

Transcranial Direct Current Stimulation Enhances Recovery of Stereopsis in Adults With Amblyopia

Daniel P. Spiegel · Jinrong Li · Robert F. Hess ·
Winston D. Byblow · Daming Deng · Minbin Yu ·
Benjamin Thompson

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Abstract Amblyopia is a neurodevelopmental disorder of vision caused by abnormal visual experience during early childhood that is often considered to be untreatable in adulthood. Recently, it has been shown that a novel dichoptic videogame-based treatment for amblyopia can improve visual function in adult patients, at least in part, by reducing inhibition of inputs from the amblyopic eye to the visual cortex. Non-invasive anodal transcranial direct current stimulation has been shown to reduce the activity of inhibitory cortical interneurons when applied to the primary motor or visual cortex. In this double-blind, sham-controlled cross-over study we tested the hypothesis that anodal transcranial direct current stimulation of the visual cortex would enhance the therapeutic effects of dichoptic videogame-based treatment. A homogeneous group of 16 young adults (mean age 22.1 ± 1.1 years) with amblyopia were studied to compare the effect of dichoptic treatment alone and

dichoptic treatment combined with visual cortex direct current stimulation on measures of binocular (stereopsis) and monocular (visual acuity) visual function. The combined treatment led to greater improvements in stereoacuity than dichoptic treatment alone, indicating that direct current stimulation of the visual cortex boosts the efficacy of dichoptic videogame-based treatment. This intervention warrants further evaluation as a novel therapeutic approach for adults with amblyopia.

Keywords Amblyopia · Plasticity · tDCS · Stereopsis · Inhibition

Introduction

Amblyopia, sometimes referred to as “lazy eye”, is a neurodevelopmental disorder of vision arising from decorrelated binocular input during early visual development (prevalence, approximately 3 %) [1]. Amblyopia results in decreased visual acuity in an otherwise healthy eye and is often associated with suppression of inputs from the amblyopic eye to the visual cortex [2, 3]. This causes an impairment of binocular visual functions such as stereoscopic depth perception. Conventional amblyopia treatment emphasizes patching or penalization of the fellow-fixing (non-amblyopic) eye to force the use of the amblyopic eye [4–6]. While effective at improving visual acuity [6, 7], current treatment is often associated with residual monocular [8] and binocular [9] deficits, and a high rate of recurrence [10]. It has been argued that the monocular treatment approach may not be maximally effective, as it does not directly address suppression [11, 12]. In fact, participants with deeper suppression may have less successful monocular treatment outcomes [13]. Moreover, the standard monocular approach to amblyopia treatment is often considered to be ineffective for adult patients who are past the critical period of visual cortex development [14].

Daniel P. Spiegel and Jinrong Li contributed equally to this work.

D. P. Spiegel · J. Li · D. Deng · M. Yu (✉)
State Key Laboratory of Ophthalmology, Zhongshan, Ophthalmic
Center, Sun Yat-sen University, Guangzhou 510060, China
e-mail: max-yu@tom.com

D. P. Spiegel · B. Thompson (✉)
Department of Optometry and Vision Science,
The University of Auckland, Auckland 1142, New Zealand
e-mail: b.thompson@auckland.ac.nz

D. P. Spiegel · W. D. Byblow · B. Thompson
Centre for Brain Research, The University of Auckland,
Auckland 1142, New Zealand

R. F. Hess
Department of Ophthalmology, McGill University, Montreal QC,
Canada

W. D. Byblow
Department of Sport & Exercise Science,
The University of Auckland, Auckland 1142, New Zealand

Recent evidence from animal models has shown that reduced cortical inhibition allows for recovery of vision in adult amblyopic eyes [15–19]. This has led to the development of amblyopia treatment interventions designed to reduce suppressive mechanisms within the human visual cortex [11, 20–26]. One approach, based on psychophysical models of binocular vision and supported by initial clinical studies in adults [11, 23, 27] and children [22] involves dichoptic (separate images to each eye) presentation of high contrast images to the amblyopic eye and lower contrast images to the fellow eye. This dichoptic treatment approach has recently been implemented in the form of a videogame that can be played using video goggles [22] or on an iPod touch equipped with a lenticular overlay screen [23]. The contrast imbalance overcomes suppression and allows patients to see with both eyes simultaneously. Repeated exposure to such stimuli results in a lasting reduction in suppression, and improvements in both binocular and monocular visual function [11, 22, 23, 27].

