Cortical Activity at Baseline and During Light Stimulation in Patients With Strabismus and Amblyopia

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ABSTRACT This research measures and compares the cortical activity at baseline and during light stimulation (LS) in patients with strabismus and amblyopia (SA) and healthy controls (HCs), to understand the differences in its functionality and propose LS as a potential brain stimulator. This observational, longitudinal, prospective study enrolled 17 SA patients and 17 HCs from Querétaro, México. Electroencephalography (EEG) and digital brain mapping (DBM) were used to identify changes in frequency, voltage, and brain coherence. A total of 68 DBM was analyzed for this purpose. Our results indicate that at baseline, patients with strabismus and amblyopia present: i) lower frequency of alpha-wave activity ($p = 0.029$) with an abnormal distribution within hemispheres, ii) theta-wave with a predominance in the frontal lobes, which relates these visual conditions to neurodevelopmental disorders, iii) higher values of low voltage ($p < 0.001$) and lower values of and high voltage ($p = 0.001$) iv) interhemispheric asynchronicity with a predominance in the left hemisphere. On the other hand, the administration of LS modulates the brain activity of SA patients by i) modifying high and low voltages ($p < 0.001$ and 0.022 respectively), which define the anteroposterior gradient ii) eliminating theta-waves, iii) distributing alpha-wave activity towards the occipital lobes iv) bringing synchronicity between hemispheres. For the HC group, LS alters the distribution of alpha waves within hemispheres, and the state of interhemispheric synchronicity. There were no statistically significant changes in the frequency of the alpha-wave or the anteroposterior gradient. To summarize, LS provokes a state of malleability in the brain of SA patients, by increasing the cortical connectivity, enhancing neural activation and bringing to balance the interhemispheric communication, which converts it into a potential brain stimulator that should be considered as a complementary therapy in the treatment of these patients.

INDEX TERMS Light stimulation, cortical activity, electroencephalography, strabismus, amblyopia.

I. INTRODUCTION

Light is an electromagnetic wave capable of being perceived by the human eye and whose frequency determines its color, representing a fraction of the electromagnetic spectrum. In general terms, the electromagnetic spectrum encompasses an increasing order of frequency: microwaves,

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radio waves, infrared rays, visible light, ultraviolet radiation, X-rays, and gamma rays. Visible light is part of a narrow band that ranges from 380 nm (violet) to 780 nm (red). The colors of the spectrum are arranged like in the rainbow, forming the so-called visible spectrum. In medicine, the major applications of light are divided into three categories [1]: i) optical diagnosis: ophthalmic imaging, endoscopy, optical mammography, implants, wearable, oximetry, intravascular imaging, colonoscopy, diffuse tomography, among others; ii) laser

surgery: refractive correction, dermatological laser treatments, dental, cystoscopic photoablation, laser hair removal, to mention a few of them; and iii) light-activated therapy or phototherapy: UV therapy, blue-light, NIR therapy, light-activated nanomedicine, etc. Concerning phototherapy, human exposure to light has demonstrated impacts both visual and non-visual, including retinal functions, circadian rhythms, metabolic processes, sleep, mood, and growth. Further, its intensity and wavelength can be modified to achieve therapeutic effects [2]. When delivered at low irradiance and fluency, light can regenerate, heal, stimulate, and protect injured tissues. This application is known as low-level light therapy or photobiomodulation. Also, infrared light has been used to enhance the cognition of patients who have undergone traumatic events (stroke, traumatic brain injury, ischemia) or developed degenerative diseases (Parkinson's disease and Alzheimer's disease) obtaining impressive results [3], [4]. Furthermore, spectral filters have been used to treat light sensitivity in visually normal individuals in a predominantly luminance-dependent manner, and exposure to light radiation of between 380-780 nm in wavelength has been recommended as a method of retinal stimulation to be administered as an adjunctive, non-invasive treatment for visual disorders [5]. On the other hand, the current literature, reports no findings on the cortical activity in humans before and after a complete session of light stimulation, as it is done in the present study, using quantitative electroencephalography (qEEG). However, visible light and brain responses have been analyzed in macaques [6], where cells responsive to luminance, color, or luminance and color, were found in the primary visual cortex (V1), whose neural brain activity and synchronization was influenced and modified by different wavelengths of visible light. Moreover, in humans, neuroplasticity can be enhanced with energy-based stimulation, including light, sound, and movement [7]. These stimulants may thus feature potential in helping to reactivate disabled neural circuits or to build new cortical networks and thereby improve brain functioning. Additionally, advances in optogenetics focused on retinal ganglion cells have enabled the expression of light-sensitive proteins on neurons. These proteins can boost neural activation through illumination or be used as a tool to address retinal disorders [8]. In particular, LED therapy of 670 nm can improve the recovery of retinal ganglion cells and the occipital cortex, as it diminishes the levels of oxidative stress and cell death [9]. Furthermore, studies using monochromatic light exposure have demonstrated that non-visual responses are maximally sensitive to blue light (459-483 nm) [10]. Based on the aforementioned, the present study, uses EEG converted to DBM to measure the impact of light stimulation on the cortical activity of patients with strabismus and amblyopia in the waking-state. Specifically, EEG studies can determine the relative strength and position of electrical activity in different brain regions and monitor the symmetry of alpha activity within hemispheres, which patterns can be modified by neuroelectric processes [11]. Moreover, DBM uses precisely determined

amplitude values, which can be used for statistical comparisons. The digitized data allows a less subjective and more efficient interpretation, which makes it possible to discover facets of the EEG that the conventional interpretation did not contemplate, such as the exact quantity of the waves in the different bands and their amplitude, as done in this research. Light stimulation has been successfully used in patients with strabismus and amblyopia in the daily clinical practice of health professionals [12], [13]. Nonetheless, the literature features sparse research on the understanding of the exact mechanism by which light stimulation affects patients with visual disorders [14], and the cortical electrical response to such stimulation. On the other hand, studying strabismus is of great importance as it is a visual disorder that could lead to abnormal development of the visual system, in particular by affecting binocularity [15]. The prevalence of strabismus varies widely in the world [16], and it is generally followed by amblyopia, a cortico-visual adaptation which affects 1–4% of the population worldwide [17]. In both visual conditions, abnormalities have not only been seen in first- (luminance based) and second-order (texture-based) processing of visual information [18], [19], but also at deeper cortical levels [20]. Differences found in brain activity patterns [21], cortical thickness [22], and functional connectivity [23] relate strabismus with changes in the white and gray matter, depending on its type and time of appearance [22]–[25].

Hence, informed by previous research on light and its impact on subcortical structures as well as limbic and cortical areas [26], we explore how light stimulation modifies the cortical electrical activity of patients with strabismus and amblyopia. More precisely, qEEG allows to collect and analyze changes in the metrics of cortical electrical activity, such as frequencies, voltages, and coherence across the administration of light therapy. This research measures the baseline and during light stimulation cortical activity of patients with strabismus and amblyopia to understand the differences in its electrical activity when compared to healthy controls, as light is considered a potential brain activator. As one study among few to use neuroimaging to investigate the impacts of light stimulation on the visual system [14], our findings help to shield light into its influence on the cortical activity of SA patients using the visual system as a vector. Besides, it can help to inform clinical decisions, e.g., to determine the extent of light stimulation required for the whole-therapy treatment of a patient with strabismus and amblyopia or other groups of patients with neurodevelopmental disorders.

II. NEURONIC™

Neuronic is a company developing technology to obtain EEG and DBM studies among others (http://www.neuronicsa.com /index.htm). The EEG Quantitative Analysis (qEEG) examines the electrical activity of the brain. The methods use EEG spectral analysis through Fast Fourier Transform (FFT) [27], producing several numerical parameters. Some characteristics of this system are the following:
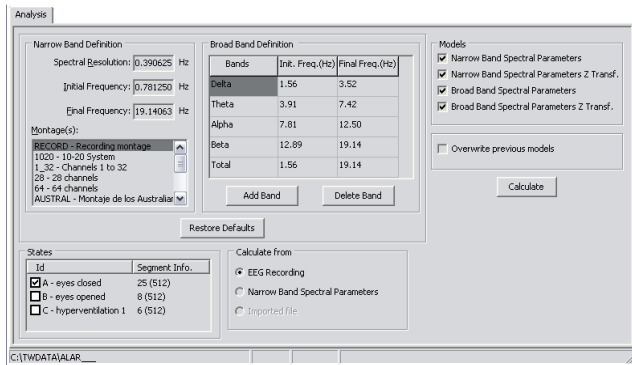
FIGURE 1. Graphical interface includes the narrow and broad bands, montage, models and states, and the option to calculate from.

