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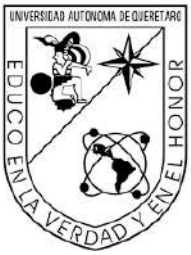

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Análisis del Efecto Syntoni en la Corteza Cerebral de Pacientes con Estrabismo y Ambliopía mediante EEG y MCD

Tesis

Como parte de los requisitos para obtener el Grado de Docotrado en Ingeniería

Presenta
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ANALYSIS OF THE SYNTONIC EFFECT ON THE CERERBAL CORTEX OF PATIENTS WITH STRABISMUS AND AMBLYOPIA USING EEG AND DBM

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This thesis is dedicated to people like me, who always manage to succeed, no matter what life brings us...

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Abstract

This research measures and compares the cortical activity at baseline, during light stimulation (LS) and after light therapy (LTH), in patients with strabismus and amblyopia (SA) and healthy controls (HCs), to understand the differences in its functionality and propose LTH as a potential brain stimulator and treatment. Quantitative electroencephalography (qEEG) was used to record the brain activity of participants. Digital brain mapping (DBM) allowed the identification of changes in frequency, voltage, and brain coherence. Clinical metrics such as the visual acuity, angle of deviation, phoria state, stereopsis, and visual fields determined the visual performance at baseline and after the LTH program.

Our research determined that at baseline, patients with strabismus and amblyopia present lower frequency of alpha-wave activity with an abnormal distribution within hemispheres; theta-wave with a predominance, in the frontal lobes, which relates these visual conditions to neurodevelopmental disorders; higher values of low voltage and lower values of and high voltage, and interhemispheric asynchronicity with a predominance in the left hemisphere. On the other hand, during the administration of LS significant improvements were seen on the anteroposterior gradient; the distribution of the alpha-wave activity towards the occipital lobes and the interhemispheric synchronicity. No theta-waves were recorded during this phase.

Nonetheless, the use of LS in HCs, altered 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. After LTH, results showed a constant higher alpha-wave frequency for HCs. Low voltages remained negative for HCs and positive for SA patients across stimulation. After LTH, high voltage increased in SA patients, and decreased in HCs. A second spectral peak, (theta-wave), was exclusively recorded in SA patients, at baseline and after LTH. Positive Spearman correlations for alpha-wave frequency, low and high voltages were only seen in SA patients. Synchronized brain activity was recorded in all SA patients stimulated with filters transmitting light in the blue but not in red spectrum.

Enhancement in the visual performance of SA patient was found, whereas deterioration of the phoria state and a decrease in the amount of stereopsis was seen in HCs. To summarize, LS and LTH 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. However, this research determined that only a suffering brain and a visual pathway which needs to be enabled can benefit from LTH.

Resumen

Esta investigación mide y compara la actividad cortical en estado basal, durante la fotoestimulación (FE) y después de la fototerapia (FT), en pacientes con estrabismo y ambliopía (EA) y controles sanos (CS), para comprender las diferencias en la funcionalidad cortical y proponer la FT como potencial estimulador y tratamiento cortico-visual. Se utilizó electroencefalografía cuantitativa (qEEG) para registrar la actividad cerebral de los participantes. El mapeo cerebral digitalizado (MCD) permitió la identificación de cambios en la frecuencia de la onda alpha, el voltaje y la coherencia cerebral. Las medidas clínicas como la agudeza visual, el ángulo de la desviación, el estado de foris, la estereopsis y los campos visuales determinaron el rendimiento visual al inicio y después del programa de FT.

Nuestros resultados indican que en estado basal, los pacientes con estrabismo y ambliopía presentan menor frecuencia de actividad de la onda alpha con una distribución anormal dentro de los hemisferios; onda theta con predominio en los lóbulos frontales, lo cúal relaciona estas condiciones visuales con difunciones de neurodesarrollo; valores más altos del voltaje bajo y valores más bajos del voltaje alto y asincronicidad interhemisférica con predominio en el hemisferio izquierdo. Por otro lado, durante la administración de la FE, cambios significantes se presentaron en el gradiente anteroposterior; la distribución de la actividad de ondas alpha hacia los lóbulos occipitales y la sincronicidad interhemisférica. No se registró actividad de ondas theta durante esta fase.

Sin embargo, la FE alteró la distribución de ondas alpha dentro de los hemisferios y el estado de la sincronicidad interhemisférica en los CS. No hubo cambios estadísticamente significativos en la frecuencia de la onda alpha o el gradiente anteroposterior.

Después de la FT, los resultados mostraron que la frecuencia de onda alpha siguió siendo más alta en los CS. Los voltajes bajos permanecieron negativos para los CS y positivos para los pacientes con EA despues de la FT. Además, el voltaje alto aumentó en los pacientes con EA y disminuyó en los CS. Un segundo pico

espectral, (onda theta), se registró exclusivamente en pacientes con EA, ene stado basal y después de la FT.

Se encontraron correlaciones positivas de Spearman para la frecuencia de la onda alpha y los voltajes altos y bajos solamente en pacientes con EA. Se registró sincronización de la actividad cerebral en todos los pacientes con EA estimulados con filtros que transmitían luz en el espectro azul pero no en el rojo. Se encontró una mejora en el rendimiento visual del paciente con EA, mientras que en los CS se observó un deterioro del estado de forias y una disminución en la cantidad de estereopsis.

En resumen, la FE y FT provocan un estado de maleabilidad en el cerebro de los pacientes con EA, al incrementar la conectividad cortical, potenciar la activación neural y equilibrando la comunicación interhemisférica, lo que convierte la luz en un potencial estimulador cerebral que debe considerarse como un terapia complementaria en el tratamiento de estos pacientes. Sin embargo, solo un cerebro que sufre y una vía visual que necesita rehabilitarse pueden beneficiarse de la FT.

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1. Introduction

1.1 Motivation

In the field of the visual science, strabismus, and amblyopia (SA) have often been seen as a cosmetic disadvantage. However, during the last decade, neuroimaging studies, have shown the implication of the neocortex, with changes found in the grey and white matter, which place strabismus and amblyopia among neurodevelopment disorders [1,2]. Additionally, remodeling of the brain connectome of these patients, is directly reflected in their visual performance, where sensorimotor adaptations, depending on the type and time of appearance are found. Likewise, strabismus and amblyopia have been proved to have a bad impact on the self-esteem and life quality of these patients [3].

Eye muscle surgery, eye patching and visual therapy have been used to treat strabismus and amblyopia during decades. However, eye muscle surgery and eye patching are frequently accompanied by unwanted outcomes. Regression, consecutive strabismus, and amblyopia of the patched eye are often presented in these situations [4]. Visual therapy on the other hand, could last from 2 to 3 years, and results are not always maintained once the therapy is over. Considering that light therapy (LTH) has been successfully used in the field of neuroscience [5,6], its introduction in the field of visual science, would impact the treatment process of patients with strabismus and amblyopia.

Results obtained during both phases of this research, support the theory of light being an important treatment to visual dysfunctions. Phase one measured and compared the cortical activity at baseline and during LS in SA patients and HCs, to understand the differences in its functionality and propose LS as a potential brain stimulator. Seventeen SA patients and seventeen HCs were enrolled for this purpose. Changes in frequency, voltage, and brain coherence were identified through DBM. A total of 68 DBM was analyzed for this purpose. At phase two, the brain activity and visual performance at baseline and after light LTH, of seventeen SA patients, and eleven HCs was assessed. Quantitative electroencephalogram analysis (qEEG) was used to record the brain activity, and clinical metrics such as

the visual acuity, angle of deviation, phoria state, stereopsis, and visual fields determined the visual performance. Our results provided brand-new information about the impact of the visible spectrum on brain activity and visual performance of SA patients and HCs. LTH, proved to bring synchronicity between hemispheres, which is the key to a healthy functional brain network. As a result, LTH should be considered the first step before any other treatment to enhance brain response and prepare the shore for the next step.

Based on the scientific data and evidence gathered through this research, a significant contribution in the field of visual health and neurodevelopment disorders is made, which broadens the understanding of the LTH effect across the brain of SA patients, and the degree at which it can be clinically reflected in the visual performance. Evidence-based decisions can then be taken to determine the extent of LTH required for the whole-therapy treatment of a patient with strabismus and amblyopia or other groups of patients with neurodevelopmental disorders.

1.2 Problem Description

In the field of biomedicine, light therapy is a concept that has gained strength over the years as it has been proven to be efficient in the treatment of Central Nervous System diseases (CNS) and has also been implemented with great success in different diagnostical, surgical and therapeutical areas [7].

In the field of optometry, Syntonic phototherapy has already been used empirically and clinically in patients with strabismus and amblyopia, but literature refers no previous scientific works related to its real impact on the brain and the visual system of these patients [8,9].

The prevalence of strabismus varies widely in the world [10], and it is generally followed by amblyopia, a cortico-visual adaptation which affects 1–4% of the population worldwide [11]. Considering improvements in perinatal and obstetric care which have been associated with the increment of premature children's survival, and/or other patients suffering neurological damages, and the near distance visual stress that is accompanied by significant binocular dysfunctions, the percentage of strabismus accompanied amblyopia is raising at a fast speed [12]. The visual system dominates over the rest of sensorial modalities, if we consider that 70% of the total sensory input to the brain comes from the two eyes. Brain research has identified 300 intracortical pathways linking over 30 different cortical areas involved in processing visual information. Taking into consideration that 50% of the cortex is related to visual processing, the treatment of visual deficiencies becomes crucial [13].

In this research, light therapy was used to modulate the brain activity and enhance the visual performance of patients with strabismus and amblyopia. Quantitative electroencephalography (qEEG) made it possible to measure and quantify the impact of different wavelengths of the visible spectrum on the cortex of SA patients. The neuro-optometric exam permitted gathering and comparing the visual performance of the participants before and after the LTH process.

Moreover, healthy controls, helped us to understand that light therapy only benefits patients who really need it, and important side-effects and disorganization can be presented in a normally functional brain with a balanced visual system.

1.3 General Objective

To calculate the Syntonic effect on the cerebral cortex and visual system of patients with strabismus and amblyopia using quantitative electroencephalography and its impact on the visual performance of the participants.

1.3.1 Specific Objectives

a) To measure the cortical electrical activity at baseline, during 20 minutes of light stimulation and after 20 sessions of light therapy in all participants.
    - Alpha-wave distribution
    - Anteroposterior gradient (low and high voltage)
    - Interhemispheric connectivity or brain coherence
b) To analyze the differences found between patients with strabismus and amblyopia and healthy controls.
c) To quantify the impact of light stimulation and light therapy on the visual system and the cerebral cortex of patients with strabismus and amblyopia.
    - Angle of strabismus
    - Visual acuity
    - Visual fields
    - Binocularity (3D perception and fusion)
d) To propose a model of how the visible spectrum affects the cerebral cortex of patients with strabismus and amblyopia.

1.4 Thesis Structure

This research measures the cortical response and brain activity of patients with strabismus and amblyopia (SA) and healthy controls (HCs) during light stimulation (LS) and after a complete cycle (twenty consecutive sessions) of light therapy (LTH), based on the theory of Syntonic Phototherapy, as well as the impact of LTH on the visual performance of the participants.

To do so, our research is organized in six important sections.

- Section I provides a general overview about the motives behind this research.
- Section II emphasizes in literature findings about the use of light in the biomedical field for diagnostic and treatment purposes.
- Section III is dedicated to the methodology followed in this research and provides all the steps followed to achieve our goals.
- Section IV explains in detail the procedure used in each phase.
- Section V analyzes the results obtained in each phase of the research as well as the discussion session.
- Section VI and VII contains the appendix of the neuro-optometric and neurological evaluation and the bibliography respectively.

2. Literature Survey

2.1 Background

Syntonic is a treatment that uses non-coherent, non-polarized, broadband light, which reaches the primary visual cortex through the retina, making it a powerful tool in the treatment of visual dysfunctions such as: strabismus, amblyopia, brain injuries, learning difficulties, and some ocular pathologies [8]. Syntonic permits local and non-local action, where long, low-energy wavelengths stimulate the sympathetic nervous system (SNS); mid frequencies balance physiology, and short, high-energy wavelengths stimulate the parasympathetic nervous system (PNS) [9].

The effectiveness of this therapy is based on its neurological action, followed by neurobehavioral reactions, often used in patients with severe visual conditions. Electroencephalography (EEG) converted to digital brain mapping (DBM) were used to measure the impact of the visible spectrum on the brain activity of SA patients and HCs in the waking-state, and the neuro-optometric evaluation determined changes in the visual performance of the participants, before and after the LTH program. 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 [14]. Changes in the brain activity aim to a better interhemispheric communication, as a balanced brain guarantees enhanced and stabilized function throughout the time [15,16]. 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. Strabismus and amblyopia are considered high-level visual dysfunctions. A visual dysfunction is defined as a decrease in the functionality of the visual system and can be manifested as a decrease in the visual acuity or contrast sensitivity, visual field loss,

photophobia, diplopia, visual distortion due to strabismus, difficulties with visual perception or any combination of the above [17].

These functional limitations can be congenital, inherited, or acquired. Visual dysfunctions can cause significant disabilities, by even interfering with a person's independence, and its interaction with the environment. Although the definition of strabismus has changed over the years, from a merely cosmetic concept to a cortical dysfunction [18], the most common definition remains to that of "a misalignment of the visual axes, which does not allow the retinal fusion of the two images perceived by each eye", breaking the binocularity of the patient [11]. However, through neuroimaging studies, it has been discovered that patients with congenital strabismus present cortical changes of the gray matter and damage to the inter-and intrahemispheric neurological pathways, depending on the type and time of its onset [1,2].

The importance of understanding strabismus lies in the fact that the visual system plays a fundamental role throughout a person´s life, directly affecting the interpretation of the outside world based on previous personal experiences [3]. Likewise, the prevalence of strabismus in preschool and primary school children is increasing due to the improvement in perinatal and obstetric care that increases the survival of premature or neurologically damaged patients. The preschool stage is the critical period of neuro-sensory-psychomotor development, considered the stage with more neuroplasticity, where intra- and inter-hemispheric connections flourish and consolidate, both in the primary visual pathway and the secondary, so any damage to the white matter, which is composed of interconnecting axons, will affect the visual performance of these patients [1, 2].

Strabismus is generally accompanied by amblyopia [11], a neuronal disorder caused by inadequate visual stimulation during the critical period of childhood development [19], which affects oculomotor abilities [20], binocularity [11,19], visual-motor skills [21] and space-time relationships [22], being all these visual abilities related to learning and academic achievement. Nonetheless, the literature features sparse research on the understanding of the exact mechanism by which light

stimulation affects patients with visual disorders such as strabismus and amblyopia [23], and the cortical electrical response to such stimulation.

Other cortical impairments accompanying strabismus include disruption of binocular synaptic integration in the striate cortex (V1), related to depth perception of space, damage to tracts connecting both hemispheres, the occipital cortex with the frontal cortex and the anterior part of the corpus callosum with the vertical occipital fasciculus that consolidate bilateral information and decreased inter- and intrahemispheric communication of the temporal and fronto-parietal lobes, related to memory, attention and learning [4]

There are two phases of processing within the visual system carried out in different areas of the neocortex. In the first stage, characteristics of retinal images such as illumination contrast, spatial orientation, color, and motion are analyzed. At higher processing levels, the selective region of interest is analyzed to perform object recognition. Through a series of circuits, the basic visual information is classified and sorted according to its spatial and temporal frequency in the occipital lobes. This is where the first visual pathway ends, and the second visual pathway begins. Not only intra- and interoccipital circuits are involved in visual perception, as well as other cortical areas which increase their activity when subjects select a spatial location for further processing [11].

Specifically, there are two regions needed to be stimulated: the ocular frontal fields and the intraparietal sulcus, which are constantly activated during the attentional process. The prefrontal cortex guides visual attention to select behaviorally relevant information. In addition, the basal ganglia are involved in the integration of information categorization. The medial temporal cortex is particularly involved in memory-based tasks, while the occipito-temporal regions are involved in stimulus comparison tasks. For their part, the temporal and parietal areas encode similarity of shape and perceived motion respectively [21, 22].

When strabismus occurs before the critical period, as in the case of congenital strabismus, the response of the V1 striate cortex changes. First, the neurons respond better to monocular information, and react better to the stimulus of one eye compared to the other. Secondly, the response to retinal disparity selectivity

decreases; this means that neurons respond uniformly; however, the disparity of the stimulus presented binocularly decreases the perception of space and objects in depth (3D). Third, there is suppression of binocular neurons, and there is a better monocular than binocular response [18]. Light as a powerful tool has been used successfully in the everyday training of patients with strabismus and amblyopia to treat suppression and enhance visual achievement.

