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Original Article

Progressive enhancement of alpha activity and visual function in patients with optic neuropathy: A two-week repeated session alternating current stimulation study

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ABSTRACT

Introduction: Repetitive transorbital alternating current stimulation (rtACS) can improve visual deficits in patients with optic nerve damage. Recent retrospective results suggest that rtACS enhances oscillatory brain activity. The exact mechanisms of rtACS are unclear and little is known about possibly frequency-specific neural-plastic mechanisms. An association between bandwidth-confined neural-entrainment and vision recovery maximization could offer a novel therapeutic option for patients with optic neuropathy.
Objectives: The goal of this prospective open-label study was to investigate if the enhancement of rhythmic brain activity over 10 days of consecutive rtACS stimulation is associated with visual field recovery. The secondary goal was to investigate neurophysiological mechanisms related to frequency dependent adaptive plasticity.
Methods: 18 Patients with visual field impairments resulting from pre-chiasmatic partial optic nerve damage received rtACS on 10 consecutive days. Daily, subject-specific treatment parameters (<500 μA, 9–37 Hz, 25–40 min/day) were defined and EEG-spectra collected prior to and after rtACS. Visual field data was collected at day 1 and 10. The change of spectral-power in classic bandwidths were investigated and correlated with visual field deficit recovery.
Results: After 10 days of rtACS alpha-power over bilateral occipital electrodes was significantly larger than at baseline ($F_{\text{Time x alpha-power}}$ $p < 0.01$). This effect was progressive over subsequent days of stimulation (cubic-fit, R^2 0.70, RMSE 0.008). Perimetric results improved significantly, but they were not associated with changes in alpha-synchronization.
Discussion: rtACS can induce cumulative bandwidth-confined changes in brain rhythms over multiple sessions. These findings are in line with the notion of brain-state dependent [1] and bandwidth-confined entrainment [2] as well as rtACS facilitated visual recovery [3].

Introduction

Visual field defects (VFD) caused by lesions to the optic nerve are responsible for substantial limitations in quality of life [4]. Spontaneous recovery occurs in about 50% of cases in the first three months, yet the remaining blindness is considered permanent without therapeutic options [5–7]. Well documented residual functionality and adaptive plasticity – even after massive loss of retino-fugal neurons [8–12] – support the notion that development of therapeutic techniques for these optic-nerve disorders poses a significant challenge for clinical neurology.

Transcranial brain stimulation techniques provide tools that have been repeatedly shown to promote long-term adaptive plasticity [13]. Stimulation-associated improvements in stroke-related functional deficits of 10–20% have been documented successfully in both animal and human studies [14–16]. These effects could be enhanced through repeated sessions on consecutive days [17]. Recently, first studies in the visual system have provided evidence for similar effects, both in healthy test-subjects [1,18,19] as well as in patients with optic neuropathy [20]. A retrospective study of 462 patients with VF-recovery following a mixed-frequency low-voltage stimulation algorithm, developed in the 1970s by Bechtereva in association with the Russian Academy of Sciences, found VF-recovery and concurrent heightened synchronization in brain rhythms [29,31].

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Table 1
OD: right eye, OS: left eye. Three patients without a post rtACS measurement dropped out before completing the visual field examination because they did not come for post-treatment perimetric evaluation but finished the 10-day rtACS treatment period.

Patient	Etiology	Age	% Detection accuracy in defective visual field sectors, at baseline	
			OD	OS
Verum group				
1	Congenital optic neuropathy	41	27.85	34.52
2	Congenital optic neuropathy	29	70.22	67.73
3	Compressive neuropathy (pituitary tumor)	47	44.58	53.19
4	Non-arteritic anterior ischemic optic neuropathy	70	12.06	22.92
5	Non-arteritic anterior ischemic optic neuropathy	58	57.71	17.49
6	Non-arteritic anterior ischemic optic neuropathy	44	36.49	43.14
7	Idiopathic optic neuropathy	70	56.12	15.95
8	Idiopathic optic neuropathy	48	14.37	31.83
9	Optic neuropathy (pseudotumor cerebri)	26	7.34	15.51
10	Inflammatory optic neuropathy	43	26.34	78.27
11	Inflammatory optic neuropathy	50	21.20	18.08
12	Glaucomatous optic neuropathy	71	29.88	9.62
13	Idiopathic optic neuropathy	30	74.47	53.74
14	Congenital optic neuropathy	28	2.13	1.29
15	Optic neuropathy after ischemic stroke	70	25.14	25.19
16	Optic neuropathy after hemorrhagic stroke	67	28.22	30.32
17	Compressive optic neuropathy (meningioma)	56	20.00	22.32
18	Compressive optic neuropathy (meningioma)	63	0.00	16.77
Placebo group				
1	Congenital optic neuropathy	71	25.71	26.90
2	Congenital optic neuropathy	70	8.33	37.04
3	Congenital optic neuropathy	62	60.29	1.33
4	Congenital optic neuropathy	44	25.77	45.10
5	Idiopathic optic neuropathy	70	41.30	18.12
6	Compressive optic neuropathy (meningioma)	56	15.86	19.38