- qEEG or DBM is the mathematical processing of digitally recorded EEG to highlight specific waveform components. qEEG estimates spectral activity at the electrodes (topography) as well as at the sources (tomography).
- Permits the user to select the frequency range limits for each band. Includes the Narrow Band Spectral Model giving the possibility of analyzing the EEG spectra at each frequency.
- Includes a normative database for obtaining a Z transformation correlated with age in the range of 5-90 years for comparison.
- qEEG allows obtaining a topographic brain mapping, looking for focal alterations, as well as identifying bands (frequencies) with greater precision, and detecting one or more spectral peaks. qEEG utilizes a discrete spline EEG inverse solution known as Variable Resolution Electromagnetic Tomography (VARETA). Anatomical constraints are incorporated using the Montreal Neurological Institute (MNI) probabilistic brain atlas [28]. Efficient methods were developed for frequency domain VARETA to estimate the source spectra for the set of 103-105 voxels that comprise an EEG/MEG inverse solution.

Figure 1 illustrates the interface to select the parameters during the study.

On the other hand, the Narrow Band 10/20 permits visualizing the models with a spatial distribution corresponding to the 10/20 system. On every window, the derivation name and the current value of the vertical cursor are displayed. The horizontal axis shows divisions indicating the limits for the bands ($\delta, \theta, \alpha, \beta$). The vertical cursor can be placed over the different frequencies using the left button mouse or selecting the frequency. Figure 9 illustrates the above description.

To visualize the DBM, the broad-band option is used which shows the BBSP and ZBBSP models, and helps to measure the next 3 parameters: absolute power, relative power, and mean frequency for every calculated band.

The system presents a matrix of plots, where the rows correspond to the measures and the columns to the bands. The first row shows the raw measure, and the second one shows

the Z transform. There are options at the information bar to select the state and to visualize PG correction as well. The raw measures are displayed using the best fit data Max-Min scale, and the Zs are displayed with a Threshold scale with 3.0 as a threshold value.

Research about the importance, specificity, reliability, Z-scores transform and qEEG normative databases, which provide a better understanding of its statistical and technical component, have already been published [29], [30]. Additionally, the electronic ability and statistical methods used in the qEEG have already been explained and analyzed in a detailed way [27]. It is important to mention that the Neuronic™ system permits obtaining DBMs from EEGs, a reason why, in this paper, the obtained data are analyzed using probabilistic studies. The specifications and conditions used to obtain the data from the patients using the Neuronic system are presented in detail in the Materials and Methods section.

III. MATERIALS AND METHODS
A. PATIENTS IN THE STUDY
A total of seventeen patients with strabismus and amblyopia participated in this study (mean age, 18.1 ± 10.5). The patients included eight females (47%; mean age, 19.4 ± 9.0 years) and nine males (53%; mean age, 14.7 ± 7.7 years). Eight patients presented esotropia (47%), one of whom also had hypertropia/hypotropia as a secondary deviation; seven (41.2%) suffered from exotropia, three of whom presented hypertropia/hypotropia as well; one had pure hypertropia/hypotropia; and one had anisometropic amblyopia. Moreover, seven patients (41.2%) presented stereopsis. One patient had gross stereopsis, and the other six presented fine stereopsis, which affected the standard deviation value (mean value 128.8 ± 252.1 arcmin). Of the seventeen patients, six (35.3%) had left-eye motor dominance, and eleven (64.7%) had right-eye motor dominance. All patients were right-handed.

B. INCLUSION CRITERIA
Diagnosis of primary strabismus and amblyopia; best-corrected visual acuity of ≥ 0.7 logMAR; age of 8–30 years; IQ score in the norm for their chronological age, as reported by their schools and confirmed by their medical histories.

C. EXCLUSION CRITERIA
Diagnosis of secondary strabismus (neurological, traumas, diseases) and/or a history of vision therapy; previous eye surgeries, dissociated and consecutive strabismus; photosensitivity; the presence of conditions such as attention-deficit/hyperactivity disorder, epilepsy, dyslexia, or depression; the use of medications that could affect the central nervous system (CNS); and premature birth. In addition, seventeen healthy controls, including nine men and eight women were matched with the patients in terms of age, sex, and economic status. All HCs met the following criteria:
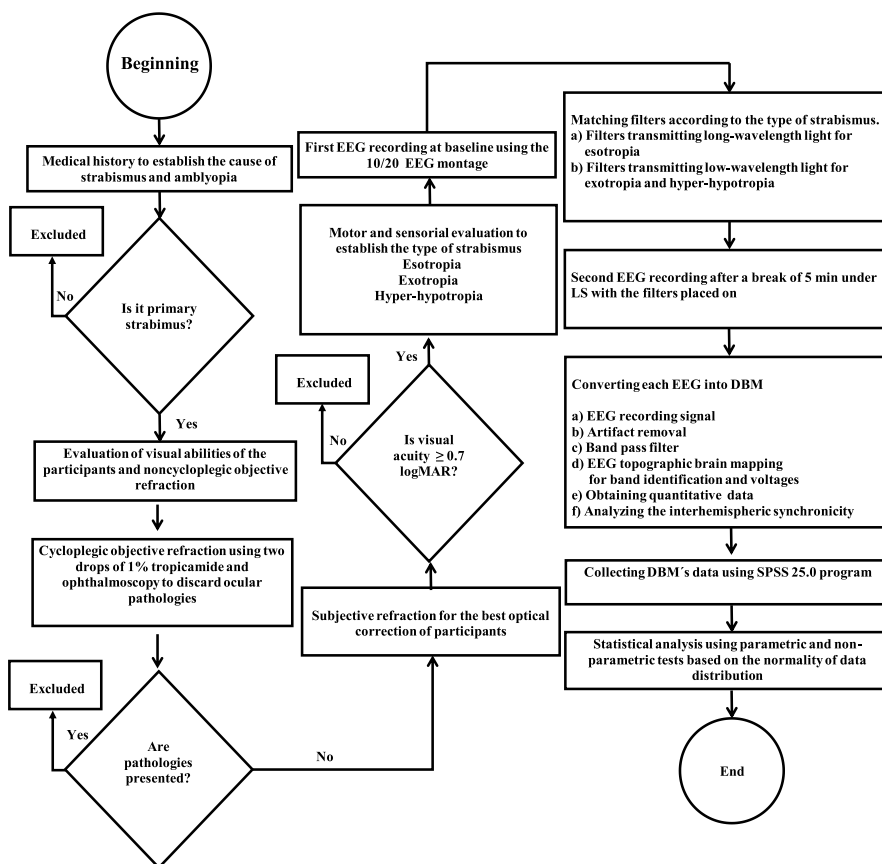
FIGURE 2. Flowchart illustrating the procedure followed in this study.

i) no history of eye disease, ii) best-corrected visual acuity (VA) ≥ 0.2 logMAR units, iii) no history of any neurological condition, nor psychiatric disease, iv) no use of medications that could alter the CNS. All HCs presented orthophoria at far and exophoria at near (mean 11.5 ± 3.9 diopters). Data on the medical histories of the patients and results from their clinical examinations were collected at the Autonomous University of Querétaro, México, from August 2019 to August 2020. The protocols were approved by our Institution's IRB with approval number 10848, and conform to the principles of the Declaration of Helsinki. Written informed consent was obtained from the participants or their parents before their enrollment in the study. Eligibility was established over a three-day period as follows.

D. DATA COLLECTION

Detailed medical histories regarding strabismus and amblyopia were collected from the patients by the neuro-optometrist in charge of the study on the first day. The following tests were performed: near and distance visual acuity, Lensometry of the optical correction of the participants. lensometry of the participants, noncycloplegic objective refraction, cycloplegic objective refraction using two drops of 1% tropicamide [31], and ophthalmoscopy to establish the type of fixation under the cycloplegic effect. To achieve better results, the optometric evaluation was performed from 10 am

to 12 pm after the participants had slept 8-9 hours. On the second day, subjective refraction for the best optical correction was performed. The following tests were then conducted: the repetition of the near and distance visual acuity examinations with the new prescriptions; measurements of the deviation and magnitude of strabismus; motor and sensory fusion; fixation and correspondence using the Macular Integration Test and Bagolini lenses; motility (paresis and paralysis); pupillary reflex; hyper-hypotropia; and the assessment of dissociated elements such as latent or manifest nystagmus, dissociated vertical deviation, angle variability, and limitation in abduction followed by horizontal incomitancies. Patients with a visual acuity of ≤ 0.3 logMAR were reexamined after wearing the newly prescribed glasses for four weeks. The type of strabismus was established based on the clinical data collected. The detailed neuro-optometric clinical testing can be found in the appendix section. On the third day, patients who met the inclusion criteria were scheduled for the baseline and during light stimulation cortical activity measurement through electroencephalography. The following flowchart represents the steps followed in this study (Fig 2).