Light as an electromagnetic wave is capable of being perceived by the human eye. Its frequency determines its color and represent a fraction of the electromagnetic spectrum which encompasses an increasing order of frequency: microwaves, radio waves, infrared rays, visible light, ultraviolet radiation, X-rays, and gamma rays. Visible light consists of a narrow band that ranges from 380 nm (violet) to 780 nm (red). The colors of the spectrum arranged like in the rainbow, form the visible spectrum. In medicine, the major applications of light are divided into three categories [24]: 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 [25]. Known as low-level light therapy (photobiomodulation), light delivered at low irradiance and fluency, can regenerate, heal, stimulate, and protect injured tissues. 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 [26,27]. 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 [28]. By contrast, the current literature, reports no findings on the electrical cortical activity in humans at baseline and after a cycle of light therapy using quantitative electroencephalography (qEEG), as presented in this research.

Nevertheless, visible light and brain responses have been analyzed in macaques [29], where cells responsive to luminance, color, or luminance and color, were found in the primary visual cortex (V1). Their neural brain activity and synchronization was influenced and modified by different wavelengths of visible light. Likewise, in humans, neuroplasticity can be enhanced with energy-based stimulation, including light, sound, and movement [30]. These stimulants may thus feature potential in helping to reactivate disabled neural circuits or to build new cortical networks and thereby improve brain functioning. Furthermore, 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 [31].

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 [32]. Additionally, studies using monochromatic light exposure have demonstrated that non-visual responses are maximally sensitive to blue light (459-483 nm) [33]. Although light stimulation has been successfully used in patients with strabismus and amblyopia in the daily clinical practice of health professionals [8,9], literature features sparse research on the understanding of the exact mechanism by which light stimulation affects patients with visual disorders [23], and the cortical electrical response to such stimulation.

Strabismus and amblyopia are a great choice to analyze the effects of light on the brain. Both are visual disorder that could lead to abnormal development of the visual system, particularly by affecting binocularity [34]. The prevalence of strabismus varies widely in the world [10], and it is generally followed by amblyopia, a cortico-visual adaptation which affects 1–4% of the population worldwide [11]. In both visual conditions, abnormalities have not only been seen in first (luminance-based) and second-order (texture-based) processing of visual information [34,35],

but also at deeper cortical levels [4]. Differences found in brain activity patterns [36], cortical thickness [37], and functional connectivity [38] relate strabismus with changes in the white and gray matter, depending on its type and time of appearance [37]-[39]. It is important to remind us that brain is the body's most complex organ and has been the object of study of the neuroscientific community for decades [40]. Nonetheless, there is a lot to be discovered about the brain network organization, its connections, and functions.

Even though LTH has been successfully used in the field of neuroscience [5,6], this is the first research to assess the afterwards effect of exposure to LTH in SA patients using qEEG analysis. The aim of this study was to measure and analyze the impact of a complete cycle of LTH in SA patients and propose its use as an essential element of the whole therapy treatment to achieve brain synchrony and enhance the visual performance of these patients.

Eye muscle surgery, eye patching and visual therapy have also been used to treat strabismus during decades. However, eye muscle surgery and eye patching are frequently accompanied by unwanted outcomes. Regression, consecutive strabismus, and amblyopia of the patched eye are often presented in these situations. Visual therapy on the other hand, could last from 2 to 3 years, and results are not always maintained once the therapy is over. These are strong reasons to introduce the use of LTH as an important tool in the treatment of SA patients [4].

The visual system dominates over the rest of sensorial modalities, if we consider that 70% of the total sensory input to the brain comes from the two eyes. Even though the visual system isn´t the first one to develop, once it reaches the maturation, it becomes dominant. Brain research has identified 300 intracortical pathways linking over 30 different cortical areas involved in processing visual information. Taking into consideration that 50% of the cortex is related to the visual processing, the treatment of visual deficiencies becomes crucial [13]. Strabismus and amblyopia were chosen for this study as both conditions relate to changes in dorsal and ventral pathways, followed by deficiencies in visual judgment, visual attention [2,18], memory and learning aspect can be altered as well [41]. Likewise, the presence of theta-waves at baseline, on different brain regions and particularly

on frontal lobes, suggests that strabismus and amblyopia are part of a neurodevelopment disorder [42], which requires deeper attention and intervention.

This research focused not only on the cortical electrical activity of SA patients at the precise moment of receiving a light stimulus [42], but also went a step forward and analyzed the permanence of the light effect on the brain activity of SA patients after a complete cycle or twenty consecutive sessions of LTH, once the stimulus is off [8,9], as well as its influence on the visual performance of these patients. A control group was used as a comparative to SA patients across the light therapy program. Quantitative electroencephalography (qEEG) was used to measure the impact of light therapy on the brain activity of SA patients and healthy controls (HCs) in the waking-state. qEEG was chosen for this research as it 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 [43,44]. This way, qEEG determined the electrical activity in different brain regions and monitor the symmetry of alpha-wave activity within hemispheres, which relates to the functionality of the human brain [45].

Visible light was used in this research as therapeutic effects can be triggered in patients with visual dysfunctions [8,9], and degenerative diseases [5,6]. Several authors have reported that the absorption of light by the visual pigments in photoreceptors triggers a cascade of chemical events that increases electrical neural activity. Visual information is transmitted in the form of electrical signals by the photoreceptors to ganglion cells. Interneurons alter electrical signals by incorporating temporal and spatial patterns of light stimulation in the retina. Information is then sent to the striate cortex (V1) through the primary visual pathway, to which the phenomenon of image forming is attributed.

Photoreceptors also send indirect inputs to intrinsically photosensitive retinal ganglion cells (ipRGC), which have a maximal sensitivity to blue light. These subsets of retinal ganglion cells feature an opsin/vitamin A-based photopigment called melanopsin, which plays a key role in mediating non-visual responses to light including the regulation of circadian rhythms and pupil constriction [46]. Additionally, ipRGC project to the hypothalamus, thalamus, striate, brainstem, and limbic system.

As these structures feature extensive cortical connectivity, it is evident that non-visual responses to light could involve diverse brain areas affect various neural functions [47].

Neuroimaging studies have shown that the wavelength, duration, and intensity of light exposure can modulate cortical responses through the visual and non-visual pathways [48]. For example, light modulated the neural activity of study participants engaged in auditory tasks during exposure and several minutes afterwards. At the cortical level, these modulations were not only detected in areas involved in the top-down regulation of attention but also in regions involved in bottom-up feedback associated with the reorientation of attention [49,50]. If light can modulate brain activity to improve performances in auditory tasks, light-induced enhancement should also be seen in the brain activity of patients with strabismus and amblyopia, reflected on their visual performance, measured through the clinical neuro-optometric evaluation.

Most research on light exposure has demonstrated that human circadian rhythmicity can influence cognitive processes, including attention, working memory, executive functions, and emotional states; specifically, the activity of cognitive processes improves across the day and declines throughout the night [51]. Exposure to bright light impacts alertness, sleep, and psychometric measures [52]. Compared to monochromatic light with a wavelength of 555 nm, monochromatic light of 460 nm reduces EEG delta power and increases alpha power during the night and reduces EEG theta power only during the day. By contrast, green light increases EEG high delta power and high alpha power during the night, while short-wavelength light increases EEG alpha power during the night [53].

Based on all the provided scientific information, but the lack of research in the field of strabismus and amblyopia, a new path was opened to understand the impact of visible light in the brain connectome of these patients. This research shields light on an unknown subject and provides us with a new tool towards the treatment of strabismus and amblyopia and other neurodevelopment disorders as well.

2.2 Understanding the Human Brain

To understand why light can induce changes in the brain after its administration, the overview of the brain anatomy, its functionality, and the connections between them, is essential.

Anatomically, the human brain is composed by the hindbrain (metencephalon and myelencephalon which regulates autonomic functions), the midbrain (mesencephalon-processes visual information), and the forebrain (telencephalon and diencephalon-regulates autonomic, endocrine, and motor functions).

2.2.1 The Brainstem and Diencephalon

The Brainstem consists of medulla, pons, and midbrain

1. The most caudal subdivision of the brainstem is the **medulla oblongata** (or “medulla” for short).
2. The **pons** is next as we proceed caudally. It would be difficult to miss the pons because of the massive enlargement on its ventral surface. (Pons means ‘bridge’; the enlargement is made up of cells with transversely oriented axons that cross the midline and could be said to form a bridge across the base of the brainstem.) A further feature that identifies the pons is its attachment to the cerebellum which lies dorsal to it. The cerebellum plays a crucial role in the coordination of movement.
3. The **mesencephalon** or **midbrain** lies just caudal to the thalamus. Prominent landmarks that can be seen on the dorsal surface of the midbrain are the superior and inferior colliculi. They are concerned with oculomotor function and postural adjustments (superior colliculi) and audition (inferior colliculi). The other prominent external feature of the midbrain is the cerebral peduncles.
4. The **diencephalon** consists of four parts arrayed from dorsal to ventral.

A. The epithalamus is a small strip of tissue to which is attached the **pineal gland**.

B. The **thalamus**, the largest part, relays most of the information going into the cortex from other parts of the brain and spinal cord. The thalamus consists of many further subdivisions, some of which you will learn about in later tutorials.

C. The **subthalamus**, a small area concerned with control of motor and cognitive functions, cannot be seen from this view since it does not extend all the way to the midline (this small diencephalic region is a frequent target of deep brain stimulation for control of movement disorders).

D. The **hypothalamus**, a small but crucial part of the brain, is devoted to the control of homeostasis and a rich variety of physiological activities that are essential for survival and reproduction. It is bounded rostrally by the optic chiasm, and its caudal extremity is made up of swellings known as the mammillary bodies. On some brain specimens, the pituitary gland or part of its stalk (the infundibulum) may still be attached to the ventral surface of the hypothalamus [54].

2.2.2 Visceral Motor System – Anatomical and Functional Divisions

I. Introduction

A. maintains the internal state of the body (homeostasis) and promotes changes (allostasis) by regulating the activity of visceral organs, glands, and blood vessels.
B. three peripheral structural/functional divisions, of which only two are the one related to the topic.

a. **Sympathetic** & **Parasympathetic** divisions
   i. two-neuron chains that connect CNS to peripheral effectors.
   ii. sympathetic division organizes involuntary responses that prepare the body for exertion (fight or flight).
   iii. parasympathetic division organizes involuntary activities of the viscera in a state of relaxation when there is a need to replenish bodily reserves.

1.Sympathetic division

a. Preganglionic neurons are arranged in the intermediolateral cell column of the thoracic/upper lumbar spinal cord.

i. most preganglionic neurons (which may be considered as ‘premotor’ interneurons project only a very short distance to the paravertebral ganglia (or sympathetic chain ganglia).
ii. some preganglionic neurons project a longer distance to reach prevertebral sympathetic ganglia (e.g., superior, and inferior mesenteric ganglia, pelvic plexus).
iii. in addition, some preganglionic axons innervate the adrenal medulla, which is considered a special sympathetic ganglion modified for endocrine function (release of catecholamines).
iv. use acetylcholine, which binds to nicotinic (ionotropic) and muscarinic (metabotropic) receptors on ganglionic neurons.

b. postganglionic neurons in the paravertebral and prevertebral ganglia directly innervate the smooth muscle of blood vessels and glands in the viscera, reproductive organs and skin, and the cardiac muscle and pacemaker nodes of the heart.
    i. postganglionic axons travel with virtually every peripheral nerve of the body to reach their widely distributed targets.
    ii. most use norepinephrine, which binds to alpha and beta adrenergic (metabotropic) receptors.
c. functional considerations
    i. generally, allow body to make maximum use of its resources in stressful or otherwise threatening circumstances.
    ii. is always some tonic activity in postganglionic sympathetic fibers.
    iii. sympathetic control of effector systems can be graded.
    iv. many sympathetic reflexes operate independently.

2. Parasympathetic division

a. preganglionic neurons are restricted to certain cranial nerve nuclei and the intermediate gray matter of the sacral cord.

    i. cranial nerve nuclei: Edinger-Westfall nucleus (midbrain), superior & inferior salivatory nuclei (pons & medulla), and nucleus ambiguous & dorsal motor nucleus of vagus (medulla).
    ii. sacral preganglionic innervation arises from neurons in the lateral portion of the intermediate gray matter.
    iii. preganglionic axons travel a long distance to innervate (parasympathetic) ganglia in or very close to end organs.
    iv. use acetylcholine (nicotinic & muscarinic effects).

b. postganglionic neurons in the parasympathetic ganglia directly innervate the smooth muscle of the eyes, viscera and reproductive organs, cardiac muscle, and the glands of the head.

i. since neurons are already in or near end targets, their axons travel a very short distance to innervate peripheral tissues.
ii. use acetylcholine.

c. functional considerations
   i. generally opposed to sympathetic activity increases reserves when conditions allow for rest and digest.
   ii. parasympathetic control of effector systems can be graded (not all-or-none) and many reflexes operate independently.

Several structures in the forebrain and have an important role in the regulation of homeostasis/allostasis; these include the amygdala, orbital and medial parts of the prefrontal cortex, insular cortex, and the hypothalamus [54].

2.2. 3 Hypothalamus

The central control of visceral motor system.

1. it is composed by several structures in the forebrain and have an important role in the regulation of homeostasis/allostasis; these include the amygdala, orbital and medial parts of the prefrontal cortex, insular cortex, and the hypothalamus; together they constitute a *central autonomic network.*
2. *Hypothalamus*
    1. comprises many distinct nuclei that subserve a broad range of integrative functions.
    2. overview of its connections:
        1. the hypothalamus is highly interconnected with the limbic forebrain, especially the amygdala, parts of the hippocampal formation and orbital-medial divisions of the prefrontal cortex.
        2. major outflow is directed toward integrative centers in the brainstem; most importantly, the periaqueductal gray (midbrain) and the reticular formation (pons and medulla).
        3. it regulates five basic functions:
            a. controls blood pressure and electrolyte balance.

b. regulates body temperature.
c. controls energy metabolism.
d. regulates reproductive activity.
e. controls emergency responses.

It´s basic mechanisms of regulation:

i. receives sensory and contextual information.
ii. compares sensory feedback with biologic set-points.
iii. activates visceral motor, endocrine and somatic motor systems to restore homeostasis or respond to crisis conditions (promote allostasis).

The nuclei of the hypothalamus are diverse anatomically and functionally for an account of several interesting examples of hypothalamic nuclei and their functions).

a. periventricular zone

arcuate and periventricular nuclei:

- scattered cells that secrete releasing or inhibiting factors into the portal circulation.

- these factors modulate the production of hormones in the anterior pituitary.

b. medial zone

paraventricular & supraoptic nuclei:

- send axons into posterior pituitary where they secrete oxytocin and vasopressin (anti-diuretic hormone) into the systemic circulation.

- paraventricular nucleus sends axons that descend to visceral motor control centers in the brainstem (reticular formation, periaqueductal gray) and spinal cord (intermediolateral cell column).

i. medial preoptic nucleus: motivational states.

ii. suprachiasmatic nucleus: receives retinal input and entrains circadian rhythms to cycles of light and dark.
iii. dorsomedial & ventromedial nuclei: receive heavy input from amygdala and orbital-medial prefrontal cerebral cortex:
    - reproductive & parenting behavior.
    - feeding behavior (target of leptin: hormone that provides feedback regulation of food intake.
    - water balance & thermoregulation.

c. lateral zone

I. loose collection of cells (not really nuclei) that can be considered a rostral. extension of the reticular formation of the midbrain tegmentum.
II. involved in feeding behaviors, arousal, and attention.
III. contains major efferent fiber bundle for hypothalamic control of brainstem and spinal cord centers [54].