In addition to behavioral interventions, non-invasive brain stimulation techniques, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), are capable of modulating inhibitory networks within targeted areas of the human brain [25, 28–31]. The use of non-invasive brain stimulation techniques for the treatment of amblyopia is developing rapidly [25, 26, 32], and tDCS is particularly attractive owing to its low cost and the possibility that it can be used in the patient's own home [33]. Anodal tDCS (a-tDCS) tends to increase and cathodal tDCS (c-tDCS) tends to decrease excitability in the stimulated region. Several mechanisms have been proposed for these effects, including alteration of the resting membrane potential [34] and N-methyl-D-aspartate receptor-dependent long term potentiation (LTP)- or long term depression (LTD)-like mechanisms [35]. Of particular relevance for amblyopia, a-tDCS has been associated with a reduction in gamma-aminobutyric acid-mediated inhibition. These effects have been observed when a-tDCS is applied to either the motor [29, 30] or visual [28] cortices. Furthermore, there is evidence that a-tDCS of the visual cortex can enhance the effects of visual rehabilitation for visual field loss following stroke [36, 37]. This is consistent with studies reporting that a-tDCS can augment physiotherapeutic interventions for motor impairments following stroke [38, 39] and enhance learning/skill acquisition [29].

The aim of this study was to determine whether a-tDCS can enhance the effects of dichoptic treatment in adults with amblyopia. To explore the potential of this multimodal treatment approach we designed a double-blind sham-controlled cross-over study in which adults with amblyopia received daily sessions of dichoptic treatment combined with a-tDCS of the visual cortex. Our hypothesis was that dichoptic treatment and a-tDCS would result in greater improvements in visual function than dichoptic treatment alone.

Methods

Participants

Sixteen adults with amblyopia (mean age 22.07 ± 1.1 years SEM) were recruited from the ophthalmology clinics at Zhongshan Ophthalmic Center, Guangzhou, China. Inclusion criteria were a visual acuity of 0 LogMar or better in the fellow fixing eye, at least 0.2 LogMar difference in visual acuity between the eyes, and no contraindications for tDCS. Five participants had previously undergone patching therapy, and 11 patients had received no previous treatment. Clinical details of all participants are summarized in Table 1. Best refractive correction was worn during all testing sessions and prismatic correction was provided when necessary. The study protocols were approved by the Ethics Committee of Zhongshan Ophthalmic Center, Sun Yat-sen University, and complied with the Declaration of Helsinki. All participants provided informed consent.

Study Design

A sham-controlled, cross-over, double-blind study design was adopted (Fig. 1). Participants were randomized into 2 groups. Both groups received an identical dichoptic treatment regimen of 10 sessions lasting 65 mins. Both groups also received tDCS during the first 15 mins of each treatment session; however, group 1 received a-tDCS of the visual cortex during the first 5 training sessions and motor cortex tDCS [sham-tDCS (s-tDCS)] during the second 5 sessions. In group 2, the order of tDCS conditions was reversed.

Measurements of best-corrected visual acuity and stereopsis were made prior to the first training session (pre), after 5 days of treatment (post-5d) and after 10 days of treatment (post-10d). In 8 available patients, visual acuity and stereopsis were also measured at 2 weeks (post-2w) and 3 months (post-3m) after the final treatment session.