E. EEG PARAMETERS AND PROCEDURE

The 10/20 EEG montage [32] was performed by a neurophysiologist at the Santo Tomas Hospital of Querétaro,

México. Two EEG recordings were performed for each patient: before (basal) and during the session of 20 minutes of light stimulation [12]. The evaluation was performed under low-light conditions with a break of 5 minutes between the two recordings. Data were recorded in the Neuronic™ Psychophysiology system. To maximize the patients' test performance, all participants were recommended to sleep 8-9 hours per day during the week preceding the EEG studies. The skin was cleaned prior to the placement of electrodes according to the international registration system 10/20: Fp1, Fp2, F3, F4, F7, F8, C3, C4, Fz, Cz, Pz, T3, T4, T5, T6, P3, P4, O1, O2. The mastoids were used as references for surface electrodes. The estimators of the parameters of the 10/20 registration system were as follows: band filter of 1-70 Hz (low- and high-pass filter), speed of 30 m/s, and sensitivity of 7 μV/mm. Fourier transformation was used for the quantitative analysis and the prerequisite conversion of the EEG into digital brain mapping by extracting 10 windows of 10 seconds in duration from the EEG and averaging the data. The baseline cortical activity recording began with 5 minutes of registration without activations during the waking-state, at rest, and while the participants' eyes were closed. We then conducted 10-minute activation, including hyperventilation and photo-stimulation, while the patients opened and closed their eyes to help measure their biological responses (biological calibration). The assessment was finished with a 5-minute segment without activation performed while the eyes of the patients were closed. After a break of 5 minutes, a second EEG recording of 20 minutes was performed, now with the filters placed as the case required. The most relevant data when analyzing a DBM are the relative and absolute power, and the average frequency. The mean and standard deviation for the baseline activity (alpha-wave) are obtained and the coherence (interhemispheric synchronicity) is checked. Spectral peaks (frequency) and voltages are also measured, with a topographic distribution of the above. The baseline values of the patient are compared with the values of the general population included in the program.

F. LIGHT STIMULATION PARAMETERS AND PROCEDURE

Fig. 1 in [12], illustrates the patient accommodation. The visible spectrum (380-780 nm), was used for LS. Of a set of 13 different glass filters of 24 mm in diameter and between 4 and 8 mm in thickness which transmit light in the blue and red spectrum were available, two or three were used in combination and mounted near the bulb according to the needs of each patient. Filters were chosen based on the patient's medical history, symptoms, and clinical findings according to the protocol for patients with strabismus and amblyopia established by the College of Syntonic Optometry (CSO). Light stimulation was administered in a 20-min session for all patients [12], [13]. For HCs, eight of whom were stimulated with filters transmitting light in the blue spectrum and the other nine, with filters transmitting light in the red spectrum, randomly chosen. The Syntonizer of the CSO used for light

stimulation features the following characteristics: a black tube of 50 cm in length, a frosted lens of 55 mm in diameter that appears as a glowing dot with saturated color, and a 115-V bulb with a vibration-series 50-W that delivers 1.4 Lux when unfiltered. The light could be presented as steady or strobed.

The light stimulation theory posits that low-energy, long-wavelength light (red) stimulates the sympathetic nervous system (used in patients with esotropia and amblyopia); mid-length wavelengths (green) balance physiology; and high-energy, short-wavelength light (blue) activates the parasympathetic nervous system (used in patients with exotropia and hyper/hypotropia), having an impact on the autonomic nervous system. The neurological pathway in charge of this process includes the retinohypothalamic tract (i.e., the non-visual pathway of light perception) and its projections to subcortical and cortical regions, which react to light stimulation [33].

G. STATISTICAL ANALYSIS

The non-parametric Mann-Whitney (U) test was used to detect differences between two independent samples. T-paired test and Wilcoxon test were used to detect changes between two related samples based on the normality of data distribution. The normality of data distribution was checked with Shapiro-Wilk (S-W) test. All statistical analysis were performed with SPSS Statistics Base 25.0. The confidence level (CI) used in this study was 95%, with an alpha of 0.05 ($\alpha = 0.05$). In this paper, DBM's data of SA patients are compared to HCs using the non-parametric Mann-Whitney (U) test, considering that the same variable, is not normally distributed in both groups. Given that SA and HCs are two independent samples, this method tests whether one variable tends to have higher values than the other. Additionally, the Mann-Whitney test is a test of both location and shape as it can detect differences in shape and spread as well as just differences in medians. It is an alternative of t-test when the data are not normally distributed. The parametric paired t-test is used in this paper to analyze the difference between two variables for the same subject, when the data are normally distributed, and the two variables are separated by time. In our case, we are measuring the cortical response at baseline and under the effect of light stimulation, having two EEG recordings, with a break of 5 minutes between them. On the other hand, the non-parametric Wilcoxon signed-rank test is used to compare two repeated measurement on a single sample when data are not normally distributed. The level of statistical significance is expressed as a p-value between 0 and 1. A p-value less than 0.05 ($p < 0.05$) is statistically significant. This indicates that the null hypothesis should be rejected and accept the alternative hypothesis. A p-value higher than 0.05 ($p > 0.05$) is not statistically significant. This means we retain the null hypothesis and reject the alternative hypothesis [34], [35]. As in this paper the distribution of data is analyzed using the Shapiro-Wilk test, parametric

TABLE 1. Demographics and clinical measurements of SA and HC groups.

Parameters	SA Mean ± SD	HC Mean ± SD	p-value
Male/female	9/8	9/8	-
Age (years)	18.1 ± 10.5	23.4 ± 4.8	0.63
Motor eye dominance	11R / 6L	15R/2L	-
Handedness	17R	16R/1L	-
Angle of esotropia (far/near)	29.0 ± 14.8 / 27 ± 17.0	-	-
Angle of exotropia (far/near)	12.7 ± 8.3 / 25.4 ± 12.5	-	-
Angle of hypertropia (far/near)	9.2 ± 3.0 / 9.2 ± 3.0	-	-
Visual Acuity OD (far/near)	0.3 ± 0.3 / 0.2 ± 0.3	0.01 ± 0.03/0.02 ± 0.04	<0.01/0.01
Visual Acuity OS (far/near)	0.3 ± 0.3 / 0.2 ± 0.2	0.0 ± 0.02/0.02 ± 0.04	<0.01/0.01
Stereopsis	128.8 ± 252.1	24.9 ± 11.3	< 0.01

*Mann-Whitney test comparing the two groups ($p < 0.05$ represented statistically significant differences). Data shown as mean standard deviation or n. *Abbreviations: SA, strabismus and amblyopia; HC, healthy control; OD, oculus dexter; OI, oculus sinister; R, right; L, left.

TABLE 2. EEG recordings of the cortical activity at baseline and during LS of SA and HC groups.

Parameters	SA baseline Mean ± SD	HC baseline Mean ± SD	SA during LS Mean ± SD	HC during LS Mean ± SD
Alpha-wave (α)	9.4 ± 1.1	10.4 ± 1.3	9.7 ± 0.8	9.7 ± 1.6
Theta-wave (θ)	4.6 ± 0.9	-	-	-
Low voltage ($< V$)	1.9 ± 2.9	-2.7 ± 0.6	3.3 ± 2.8	-3.1 ± 1.9
High voltage ($>V$)	3.5 ± 1.1	4.7 ± 0.8	5.5 ± 1.9	4.7 ± 1.4

* Data shown as mean standard deviation. *Abbreviations: LS, light stimulation SA, strabismus and amblyopia; HC, healthy control

TABLE 3. Mann-Whitney test comparing EEG measurements of the cortical activity at baseline and during LS of SA and HC groups.

Parameters	U of Mann-Whitney	p-value
Alpha-wave activity at baseline	81.0	0.029
Alpha-wave activity during LS	139.0	0.865
Low voltage at baseline	0.0	< 0.001
Low voltage during LS	1.0	< 0.001
High voltage at baseline	50.0	0.001
High voltage during LS	107.0	0.205

* Mann-Whitney test comparing the two groups ($p < 0.05$ represented statistically significant differences. *Abbreviations: LS, light stimulation

and non-parametric tests are used to provide a precise and robust statistical analysis.

IV. RESULTS

A. DEMOGRAPHIC AND VISUAL MEASUREMENTS

No significant age differences ($p = 0.63$) were detected between the two groups. By contrast, the differences observed between the two groups in the best-corrected visual acuity of both eyes at far ($p < 0.01$) and near ($p = 0.01$) and the amount of stereopsis ($p < 0.01$) were statistically significant (Table 1).