2.2.4 The Visual System

Central Visual Processing

I. Functional organization of V:

A. the primary visual cortex (V1) is also known as the “striate cortex”.
    1. “striate” because of a prominent band of white matter (stria of Genari) that runs through the middle of cortical layer 4, giving this region of the cortex a distinctive appearance.
    2. Brodmann recognized this cortical region as Area 17.
B. neurons in V1 show response properties that are not elaborated at previous stages of neural processing (some of the best examples of “computational” functions of the cerebral cortex are known from neurophysiology studies of V1).
C. receptive field properties of cortical neurons in V1:

    1. V1 neurons respond best to moving edges of light and shadow.

a. small spots of light that evoke vigorous discharges in retinal ganglion cells and LGN neurons are not very effective in driving V1 neurons.
b. V1 neurons respond best to a moving edge that is within a narrow range of orientations in space (e.g., horizontal, vertical, oblique); this property is known as orientation selectivity.
c. many V1 neurons respond best when a particular orientation moves in only one direction (e.g., a vertical edge moving from right to left); this property is known as direction selectivity.

    2. organization of the retina:
        a. the retinal inputs to the LGN terminate in separate layers, so that individual neurons in the LGN are monocular.
        b. the projections of these monocular LGN neurons to layer 4 of V1 remain segregated within layer 4.

(i) LGN afferents terminate in alternating bands or columns in layer 4, called ocular dominance columns.

(ii) monocular neurons in the ocular dominance columns of layer 4 converge onto neurons in layers 2 and 3, where binocularity is first established in the visual pathway.

3. stereopsis:
    a. because neurons in V1 (after layer 4) are binocular, neural signals are generated that take advantage of the fact that, for near objects, the lines of sight of the two eyes are slightly different.
    b. for all objects near or far from the plane of fixation, images of the objects fall on "non-corresponding" locations in the two retinas.
    c. many cells in V1 (and in other visual cortical areas) are sensitive to such retinal disparities.
    d. these neural signals are the basis of stereopsis, which provides one important clue about the location of objects in depth (this computational property in V1 is necessary for the 3D effect in visual media).
    e. other cues about depth include motion parallax and size constancy.

D. parallel pathways:

1. there are distinct anatomical and physiological classes of retinal ganglion cells, each of which is organized into ON and OFF center-surround subtypes.
2. three important classes are the M, P and K ganglion cells:
    a. M ganglion cells have larger cell bodies, dendritic arbors and axons compared to P cells; thus, M cells have larger receptive fields, and their axons conduct faster than P cells.
    b. M cells respond transiently (phasically) to visual stimuli, while P cells show a more sustained (tonic) response.
    c. P cells are sensitive to color, while M cells are "color-blind":

(i) receptive field centers and surrounds of P cells are driven by different types of cones (e.g., red, and green).

(ii) P cells respond best to differences in color striking their centers and surrounds (e.g., red center and green surround).

(iii) the centers and surrounds of M cells are both driven by different types of cones.

3. M and P ganglion cells terminate in different sets of layers in the LGN, the magnocellular ("large cell") layers (layers 1 and 2) and parvocellular ("small cell") layers (layers 3-6), respectively.
4. In V1, the inputs from magnocellular and parvocellular LGN neurons are partially segregated into functional "streams" of processing, a magnocellular stream for detecting quickly moving stimuli and a parvocellular stream for detailed examination of form (acuity) and color.
5. there are also K ganglion cells that project to small clusters of "konio" cells that reside between the major laminae of the LGN; this so-called koniocellular pathway is conveyed to V1 in projections that terminate in patches in layer 2/3 (an exception to the thalamus-to-layer 4 rule).

Extrastriate Visual Cortex:

A. beyond V1 (= "striate cortex"), there are multiple areas in the occipital, parietal and temporal lobes that process visual information.
B. these areas are arranged into two broad functional pathways that feed visual information from V1 into associational cortical areas in the parietal and temporal lobes:
    1. dorsal or lateral parietal pathway: responsible for spatial aspects of vision, such as the relationships between objects and ourselves and the movements of objects (including ourselves) through the environment (i.e., "where?").

2. ventral or inferior temporal pathway: responsible for high-resolution form vision, color processing and object recognition (i.e., “what?”).

C. although both pathways receive input from both parvocellular and magnocellular streams in V1, there tends to be more ‘magnocellular’ influence on the parietal pathway and more ‘parvocellular’ influence on the temporal pathway.

D. damage to cortical areas in the parietal and temporal pathways produce different visual deficits, such as the selective loss of color vision or an inability to recognize a familiar face (ventral temporal pathway), or the loss of motion perception (parietal pathway, involving lesions in visual areas MT/MST in particular).

Central Visual Pathways

I. Overview of Central Visual Pathways:

A. central projections of the retina arise from retinal ganglion cells.

B. projections terminate on a variety of structures in the diencephalon and midbrain:

1. diencephalic targets

a. dorsal lateral geniculate nucleus (LGN):

(i) principal target of retinal ganglion cells

(ii) relays visual signals to the primary visual cortex (V1)

(iii) this pathway, is responsible for most aspects of what we know as visual perception

b. suprachiasmatic nucleus of the hypothalamus:

(i) responsible for entraining endogenous circadian (daily) rhythms to natural day-night cycle. For this reason, light stimulation affects visual system and its connections with the rest of the brain areas.

(ii) the light-sensing elements in this visual projection are a special class of photosensitive ganglion cells that contain another photopigment, melanopsin.

2. midbrain targets:

a. superior colliculus

(i) involved in coordinating orienting movements of the head and eyes to a visual stimulus and other sensory stimulus.

b. pretectum

(i) involved in pupillary light reflex.

(ii) pretectum is also involved in coordinating the activities of the preganglionic neurons that innervate the ciliary muscles and allow for accommodation.

C. **parallel processing** in visual pathways begins with distinct anatomical and physiological classes of retinal ganglion cells and continues into the array of cortical areas that process different aspects of visual information.

II. The pathway from the retina to V1 in more detail:

A. from retina to brain:
    1. ganglion cell axons leave the retina at the optic disk and project centrally in the optic nerve ("CN" II—not really a nerve, but an extension of the brain).
    2. about 55% of the optic nerve axons cross the midline (i.e., decussate) in the optic chiasm and project to the contralateral hemisphere; the other 45% remain ipsilateral (see below for consideration of retinotopy).

3. central to the optic chiasm, ganglion cell axons form the optic tract, which is simply the central continuation of optic chiasm.
4. axons (and branches of axons) exit the optic tract and terminate in central targets in the diencephalon and/or midbrain
5. the principal projection to the visual parts of the cerebral cortex originates in the LGN and terminates in V1, Brodmann's Area 17 (also called the "striate cortex", for its prominent striation in the human brain), which is in the banks of the calcarine fissure on the medial aspect of the occipital lobe.

B. retinotopic organization of the visual field projections:

The nearest neighbor relationships within each half-retina are maintained throughout the projections to the LGN and primary visual cortex; this is termed "visuotopy" or "visual topography". *However, each hemisphere (LGN and V1) represents the contralateral visual hemifield.*

a. each retina sees overlapping regions of visual space that includes portions of both visual hemifields:

(i) **binocular visual field** is seen by nasal and temporal parts of both retinas.

(ii) **monocular crescents** of visual space (far temporal in visual space) are seen only by the extreme medial portion of the nasal retina. The lens inverts and reverses the optical image: the superior part of the visual field is seen by the inferior part of the retina, and the temporal half of the visual field is seen by the nasal half of the retina

b. how are the central projections from "corresponding" points in each retina that see the same position in visual space brought together in the brain?
    1. axons of ganglion cells in the nasal retina decussate in the optic chiasm and project to the contralateral hemisphere.

2. the axons of ganglion cells in the temporal retina do not cross and remain ipsilateral.
3. the line of decussation in the retina runs through the fovea the LGN
4. in the LGN, each optic tract terminates in an orderly fashion, so that each LGN contains an orderly map of the contralateral visual hemifield. However, the axons from each retina terminate in distinct layers.

c. In the V1:

1. the projections of the LGN to V1 terminate in proper topographic order in cortical layer 4.

2. the fovea is represented in the posterior part of the calcarine sulcus, with more peripheral parts of the contralateral visual hemifield represented in progressively more anterior locations.

3. the upper visual field is represented in the inferior bank of the calcarine sulcus, while the lower visual field is represented in its superior bank.

4. the representation of the fovea is disproportionately large (like the “over-representation” of the hand in S1).

5. on the way to V1, the projection of the LGN is called the optic radiation:

(i) the lateral-inferior part, called Meyer’s loop, “loops” into the white matter of the temporal lobe before projecting onto the inferior bank of the calcarine sulcus (terminating in the lingual gyrus).

(ii) the more medial-superior fibers course through the white matter of the parietal lobe before projecting onto the superior bank of the calcarine sulcus (terminating in the cuneus gyrus).

Beyond V1:

A. As already mentioned, extrastriate cortex it goes beyond V1 (= “striate cortex”), there are multiple areas in the occipital, parietal and temporal lobes that process visual information.

   these areas are arranged into two broad functional pathways that feed visual information from V1 into associational cortical areas in the parietal and temporal lobes.

   1. dorsal or lateral parietal pathway: responsible for spatial aspects of vision, such as the relationships between objects and ourselves and the movements of objects (including ourselves) through the environment (i.e., “where?”).

   2. ventral or inferior temporal pathway: responsible for high-resolution form vision, color processing and object recognition (i.e., “what?”) [54].

Eye Movements:

A. General oveview:
    1. because good visual acuity is restricted to a very small part of the visual field (about two degrees), eye movements are necessary to:
        a. maintain foveal fixation on a moving target
        b. maintain foveal fixation on a target during head movements
        c. acquire and fixate a new visual target
    2. eye movements are a relatively simple set of somatic motor behaviors; there are only 6 pairs of muscles involved and five patterns of movement.

B. Extraocular muscles and patterns of innervation:
    1. for each eye, there are three pairs of striated muscles that move the eye along the three axes of rotation.
    2. innervation by three cranial nerves:
        a. **abducens** (CN VI): ipsilateral lateral rectus muscle
        b. **trochlear** (CN IV): contralateral superior oblique
        c. **oculomotor** (CN III): supplies the remaining four ipsilateral muscles (medial rectus, inferior rectus, superior rectus, and inferior oblique)

            - distinct columns of motor neurons in the oculomotor complex supplies each of these four extraocular muscles (a separate pool of motor neurons also innervates elevator muscles of the eyelid).

            - Addition ally, the Edinger-Westphal component supplies preganglionic parasympathetic innervation to the constrictor muscles of the iris.

C. Types of Eye Movements:

1. *Conjugate* eye movements: eyes move together in the same direction.

a. **saccades:**
   - rapid movements of the eye that abruptly change the point of fixation
   - can be voluntary, but most are involuntary
   - after decision to saccade (or onset of a target), there is an obligatory delay of ~200 msec before the onset of movement
   - movement is ballistic, sudden forceful motion, without ongoing visual guidance toward target)
   - during a movement, visual information is suppressed from perception (demonstrate this fact for yourself!)

b. smooth pursuit movements:
   - much slower eye movements designed to track a moving stimulus
   - voluntary, (usually) requiring a moving target

c. optokinetic movements:
   - movements of the eyes to compensate for large-scale motion of the visual field
   - operate at low stimulus frequencies when vestibulo-ocular gain slow
   - very large-scale motion patterns (e.g., waiting at a railroad crossing for a train to pass) may induce optokinetic nystagmus:
     - smooth pursuit movement to track a stimulus to the limit of ocular rotation (movement in the direction of stimulus motion)
     - saccade to acquire a new element of the visual scene for fixation (movement opposite the direction of stimulus motion)

d. **vestibulo-ocular movements:**

   i. in brief, rotational movements of the head induce eye movements opposite to the direction of rotation, thus allowing maintained visual fixation of both eyes

2. *Disconjugate* eye movements: eyes move in opposite directions:

a. **vergence movements:**

- eyes rotate inward (convergence) or outward (divergence) so that the lines of fixation intersect on ‘near’ or ‘far’ visual targets, respectively
- recall that along with vergence movements, accommodation of the lens and adjustments of pupillary diameter are reflexively yoked when fixation shifts from near to far, and vice versa

D. Neural control of eye movements:

1. **amplitude** of movement:
    a. encoded by duration of action potential firing in the appropriate lower motor neurons
    b. when eye is moved in the opposite direction, the same lower motor neurons become transiently silent (i.e., inhibited)
2. **direction** of movement:
    a. specified by which eye muscles are activated
    b. horizontal and vertical eye movements are coordinated by two gaze centers in the brainstem reticular formation
        - these centers are sets of highly interconnected interneurons whose output is directed toward lower motor neurons
        - horizontal gaze center (paramedian pontine reticular formation): coordinates horizontal eye movements
        - vertical gaze center (rostral interstitial nucleus in the midbrain): coordinates vertical eye movements
        - activation of both gaze centers produces oblique movements

3. “**Upper motor neurona**l” control of saccades:

a. horizontal and vertical gaze centers are influenced mainly by two sources of descending control: the superior colliculus and the frontal eye field **(**Brodmann’s Area).

- neurons in both structures fire just prior to making a saccade
- both structures contain a motor map so that activation of a discrete site produces a saccade in a specific direction for a specific distance in the *contralateral* visual hemifield
- both structures contain a sensory map that represents visual space

a. role of superior colliculus:
    - in the superior colliculus, certain ganglion cells in the retina provide direct input that is retinotopically mapped
    - the sensory map is in register with a deeper map of motor error that generates a shift in gaze direction
    - the saccade related burst neurons, however, are not laid out in a *retinotopic* map, but in a *map of motor error*
    - the superior colliculus also contains systematic representations of the body surface (via the anterolateral system) and auditory space (via the inferior colliculus)
    - in a similar manner, somatic sensory or acoustic stimuli may lead to a saccade toward the source of the stimulus (a particular location on the body surface or in the environment)

b. role of frontal eye field:
    - parts of the parietal or dorsal visual stream “where stream “project to Area 8 and provide a visuotopic map, but the map is less precise than in the superior colliculus
    - nevertheless, activation of a particular column of neurons in the frontal eye field drives a saccade to the location in contralateral visual space represented by that same column of cells

- the frontal eye field projects directly to the (contralateral) gaze centers in the brainstem and indirectly via projections to the (ipsilateral) superior colliculus

c. damage to one or the other structure produces only transient deficits in saccadic eye movements; this suggests that both are involved in specifying saccadic behavior.
d. upper motor neurons in the frontal eye fields and superior colliculus are modulated by neural circuits in the basal ganglia and cerebellum:
    - basal ganglia: involved in the initiation of appropriate saccadic behavior and suppression of inappropriate saccades
    - cerebellum: coordination of ongoing saccadic activity and adjustment of gain as needed (sensory-motor learning) [54].

2.2.5 Modification of Neural Circuits in Early Neonatal Life

I. Introduction:

A. mechanisms of neural development:
    1. **genetic specification**: phenotypes produced by spatial and temporal patterns of gene expression in cells derived from common precursors
    2. **self-organization**: phenotypes produced by cell-cell interactions mediated by endogenous patterns of activity in neural networks
    3. **sensorimotor experience**: the modulation of endogenous neural activity by the activation of sensory receptors during environmental interactions
B. each of these basic mechanisms is subject to modification due to the consequences of genetic mutation, disease, exposure to environmental and dietary toxins, and normal and abnormal sensorimotor experience.

II. **Sensorimotor experience** in early brain development: "precritical" circuit construction and modification in a critical period.

A. subcortical brain circuits and circuits set-up by the topographic mapping of thalamic projections to the cerebral cortex.

1. overview:
    a. such circuits develop in a formative "*precritical*" phase, under the influence of genetic specification and self-organization, without the need for sensorimotor experience
    b. however, in a later "**critical period**" phase of development, such circuits are plastic for a period of early life
2. evidence for this view has come mainly from studies of ocular dominance columns in the visual cortex of animal models:
    a. ocular dominance columns are alternating patches of monocular inputs from the lateral geniculate nucleus to cortical layer 4 (recall that

binocular interactions do not occur until layer 4 signals are passed on to cortical layer 2/3).

b. ocular dominance column plasticity:
    i. ocular dominance columns develop early (in utero in primates), even in animals (carnivores) raised in complete darkness
    ii. thus, sensory experience (vision) is not needed for the formation of these circuits
    iii. however, once established in visual cortical circuitry, ocular dominance columns are plastic in early life
        - a brief period of monocular vision in early life can lead to permanent blindness (amblyopia)
        - amblyopia is explained by a dramatic shift in the size of ocular dominance columns in V1
        - open-eye columns expand (grow new connections)
        - deprived-eye columns shrink (lose connections)
        - these effects are not (usually) seen in adults
    iv. ocular dominance column plasticity has been the dominant paradigm for understanding the construction of neural circuits within critical periods of early postnatal life; indeed, this paradigm has been the “gold standard” for evaluating mechanisms of neural plasticity for more than 5 decades.

