineate the locus of the effect within the pTC of each hemisphere and may help to optimize electrode placement for clinical applications of tDCS in dyslexia.

The activation state of networks during brain stimulation impacts the physiologic effect of stimulation,[31] and tDCS in particular has a purely modulatory effect on neuronal populations likely making its effect dependent on the activity state of the neurons impacted by the EF.[32] Thus, the effect of tDCS on reading efficiency could potentially be optimized by pairing stimulation with behaviors that engage the specific cognitive processes, and hence the neuronal populations, maximally impacted by stimulation.
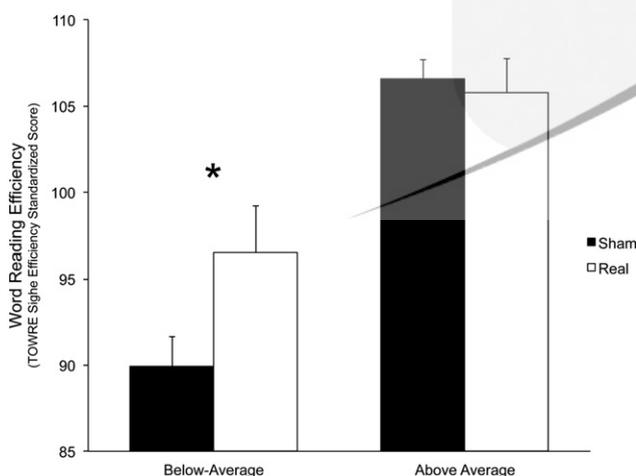

Figure 3   Word reading efficiency results by reading ability. Standardized scores have a population mean of 100 and SD of 15. *P = 0.001.

We elected to use standardized reading measures in this study because these scores would provide a metric of the tDCS effect that is meaningful to clinicians and educators. The fact that tDCS induced changes in these gross measures reinforces the possibility of practical applications for dyslexia, but using these measures limited our ability to control for word regularity, concreteness, or other variables that might help to clarify the specific cognitive operations impacted by tDCS. However, the specific effect of tDCS in improving word but not nonword reading efficiency suggests improved access to lexical or semantic representations necessary for word, but not nonword reading.[6,33] In this study, subjects performed tasks during tDCS that do not require engagement of lexical or semantic systems and the effect of tDCS did not interact with the specific task performed. For the purpose of optimizing clinical efficacy, pairing stimulation with behaviors that require lexical or semantic access should be investigated.

Conversely, activity-state dependent neuromodulatory effects of tDCS might potentially be exploited clinically. Selectively engaging neuronal populations involved in specific reading subprocesses (e.g., grapheme-to-phoneme conversion) during stimulation might sensitize them to the effect of tDCS. Thus, by pairing stimulation with specific approaches to reading remediation, the effect of tDCS might be tuned to improve a specific individual's area of weakness. Clinical investigations of tDCS for dyslexia should thus pair stimulation with different instructional remediation strategies to evaluate these interactions. Optimizing the effect of tDCS for reading remediation in dyslexia will depend on further basic and clinical investigations into the physiologic and cognitive effects of stimulation in different behavioral contexts.

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