Clinical Assessment

Visual acuity was measured using a tumbling E chart with decimal progression presented using a Topcon ACP-8 projector and viewed from a distance of 3 m. A forced-choice testing method was employed. Lines 1.0–0.2 contained 5 optotypes, lines 0.18–0.05 contained 3 optotypes, and visual acuity was scored using the standard technique of subtracting 0.02 or 0.03 logMAR units, respectively, for each correctly identified optotype. Stereopsis was assessed using the Randot Stereo Test at a 40-cm viewing distance. This test relies on dichoptic separation of 2 disparity-shifted images using polarized glasses and requires patients to detect shapes presented in depth. Measurements of stereopsis can be made in the range of 800 to 40 seconds of arc. Clinical data were

Table 1 Clinical details of the study participants

Identification	Age/ sex	History and previous treatment	Type of amblyopia	Visual acuity (logMAR)	Current refraction
G1-1	18/M	Not known, patching	RE LE Aniso	0.0 0.73	Plano +5.75 -1.25×5
G1-2	20/F	Not known, none	RE LE Strab	0.0 1.03	+0.25 Plano
G1-3	19/F	Detected age 8 years, patching	RE LE Aniso	0.0 0.22	-1.25 -0.25 -0.5×145
G1-4	22/F	Not known, patching	RE LE Aniso	0.0 0.4	-1.5 +3.0
G1-5	22/M	Not known, none	RE Aniso LE	0.16 0.0	+5 -0.5×35 +2.5 -0.5×155
G1-6	25/F	Detected age 7 years, surgery	RE Strab LE	0.75 0.0	-1.25 -0.75
G1-7	31/F	Not known, none	RE LE Strab	0.0 0.42	-3.25 -2.25
G1-8	20/M	Detected age 5 years, patching	RE LE Aniso	0.0 1.0	+1.25 -0.75×15 +6.5 -1.0×95
G2-1	21/F	Not known, none	RE LE Aniso	0.0 0.15	-0.5 +3.25 -1.0×80
G2-2	23/F	Not known, patching	RE LE Strab	-0.8 1.03	+4.75 -1.0×10 +4.5 -1.25×5
G2-3	17/M	Not know, none	RE Mixed LE	1.05 0.0	+4.25 -0.5×50 -0.25
G2-4	31/M	Not known, none	RE Aniso LE	0.58 0.0	+5.0 -2.0×120 +7.75 -1.0×30
G2-5	19/M	Detected age 6 years, surgery	RE LE Strab	0.0 0.55	0 -0.5×165 -1.0 -0.75×15
G2-6	24/F	Not known, none	RE Strab LE	0.7 0.0	-5.0 -0.75×180 -4.5 -1.25×170
G2-7	19/F	Not known, none	RE Aniso LE	0.38 0.0	+8.0 -2.0×175 +3.25 -1.5×165
G2-8	29/F	Detected age 8 years, none	RE Aniso LE	1.0 0.0	-1.25 -1.0×85 +3.75 -0.75×165

G1 participants who received anodal-transcranial direct current stimulation (tDCS) first (group 1), *G2* patients who received sham-tDCS first (group 2), *M* male, *F* female, *RE* right eye, *LE* left eye, *Aniso* anisometropic amblyopia, *Strab* strabismic amblyopia

collected by an investigator masked to the grouping of the participants.