B. EEG DIFFERENCES COMPARING THE TWO GROUPS USING THE MANN-WHITNEY TEST

In the SA group, the alpha-wave activity ($p = 0.029$) and the high-voltage values ($p = 0.001$) recorded at baseline, were significantly lower compared to the HC group (Fig. 3 and Fig. 4). No statistically significant differences were found in these values during the administration of LS. By contrast, the low-voltage values were significantly higher in both states, at baseline and during LS ($p < 0.001$), (Table 2, Table 3, Fig. 5, and Fig. 6). A remarkable finding was the presence of theta-wave recorded at baseline and its absence during the administration of LS in the SA group (Table 2).
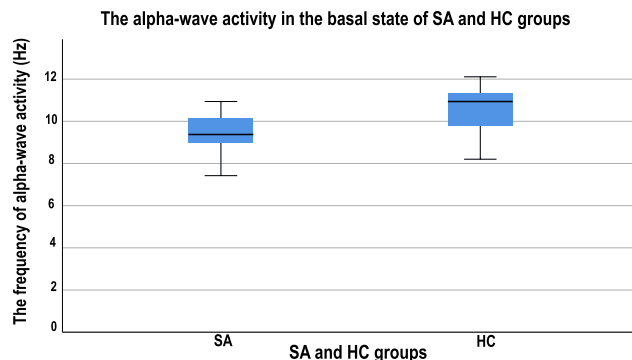

FIGURE 3. The frequency of alpha-wave activity of SA and HC groups recorded at baseline.

C. EEG DIFFERENCES INSIDE THE SAME GROUP USING T-PAIRED TEST AND WILCOXON TEST

The frequency of alpha-wave activity and low and high-voltage values were analyzed for each group separately, at baseline and during the administration of LS. Normal data distribution was found for the frequency of alpha-wave activity and high-voltage power in the HC group and high voltage in the SA group. Non-normal distribution was found
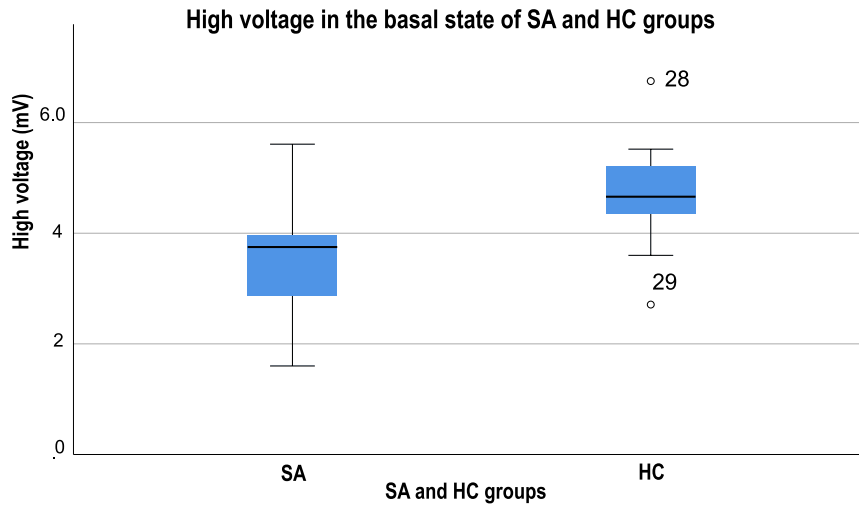
High voltage in the basal state of SA and HC groups

FIGURE 4. The high voltage of SA and HC groups measured at baseline.

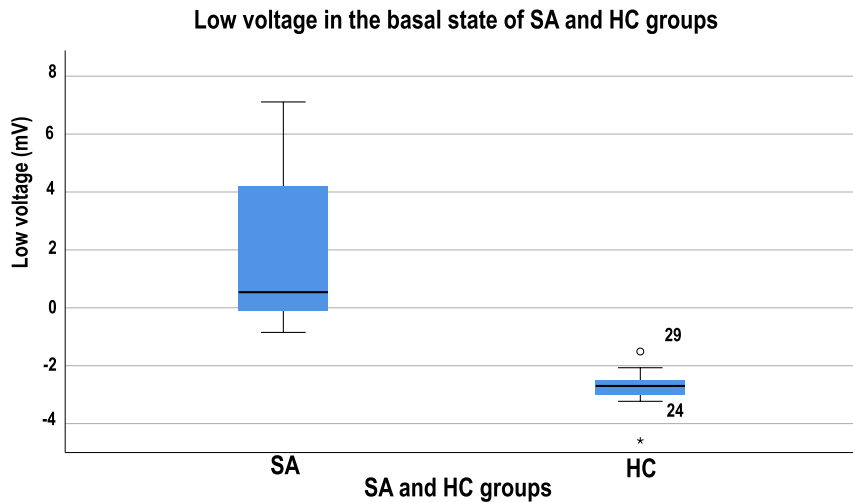## Low voltage in the basal state of SA and HC groups

FIGURE 5. The low voltage of SA and HC groups recorded at baseline.

TABLE 4. T-paired test and Wilcoxon test comparing EEG data inside the same group at baseline and during LS.

Parameters	Z-value	t-value	p-value
Alpha-wave of SA group	-1.651	-	0.099
Low voltage of SA group	-2.293	-	0.022
High voltage of SA group	-	-4.683	< 0.001
Alpha-wave of HC group	-	1.923	0.072
Low voltage of HC group	-0.308	-	0.758
High voltage of HC group	-	0.011	0.991

*T-paired test and Wilcoxon test comparing EEG data inside the same group ($p < 0.05$ represented statistically significant differences).

for low-voltage in both groups (HC and SA) and alpha-wave activity only in the SA group. The T-paired test was used for normal distribution and the Wilcoxon test for non-normal. Statistically significant differences were only seen in the low and high-voltage values of the SA group (Fig. 7 and Fig. 8). There was a statistically significant increase in both parameters during LS ($p = 0.022$ and $p < 0.001$ respectively), (Table 4).

D. EEG DIFFERENCES IN THE DISTRIBUTION OF THE ALPHA-WAVE ACROSS THE BRAIN, AT BASELINE, AND DURING THE ADMINISTRATION OF LS IN THE SA GROUP

When analyzing the baseline EEG and digital brain mapping of a healthy patient in the waking-state, alpha waves should be found in the posterior and occipital regions [36]. Table 5 shows that only 41.2% of the patients followed this pattern, suggesting an irregular alpha-wave distribution, with a predominance in the left hemisphere, showing an asymmetric activity pattern. By contrast, a homogenous distribution of the alpha waves towards the occipital brain regions was seen during the administration of LS in 88.2% of the patients (Table 6, followed by parietals regions in 11.8% of the patients.

E. EEG DIFFERENCES IN THE STATE OF BRAIN COHERENCE AND INTERHEMISPHERIC SYNCHRONICITY AT BASELINE AND DURING THE ADMINISTRATION OF LS IN THE SA GROUP

76.5% of the patients exhibited interhemispheric asynchronicity (absence of brain coherence) at baseline (Table
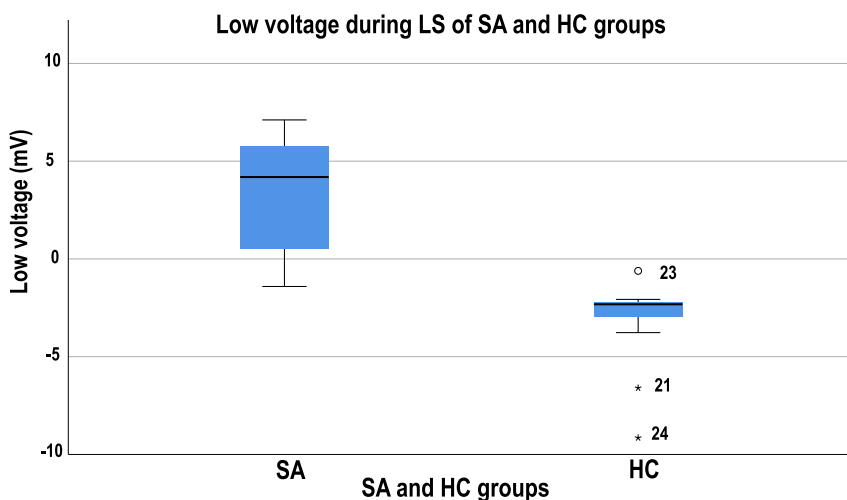
Low voltage during LS of SA and HC groups

FIGURE 6. The low voltage of SA and HC groups measured during the administration of LS.

