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Research report

Transcranial direct-current stimulation (tDCS) improves detection of simple bright stimuli by amblyopic Long Evans rats in the SLAG task and produces an increase of parvoalbumin labelled cells in visual cortices

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HIGHLIGHTS

- Monocular occlusion was used as model of amblyopia in Long-Evan rats.
- Monocular and Binocular visual acuity was affected.
- Anodal tDCS during 8 days improved visual acuity of amblyopic rats.
- Anodal tDCS technique in a controlled way can be an effective treatment for amblyopia.
- Anodal tDCS increase GABA levels in visual cortex.

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ABSTRACT

In this work visual functional improvement of amblyopic Long Evans rats treated with tDCS has been assessed using the "slow angled-descent forepaw grasping" (SLAG) test. This test is based on an innate response that does not requires any memory-learning component and has been used before for measuring visual function in rodents. The results obtained show that this procedure is useful to assess monocular but not binocular deficits, as controls and amblyopic animals showed significant differences during monocular but not during binocular assessment. On the other hand, parvoalbumin labelling was analysed in three areas of the visual cortex (V1M, V1B and V2L) before and after tDCS treatment. No changes in labelling were observed after monocular deprivation. However, tDCS treatment significantly improved vision through the amblyopic eye, and a significant increase of parvoalbumin-positive cells was observed in the three areas, both in the stimulated hemisphere but also in the non-stimulated hemisphere. This effect occurred both in control and amblyopic animals. Thus, tDCS induced changes are similar in controls and amblyopic animals, although only the last one showed a functional improvement.

1. Introduction

Amblyopia is a visual disorder caused by a functional imbalance between both eyes during development. Thus, the visual cortex does not process information coming from one of the eyes properly, and that pathway becomes inhibited, resulting in a severe decrease of visual acuity, contrast sensitivity and stereopsis. In humans, this pathology affects to 1–5% of population, and for long time it has been stated that amblyopia becomes untreatable after childhood. However, recent research both in animal models and in clinical studies have challenged this assumption (Castaño-Castaño et al., 2017; Ding et al., 2016; Li et al., 2015). In this line, non-invasive stimulation procedures using anodal tDCS have been shown to recover contrast sensitivity (Ding et al., 2016), and improve stereopsis and visual acuity (Bocci et al., 2018; Spiegel et al., 2013) in adult amblyopic patients. Visual acuity improvement after anodal tDCS has also been reported in animal models of amblyopia (Castaño-Castaño et al., 2017).

Much of the knowledge available about the neural mechanisms

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underlying amblyopia come from studies on animal models. Monocular deprivation during the sensitive period affects the expression of parvoalbumin (PV) in the binocular region of the visual cortex (Cellerino, 1992). Pharmacological strategies have been used to restore the excitatory/inhibitory balance of visual cortex in amblyopia. For instance, pharmacological reduction of GABA transmission in the adult visual cortex has proved to be a suitable treatment for restoring cortical plasticity and the recovery of visual function after the critical period for visual development (Baroncelli et al., 2011, 2012; Maya-Vetencourt et al., 2008).

Although tDCS effects are dependent on the NMDA system, which is involved in synaptic plasticity, GABAergic, dopaminergic, serotonergic and cholinergic systems have also been proposed to play a role (Medeiros et al., 2012; Stagg and Nitsche, 2011). Thus, Spiegel et al. (2012) have reported that anodal tDCS reduces intracortical inhibition in the human visual cortex. More recently, Bocci et al. (2014a) have described metaplasticity mechanisms in visual cortex following both anodal and cathodal tDCS, which can modulate the strength and direction of synaptic plasticity.

Much of the research using animal models have tested visual acuity or contrast sensitivity following postnatal monocular deprivation (Castaño-Castaño et al., 2017; Fischer et al., 2007; Fong et al., 2016; Toginini et al., 2012). Evaluation procedures are usually based on innate behaviors depending on visual capabilities like the optokinetic reflex (Balkema et al., 1984; Castaño-Castaño et al., 2017; Tabata et al., 2010), the visual placing reflex (Allam and Abo-Eleneen, 2012), the Cliff test (Fox, 1965), the raised arms maze (Handley And Mithani, 1984) or visual evoked potentials (Porciatti et al., 1999). However, animals' performance can be influenced by alternative strategies to perceive distances, or their innate response like fear or impulsivity during the execution of exploratory tasks (Flint et al., 1995).