In apparent reversal of the notion of clinical research derived from basic science, non-invasive brain stimulation techniques are investigated while often lacking a comprehensive explanatory model of the underlying mechanisms. For direct current stimulation it is understood that the firing rate probability of neurons is modified [21]. In contrast, alternating current stimulation is understood to entrain oscillatory activity in neuronal structures of the brain [2,22], induce coherent oscillations in cortico-thalamo-cortical loops [21,23] and heightened synchronization [24], which can be associated with STDP-like [2] and frequency-dependent plasticity [25]. Further, these in sum non-depolarizing oscillatory currents are arguably safer, independent of stimulus orientation [21] and more reliable due to subject specificity [26,27].

The primary aim of this intention-to-treat prospective open-label study was to investigate if EEG power spectra offer an objective measure that can be associated with the visual improvements previously described after rtACS stimulation in patients with a circumscribed pre-chiasmatic lesion of the optic nerve. We hypothesized that rtACS would induce i) heightened alpha-synchronization over visual brain regions ii) related to VF-field recovery. A further motivation was that a study with mixed-frequency AC-stimulation and simultaneous EEG could make inferences about the mechanisms of possibly frequency-specific entrainment of cortical structures.

Methods

Subjects

The patient population consisted of 26 patients (mean age 53.51, SD = 15.32) with circumscribed pre-chiasmatic optic nerve lesions. One patient was excluded from the analysis because of discontinuation of therapy after day 5. Another was excluded due to technical artifacts in the EEG-data. Patients were assigned to either a rtACS-group (n = 18) or sham-group (n = 6). Thus the rtACS-patient population for analysis consisted of 18 patients (mean age 50.56, SD = 15.73), with 12 men (mean age 51.67, SD = 16.88) and 6 women (mean age 48.33, SD = 14.35). All rtACS-patients were treated according to the ethical standards of the Declaration of Helsinki (1964). Approval was obtained from the local ethics committees. All eligible patients were stimulated with tACS after providing signed informed consent. Six patients received sham-stimulation (mean age 62.33, SD = 10.67), with 5 men (mean age 63.60, SD = 11.41) and 1 women (age 56).

The primary inclusion criterion was the presence of a lesion of the optic nerve with a stable partial visual field (VF) loss and detectable residual vision. The minimal lesion age was 6 months, except in two patients with a lesion age of at least 3 months with well documented non-fluctuating visual function after the initial event. The mean lesion age was 8 years. All subjects had binocular partially damaged visual fields, of which 9 were clearly lateralized with respect to the defect depth (n = 5 better residual vision on the right, n = 4 on the left, relative to > 50% difference), also see Table 1.

A lesion was defined as chronic and spontaneous remission considered complete if the patient documented unchanged visual function for at least 6 months. Visual field improvements subsequent to an early baseline measure were attributed to therapeutic stimulation. Exclusion criteria included electrical and electronic implants, epileptic seizures in the last ten years, addictive disease, brain tumor, electrophysiological evidence for photosensitivity, psychiatric disorders, diabetic retinopathy, high blood pressure (maximum 160/100 mmHg), macular degeneration, pathological nystagmus, unstable or high intraocular pressure (>27 mmHg), retinitis pigmentosa and pregnant or nursing women.

Stimulation

Repetitive sessions of rtACS were applied as described elsewhere in more detail [3,28,29]. In brief, the stimulation procedure used in this study was developed for patients with visual deficits caused by lesions to the pre-chiasmatic visual pathway [30] based on invasive electrical stimulation of injured optic nerves during