High voltage of SA group in the basal state and during LS

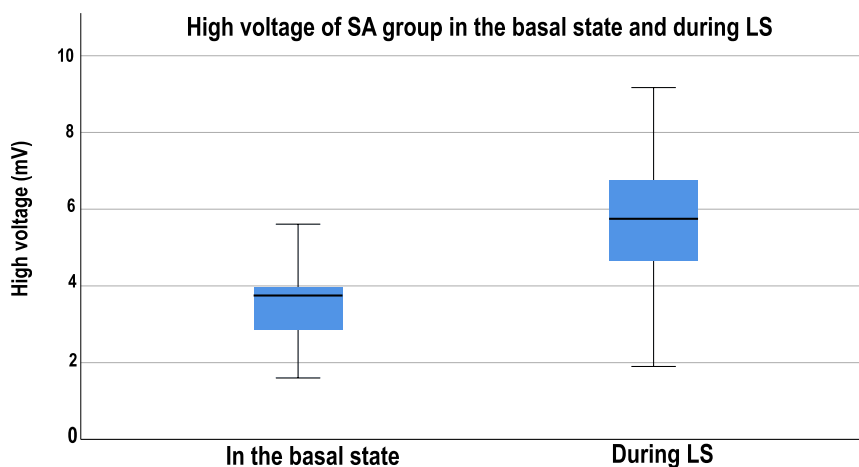

FIGURE 7. The high voltage of SA group measured at baseline and during the administration of LS.

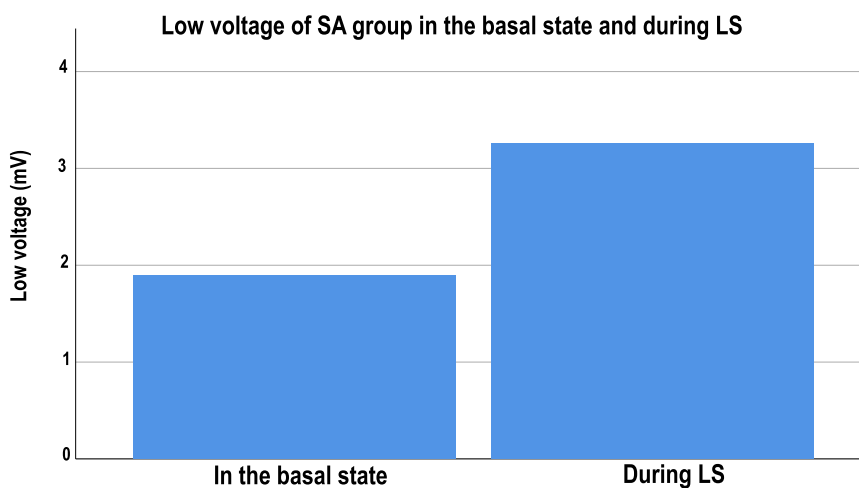**Low voltage of SA group in the basal state and during LS**

FIGURE 8. The low voltage of SA group measured at baseline and during the administration of LS.

5). By contrast, a state of interhemispheric synchronicity was found in all patients during the administration of LS (Table 6), indicating the heightened synchronization between the two hemispheres. Hence, light stimulation can help to balance the activity in the two hemispheres and promote synchronicity across the whole brain. The wavelength of

TABLE 5. Distribution of alpha and theta-waves and the state of brain coherence at baseline of SA group.

Patients	Distribution of (α)	Distribution of (θ)	Brain Coherence
001	Occipitals	Frontals	Synchrony
002	Parieto-occipitals	Fronto-centrals, predominating at centrals	Synchrony
003	Occipitals	Frontals and occipitals	Asynchrony of right temporal lobe
004	Frontals and left center-parietal lobe	Left frontal and right parietal lobe	Asynchrony
005	Right fronto-temporal and left parieto-occipital lobe	Frontals	Asynchrony of left temporal lobe
006	Occipitals	Right parieto-occipital lobe	Asynchrony of left temporal lobe
007	Frontals and occipitals	Frontals and centrals	Asynchrony of frontals and parieto-occipitals
008	Center-parietals	Right frontal and right parietal lobe	Synchrony
009	Left parietal lobe	Frontals and occipitals	Asynchrony of left parietal lobe
010	Left center-parietal lobe	Right frontal and right parietal lobe	Asynchrony of left centro-parietal lobe
011	Occipitals	Parieto-occipitals	Asynchrony of fronto-temporal and left parietal lobe
012	Left center-parietal lobe	Left parietal lobe	Asynchrony of left central and parietal lobe
013	Occipitals	Parietals and occipitals	Asynchrony of left frontal lobe
014	Left parieto-occipital lobe	Left parieto-occipital lobe	Asynchrony of left fronto-temporal lobe
015	Occipitals	Occipitals	Asynchrony of fronto-temporals
016	Occipitals	Right frontal lobe	Synchrony of occipitals
017	Parietals	Parietals	Asynchrony of left parietal lobe

*Red represents patients who used filters transmitting long-wavelength light (red-orange-yellow) and blue the patients who used filters transmitting low-wavelength light (from bright to dark blue and the combination of grey-blue and violet-blue). Filters transmitting medium-wavelength light (green) are stabilizing filters and were combined either with red or blue filters according to the needs of each patient.
*EEG recordings were carried-out in the waking-state.
*Abbreviations: (α), alpha-wave; (θ), theta-wave

TABLE 6. Distribution of alpha-wave and the state of brain coherence during light stimulation of SA group.

Patients	Distribution of (α)	Brain Coherence
001	Occipitals	Synchrony
002	Occipitals	Synchrony
003	Occipitals	Synchrony
004	Occipitals	Synchrony
005	Occipitals	Synchrony
006	Occipitals	Synchrony
007	Occipitals	Synchrony
008	Occipitals	Synchrony
009	Occipitals	Synchrony
010	Occipitals	Synchrony
011	Parietals	Synchrony of parietals
012	Occipitals	Synchrony
013	Occipitals	Synchrony
014	Occipitals	Synchrony
015	Occipitals	Synchrony
016	Occipitals	Synchrony
017	Parietals	Synchrony of parietals

*Red represents patients who used filters transmitting long-wavelength light (red-orange-yellow) and blue the patients who used filters transmitting low-wavelength light (from bright to dark blue and the combination of grey-blue and violet-blue). Filters transmitting medium-wavelength light (green) are stabilizing filters and were combined either with red or blue filters according to the needs of each patients. *EEG recordings were carried out in the waking-state. *Abbreviations: (α), alpha-wave

light transmitted by the filters could not be associated with changes in the activity of a specific brain region or the state of coherence.

F. A REMARKABLE EEG FINDING WAS THE PRESENCE OF THETA WAVES RECORDED AT BASELINE AND ITS DISTRIBUTION ACROSS THE BRAIN IN THE SA GROUP

Theta waves (4-7 Hz) occur primarily during sleep or relaxed wakefulness; their presence in the waking-state is associated with clinical conditions. The distribution of the theta-wave favored the frontal lobe, followed by the occipital and parietal lobes, suggesting that the patients' conditions may have compromised brain function in the specific cortical areas where

theta-wave activity was observed (Table 5. Less theta-wave activity was recorded in the central regions, related to motor areas. No theta-wave was recorded during the session of 20 minutes of LS.

G. EEG DIFFERENCES IN THE DISTRIBUTION OF THE ALPHA-WAVE ACROSS THE BRAIN, AT BASELINE, AND DURING THE ADMINISTRATION OF LS IN THE HC GROUP

At baseline, alpha waves were mostly found in the occipital lobes, as expected. Nevertheless, the distribution of alpha-wave activity shifted towards the parietal, frontal, and temporal regions of both hemispheres during the administration

TABLE 7. Distribution of alpha-wave and the state of brain coherence at baseline and during light stimulation of HC group.

Patients	Distribution of (α) at baseline / during LS	Brain Coherence at baseline / during LS
001	Occipitals / Occipitals	Synchrony of occipitals / Synchrony of occipitals
002	Occipitals / Parietals	Asynchrony of parieto-occipitals / Asynchrony of frontals
003	Occipitals / Parietals	Synchrony of parieto-occipitals / Asynchrony of fronto-parieto-occipitals
004	Occipitals / Occipitals	Asynchrony of parieto-occipitals / Asynchrony of parieto-occipitals
005	Parieto-occipitals / Occipitals	Asynchrony of parieto-occipitals / Asynchrony of fronto-parieto-occipitals
006	Parieto-occipitals / Frontals and parieto-occipitals	Asynchrony of parieto-occipitals / Asynchrony of fronto-parieto-occipitals
007	Parietals / Frontals and Parietals	Synchrony of parietals / Synchrony of parietals
008	Parietals/Parietals	Synchrony of parietals / Synchrony of parietals
009	Occipitals / Parietals	Synchrony of parietals / Synchrony of parietals
010	Occipitals / Parietals	Synchrony of parieto-occipitals / Synchrony of parietals
011	Occipitals / Parieto-occipitals	Synchrony of occipitals / Synchrony of occipitals
012	Parieto-occipitals / Center-parietals	Synchrony of parieto-occipitals / Synchrony of parieto-occipitals
013	Fronto-parieto-occipitals / Temporo-parietals	Synchrony of parieto-occipitals / Synchrony of occipitals
014	Occipitals / Occipitals	Synchrony of occipitals / Synchrony of occipitals
015	Occipitals / Temporo-occipitals	Synchrony of occipitals / Synchrony of occipitals
016	Occipitals / Occipitals	Synchrony of occipitals / Synchrony of occipitals
017	Occipitals / Occipitals	Synchrony of occipitals / Synchrony of occipitals

*EEG recordings were carried out in the waking-state. *Abbreviations: (α), alpha-wave; LS, light stimulation

of LS, suggesting an altered state of brain activity induced by the LS. A 23.5% of the HC group presented a state of asynchrony of parieto-occipital lobes at baseline without any clinical manifestation 21, which shifted towards an asynchrony of fronto-parieto-occipital lobes during LS. The state of brain coherence did not change for the rest of the HC group during the administration of LS (Table 7). The wavelength of light transmitted by the filters could not be associated with changes in the activity of a specific brain region or the state of coherence.