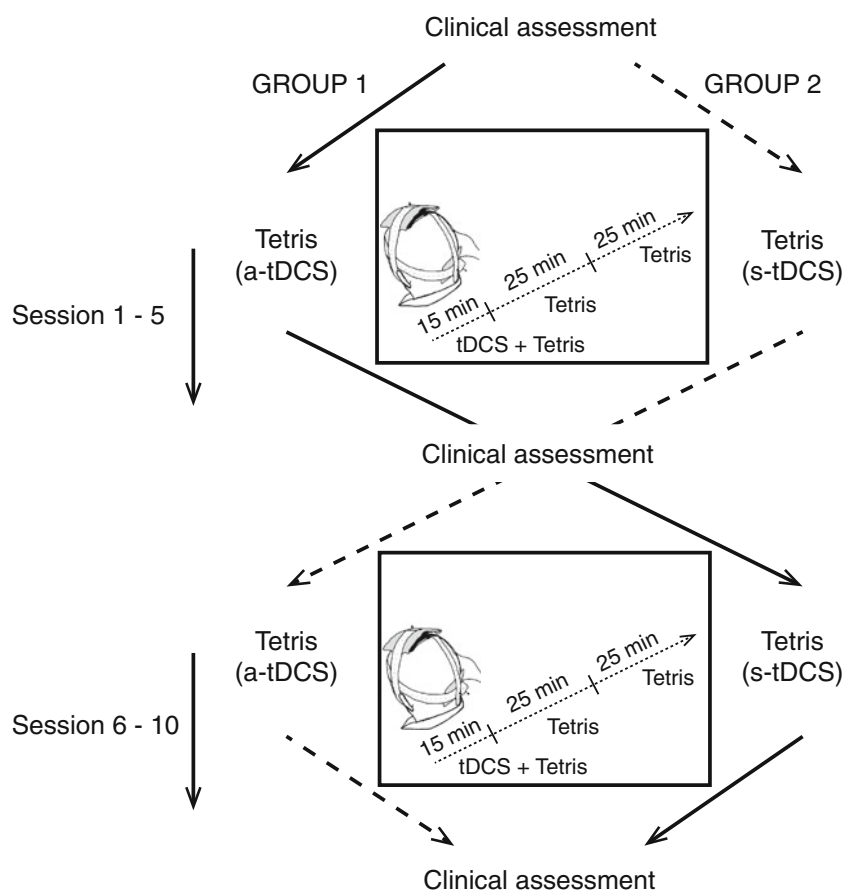
Dichoptic Treatment

Dichoptic treatment was administered in a clinical assessment room using an iPod touch equipped with a lenticular overlay screen. The videogame-based treatment is described in detail elsewhere [23]. In brief, it consists of a modified version of *Tetris*, which requires the player to tessellate falling blocks together [23]. Some blocks are presented to the amblyopic eye at high contrast, some to the fellow eye at low contrast, and some to both eyes to aid fusion. Successful game play can only occur if suppression of the amblyopic eye is

overcome, thereby allowing all blocks to be perceived simultaneously.

Participants were seated in a chair with their head placed in a chinrest to ensure exact alignment of the lenticular screen. The iPod touch was controlled using a Bluetooth keyboard. Interocular suppression was assessed at the start of each treatment session using an established psychophysical technique that provides a measurement of the interocular contrast difference required to overcome suppression of the amblyopic eye [13, 40, 41]. This technique has recently been modified to allow for measurements to be made in the context of high anisometropia [42]. The suppression measurement was used to set the contrast of the Tetris blocks presented to the fellow eye; amblyopic eye blocks were always presented at 100 % contrast.

Fig. 1 Experimental design. A sham-controlled, cross-over, double-blind study design was adopted. Group 1 (solid line) received anodal-transcranial direct current stimulation (a-tDCS) of the visual cortex during the first 5 treatment sessions and sham-tDCS (s-tDCS) during the second 5 sessions. The order of tDCS conditions was reversed for group 2 (dashed line). Visual functions were assessed before treatment (baseline), after 5 treatment sessions, and after 10 treatment sessions. tDCS was administered during the first 15 mins of dichoptic training. This was followed by two 25-min training blocks. A 5-min break was provided between each block



Each treatment session was divided into 3 blocks of Tetrakis play. The first block lasted 15 mins and the second 2 blocks lasted 25 mins. Each block was separated by a 5-min break (Fig. 1). tDCS was delivered during the first block.

tDCS

tDCS was administered using a direct current stimulator (Chattanooga Ionto DJO International, Guildford, Surrey, UK) according to established safety guidelines [43]. This device complies with international electrotechnical commission (IEC) 60601 and is CE-approved. The device is not Food and Drug Administration-approved for tDCS. The stimulating current was delivered via 2 rubber electrodes housed in saline-soaked sponge pockets (Chattanooga Intelect). The sizes of the stimulating and reference electrode were 4×6 cm and 8×12 cm, respectively. The large size of the reference electrode was chosen to render the electrode inert owing to a low current density [44].

For the a-tDCS condition the stimulating and reference electrode were positioned over Oz and Cz, respectively [28, 45–50], as defined by the 10–20 electroencephalography coordinate system [51]. The direct current was ramped up to 2 mA, kept constant for 15 mins, and then ramped down.