B. intrinsic neural circuits of the cerebral cortex (beyond the input layer, layer 4):

1. more recently, developmental neuroscientists have studied the formation of intrinsic cortical circuits (columnar circuits that compute new functional properties within the middle and upper layers of the visual cortex), and results suggest a more important role for experience in circuit construction.
2. two important model circuits for these studies (also in visual cortex):
    1. orientation columns: columnar circuits in the visual cortex that compute the orientation (axis of motion) of contours in visual stimuli

2. direction columns: columnar circuits in the visual cortex that compute the direction of motion of visual stimuli

3. studies of orientation columns:
    1. orientation preference maps in different species share a common design, with a pinwheel density of π
        i. this strongly suggests that the neural networks in the visual cortex that compute orientation preference *self-organize*
        ii. essential factors are (1) activity-dependent development; and (2) long-range connections across the developing network
    2. orientation columns are present at the onset of visual experience in animals reared normally and in animals reared in complete darkness as predicted by models of self-organizing cortical networks.
    3. *however:*
        i. in animals reared in darkness, orientation selectivity is weak, indicating some benefit of normal sensory experience
        ii. in animals reared with abnormal experience (through closed eye-lids), orientation selectivity is so weak that orientation columns are barely discernible (*bad experience is worse than no experience*)

d. Conclusions:

i. normally, self-organization operates *synergistically* with sensorimotor experience to promote full functional maturation.

ii. when experience is rendered abnormal, this synergy is broken, self-organization goes awry, and the neural circuits are functionally impaired.
    - in other words, neural circuits self-organize to adapt to the quality of the incoming sensory signals
    - not only do neural circuits fail to benefit from normal experience, but they could be harmed by abnormal experience

4. studies of direction columns:

   a. direction columns are absent at the onset of visual experience in animals reared normally and emerge after 1-2 weeks of vision
   b. direction columns fail to form in complete darkness
   c. the critical period for the development of direction columns is remarkably brief: only animals that experience vision in the first 1-2 weeks after eye-opening (neonates) develop direction columns
   d. early vision drives the development of direction columns (and neuronal direction selectivity)
      i. experience with motion energy is necessary
      ii. changes can happen quickly (hours)
      iii. for some cells, this requires reversing an initial direction preference
   e. *conclusions:*

i. the neural circuits that underlie direction columns cannot self- organize, but must be instructed (trained) by visual experience with moving stimuli

ii. the window of opportunity for this motion training is very brief, so *early experience is critical* [54].

2.2.6 Synaptic Plasticity

I. Introduction:
   A. plasticity: the capacity of the nervous system to change
   B. plasticity occurs at all levels of organization (i.e., synapses, neural circuits, neural systems).
   C. plasticity is the basis of all neural functions that involve change (e.g., memory, acquisition of motor skill or cognitive skills, adaptation to and recovery from injury or disability).

II. Overview of long-term synaptic plasticity:
   A. changes in synaptic function that occur over a very long-time frame: hours, days, months (and maybe years).
   B. changes in synaptic function are the cellular correlates of learning and memory.
   C. general cellular mechanisms for synaptic change:
      1. neural activity triggers the activation of postsynaptic, second messenger systems.
      2. the trigger is usually a specific alteration in the levels of intracellular calcium in the postsynaptic neuron.
      3. Ca-dependent second messenger systems alter the activity of protein kinases (phosphorylate target proteins) and phosphatases (dephosphorylate target proteins).
      4. alterations in protein phosphorylation mediate the early stages of long-term synaptic plasticity (changes in phosphorylation induce changes in protein function).
      5. the more long-lasting changes in synaptic strength are brought about by alterations in gene transcription induced by second messenger systems.

III. Long-term potentiation (LTP):

A. a long-lasting increase in postsynaptic currents induced by brief, *high-frequency* stimulation of an afferent pathway.
B. characteristics:
    1. *the postsynaptic neuron must depolarize*
        a. induction of LTP requires pairing of presynaptic activity *and* postsynaptic depolarization (satisfies Hebb's postulate).
        b. mediated by NMDA receptors.
    2. *LTP only occurs at active synapse.*
    3. *other inputs that are concurrently active, even weakly active, may become potentiate.*
        a. This allows for the selective enhancement of two distinct inputs onto the same postsynaptic neuron.
        b. provides for the basis of associative learning (classical conditioning).
    4. persists for at least many weeks.
    5. studied primarily in the hippocampus, but basic phenomenon is assumed to occur throughout the cerebral cortex (and subcortical circuits).

IV. Long-term depression (LTD):

A. a long-lasting decrease in postsynaptic currents induced by relatively prolonged, *low- frequency* stimulation of an afferent pathway.
B. LTD in the cortex
    1. characteristics:
        1. induction of LTD requires pairing of presynaptic activity and postsynaptic depolarization
        2. phenomenon persists for at least many weeks

C. LTD in the cerebellum:

1. induction of LTD requires pairing of parallel fiber (cerebellar granule cell) and climbing fiber activity (climbing fibers provide the ‘learning signal’; these inputs originate in the inferior olivary nucleus in the medulla).
2. phenomenon persists for at least many weeks [54].

2.2.7 Changes in the Brain due to the Process of Neuro-Plasticity

Plasticity: the capacity of the nervous system to change. The general cellular mechanism for synaptic change is explained as follows:

1. neural activity triggers the activation of postsynaptic, second messenger systems

2. the trigger is usually a specific alteration in the levels of intracellular calcium in the postsynaptic neuron

3. Ca-dependent second messenger systems alter the activity of protein kinases (phosphorylate target proteins) and phosphatases (dephosphorylate target proteins)

4. Alterations in protein phosphorylation mediate the early stages of long-term synaptic plasticity (changes in phosphorylation induce changes in protein function)

5. The more long-lasting changes in synaptic strength are brought about by alterations in gene transcription induced by second messenger systems

Spike-timing dependent plasticity (STDP):

A. explains how synaptic plasticity can occur in the brain *one postsynaptic spike at a time*

1. seldom do patterns of neural activity in real brain circuits resemble the artificial spike trains that were used in the classical studies of the LTP and LTD.

2. For example, if real synapses seldom (if ever) experience brief trains of 500 Hz stimulation, how does plasticity (LTP) work?

3. STDP provides a framework for understanding how synaptic plasticity can occur (LTP in this case) without the need for brief, high-frequency trains of stimulation.

B. mechanisms: precision timing matters:

1. synapses strengthen when presynaptic activity *precedes* postsynaptic activity by ~20 msec or less
    1. this sequence of “pre- before post”, and the short interval between the two, implicates the presynaptic input in question as the principal source of depolarization that resulted in the generation of a postsynaptic action potential.
    2. this regime is consistent with the Hebbian notion of “coordination” between pre- and post-synaptic activity (more on this in next tutorial)
    3. for sensory circuits, structured experience with the sensory environment (e.g., training) may provide one means for coordinating spatial and temporal patterns of activity
2. synapses weaken when presynaptic activity *follows* postsynaptic activity by up to ~40 msec.

    a. This sequence of “post before pre-” implicates some other presynaptic input as the principal source of depolarization that resulted in the generation of a postsynaptic action potential. Most neurons receive 1000s of synaptic input.
    b. This “post before pre- “sequence indicates that the postsynaptic neuron was driven to fire an action potential by some other input, not the input in question.
    c. This regime is consistent with the Hebbian notion of “incoordination” between pre- and post-synaptic activity.

3. The interval between pre- and post-synaptic neuron firing that leads to LTD is roughly twice the interval that leads to LTP.

- this suggests that random firing will tend toward LTD and the weakening of synaptic connections.
- thus, unstructured activity in sensory circuits would be expected to favor LTD over LTP [54].

2.2.8 Brain Changes during Life

A. The mechanisms of neural development:
    1. **genetic specification**: phenotypes produced by spatial and temporal patterns of gene expression in cells derived from common precursors
    2. **self-organization**: phenotypes produced by cell-cell interactions mediated by endogenous patterns of activity in neural networks
    3. **sensorimotor experience**: the modulation of endogenous neural activity by the activation of sensory receptors during environmental interactions

B. As development proceeds across the lifespan, these fundamental forces continue to shape the structure of function of neural circuits albeit with limited capacity to learn, repair and regenerate outside of the critical periods that characterize early life.

Ongoing development of the human brain throughout childhood:

A. commensurate with the onset and duration of many known critical periods in early life, there is an explosive increase in synaptogenesis across the cortical mantle.

1. in rhesus monkey (and presumably in humans):

a) there is an explosive increase in synapse formation (synaptogenesis) in the neonatal period that continues through early childhood
b) although there is likely both synapse construction AND synapse pruning occurring concurrently, the major developmental theme of early life is the *construction of neural circuits* with a several-fold increase in the total numbers of synaptic connections in most gray matter structures

2. presumably, the capacity to build new synaptic connections is an important component to critical period plasticity and the rapid learning that occurs in early life.

3. however, the rate of synaptogenesis and/or the proper construction of functional, adaptive neural circuits may be altered in disorders of cognition and behavior, such as autism spectrum disorders, schizophrenia, and attention deficit-hyperactivity disorder (ADHD)

a. autism spectrum disorder:
    i. there appears to be an accelerated rate of synaptogenesis in the frontal and temporal lobes, and in the amygdala and cerebellum, resulting in an overgrowth of neural circuits and an early increase in overall brain size
    ii. by adolescence, differences in gray matter trend toward normal volumes
    iii. however, aberrant wiring patterns of cortical and subcortical networks are likely to persist, especially in networks subserving social cognition and verbal and non-verbal communication
b. attention deficit-hyperactivity disorder (ADHD):
    i. there appears to be decreased rate of synaptogenesis resulting in a developmental delay in circuit construction and an overall decrease in the thickness of cortical gray matter, especially in the frontal and temporal lobes.

B. beginning in later childhood (pre-adolescent), there is a *net reduction* in the numbers of synapses in the cerebral cortex.

1. in most cortical areas, there is 20-50% reduction in the numbers of synaptic connections from the peak in early childhood to a stable plateau in young adulthood.

2. this reduction in synaptic connections is the major factor responsible for a reduction in the volume of gray matter in the cerebral cortex observed in the same time frame.

a. In ADHD, there appears to be a modest increase in the rate of gray matter thickness reduction.

b. Consequently, cortical gray matter volumes are (on average) reduced in adults with ADHD.

C. throughout childhood and into adulthood, there is an increase in white matter volume.

1. this increase likely reflects an increase in myelination of axonal pathways in the brain; and it could also reflect an increase in the numbers of axons within pathways

D. thereafter, overall brain size gradually decreases throughout adulthood, presumably reflected the loss of synaptic connections, axons and myelin.

1. however, a loss of neurons is not typical in adult aging, unless neurodegenerative disease is manifest

Plasticity in sensory and motor maps:

1. the organization of sensory and motor maps may be altered by damage to peripheral nerves and/or changes in ongoing patterns of neural activity
2. the degree of plasticity is much greater during early critical periods, but some plasticity in map structure persists into adulthood
3. in the somatic sensory cortex:
    1. when peripheral nerves are lesioned, central representations reorganize
        a. in the short-term, newly deafferented cortical zones become unresponsive
        b. however, over time, deafferented cortical zones become responsive to sensory stimuli that drive adjacent regions of cortex

2. reorganization may also be seen in an intact system when patterns of neural activity are habitually reinforced (e.g., with extensive practice or non-use).

4. in the motor cortex:
    1. over training can expand the motor representation of practiced movements in the primary motor cortex.
    2. similar plasticity has been observed in animals recovering from brain injury (e.g., stroke) who were rehabilitated using specific motor sequences
5. mechanisms of circuit plasticity in the cerebral cortex:
    1. plasticity may occur at multiple stations along a sensory or motor pathway
    2. however, plasticity is understood best at the level of the cerebral cortex where intrinsic cortical circuits are modified by experience
    3. long-range horizontal connections are a likely mediator of cortical plasticity in sensory and motor maps

       a. horizontal connections span many cortical columns and interconnect different parts of maps that are functionally synergistic

       (i) normally, effects of horizontal connections are weak

       (ii) in response to deafferentation (see below), disuse or overuse, the synapses made by horizontal connections may become strengthened and more effective at driving neuronal responses; they may mediate at least the early phases of cortical reorganization

       (iii) long term consequences may involve growth of new connections that reinforce longer lasting effects on the structure of cortical maps.

Peripheral nerve regeneration:

1. following damage (severing, evulsing or crushing a nerve), a sequence of events plays out that results in partial restoration of sensory and motor function.
2. macrophages rapidly remove myelin and axonal debris as the distal portion of the axon degenerates
3. Schwann cells proliferate, express adhesion molecules and other growth- promoting signals
4. the neuronal cell body expresses genes that reactivate growth programs that allow for the formation of a growth cone and the transduction machinery that is necessary to respond to factors produced by Schwann cells
5. regenerating axons elongate as growth cones migrate along extracellular matrix and the relatively orderly array of Scwhann cells that guide growth cones to their peripheral targets
6. for motor axons and some sensory afferents (e.g., Merkel cell-neurite complexes), synapses form on target tissues using similar mechanisms that established synaptic connectivity in development
7. however, the fidelity of regeneration is limited, and full functional recovery may not be achieved.

Plasticity of neural circuits in response to brain injury:

A. in response to brain injury (following trauma, hypoxia, or the onset of neurodegenerative disease), neuronal loss is often exacerbated by programmed cell death and the inability to restore long axonal projections.

1. fatally injured neurons die acutely or undergo apoptosis:

a. cell death may be triggered by over-activation of glutamatergic synaptic inputs.

b. cell death may be triggered by inflammatory mediators (cytokines), DNA damage, loss of neurotrophic support, and other means of cellular stress.

c. whatever the trigger, lost neurons cannot be replaced via mitosis and differentiation of neuroblasts.

2. in compact white matter structures, damage to long pathways in the CNS have *limited capacity to regenerate:*

a) glial cells respond to signals produced by damaged tissues and immune cells that infiltrate the region of damage and proliferate forming scars that congest the local volume of brain tissue.
b) glial reactions create an environment which is nor permissive for the regrowth of long axonal projections.
c) oligodendrocytes produce signaling molecules (myelin associated proteins) that inhibit axonal growth and elongation.

B. however, in gray matter, surviving circuit elements may undergo functional and structural plasticity; the key to recovery is the capacity of these elements to reorganize and reshape the strength and distribution of their synaptic connections.

1. cortical (and subcortical) connections may be modified by central injury, e.g., following stroke:

a. injury to brain tissue surrounding the core of infarction will undergo a sequence of activity-dependent changes in:
    i. patterns of neural activity
    ii. patterns of gene expression
    iii. patterns of synapse formation and axonal outgrowth
b. changes in the patterns of gene expression (and their consequences) often involve expression of the same genes (i.e., encoding tropic molecules, trophic molecules, and their receptors) that were initially induced in the early construction of neural circuits

c. *thus, the plastic response of injured neural tissue likely involves the reactivation of developmental programs*

C. the capacity for neuronal regeneration (i.e., mitosis and production of new neurons) is *limited* to special populations of neural stem cells close to the lateral wall of the lateral ventricle:

1. These new neurons provide interneurons for local circuits in the dentate gyrus (a component of the hippocampus).
2. despite some recent controversy, it now appears clear that few if any new neurons contribute to neural circuits in the neocortex.
3. nevertheless, the addition and integration of new neurons in the dentate gyrus may be important for neuropsychiatric disease and treatment [54].