V. DISCUSSION

The present study uses EEG converted to DBM to collect and analyze changes in the metrics of cortical activity, such as frequencies, voltages, and coherence during the administration of LS in 17 patients with strabismus and amblyopia, and 17 healthy controls, aged 8-30 years. The visible spectrum of light is used for this purpose, as exposure to light radiation of between 380-780 nm in wavelength has been recommended as a retinal stimulation method to be administered as an adjunctive, non-invasive treatment for visual disorders [37]. Considering that light reaches the visual cortex through the retina and the possibility to modify EEG patterns by hormonal, biochemical, and neuroelectric processes [11], it is expected that LS has an impact on the brain activity, measured in the waking-state. Four parameters helped to identify the cortical activity of SA and HC groups: 1) the activity and distribution of the alpha-wave, 2) the interhemispheric synchronicity which represents the state of neural brain coherence (Figs 9-11), 3) the unexpected discovery of the theta-wave recorded at baseline in the SA group, and 4) the anteroposterior gradients which indicates low (anterior brain regions) and high (posterior brain regions) voltages in the brain.

A. FIRST AND SECOND PARAMETER

In the present study, particular interest is shown in measuring and monitoring the symmetry of alpha-wave activity and its distribution within hemispheres. Its activity in the waking-state represents the cortical functionality. By contrast, the beta-wave activity which is found in frontal lobes, is not considered for the statistical analysis, as not being directly related to the electrical functionality of the brain [38]. Alpha waves (8-12 Hz) predominately originate from the occipital lobe (visual cortex) and posterior regions (associated areas) of the brain during wakeful relaxation while eyes are closed. Alpha-wave activity decreases when eyes are open and during drowsiness and sleep [36]. The alpha-wave activity measured at baseline was higher in the HC group compared to the SA group. Based on the physiology of the visual system, these differences could be related to the integrity and functionality of visual pathways, as well as the levels of visual attention [39]. Under normal circumstances, alpha-wave activity should decrease when eyes are open, as recorded in HCs. However, during LS, the frequency of alpha-wave activity was incremented in SA patients. These findings hypothesize that visual attention is voluntarily directed to the visual stimulus when presented to SA patients. Changes in the alpha-wave activity should then be proportional to the amount of visual attention given to the light stimulus. Clinically, it could be an indicator of higher levels of visual engagement and enhancement on the functionality and integrity of visual pathways. When it comes to its distribution within hemispheres, several variants of atypical alpha-wave activity, such as frontal, temporal, central, and parietal were observed prior to LS. As different brain areas are associated with specific brain activities (e.g., Cz, C3, and C4 have been associated with sensory and motor functions; Pz, P3, and P4 with perception and differentiation;
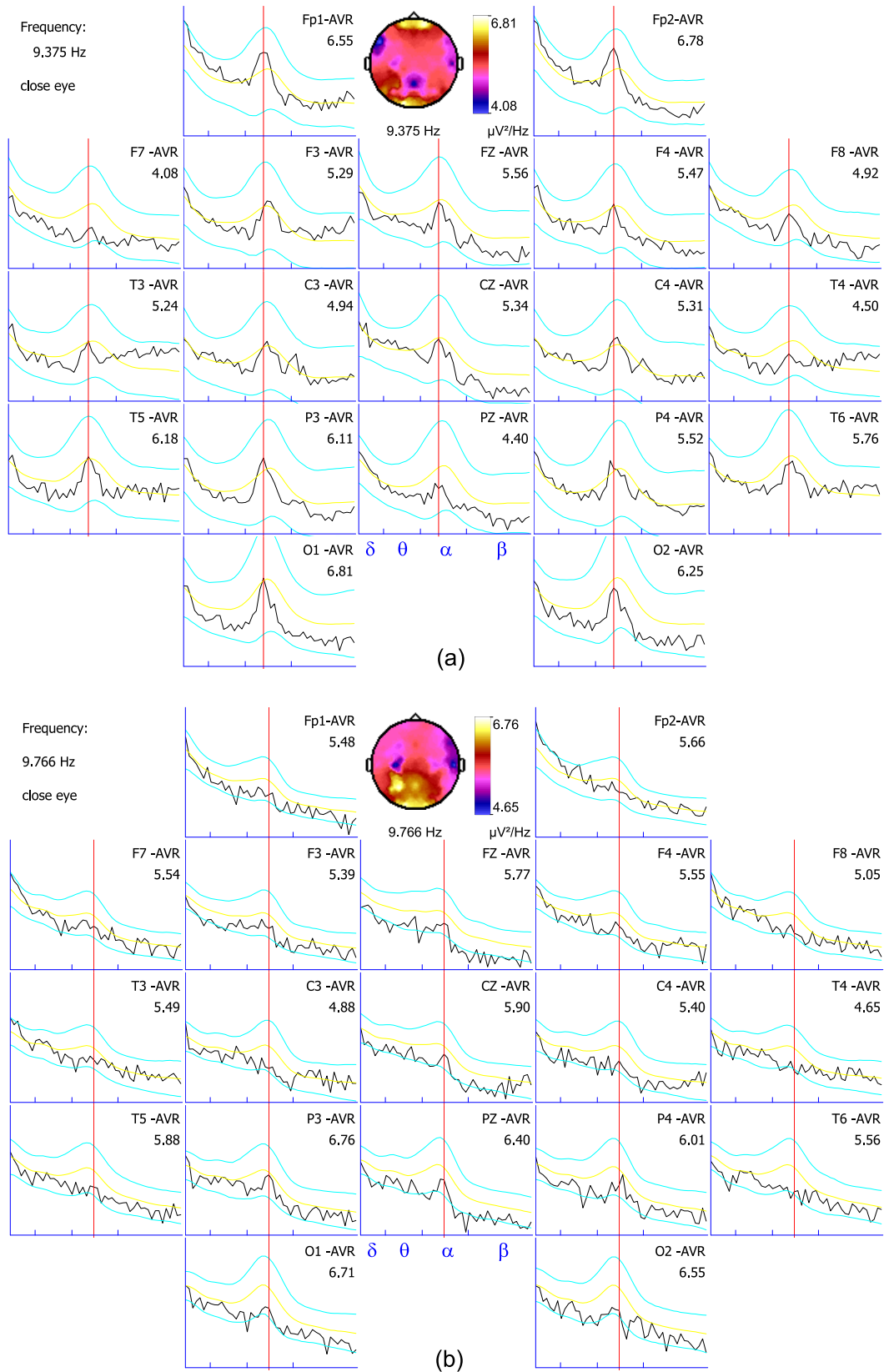
FIGURE 9. The distribution and frequency of alpha-wave activity at baseline (a) and during (b) light stimulation through digital brain mapping.
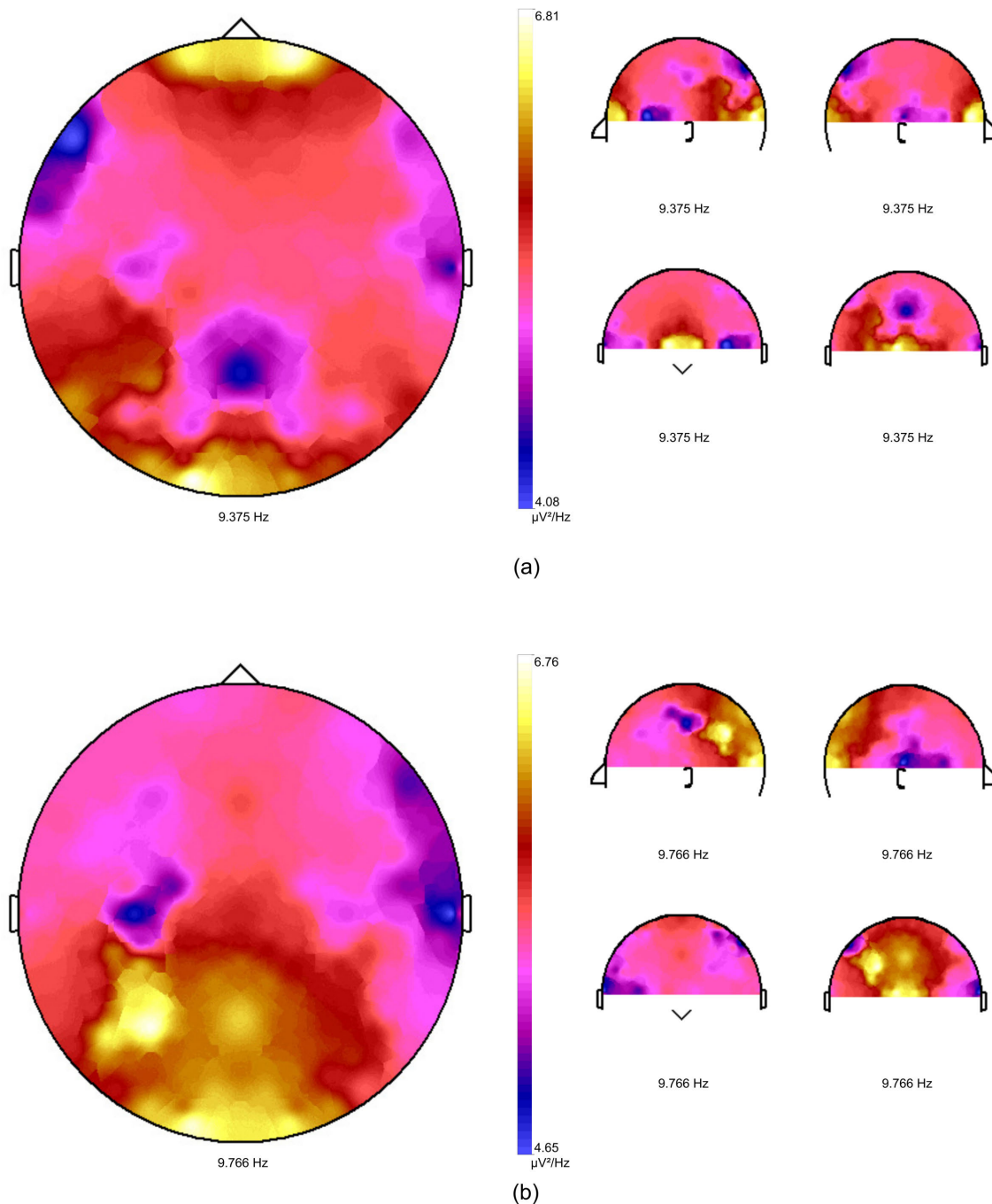
(a)