Sham stimulation differed from real stimulation in 2 ways. First, sham tDCS was only delivered for 30 s, whereby the current was ramped up to 2 mA and then turned off out of view of the patient [51]. Second, the tDCS electrodes were placed over the motor cortex to ensure that the 30-s period of stimulation could not influence visual cortex function. The stimulating electrode was placed over the nondominant primary motor cortex and the reference electrode was placed over the dominant primary motor cortex (corresponding to 10–20 electroencephalography positions C3 and C4).

Statistical Analysis

Prior to statistical analysis, visual acuity measurements were converted to logMAR units and stereoacuity values were converted to stereosensitivity (stereosensitivity = stereoacuity⁻¹), as many patients had no measurable stereopsis prior to treatment (sensitivity of 0). Visual acuity and stereosensitivity measures made after 5 treatment sessions were normalized to baseline measurements (pretreatment) by subtraction. Measurements made after 10 treatment sessions were normalized to the measurements made after 5 treatment sessions by subtraction. In order to assess any a-tDCS-specific effects on the results of dichoptic treatment, mixed analyses of variance were conducted on normalized data with a between-

subject factor “group” (group 1 vs group 2) and within-subject factor “time” (post-5d and post-10d). *Post hoc* analyses were conducted using paired sample *t* tests. Means and standard error are reported in the text.

Results

No participants reported any adverse effects apart from a slight tingling sensation under the electrodes.

In agreement with previous studies [11, 23, 24], dichoptic training resulted in improved visual acuity and stereopsis. After all 10 treatment sessions 14 of the 16 participants (78.8 %) exhibited improved stereopsis, including 12 participants who had no measurable stereopsis prior to treatment. The mean improvement was $0.003 \pm 0.0004 \text{ arc sec}^{-1}$ ($t_{15} = -3.382$, $p = 0.004$) (Fig. 2a). The improvement in amblyopic eye visual acuity ranged from 0.16 to 0.53 logMAR and the mean improvement was $0.34 \text{ logMAR} \pm 0.04 \text{ SEM}$ ($t_{15} = 8.725$, $p < 0.0001$) (Fig. 2b). There was a strong positive correlation (Pearson's $r = 0.955$, $p < 0.0001$) between each patient's baseline visual acuity (pre) and their visual acuity improvement, indicating that patients with deeper amblyopia exhibited

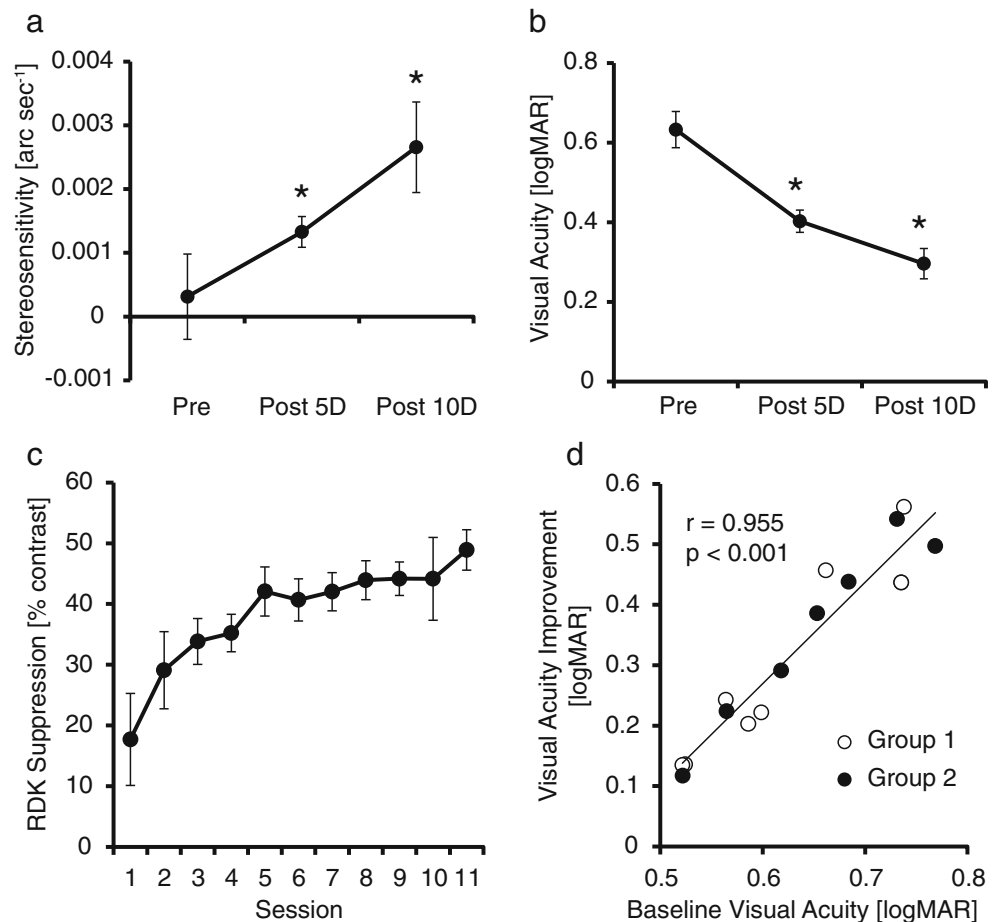
greater acuity improvements (Fig. 2c). This correlation remained significant when each patient's average acuity before and after treatment (mean of pre and post-10d measurements) was compared with their improvement in visual acuity ($r = 0.866$, $p < 0.0001$).