2.2.9 The Circadian Rhythm

A. Is responsible for diverse physiological (homeostatic) functions and overt patterns of behavior cycle with a period of approximately 24 hours:
    1. oxidative metabolism and core body temperature decline during (or just prior to) the onset of sleep
    2. certain hormones, such as cortisol, growth hormone, “spike” in relation to intervals of nightly sleep
    3. daily cycles of activity and sleep:
        a. average 24.0 hours
        b. if isolated from external cues, daily cycles “free-run” with a period of just longer 24 hours
        c. indicates that circadian rhythms are generated internally, but entrained to environmental cycles of day and night

B. Suprachiasmatic nucleus (SCN) and photoentrainment:
    1. The SCN is in the periventricular zone of the anterior hypothalamus, just above the optic chiasm.
    2. SCN neurons maintain an intrinsic circadian rhythm:
        a. SCN lesions abolish circadian rhythms of sleep and wakefulness
        b. isolated SCN neurons show circadian rhythms
    3. neural mechanism of photo-entrainment:
        a. SCN receives retinal input via the retino-hypothalamic tract from newly discovered, photosensitive ganglion cells
        b. SCN activates projection neurons in the paraventricular nucleus (medial hypothalamus) that innervate sympathetic preganglionic neurons in the intermediolateral cell column
        c. sympathetic postganglionic neurons in the superior cervical ganglion innervate the pineal body (gland), which synthesizes and secretes the sleep promoting hormone, melatonin
        d. melatonin modulates the activity of hypothalamic and reticular formation centers that, in turn, regulate the sleep-wake cycle

III. Sleep stages:

A. sleep comprises a series of successive stages that occur in a characteristic sequence and cycle during a normal night´s sleep
B. first, a primer on electroencephalography (EEG):

i. electrical activity generated by the billions of neurons and their synaptic connections within the cerebral cortex is reflected in the electrical potentials that can be recorded from the surface of the scalp
ii. the amplitude and frequency of the surface EEG brain waves is a function of:

- the number of active neurons that underlie any electrode
- the firing rate of the active neurons
- the synchrony of the active population

iii. EEG activity is conventionally recognized in one of several frequency bands that have characteristic amplitudes:

- delta rhythms = 1-4 Hz, high amplitude (slow-wave sleep)
- theta rhythms = 4-7 Hz, moderate amplitude (active exploration)
- alpha rhythms = 8-12 Hz, moderate-to-high amplitude (quiet rest)
- beta rhythms = 12-60 Hz, low amplitude (attentive, concentrating)

iv. EEG recordings are used to diagnosis normal (e.g., sleep, wakeful conscious) and pathological (e.g., seizure, coma, persistent vegetative) brain states, a reason why qEEG was used in our study to measure the cortical activity of SA patients before and after the treatment, considering that strabismus and amblyopia are considered as neurodevelopment disorders [54].

2.2.10 Waking EEG Record

To analyze the brain functionality of the participants, the frequency and distribution of the alpha rhythm was determined. The alpha rhythm, which is found in posterior lobes, from eight to ten years old, reaches a mean frequency of around 10 Hz, which equals the mean frequency of the mature adult EEG. In general, girls show a statistically significant faster acceleration of the posterior alpha frequency. The posterior alpha rhythm is usually of higher amplitude over the nondominant hemisphere and thus larger on the right side.

Slow rhythm (5 Hz rhythm), which is a special entity of posterior slowing, is not demonstrable during the first decade. Very rhythmical high-voltage 3- to 4-Hz waves may occur in prolonged runs in children with absence epilepsy and is referred to as occipital intermittent rhythmic delta activity. Likewise, the prevalence of anterior rhythmical 6- to 7-Hz theta activity increases between the age of 6 and 12 years before reaching a peak at the age of 13 to 15 years. If a 4- to 6 Hz theta rhythm activity is found in the frontal lobes, a predisposition to primary generalized epilepsy can be confirmed, as well as the predominantly centroparietal theta activity is considered abnormal.

From six to twelve years old, the *hyperventilation* shows particularly pronounced high-amplitude slowing. The slowing starts over posterior areas and gradually becomes diffusely distributed with a frontal maximum; rhythmical slow activity usually ranges from 1.5 to 4 Hz. Likewise, *intermittent photic-stimulation* shows a more mature type of occipital driving response, less prominent at low flash rates, and more impressive in the medium range (6 to 16 Hz) [45].

3.Metodology

3.1 Specification

This study was divided in two phases and measures were recording at three different times.

a. Phase one (1): EEG recordings at basal state and during 20 min of light stimulation with the filters placed on. This phase includes Time one (1) and two (2), corresponding to the first day of the experiment.
b. Phase two (2): EEG recordings after 20 sessions of light therapy without filters, which includes Time three (3), and corresponded to the last day of our experiment.

   EEG data were recorded using Neuronic.

3.2 Implementation

3.2.1 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) [55], producing several numerical parameters. Some characteristics of this system are the following:

a. 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).
b. 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.
c. Includes a normative database for obtaining a Z transformation correlated with age in the range of 5-90 years for comparison.
d. 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 [56]. 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 used to select the parameters during the study.

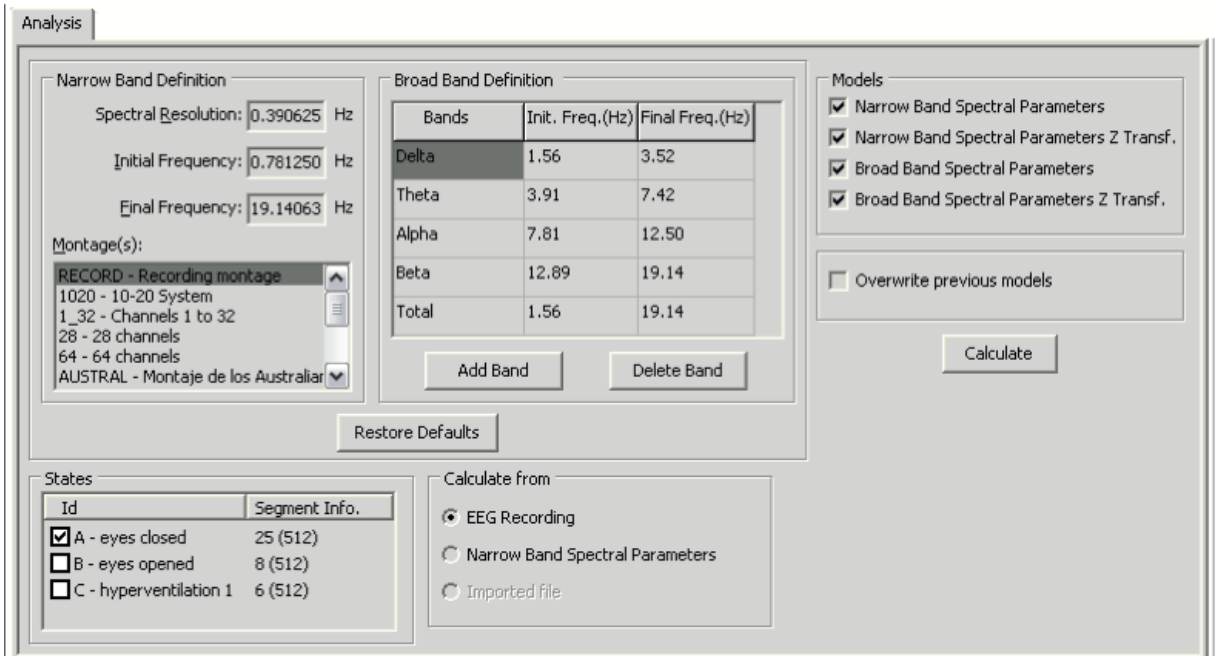

***Figure 2**. Graphical interface includes the narrow and broad bands, montage, models and states, and the option to calculate from.*

Likewise, 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 (δ, θ, α, β). 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 [57,58]. Additionally, the electronic ability and statistical methods used in the qEEG have already been explained and analyzed in a detailed way [55]. It is important to mention that the Neuronic ™ system permits obtaining DBMs from EEGs, a reason why, in this research, the obtained data are analyzed using probabilistic studies.

4. Design

This study included two phases. Each phase had its own design and specifications for each phase are presented bellow as follows:

4.1 Procedure used in Phase One

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. Additionally, 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.

Inclusion Criteria

Diagnosis of primary strabismus and amblyopia; best- corrected visual acuity of ≥ 0.7 logMAR; age of 8–30 years (considering that the brain activity of patients in this range is similar); IQ score in the norm for their chronological age, as reported by their schools and confirmed by their medical histories.

Exclusion Criteria

Diagnosis of secondary strabismus (neurological, traumas, systemic diseases) and/or a history of vision therapy; previous eye surgeries, dissociated and consecutive strabismus; photo-sensitivity; 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: 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:

Data Collection

Detailed medical histories regarding strabismus and amblyopia were collected from the patients on the first day. The following tests were performed: near and distance visual acuity, lensometry of the optical correction of the participants. noncycloplegic objective refraction, cycloplegic objective refraction using two drops of 1% tropicamide [59], 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. Neuro-optometric evaluation was 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 to see its influence of the visual system. The type of strabismus was established based on the clinical data collected.

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).

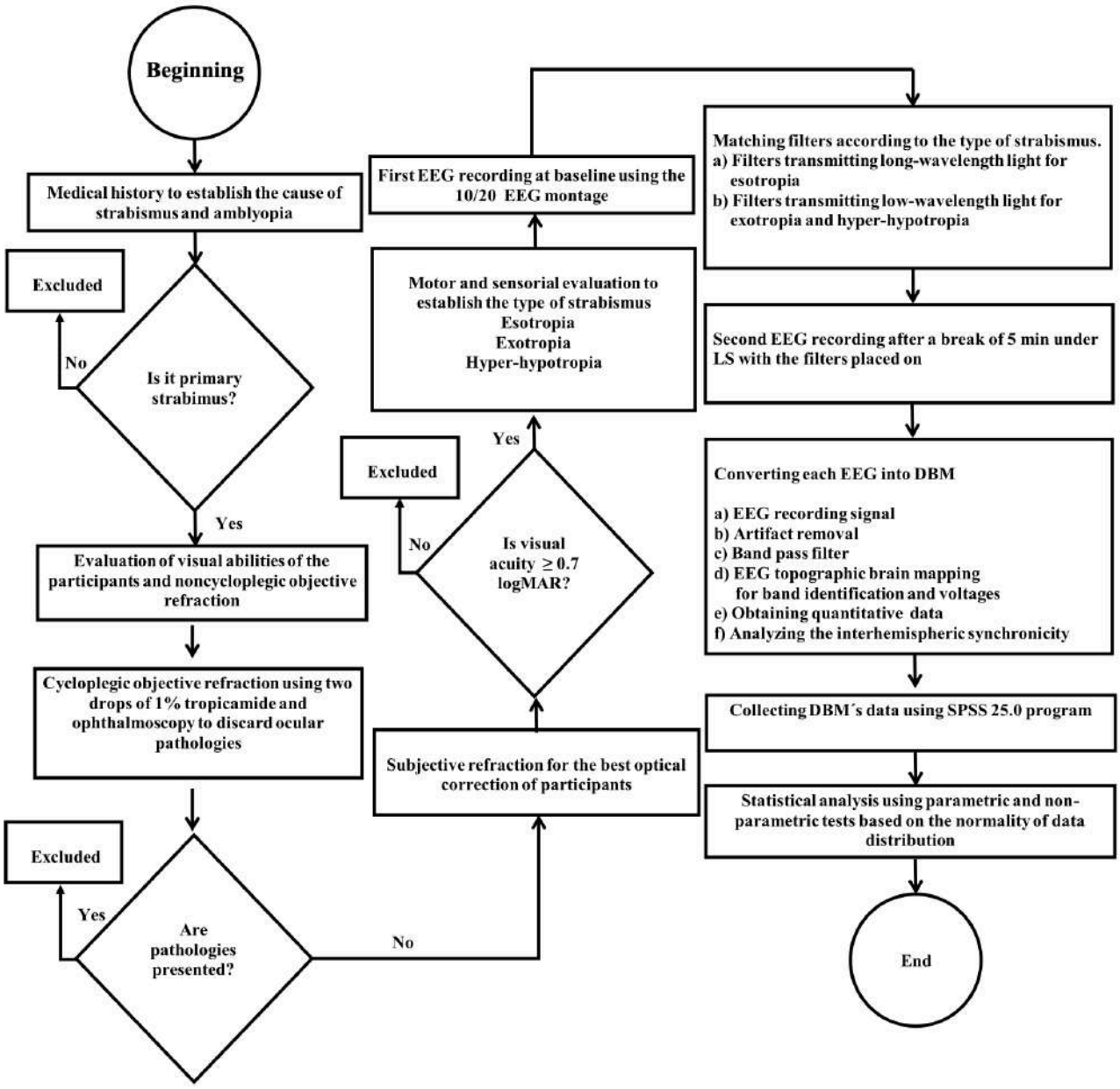

Figure 3. Flowchart illustrating the procedure followed during phase one of the study.

EEG Parameters and Procedure

The 10/20 EEG montage [60] was performed by the neurophysiologist in charge 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 [8]. 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. A 10-minute activation was then conducted, 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 with eyes 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 of a DBM were the relative and absolute power, and the average frequency.

The mean and standard deviation for the baseline activity (alpha-wave) were obtained and the coherence (interhemispheric synchronicity) was checked. Spectral peaks (frequency) and voltages were also measured, including a topographic

distribution of the above parameters. The baseline values of the patient were compared with the values of the general population included in the program.

Light Stimulation Parameters and Procedure

Fig. 1 in [8], 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 [8, 9]. 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 (exotropia and hyper/hypotropia) or strobed (esotropia and amblyopia).

As already explained in chapter two of this research, 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 retino-hypothalamic tract (i.e., the non-visual pathway of light perception) and its projections to sub-cortical and cortical regions, which react to light stimulation [61] explain all the changes found on the brain connection system and visual response.

Statistical Analysis for Phase One

For this purpose, both, parametric and non-parametric test were used to provide a precise and robust statistical analysis. The non-parametric Mann-Whitney (U) test was used to detect differences between two independent samples, as it is a test of both location and shape which 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.

Likewise, T-paired test and Wilcoxon test were also used to detect changes between two related samples based on the normality of data distribution. The parametric paired t-test was used in this phase to analyze the difference between two variables of the same subject, when the data are normally distributed, and the two variables are separated by time. In our case, we were 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 was used to compare two repeated measurements on a single sample when data were not normally distributed.

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 research was 95%, with an alpha of 0.05 ($\alpha = 0.05$). The level of statistical significance was 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 [62,63].

4.2 Procedure used in Phase Two

All strabismic patients included in phase one continued to phase two. However, only 11 healthy controls made it two phase two.

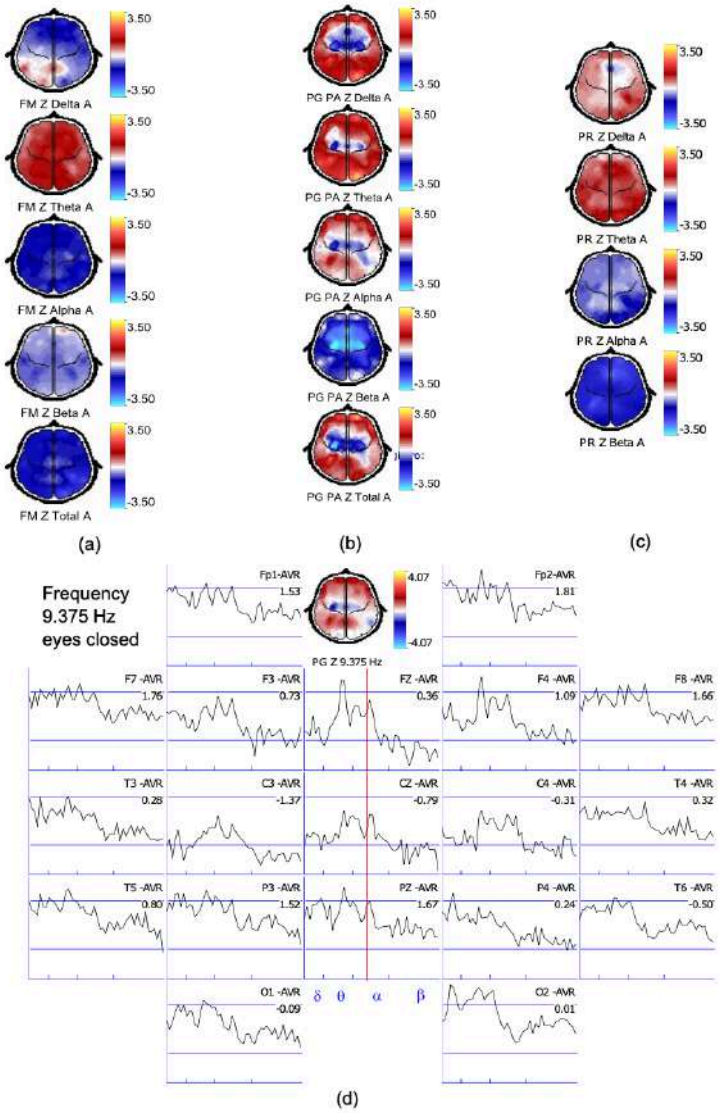

Figure 4. Images obtained from Neuronic software after the LTH program. (a) the mean frequency; (b) absolute power; (c) relative power; (d) FFT result.