(b)

FIGURE 10. The anteroposterior gradient at baseline (a) and during light stimulation (b), as measured in μV2/Hz, through digital brain mapping. Lower voltage is represented in blue-pink, while higher voltage is indicated by bright yellow red.

F7 with rational activities; T5 and T6 with memory; T3 and T4 with emotional situations; and O1 and O2 with visual processes [11]) the spatial distribution of the alpha-wave activity could indicate the relative activity of various cognitive processes. During the administration of LS, the distribution of the alpha-wave was prompted towards the posterior and occipital brain regions and a state of interhemispheric symmetry and synchronicity was established in all patients. So, coherence, which describes the networks of functional and anatomical

connections across the brain and the synchronous activations of the neurons was established [40]. By contrast, LS altered the distribution of alpha waves within hemispheres, and the state of synchronicity in HCs. Considering that HCs possess a functional visual system without clinical manifestations, there is no need for rehabilitation. LS acts in this case as a destabilizing stimulus for the brain, as recorded by the EEG. Additionally, the observed changes were independent of the wavelength of light transmitted by the filters. Based on the
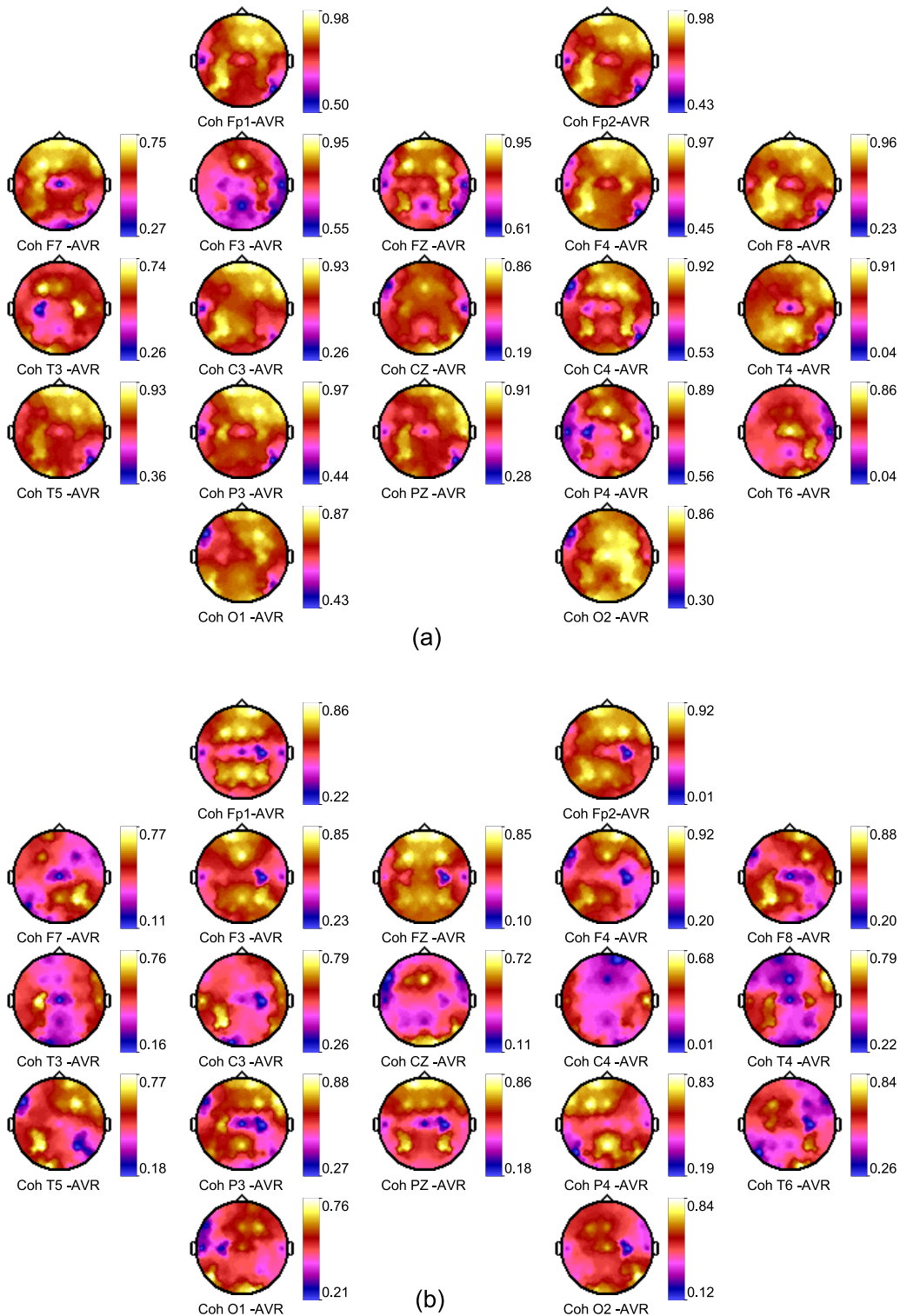
FIGURE 11. The interhemispheric coherence at baseline (a) and during light stimulation (b) measured through digital brain mapping. Fz, Cz, and Pz are situated along the midline of the scalp and thus divide the hemispheres.

physiology of the visual development and its functionality, dysfunction visual pathways that need to be rehabilitated react positively to an adequate stimulus. Using LS we provide the visual system with a stimulus to react and overcome its status "quo." The aforementioned could be the reason behind the differences recorded in the brain activity of SA and HCs. Likewise, knowing that neuroplasticity exists throughout life, with different responses according to age [41], changes can be produced to the visual system as the rest of the sensory and motor modalities.