A mixed analysis of variance conducted on the normalized stereopsis data revealed an interaction between time and group ($F_{1, 14} = 10.5$, $p = 0.006$), indicating that the effect of a-tDCS differed significantly from the effect of s-tDCS. As shown in Fig. 3a, a-tDCS enhanced the improvement in stereoacuity (group 1 pre to post-5d $t_7 = -2.553$, $p = 0.038$; group 2 post-5d to post-10d $t_7 = -3.55$, $p = 0.009$), whereas s-tDCS did not (group 1 post-5d to post-10d $t_7 = -1.256$, $p = 0.250$; group 2 pre to post-5d $t_7 = -1.323$, $p = 0.227$). It is notable that across both groups 12/16 patients experienced improved stereopsis when dichoptic treatment was combined with tDCS compared with 4/16 when dichoptic treatment was delivered alone.

Unlike the stereosensitivity measurements, there was no interaction between time and group for the amblyopic eye visual acuity data (Fig. 3b), indicating no difference between a-tDCS and s-tDCS for this measure.

Clinical measurements made at post-2w and post-3 m after the combined treatment in a subset of 8 available patients

Fig. 2 Overall improvements in visual function. (a, b) Stereopsis and amblyopic eye visual acuity measurements averaged across all 16 participants at baseline (Pre) and after 5 (post-5d) and 10 (post-10d) treatment sessions. *Significant change from baseline ($p < 0.05$, 2-sample paired *t* test). (c) Suppression measured as the Weber contrast that could be tolerated in the fellow eye when the amblyopic eye was presented with a random dot kinematogram (RDK) stimulus at 100 % contrast. Larger values indicate weaker suppression (less contrast difference between the eyes was required to overcome suppression). Error bars represent \pm within-subject SEM. (d) Correlation between baseline visual acuity and change in visual acuity after 10 sessions. Each data point represents an individual participant. The positive correlation indicates that the treatment effect was smallest for participants with mild amblyopia and largest for those with more severe amblyopia