The SLAG task is a simple and inexpensive test based on an innate response that serves to evaluate the visual function of rodents, and has been validated in mice (Gil-Pagés et al., 2013). In such task the animal is slowly descended while passing close to an illuminated wire lid. When this bright stimulus is detected the animal extends the forepaws and grasps the wire lid. The results obtained with mice show that it is an effective test to identify if they have functional vision, and has been used as a screening method for research procedures requiring a proper function of the visual system (Gil-Pagés et al., 2013). Nevertheless, to the best of our knowledge the ability of amblyopic rats to detect simple bright stimuli has not been evaluated yet. For such reason we have decided to use this test in postnatally deprived Long Evans rats to assess their visual performance. Subsequently, the effect of anodal tDCS will be assessed using the same task to test possible visual recovery of amblyopic animals following stimulation. Finally, immunohistochemistry labelling of parvoalbumin positive GABAergic neurons in cortical areas will be conducted to investigate the involvement of such neurotransmitter in monocular deprivation induced amblyopia, as well as the subsequent tDCS treatment.

2. Results

Treatment with tDCS showed no significant effects on binocular performance $F(1.32) = 0.0157$, $p > 0.05$. However, tDCS treatment produced a significant effect for monocular assessment $F(1,32) = 35.346$, $p < 0.001$. A significant interaction TREATMENT x GROUP was also observed for monocular assessment $F(3.32) = 23.669$, $p < 0.001$. Figs. 1 and 2 illustrate binocular and monocular performance respectively.

2.1. Analysis of binocular performance in the SLAG task

GROUP x TREATMENT comparisons did not show significant differences during the binocular test among the four groups before tDCS treatment: CONTROL and AMBLYOPIC (mean difference = 0.089, $p > 0.05$); CONTROL and AMBLYOPIC-tDCS (mean difference = 0.111; $p > 0.05$); AMBLYOPIC and AMBLYOPIC-tDCS (mean difference = 0.022, $p = 1.00$); CONTROL and CONTROL-tDCS (mean

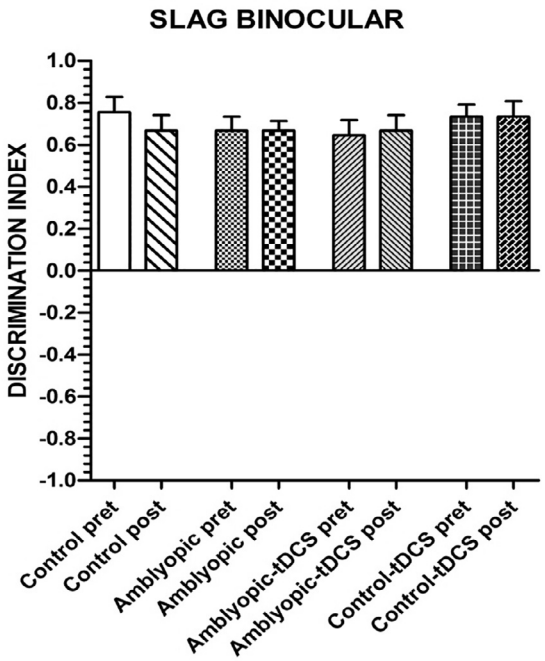

Fig. 1. No significant differences between groups are observed for the binocular assessment both at the pre- and post-treatment phases.

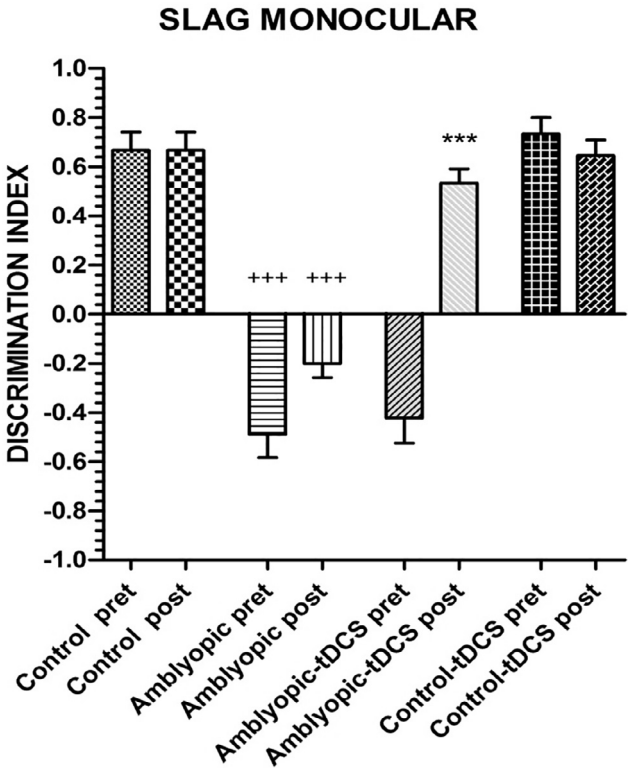

Fig. 2. During monocular assessment there is a significant visual deficit when comparing the amblyopic groups with respect to the control group (where "+++" means significant differences with regards to the control group, $P < 0.001$). It is also observed that visual recovery occurs in amblyopic group treated with tDCS (where "***" means significant differences with regards to the pretreatment phase for the Amblyopic-tDCS group, $p < 0.001$).