B. THIRD PARAMETER

A remarkable finding of the EEG recordings is the presence of the theta-wave at baseline, in patients with strabismus and amblyopia. Theta waves do not typically present in the waking-state, as they indicate slower neural processing and are an indirect marker of age [36]. Its distribution featured a frontal predominance in most of the patients with strabismus and amblyopia. Considering that the presence of theta waves in the frontal lobes is generally observed in patients with neurodevelopmental disorders, our findings suggest that strabismus and amblyopia might also be considered as the result of dysfunctional cortical maturation. Further, the depression of the brain activity in a specific region may indicate aberrations in functions associated with this brain area [36]. Based on the neurology of the brain functionality, theta-wave is generally observed during drowsiness, and its appearance during wakefulness can indicate focal, regional, or generalized cerebral dysfunction. However, the present study is limited in so far as it did not perform any clinical neuropsychological studies, and potential associations between neurological features and our neuroimaging data could not, therefore, be identified. By comparison, no theta-wave was recorded during the administration of LS in the SA group, which indicates that light could be an activating stimulus for the brain.

C. FOURTH PARAMETER

The brain voltage expresses neural activation and indicates the sum of the recorded action potentials of neurons across electrodes. It must be symmetrical and synchronous across the brain hemispheres and is typically lower in the anterior region and higher in posterior areas. The anteroposterior gradient indicative of the low and high voltages in the brain presented statistically significant differences when comparing the two groups. In the qEEG, no specific value is provided for the measured voltage. What should be highlighted, however, is that low voltage took negative values in HCs but positive ones in most of SA patients, both at baseline and during the administration of LS. The difference between the two values (high voltage - low voltage value) was bigger in HCs when compared to SA patients. Additionally, low and high voltage values increased significantly during LS in SA patients, without statistically significant changes in HCs. Higher voltage in a developed and functional brain is indicative of a greater neural activation. It can be an indirect measure of the number of synapses, which in turn defines the neural networks and cortical plasticity [41]. These results can be translated into a defined anteroposterior voltage gradient in the SA group, followed by an increased cortical activity and functionality during LS. The neurophysiological changes mentioned above help the continuous remodeling of neurosynaptic organization that optimizes the functioning of neural networks. The more signals are sent between neurons, the stronger the connections grow. This phenomenon accounts for why each new experience or event can help the brain to re-wire its physical structure [41]. Based on the aforementioned, when a specific pattern of light stimulation is offered to a dysfunctional visual

pathway, it could trigger new responses in benefit of the brain's re-wiring process.

Complementing previous studies on light exposure, our research shows that during LS, SA patients established a perfect state of interhemispheric synchronicity, suggesting a balanced communication between the hemispheres with a total lack of theta rhythm. Likewise, higher brain voltage which indicates greater neural activation, and a symmetric distribution of the alpha-wave towards the posterior and occipital lobes was also recorded. Statistically, LS did not provoke any significant changes in alpha-wave activity as already reported in a previous study [5], but clinically there were measured higher levels of alpha-wave activity in the brain of SA patients. qEEG is used as a method of study in the present research, as literature features little information about the cortical electrical activity of strabismic and amblyopic patients [41]. Nevertheless, other techniques have been used to study the brain's functionality of strabismic patients. Differences found in the brain activity patterns [21], [42], cortical thickness [22], and functional connectivity [23] relate strabismus to changes in the white and gray matter, depending on its type and time of appearance. Through this research, we provide new information about the cortical activity in the waking-state of strabismic and amblyopic patients at baseline and during the administration of light stimulation, and its role as a potential brain modulator, to help brain synchronization. The synchronization between different brain areas is characteristic to a normative neurophysiological organization and is a target outcome of many therapies related to the child neurodevelopment process [43], [44]. Our results might help to inform the future development of clinical treatments and practice. Additionally, considering the multiple projections of the non-visual pathway throughout the brain, the potential of light-stimulation therapy should be considered in the context of treating SA patients and other neurodevelopmental disorders as well. Finally, this research comes to complement what the studies mentioned above have shown; that strabismus comes with changes in the whole brain, reflected in the cortical electrical activity of these patients. Based on these results, LS should be considered as a possible non-invasive treatment.

VI. CONCLUSION

Significant differences were seen in the cortical electrical activity of patients with strabismus and amblyopia when compared to healthy controls, at baseline and during the administration of LS. Specifically, at baseline, patients with strabismus and amblyopia present: i) lower frequency of alpha-wave activity ($p = 0.029$) with an abnormal distribution within hemispheres, ii) theta-wave with a predominance in the frontal lobes, which relates these visual conditions to neurodevelopmental disorders, iii) higher values of low voltage ($p < 0.001$) and lower values of and high voltage ($p = 0.001$) iv) interhemispheric asynchronicity with a predominance in the left hemisphere. On the other hand, the administration of LS modulates the brain activ-

ity of SA patients by i) modifying high and low voltages ($p < 0.001$ and 0.022 respectively), which define the antero-posterior gradient), ii) eliminating theta-waves, iii) distributing alpha-wave activity towards the occipital lobes iv) bringing synchronicity between hemispheres. For the HC group, LS alters the distribution of alpha waves within hemispheres, and the state of interhemispheric synchronicity. There were no statistically significant changes in the frequency of the alpha-wave or the anteroposterior gradient. To conclude, LS provokes positive changes in the cortical electrical activity of strabismic and amblyopic patients by increasing the cortical connectivity, enhancing neural activation, and bringing to balance the interhemispheric electrical activity. This evidence converts it into a potential brain stimulator and should be considered as a complementary therapy in the treatment of these patients and other neurodevelopmental disorders.

APPENDIX A
NEURO-OPTOMETRIC CLINICAL TESTING
Identical for all patients, the testing procedures were divided into motor and sensorial components to diagnose each patient accurately.

Motor clinical testing: The direction and magnitude of deviation were established using the cover and Krimsky tests. While the cover test is considered the most reliable means of measuring the angle of strabismus [45], the Krimsky test better suited for children who have difficulty collaborating. Both tests were performed with the help of the ophthalmologist who participated in the evaluation processes.

Two versions of the distant and near cover test were conducted with the Spielmann translucent occluder. The cover-uncover test indicated the presence of a tropia state, and the deviation was neutralized with the Berens prism bar. The alternating cover test was performed to determine the total magnitude of the deviation on the basis of the phoria and tropia state of the patient. The maneuver of Posner was used to define the exact amount of hyper-hypotropia in the presence of dissociated vertical deviation. Two translucent Spielmann occluders and the Berens prism bar were used.

Both the direct and indirect versions of the Krimsky test were used by placing the Berens prism bar in front of the deviated and non-deviated eyes, respectively.

Hyper- and hypo-functioning extraocular muscles were classified with crosses of $+1$ to $+4$ and -1 to -4, respectively. The Maples Oculomotor Test was employed to evaluate saccades and pursuit movements [46].

Sensorial clinical testing: Distance and near visual acuity were measured using logMAR charts at distances of 3 m and 40 cm, respectively. A difference of 0.20 logMAR (best-corrected visual acuity) between the two eyes was defined as unilateral amblyopia, while a best-corrected visual acuity of $= 0.20$ logMAR relative to age-corrected standards indicated bilateral amblyopia [47].

The Worth Dot test was used to evaluate flat and peripheral fusion and detect any suppression by applying red-green

lenses over the optical correction of the patient at three different distances: close, intermediate, and distant [48], [49].

The Lang Test, which detects disparities of between 1200 and 550 arcmin, was used to evaluate gross fusion in patients without polarized lenses that could dissociate the binocular system. Although the test avoids monocular contours, it offers monocular cues when the patient does not remain stationary relative to the image. The test was repeated under monocular viewing conditions to confirm the result. Patients who obtained the same score under monocular and binocular viewing and had no stereopsis, as assessed with the Random Dot test (see below), were considered to exhibit stereoblindness.

The Random Dot test was used to evaluate depth perception using contour (local) and global stimuli to measure stereopsis. The test was applied only at close distances and with polarized glasses placed over the patients' optical-correction glasses. The test detects disparities ranging from gross to fine stereopsis (2000–40 arcmin).

Fixation was first measured in all patients with direct ophthalmoscopy under cycloplegia.

The Bagolini lens test was performed to assess sensory correspondence and detect suppression. Striated lenses were used over the optical correction of the patient with the spotlight situated at 40 cm.

The Macular Integration Test was performed to confirm sensory correspondence and fixation in patients with a visual acuity of $= 20/100$. The test was conducted in a dimly lit room, and the patients wore correction glasses. An afterimage was used for this purpose according to the proposal advanced by Bielchowsky [48], [49].

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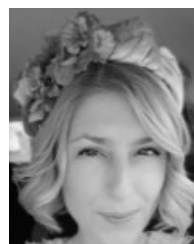
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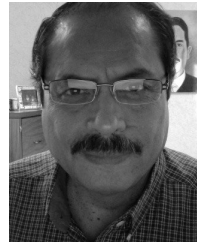
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