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Neurophysiological effect of transorbital electrical stimulation: Early results in advanced optic atrophy

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Dear Editor,

Transorbital alternating current stimulation (trACS) is becoming a new option for low vision restoration [1]. Nevertheless, its exact mechanism of action is still not completely known. Previous studies demonstrated that by delivering current with a transorbital montage, the vast majority of it flows through the eye ball and the optic nerve, not directly reaching the primary visual cortex [2]. It was shown that trACS can generate visual evoked potentials (VEP), that can be inhibited in rats by blocking the retinal ganglion cell with tedrototoxin [3], suggesting that the retina could represent the entry gate for the current in the brain [3]. Moreover, in patients with low vision, a reduction of power density, coherence and connectivity of alpha EEG activity was demonstrated, that can be in part reversed by trACS [4].

To the best of our knowledge, there are no studies exploring the effect of trACS on electroretinogram (ERG) and VEP. For this reason we report a preliminary multimodal evaluation of neurophysiologic changes along visual pathway in response to trACS.

In order to study the neurophysiological effects of trACS in patients with low vision, we recruited 11 male patients (mean age 51,7 years), all affected by chronic visual deficit. Six had a pre-chiasmatic (2 glaucoma, 2 ischemic opticopahty, 2 traumatic optic-opathy) and 5 a post-chiasmatic damage (4 occipital stroke and 1 cerebral glioma). Each patient underwent a baseline evaluation with a comprehensive neurophysiological examination and a patient-oriented questionnaire, performed a treatment with trACS, and finally underwent a post-treatment evaluation with the same exams performed at the baseline.

Primary outcome measures were: flicker VEP assessing the peak to peak amplitude of the 8 Hz component measured thanks to the Fourier transform, corresponding to the primary visual cortex activation; a and b waves amplitude of the flash-ERG in a light adapted condition, corresponding to the activation of cones and bipolar cells; the photopic negative response (PhNR), corresponding to the activity of ganglion cells and their axons [5]. Moreover the patients were asked to answer the patient global impression of change questionnaire (PGIC) [6].

TrACS was performed with two bipolar channels placing the cathode and the anode respectively over and below the eyeballs. The frequency of stimulation was 10 Hz. The intensity of stimulation was set at the phosphene threshold or, if not possible because of the patient condition, at 1 mA. The duration of the treatment was 20 minutes per day for 10 consecutive days excluding the weekend.

The statistical analyses were performed with the SPSS (v.21) and R software.

Flickr-VEP mean amplitude was increased in 10 out of 11 patients after the treatment. Mean VEP pre-treatment amplitude was 1.52mV (±0.89) and mean VEP post-treatment amplitude was 2.70 mV (±1.59). The Wilcoxon Signed-Rank test, used to compare VEP amplitude before and after the treatment, highlighted a statistically significant difference ($p = 0.004$). The comparison of VEP amplitude in the two groups of damage (pre- and post-chiasmatic) before and after the treatment, performed with the Mann-Whitney test, did not show any statistical significant difference ($p = 0.177$) (see Fig. 1a and d).

ERG amplitude for the worst eye was increased in 7 out of 11 patients with a mean ERG amplitude of 3.4μV (±1.3) at baseline and of 3.9μV (±1.8) after the treatment. However the Wilcoxon signed-rank test did not show any statistically significant change of ERG amplitude before and after the treatment ($p = 0.213$) (see Fig 1 b).

The analysis of PhNR for the worst eye showed an increase of the amplitude in 6 out of 11 patients with a mean PhNR pre-treatment amplitude of 5.2μV (±3) and a mean PhNR post-treatment amplitude of 5.6μV (±2.5). The Wilcoxon Signed-Rank test, used to compare PhNR amplitude before and after the treatment, did not show any statistically significant difference ($p = 0.508$) (see Fig. 1c).

According to the PGIC, 10 out 11 patients reported a clinical improvement and only one patient claimed to have experienced no changes at all. The most frequent score was 4, corresponding to "Somewhat better …" with a mean value of 3.64 (±1.2) (see Fig. 1 e).

According to our results, in patients with severe visual impairment, trACS is able to generate a statistically significant increase of VEP amplitude, while the amplitude of ERG and PhNR did not change. Our findings support the hypothesis that, at least in part, the effects of trACS could be related to the increase of excitability of the primary visual cortex. Making a parallelism with the

Abbreviations: trACS, transorbital alternating current stimulation; VEP, visual evoked potentials; ERG, electroretinogram; PhNR, photopic negative response; PGIC, patient global impression of change questionnaire.