As already mentioned, Neuronic was used in both phases to record the EEG activity of the patients. Figure 1. represents broad and narrow band measures through qEEG using FFT. All the seventeen SA patients who participated in phase one, made it to phase one.

On the contrary, only eleven healthy controls (HCs) which were matched with the patients in terms of age, sex, and economic status, continued to phase two; of whom 54.5% were male and 45.5% female. All HCs patients presented orthophoria at far and exophoria at near (mean 12.27 ± 5.69 diopters). Of the eleven patients, ten were right-handed and one was left-handed. Nine of the eleven patients had right-motor dominance and two left-motor dominance (see Table 1). The small number of HCs was due to the time frame of the LTH program. Apart from the electrical activity of the brain, changes in the visual performance of the patients (the amount of the visual acuity, degree of stereopsis, angle of deviation and dynamic visual fields) were also measured and compared to the results obtained at phase one.

Table 1. Demographics and clinical measurements at baseline of SA and HC groups.

Parameters	**SA Mean ± SD**	**HC Mean ± SD**	***p-value***
Male/Female	9/8	6/5	-
Age (Years)	18.1±10.5	22.3±5.9	0.49
Motor Eye Dominance	11R/6L	9R±2L	-
Handedness	17R	10R±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	-	-
Visual Acuity OD (far/near)	9.2±3.0 / 9.2±3.0	0.01±0.03/0.03±0.05	0.001/0.004
Visual Acuity OS (far/near)	0.3±0.3 / 0.2±0.2	0.01±0.03/0.03±0.05	0.001/0.002
Stereopsis	128.8±252.1	25.8±12.8	<0.001

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.

Data collection was divided in five phases:

For better results, the visual performance, EEGs, and the LTH program were performed from 10 am to 12 am and participants were recommended to maintain a constant sleep cycle which included 8–9 h of sleep per day.

Phase one: Detailed medical histories to establish the cause of strabismus and amblyopia were collected. Near and distance visual acuity and noncycloplegic objective refraction were performed. Cycloplegic objective refraction using two drops of 1% tropicamide, and ophthalmoscopy to establish the type of fixation under the cycloplegic effect was carried out.

Phase two: Subjective refraction for the best optical correction was performed. Posteriori, the visual efficiency exam was carried out. It included near and distance visual acuity with the new prescription ; 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) [15]; 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 [15,17]. Patients with a visual acuity of ≤0.2 logMAR were reexamined after wearing the newly prescribed glasses for four weeks [64]. The type of strabismus was established based on the clinical data collected. Visual field measures were performed using the Functional Color Field Tester (FCFT) devised by the Bernell Corporation with the best optical correction. Visual field measures are explained below as follows:

Visual field measures were performed in monocular and under scotopic conditions, using the best optical correction of the patient. For this purpose, a 19″ screen with a minimum resolution of 768–1024 as recommended by the FCFT manufacturers was used. The movement perception (white target), the functional visual fields (red-blue-green targets), and the blind spot were evaluated through the FCFT. The estimators of the parameters were as follows: diameters of 3.2 and 1.6

mm for the white target and the red, blue, and green targets, respectively. The target-presentation speed was of 36 mm/s; target brightness setting of 176 (no unit), and a random order of presentation regardless of target color. Targets were initially presented at 15 degrees from the center of the screen. The central fixation target was a single digit that randomly flashed at intervals of 1500 ms. Visual field measures were obtained before beginning any treatment (basal), after eight treatment sessions (to monitor progress), and after 20 sessions of LTH program (final) [8,9].

Phase three: Only patients who met the inclusion criteria were scheduled for the baseline brain activity measurement through electroencephalography (EEG), and the subsequent twenty sessions of LTH program. Filters were matched according to the type of strabismus and the visual clinical manifestations as shown in the flowchart in Figure 2 which illustrates the steps followed in this research.

Phase four: A new EEG recording after twenty consecutive sessions of LTH was performed. Visual performance and visual field measures were repeated after the complete cycle of LTH treatment.

Phase five: qEEG data were obtained and the statistical analysis using the SPSS 25.0 program was performed.

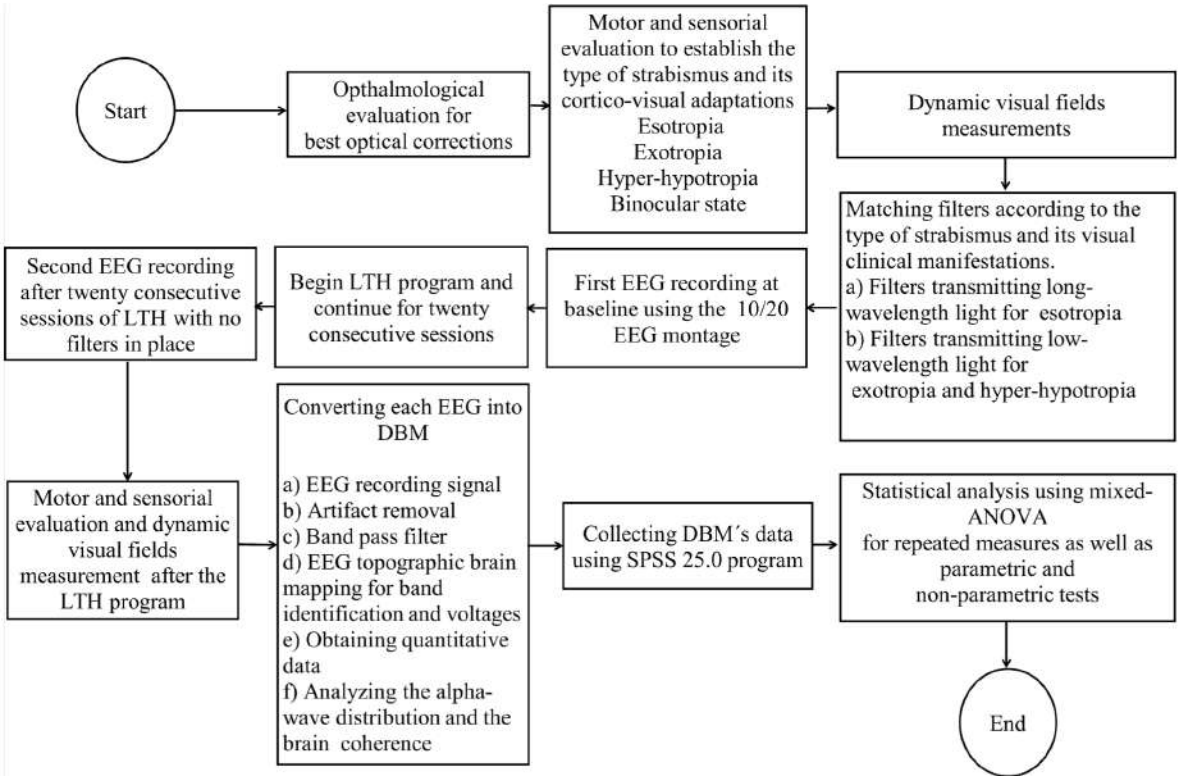

Figure 5. The flow diagram illustrates the steps followed in this research at phase two.

EEG and LTH Parameters and Procedure

As in phase one, the international 10/20 EEG montage [60] was used to record the brain electrical activity of participants. The evaluation was performed under low-light conditions in both recordings. Data were recorded in the Neuronic™ Psychophysiology system. Two waking EEG recordings were performed for each patient: before (at baseline) and after twenty sessions of LTH (a total cycle of light therapy program) [8]. The LTH accommodation using the visible spectrum (380–780 nm) is illustrated in Figure 1 [8]. The visible spectrum (380–780 nm), was used for LTH. Data about the Syntonizer of the CSO used for light stimulation was already explained in phase one [8,9].

Statistical Analysis for Phase Two

Mixed ANOVA for repeated measures was used to analyze and compare the mean differences of the data collected through the qEEG, between SA patients and HCs at Time 1 (at baseline) and Time 2 (after 20 sessions of LTH). Spearman correlation was used to assess the relationship between two variables using a monotonic function. Adjustment for multiple comparison was performed using Bonferroni. The normality of data distribution was checked with Shapiro-Wilk (S-W) test. For the visual performance, T-paired test and Wilcoxon tests were used to detect changes between two related samples based on the normality of data distribution. The level of statistical significance is expressed as a *p*-value between 0 and 1. All statistical analyses were performed with SPSS Statistics Base 25.0. The confidence level (CI) used in this study was 95%, with an alpha of 0.05 ($\alpha = 0.05$).

5. Results and Discussion

5.1 Results obtained at Phase One

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).

Table 2. 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	-	-
Visual Acuity OD (far/near)	9.2±3.0 / 9.2±3.0	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.

qEEG Differences Comparing the two Groups Using the Mann-Whitney Test

The alpha-wave activity (p = 0.029) and the high-voltage values (p = 0.001) recorded at baseline In the SA group, were significantly lower compared to the HC group (Fig. 5 and Fig. 6). There were no statistically significant differences between 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 3, Table 4, Fig. 7, and Fig. 8). What mostly stood out in this phase, was the presence of theta-wave recorded at baseline and its absence during the administration of LS in the SA group (Table 3).

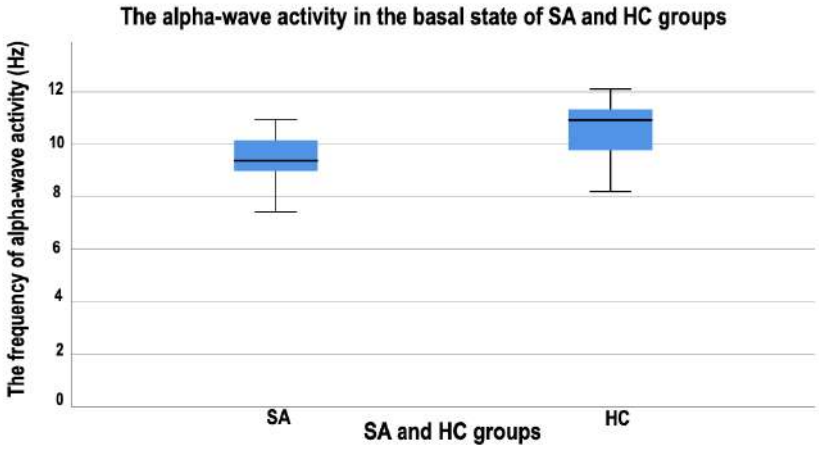

Figure 6. The frequency of alpha-wave activity of SA and HC groups recorded at baseline.

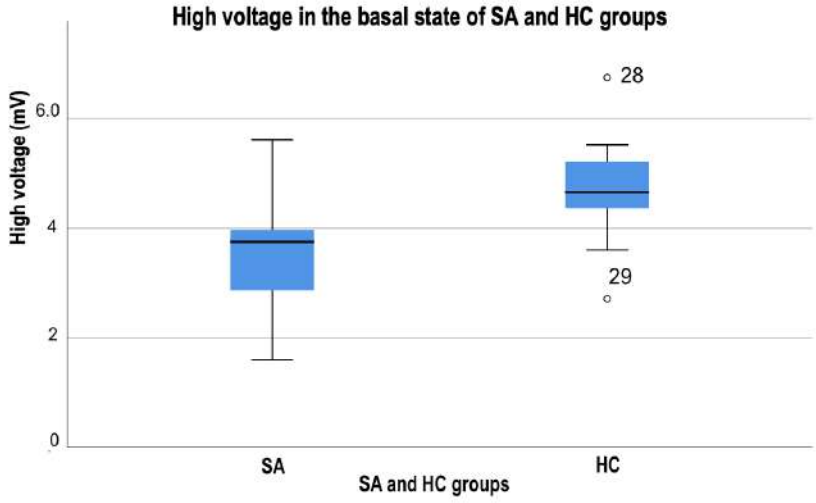

Figure 7. The high voltage of SA and HC groups measured at baseline.

Table 3. EEG recordings of the cortical activity at baseline and during LS of SA and HC groups.

Parameters	SA Baseline	HC Baseline	SA During LS	HC During LS
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Alpha-Wave	9.4 ± 1.1	10.4 ± 1.3	9.7 ± 0.8	9.7 ± 1.6
Theta-Wave	4.6 ± 0.9	-	-	-
Low Voltage (<V)	1.9 ± 2.9	3.3± 2.8	3.3 ± 2.8	-3.1 ± 1.9
High Voltage (>V)	3.5 ± 1.1	5.5 ± 1.9	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 4. Mann-Whitney test comparing EEG measurements of the cortical activity at baseline and during LS of SA and HC group.

Parameters	U of Mann-Whitney	*p-value*
Alpha-wave activity at baseline	81.0	0.029
Alfa wave activity during LS	1.39.0	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

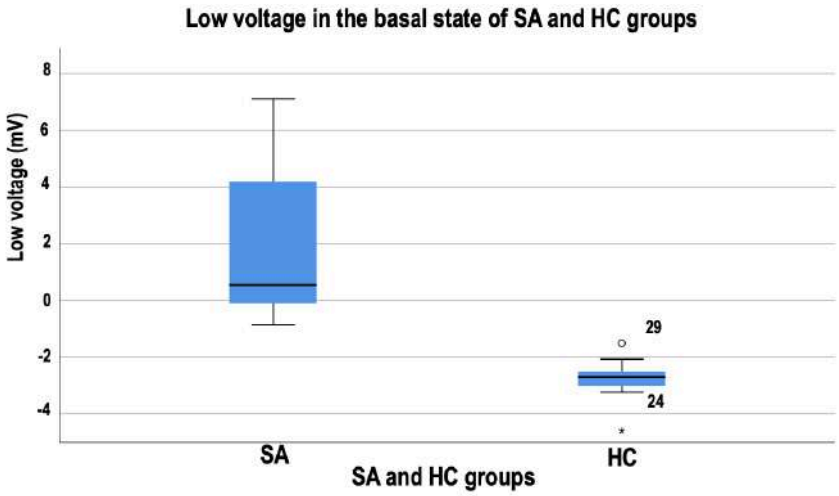

Figure 8. The low voltage of SA and HC groups recorded at baseline.

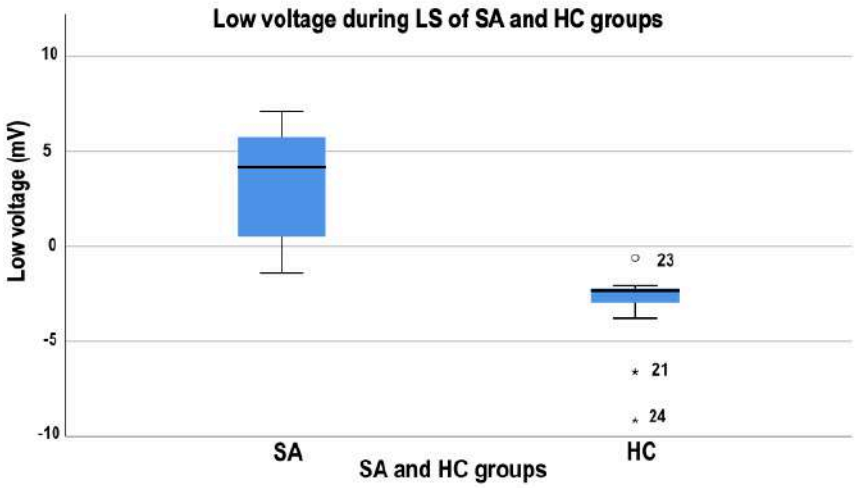

Figure 9. The low voltage of SA and HC groups measured during the administration of LS.

qEEG Differences Within the Same Group Using T-Paired Test and Wilcoxon Test

Within each group, the frequency of alpha-wave activity and low and high-voltage values at baseline and during the administration of LS were analyzed. 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 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. 9 and Fig. 10). There was a statistically significant increase in both parameters during LS ($p = 0.022$ and $p < 0.001$ respectively), (Table 5).