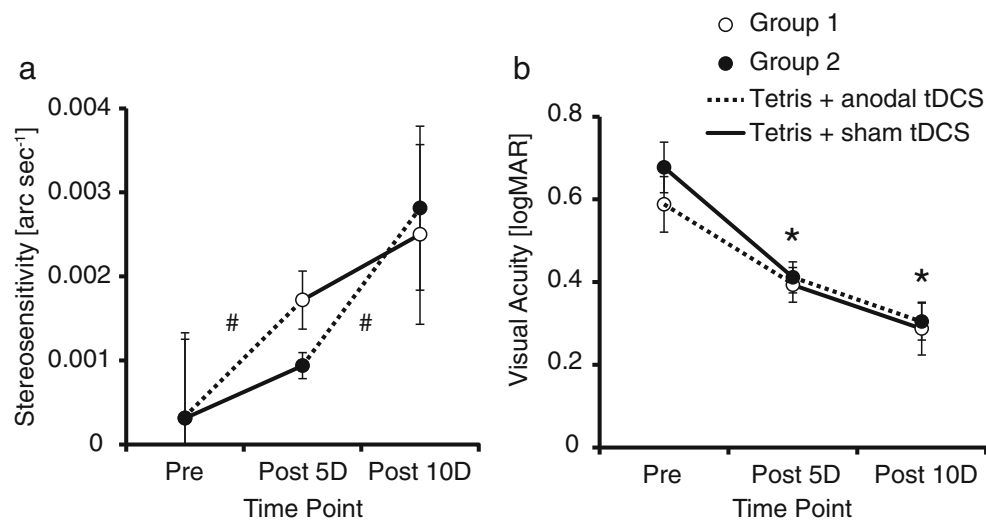


Fig. 3 Mean stereosensitivity and visual acuity. Mean stereosensitivity (a) and visual acuity (b) for group 1 [open circles; anodal-transcranial direct current stimulation (tDCS) followed by sham-tDCS] and group 2 (filled circles; s-tDCS followed by a-tDCS) at baseline (pre) and after 5 (post-5d) and 10 (post-10d) days of dichoptic treatment. Dashed lines

represent dichoptic treatment combined with a-tDCS and solid lines represent dichoptic treatment combined with s-tDCS. *Improvement in visual acuity from baseline ($p < 0.05$, 2-sample paired t test). # Improvement in stereopsis from pre to post-5d in group 1 and post-5d to post-10d in group 2 ($p < 0.05$). Error bars represent \pm within-subject SEM

indicated that the improvements remained stable for both stereopsis (pre to post-2w $t_5 = -2.611$, $p = 0.048$; pre to post-

3 m $t_5 = -2.445$, $p = 0.058$) and visual acuity (pre to post-2w $t_7 = 5.36$, $p = 0.001$; pre to post-3 m $t_7 = 5.841$, $p = 0.001$)

Table 2 Individual participant results

ID	Amblyopic visual acuity (logMAR)					Stereosensitivity (arc s ⁻¹)					RDk suppression (% contrast)		
	Pre	Post-5d	Post-10d	Post-2w	Post-3 m	Pre	Post-5d	Post-10d	Post-2w	Post-3m	Pre	Post-5d	Post-10d
G1-1	0.70	0.48	0.48	0.45	0.40	0	0.00125	0.00125	0.00125	0.00125	0	28	22
G1-2	1.00	0.57	0.55	0.55	0.52	0	0	0	0	0	10	29	38
G1-3	0.22	0.15	0.10	0.10	0.08	0.00125	0.00500	0.01000	0.00500	0.00250	34	50	78
G1-4	0.40	0.21	0.21	0.22	0.22	0	0	0	0	0	2	15	20
G1-5	0.16	0.12	0.08	–	–	0.00125	0.00500	0.00500	–	–	32	65	77
G1-6	0.73	0.57	0.30	–	–	0	0.00125	0.00125	–	–	28	36	40
G1-7	0.42	0.33	0.18	–	–	0	0.00125	0.00250	–	–	45	100	100
G1-8	1.00	0.70	0.42	–	–	0	0	0	–	–	0	13	14
G2-1	0.15	0.05	0.03	0.00	-0.05	0.00125	0.00500	0.01000	0.01000	0.01000	2	33	41
G2-2	1.00	0.57	0.55	0.45	0.42	0	0	0.00125	0.00125	0.00250	19	100	100
G2-3	1.00	0.60	0.55	0.52	0.60	0	0	0.00125	0.00250	0.00250	2	15	20
G2-4	0.57	0.35	0.27	0.30	0.38	0	0	0.00125	0.00125	0.00125	26	37	69
G2-5	0.55	0.33	0.17	–	–	0	0	0.00250	–	–	25	37	54
G2-6	0.38	0.25	0.15	–	–	0.00125	0.00250	0.00500	–	–	35	48	51
G2-7	0.70	0.42	0.25	–	–	0	0	0.00125	–	–	24	29	40
G2-8	1.00	0.70	0.48	–	–	0	0	0	–	–	0	16	19