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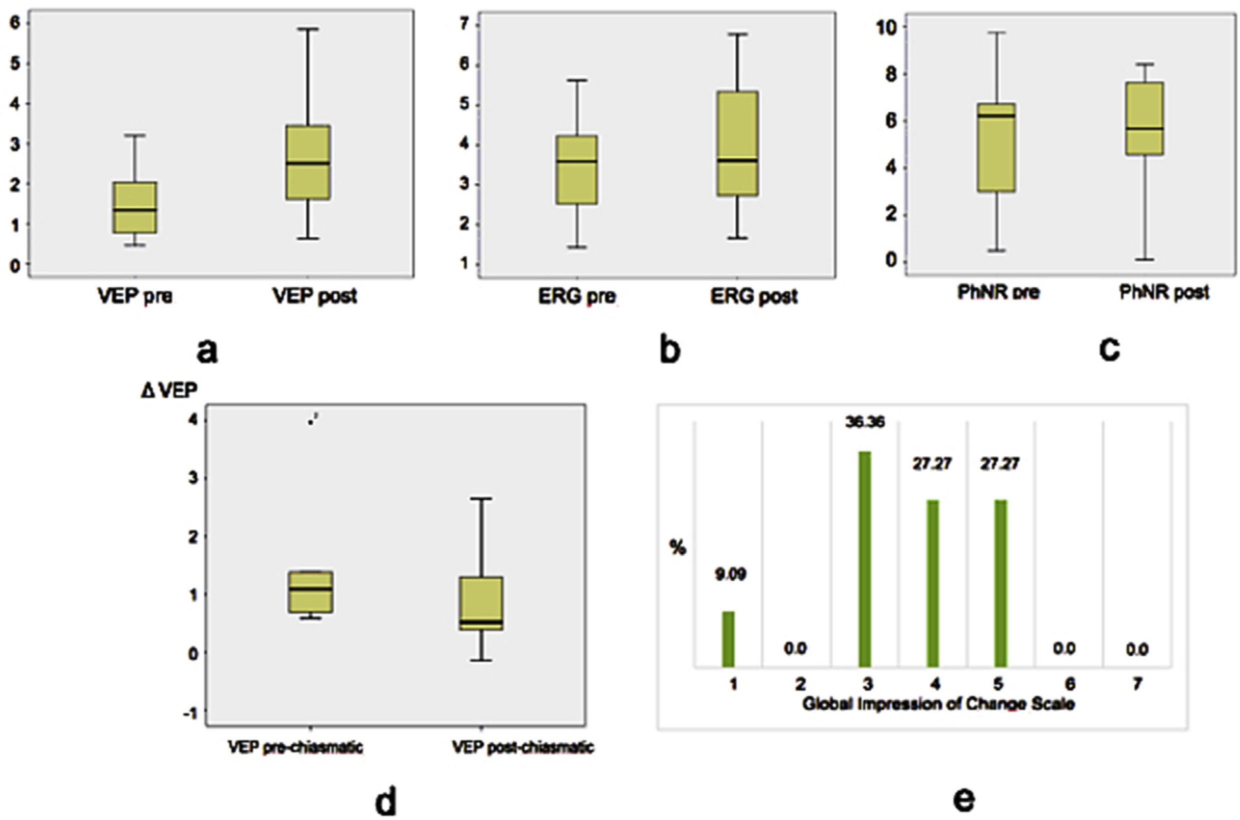

Fig. 1. VEP (1a), ERG (1b) and PhNR (1c) amplitude before and after trACS treatment. Separate analysis of VEP amplitude in patients with pre- and post-chiasmatic damage (1d). Patients subjective improvement according the global impression of changes questionnaire (1e).

high frequency transcranial magnetic stimulation (that is usually performed at 10 Hz, the same frequency of stimulation that we used) it is possible to hypothesize the Long Term Potentiation as the mechanism responsible for this effect. Moreover most of the included patients reported a mild clinical improvement according the PGIC and interestingly all patients but one asked to continue the stimulation after the study.

The study is affected by several limitations, the main is the absence of a sham group. However, on this purpose, it could be important to consider that a previous work using the same methodology and instruments of our work already demonstrated the absence of substantial fluctuation of VEP amplitude in patients with severe visual impairment [7]. Other limitations are the small sample size and the only inclusion of patient with severe clinical picture and without homogeneous pathologies. Nevertheless, this study was the first to explore the effects of trACS on retina and primary visual cortex excitability opening to a possible mechanism of action of this technique and suggesting an objective method for the evaluation of its effect. Future studies will be needed in order to confirm these results, possibly including a sham group and a larger cohort of patients.

Declaration of interest

None.

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