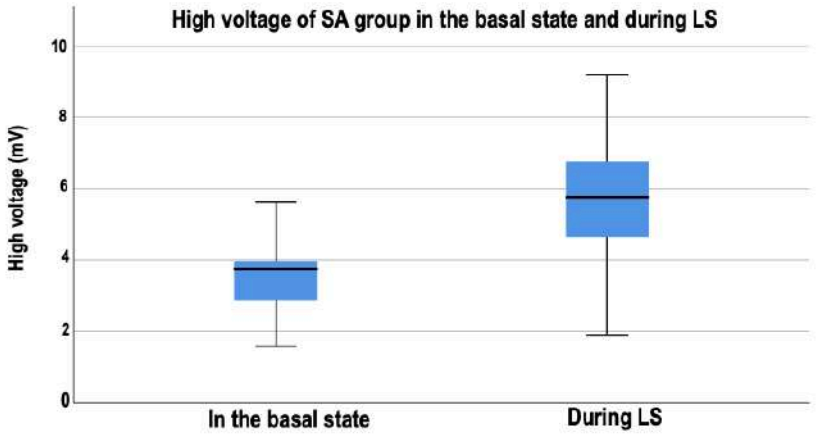

Figure 10. The high voltage of SA group measured at baseline and during the administration of LS.

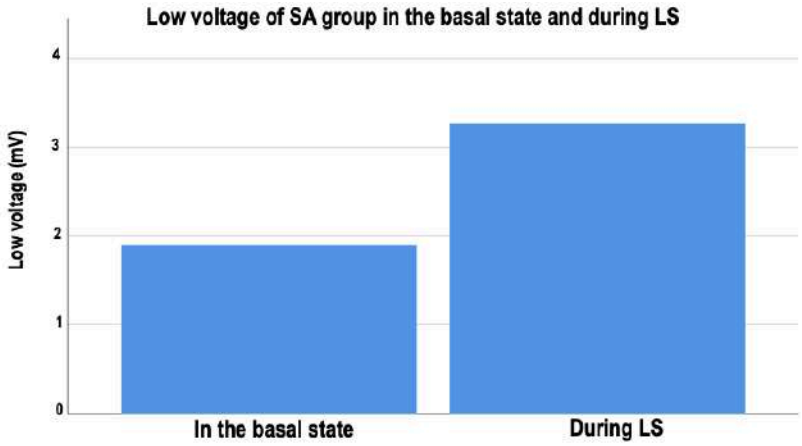

Figure 11. The low voltage of SA group measured at baseline and during the administration of LS.

Table 5. 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 SA group	-	1.923	0.072
Low voltage of SA group	-0.308	-	0.758
High voltage of SA 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).

qEEG 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 qEEG of a healthy patient in the waking-state, alpha waves should be found in the posterior and occipital regions [36]. Table 6 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 more 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 7), followed by parietals regions in 11.8% of the patients.

Table 6. 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 center-occipitals 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 7. 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 patient. *EEG recordings were carried out in the waking- state. *Abbreviations: (α), alpha-wave

Table 8. 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

qEEG Differences in the State of Brain Coherence and Interhemispheric Synchronicity at Baseline and During the Administration of LS in the SA Group.

At baseline (Table 6), 76.5% of the patients exhibited interhemispheric asynchronicity (absence of brain coherence). By contrast, a state of interhemispheric synchronicity was found in all patients during the administration of LS (Table 7), 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 light transmitted by the filters could not be associated with changes in the activity of a specific brain region or the state of coherence.

A remarkable qEEG Finding was the Presence of Theta Waves Recorded at Baseline and its Distribution across the Brain in the SA Group.

Theta-rhythm (4-7 Hz) is considered a slow brain rhythm and occurs primarily during sleep or relaxed wakefulness. Its 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 6).

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 (Table 7).

qEEG 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 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 8). 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.

5.2 Results Obtained at Phase Two

Demographic and Visual Measurements at Baseline

No significant age differences (p = 0.49) 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 = 0.001) and near (p = 0.004 and 0.002 for OD and OI respectively) and the amount of stereopsis (p < 0.001) were statistically significant (Table 1).

qEEG Measurements for the alpha-wave, low and high-voltage

A 2 (Time) × 2 (Groups) mixed-model ANOVA for alpha-wave, revealed that the main effect for Groups was statistically significant F (1.26) = 23.03, p < 0.001, Eta-squared = 0.47 (Table 9). Thus, there was a significant overall difference in its value when SA (m = 9.62) was compared to HC (m = 11.20) group (Table 10). A significant main effect for Time was also obtained, F (1.26) = 4.54, p = 0.043, Eta-squared = 0.15 (Table 11). Alpha-wave values after LTH (m = 10.59) were higher than at baseline (m = 10.21) (Table 12). However, the Time × Groups effect was not statistically significant F (1.26) = 0.005, p = 0.94, Eta-squared < 0.001.

Table 9. Tests of Between-Subjects Effects for Alpha-Wave.

Source	Type III Sum of Squares	F	Sig.	Partial Eta Square
Intercept	5776.835	4072.123	0.000	0.994
Groups	32.667	23.027	0.000	0.470
Error	36.884			

* Transformed Variable: Average.

Table 10. Estimates for Groups.

			95% CI	
SA and HC Groups	Mean	Std.Error	Lower Bound	Upper bound
SA	9.616	0.204	9.196	10.036
HC	11.180	0.254	10.658	11.702

Table 11. Tests of Within-Subjects Effects for Alpha-Wave.

	Source	F	Sig.	Partial Eta Square
Time	Sphericity Assumed	4.542	0.043	0.149
	Greenhouse-Geisser	4.542	0.043	0.149
	Huynh-Feldt	4.542	0.043	0.149
	Lower-bound	4.542	0.043	0.149

Table 12. Estimates for time.

			95% CI	
Time	**Mean**	**Std.Error**	**Lower Bound**	**Upper bound**
1	10.209	0.206	9.786	10.632
2	10.587	0.163	10.253	10.922

Table 13. Descriptive statics for Alpha-Wave.

	SA and HC Groups	Mean	Std.Deviation	N
Alpha-wave activity at baseline	SA	9.42100	1.103814	17
	HC	10.99718	0.996305	11
	Total	10.04021	1.305439	28
Alpha-wave activity after LTH	SA	9.81153	0.815620	17
	HC	11.36309	0.880818	11
	Total	10.42107	1.130057	28

Examination of the cell means indicated that qEEG values of alpha-wave obtained at baseline, and after the LTH program were statistically significant for Time and Groups, but Time × Groups interaction was not statistically significant (see Figure 11). The descriptive statistics of alpha-waves of SA and HC groups, before and after the complete cycle of LTH can be seen at Table 13.

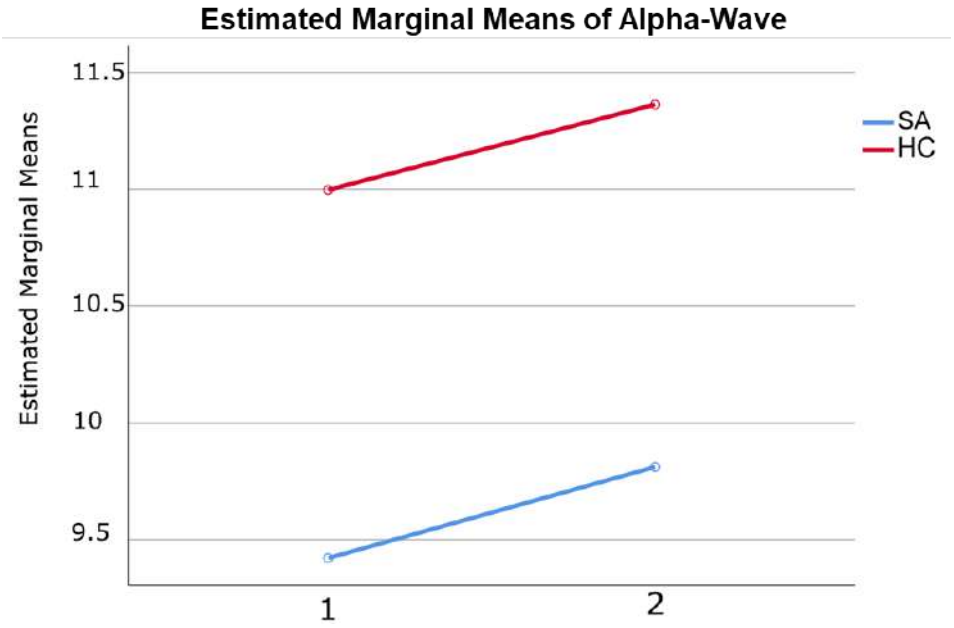

Figure 12. Displayed means for alpha-wave measured at Time 1 (baseline) and Time 2 (after 20 sessions of LTH) for SA (shown in blue color) and HC (shown in red color) groups.

When the values of low voltage were analyzed, the 2 (Time) × 2 (Groups) mixed- model ANOVA reveled that the main effect for Groups was statistically significant F (1.26) = 42.99, $p < 0.001$, Eta-squared = 0.62 (Table 14). Thus, there was a significant overall difference in the value of the low voltage measured for SA (m = 2.03) and HC (m = −2.24) group respectively (Table 15). However, no statistically significant effect for Time was found when SA (m = −0.45) was compared to HC (m = 0.25) group, F (1.26) = 1.54, $p = 0.23$, Eta-squared = 0.06. Nor Time × Groups interaction showed any statistical interest, F (1.26) = 0.56, $p = 0.46$, Eta-squared = 0.02 (see Figure 12).

Table 14. Tests of Between-Subjects Effects for Low Voltage.

Source	Type III Sum of Squares	F	Sig.	Partial Eta Square
Intercept	0.574	0.101	0.753	0.004
Groups	243.228	42.986	0.000	0.623
Error	147.116			

*Transformed Variable: Average.

Table 15. Estimates for Groups.

			95% CI	
SA and HC Groups	**Mean**	**Std.Error**	**Lower Bound**	**Upper bound**
SA	2.030	0.408	1.191	2.869
HC	-2.237	0.507	-3.280	-1.195

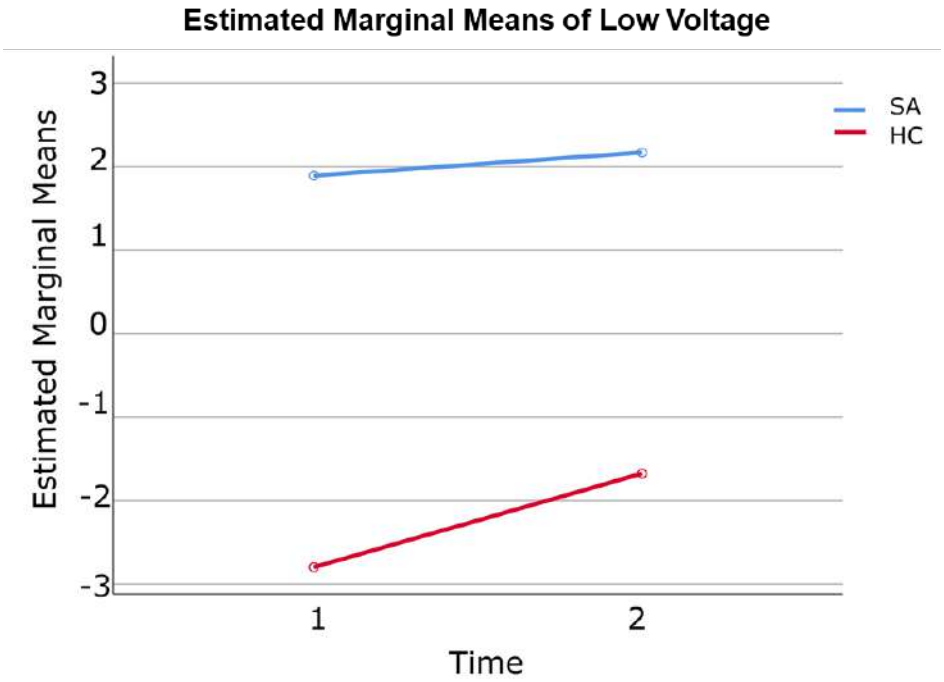

Figure 13. Displayed means for low voltage measured at Time 1 (baseline) and Time 2 (after LTH) for SA (shown in blue color) and HC (shown in red color) groups.

Examination of the cell means indicated that qEEG values of low voltage obtained at baseline, and after the LTH program were statistically significant only for Groups. Table 16 illustrates the descriptive statistics of low voltage values before and after the LTH program for both groups (SA and HCs).

Table 16. Descriptive Statistics for Low Voltage.

	SA and HC Groups	**Mean**	**Std.Deviation**	**N**
Low-voltage activity at baseline	SA	1.8912	2.86705	17
	HC	-2.7982	0.66296	11
	Total	0.0489	3.23623	28
Low-voltage activity after LTH	SA	2.1688	2.46504	17
	HC	-1.6764	1.56305	11
	Total	0.6582	2.85709	28

The 2 (Time) × 2 (Groups) mixed-model ANOVA for high voltage, revealed a significant Time × Groups effect F (1.26) = 8.11, p = 0.008, Eta-squared = 0.24 (see Table 17). To analyze its significance, the Wilcoxon test was used, which revealed a (p = 0.04 and 0.01) for SA and HCs respectively. Figure 13 illustrates that while high voltage values for the SA group incremented from Time 1 (m = 3.47) to Time 2 (m = 4.70), they decreased for the HC group (m = 4.71 and 3.83 respectively) (Table 18). While high voltage values measured at baseline (Time 1) were greater for HC group when compared to SA group, the result was inverted when measured after the LTH program (Time 2), where SA high voltage values were higher when compared to HC ones.

Table 17. Tests of Within-Subjects Effects for High Voltage.

Source		F	Sig	Partial Eta Squared
Time* Groups	Sphericity Assumed	8.114	.008	.238
	Greenhous-Geisser	8.114	.008	.238
	Huynh-Feldt	8.114	.008	.238
	Lower-bound	8.114	.008	.238

Table 18. SA and HC Groups * Time.

				95% CI	
SA and HC Groups	**Time**	**Mean**	**Std.Error**	**Lower Bound**	**Upper bound**
SA	1	3.473	0.224	3.013	3.933
	2	4.699	0.460	3.754	5.643
HC	1	4.709	0.278	4.137	5.281
	2	3.832	0.571	2.658	5.006

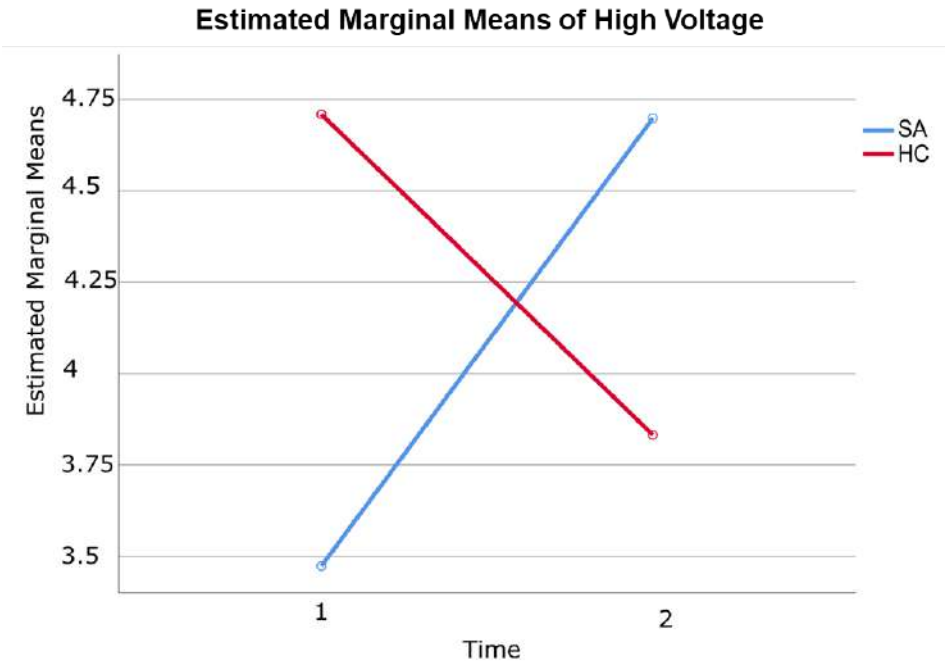

Figure 14. Displayed means for high voltage measured at Time 1 (baseline) and Time 2 (after 20 sessions of LTH) for SA (shown in blue color) and HC (shown in red color) groups.

However, no statistically significant effect was seen for Groups F (1.26) = 0.17, *p* = 0.68, Eta-squared = 0.007, where the obtained values for SA patients (m = 4.09) were no different form, the ones obtained for HC (m = 4.27). Additionally, the effect of Time was not statistically significant either F (1.26) = 0.22, *p* = 0.64, Eta-squared = 0.009. The mean value of high voltage for SA patients (m = 4.09) compared to HCs (m = 4.26) were alike. Examination of the cell means indicate that qEEG values of high voltage obtained at baseline, and after the complete cycle of LTH only presented a statistically significant Time × Groups interaction. Table 19 presents the descriptive statistics of high voltage of SA and HC groups, before and after the LTH program.