Measurements of visual acuity, stereosensitivity (s arc⁻¹) and suppression for individual participants. Suppression was measured as the Weber contrast that could be tolerated in the fellow eye when the amblyopic eye was presented with a stimulus at 100 % contrast and larger values indicate weaker suppression (less contrast difference between the eyes was required). Measurements are provided prior to treatment (Pre) after 5 days (post-5d), after 10 days (post-10d), 2 weeks after the final treatment session (post-2w) and 3 months after the final treatment session (post-3 m)

G1 participants who received anodal-transcranial direct current stimulation (tDCS) first (group 1), G2 patients who received sham-tDCS first (group 2); RDk random dot kinematogram

(Table 2). Although the post-3 m results for stereopsis were statistically marginal, none of the patients that improved returned to their baseline levels of stereopsis (Table 2).

Discussion

This study has produced confirmatory and novel results. First, in agreement with previous work [11, 22–24, 52], we found that a short period (2 weeks) of dichoptic treatment resulted in pronounced and lasting gains in visual acuity and stereopsis in adult patients with amblyopia, and, second, the novel finding that a-tDCS enhances the effect of dichoptic treatment on stereopsis. These results are consistent with the idea that the adult visual cortex has sufficient plasticity to recover function in adulthood [53–55] and provide the first evidence that brain stimulation techniques can augment treatment interventions for amblyopia.

The dichoptic treatment approach used in this study is based on psychophysical studies demonstrating that information from the amblyopic eye is subject to a strong inhibitory drive from the fellow eye prior to binocular combination [56]. The treatment is designed to reduce suppression of the amblyopic eye and therefore improve binocular functions, such as stereopsis [11, 23]. The fact that monocular function also improves, even though the fellow eye is never occluded during treatment, emphasizes the importance of binocular dysfunction in the visual deficits associated with amblyopia [57–59].

Significant gains in visual function achieved by both groups of patients in this study further support the argument that dichoptic treatment is an effective approach to amblyopia therapy [11, 23, 24]. The magnitude of the stereopsis improvements we report after 2 weeks of dichoptic treatment are consistent with previous studies using this technique in adult patients for comparable periods of time [20, 21, 23, 52]. Interestingly, the improvements in visual acuity were 0.15 log units larger than those reported in previous studies using dichoptic treatment and those using patching of the fellow combined with extended periods (40 h) of videogame play [60]. The protocol in the current study allowed for training sessions to be precisely timed and closely monitored. In addition, the interocular contrast offset used within the videogame was calibrated at the start of every session. These factors may have optimized the treatment effects on visual acuity. The fact that 11/16 (69 %) of the patients in the current study had not previously received treatment may also have resulted in large acuity gains as greater improvements may occur in older patients who have not previously been treated [61].

A novel finding of this study was that a-tDCS enhanced the effects of dichoptic treatment for stereopsis. The rationale for the application of a-tDCS to amblyopia is based on previous work showing that a-tDCS reduces gamma-aminobutyric acid-mediated inhibition [28–30], a key mechanism underlying

suppression of the amblyopic eye [3, 57]. A reduction in inhibition may also enhance the potential for experience dependent plasticity [15, 29, 62, 63]. It is possible that a-tDCS further reduced suppression of the amblyopic eye, therefore enhancing the effects of dichoptic treatment on stereopsis, which requires precise binocular integration. a-tDCS did not appear to enhance the effects of dichoptic treatment on amblyopic eye visual acuity in this study; however, it is likely that any effect of a-tDCS was masked by the pronounced improvements in visual acuity that occurred with the dichoptic treatment alone.

a-tDCS of the visual cortex has been reported to enhance the rehabilitation of visual field deficits following stroke [36, 37] and non-invasive transorbital alternating current stimulation has been applied to patients with chronic optic neuropathy [64]. Here we have shown for the first time that a-tDCS can enhance treatment effects in adults with amblyopia, raising the possibility that a-tDCS can improve outcomes for adult patients with amblyopia who are typically left untreated.

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Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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