Table 19. Descriptive Statistics for High voltage.

	SA and HC Groups	Mean	Std.Deviation	N
High-voltage activity at baseline	SA	3.4729	1.09514	17
	HC	4.7091	0.54662	11
	Total	3.9586	1.09515	28
High-voltage activity after LTH	SA	4.6988	2.33463	17
	HC	3.8318	0.78249	11
	Total	4.3582	1.90857	28

A second spectral peak, (theta-wave) was exclusively recorded in SA patients, both, at baseline and after the LTH treatment. The Wilcoxon-test (considering the non-normal distribution of the data analyzed with Shapiro-Wilk test) was used to compare means, with no statistically significant differences between their values (m = 4.62 ± 0.96 and 4.96 ± 1.51 before and after LTH respectively, where p = 0.30). However small the difference, it could make a change in the clinical performance of SA patients.

Spearman Correlation Coefficients

This analysis was used to determine the relationship between two variables based on a monotonic function. Positive Spearman correlations for alpha-wave frequency at baseline and after the LTH program (p = 0.002), as well as baseline and after LTH low and high voltages (p = 0.001 and <0.001 respectively) was found in SA patients. The results are presented in Table 20 and illustrated by Figures 14–16. No statistically significant correlations were found for HCs.

Table 20. Spearman correlations of SA group.

			Alpha-wave activity after LTH
Spearman's rho	Alpha-wave activity at baseline	Correlation coefficient Sig.(2-tailed)	0.692** 0.002
			High voltage at baseline
Spearman's rho	Low-voltage at baseline	Correlation coefficient Sig.(2-tailed)	0.729** 0.001
			High voltage after LTH
Spearman's rho	Low-voltage after LTH	Correlation coefficient Sig.(2-tailed)	0.886** <0.001

** Correlation is significant at the 0.01 level (2-tailed); N = 17.

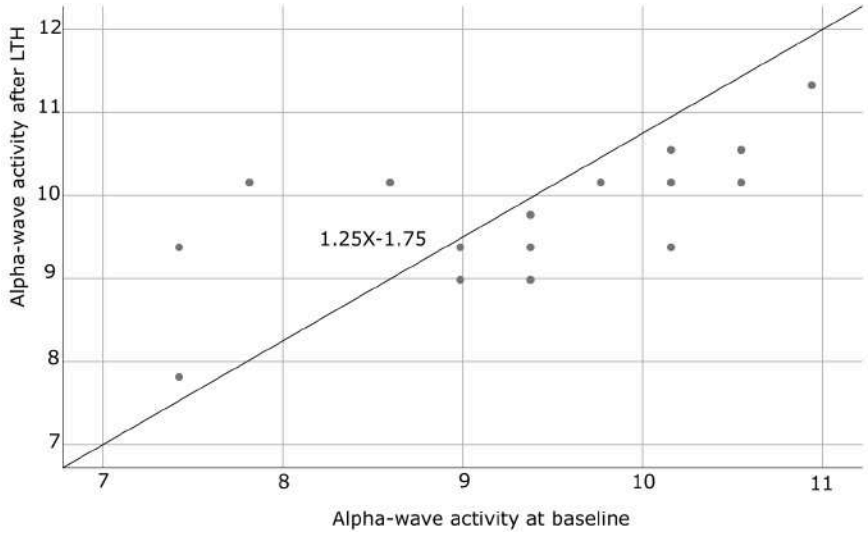

Figure 15. Illustrates the correlation between the alpha-wave activity measured at baseline and after LTH of SA patients.

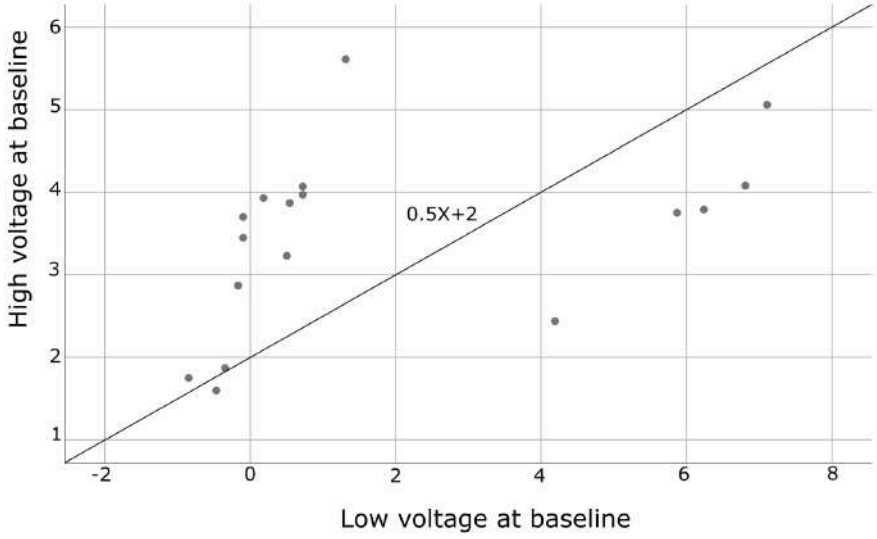

Figure 16. Illustrates the correlation between low and high voltage values measured at baseline of SA patients.

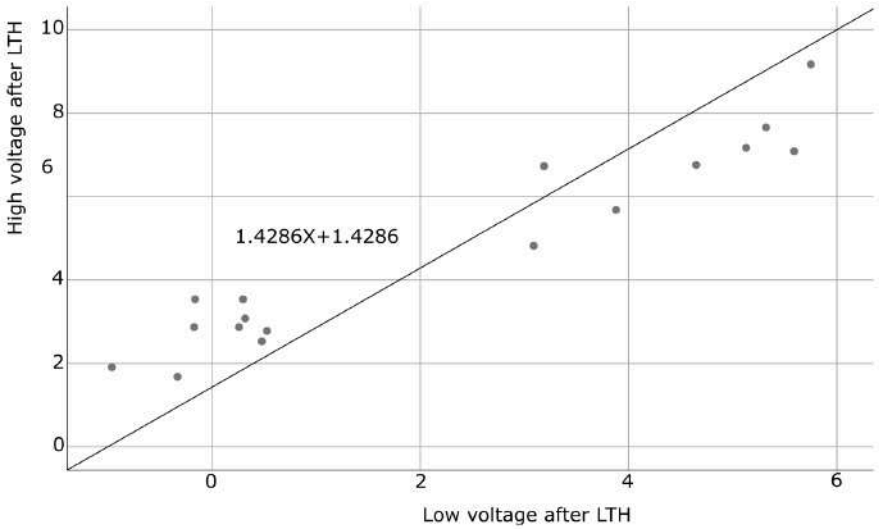

Figure 17. Illustrates the correlation between low and high voltage values measured after LTH of SA patients.

qEEG Differences in the Distribution of Alpha and Theta-Waves across the Brain, at Baseline, and after the Complete Cycle of LTH in SA Patients.

It was already emphasized that in the baseline qEEG of a healthy patient, alpha waves should be found in the posterior and occipital regions [33]. Table 21 shows that only 41.2% of the patients followed this pattern, suggesting an irregular alpha-wave distribution and asymmetric activity pattern, with a predominance in the left hemisphere. By contrast, a better distribution of alpha waves towards the occipital brain regions was seen after the LTH program in 70.6% of the patients (Table 22). An important qEEG finding was the presence of theta waves recorded at baseline and after LTH and its distribution across the brain in SA patients. Theta waves (4–7 Hz) occur primarily during sleep or relaxed wakefulness; their presence in the waking-state is associated with clinical conditions, depending on the area of its concentration.

The distribution of the theta-wave was mostly concentrated in the frontal lobe (cognitive functions), followed by the occipital (visual analysis) and parietal lobes (spatial orientation), suggesting that the patients' conditions may have compromised brain function in the specific cortical areas where theta-wave activity was observed (Tables 21 and 22). Less theta-wave activity was recorded in the central regions, related to the control of motor areas. After LTH, theta waves were also observed to a limited extent in temporal regions (memory funtions). Nevertheless, its distribution became more homogenous after the LTH treatment.

Table 21. 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 right 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 center-occipitals lobe	Left parieto-occipital lobe	Asynchrony of left fronto-temporal lobe
015	Occipitals	Occipitals	Asynchrony of fronto-temporals
016	Occipitals	Right frontal lobe	Asynchrony 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 22. Distribution of alpha and theta-waves and the state of brain coherence after LTH of SA group.

Patients	Distribution of (*α*)	Distribution of (*α*)	Brain Coherence
001	Occipitals	Frontals	Asynchrony of left temporal lobe
002	Occipitals	Fronto-centrals and occipitals	Synchrony
003	Occipitals	Frontals and occipitals	Synchrony of occipitals
004	Occipitals	Fronto-temporals and occipitals	Synchrony of occipitals
005	Occipitals	Frontal	Synchrony of occipitals
006	Occipitals	Right parieto-occipital lobe	Synchrony of occipitals and parietals
007	Occipitals and parietals	Frontals and centrals	Synchrony of occipitals and parietals
008	Frontals and right centro-parietal lobe	Right frontal and right parietal lobe	Asynchrony of left frontal and centro-parietal lobe
009	Centro–parietals, predominating at centrals	Frontals and occipitals	Synchrony of centro-parietals
010	Occipitals	Right frontal lobe	Asynchrony of left temporal lobe
011	Occipitals and parietals	Fronto-temporals	Synchrony of parietals and occipitals
012	Occipitals	Temporals	Synchrony of occipitals
013	Occipitals	Parietals and occipitals	Asynchrony of left frontal lobe
014	Occipitals	Left frontal, parietal, temporal and occipital lobe	Synchrony of parieto-occipitals
015	Parietals	Frontal	Synchrony of occipitals
016	Occipitals	No theta-wave registered	Synchrony of occipitals
017	Parietals	Parietals	Synchrony 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 patient. * EEG recordings were carried-out in the waking-state. * Abbreviations: (*α*), alpha-wave; (*θ*), theta-wave.

qEEG Differences Related to the Brain Coherence at Baseline and after the Complete Cycle of LTH in SA Patients.

At baseline, 76.5% of the patients exhibited interhemispheric asynchronicity (absence of brain coherence) (Table 21). By contrast, a better state of interhemispheric synchronicity was found in 76.5% of the patients after LTH (Table 22), indicating the heightened synchronization between the two hemispheres. Hence, light can act as a vector to balance the activity between hemispheres and promote synchronicity across the whole brain. Additionally, the state of brain coherence is affected by the wavelength of light transmitted by the filters. After LTH, all patients stimulated with filters transmitting light in the blue spectrum had defined interhemispheric synchronicity of parietal and occipital lobes ("where" aspects of the visual processing). Only 62.5% of patients stimulated with filters transmitting light in the red spectrum showed a state of interhemispheric synchronicity after treatment. Even though, no specific brain region could be associated with the asynchronous interhemispheric state of these patients (frontal, temporal, central, parietal, and occipital brain regions were all involved-general disfunction on the brain connectome).

However, the asynchronous state was mostly observed in the left hemisphere, being related to the learning process and detailed analysis. In presence of strabismus, visual and cortical adaptations are not only seen in the amblyopic eye, but in the fellow eye as well (trying to compensate for both). All SA patients were right-handed and 64.7% of them had right eye dominance as well (controlled by the left hemisphere). We contribute the irregular alpha-wave distribution to the hemisphere in charge of the visual processing information. The fellow eye is struggling to compensate for the visual deficiencies presented in the strabismic eye. Therefore, the left hemisphere takes charge of most of the sensorial processing, including eye and hand dominance. Alpha-wave distribution then could be related to the challenges presented to the left hemisphere to maintain the brain functionality at its most.

At baseline, relatively increased alpha-wave activity was observed in the left occipital and parietal lobes; increasingly less activity was observed in the right occipital, left central, frontal, and right parietal lobes, respectively. Relatively increased theta-wave activity was observed in the frontal lobe; increasingly less activity was observed in the occipital and right parietal lobes, left parietal lobe, and central regions (associated with sensory and motor functions), respectively. After 20 sessions of LTH, the alpha-wave locates mostly on occipitals, followed by parietals, centrals, and frontals, whereas theta-wave is more present in frontals, followed by occipitals, temporals, parietals, and central regions. It can be concluded that the

distribution of the alpha and theta-waves became more homogenous following LTH, indicating the heightened synchronization between the two hemispheres.

qEEG Differences in the Distribution of the Alpha-Wave across the Brain, and the State of Interhemispheric Synchronicity at Baseline, and after the Administration of LTH in HCs.

At baseline, alpha waves were mostly found in the occipital lobes, followed by parietals, as expected. Nevertheless, a 27.3% of HCs presented a state of asynchronicity of parieto-occipital lobes at baseline without any clinical manifestation [34]. However, a shift to synchronicity was observed after LTH. (Table 23). To conclude, after LTH, both, the distribution of the alpha-wave and the state of brain coherence, followed normality. 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.

Table 23. Distribution of alpha-wave and the state of brain coherence at baseline and after LTH of HC group.

Patients	Distribution of (α) at Baseline/after LTH	Brain Coherence at Baseline/after LTH
001	Occipitals/ Occipitals	Synchrony of occipitals/ Synchrony of occipitals
002	Occipitals/ Occipitals	Asynchrony of parieto-occipitals/ Synchrony of occipitals
003	Occipitals/ Occipitals	Synchrony of parieto-occipitals/ Synchrony of occipitals
004	Parieto-occipitals/ Parietals	Asynchrony of parieto-occipitals/ Synchrony of occipitals
005	Parieto- occipitals/ Occipitals	Asynchrony of parieto-occipitals/ Synchrony of occipitals
006	Parietals/ Occipitals	Synchrony of parietals/ Synchrony of occipitals
007	Parietals/ Occipitals	Synchrony of parietals/ Synchrony of occipitals
008	Occipitals/ Occipitals	Synchrony of parieto-occipitals/ Synchrony of occipitals
009	Occipitals/ Occipitals	Synchrony of occipitals/ Synchrony of occipitals
010	Occipitals/ Occipitals	Synchrony of occipitals/ Synchrony of occipitals
011	Occipitals/ Occipitals	Synchrony of occipitals/ Synchrony of occipitals

* 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; LTH, light therapy.

Assessment of the LTH Effect on Clinical Metrics, Such as the Angle of Strabismus, Phoria State, Visual Acuity, Amount of Stereopsis, and Visual Fields.

Visual performance was analyzed using both, parametric and non-parametric tests. The angle of strabismus, visual acuity of SA patients, stereopsis and phoria state were analyzed using the Wilcoxon test, considering the non-normal distribution of the data. Normal data distribution was found for visual fields (for both groups), and visual acuity of HCs. T-paired test was used in this case. The statistical analysis showed that LTH had a great impact

on the visual performance of SA patients. It induced enhancements in the visual acuity of both eyes, at far and near distances, increased the amount of stereopsis and 3D perception, decreased the angle of deviation, at both far and near, and enlarged visual fields in response to white, red, green, and blue stimulus (see Table 24). LTH destabilized some of the visual abilities of HCs. More specifically, the amount of stereopsis decreased and phoria state was deteriorated, without statistically significant changes in the visual acuity.

On the other hand, visual fields become larger in response to all four colored stimuli used. These clinical findings suggest that in patients with strabismus and amblyopia, brain patterns can be actively changed, fostering new visual abilities, and improving old ones to secure improved patient outcomes. On the contrary, when no necessary, LTH can act as an aggressor to the visual system when used in healthy population, as seen in HCs.

Table 24. Clinical measurements of SA and HC groups, at baseline and after 20 sessions of LTH.

Parameters	HCs at baseline	HCs after LTH	*p*-Value	SA at Baseline	SA after LTH	*p*-Value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
VA OD Far	0.01 ± 0.03	0.01 ± 0.03	$p > 0.05$	0.32 ± 0.37	0.16 ± 0.24	$p < 0.001$
VA OD Near	0.03 ± 0.05	0.03 ± 0.05	$p > 0.05$	0.24 ± 0.36	0.12 ± 0.23	$p < 0.001$
VA OI Far	0.01 ± 0.03	0.01 ± 0.03	$p > 0.05$	0.35 ± 0.33	0.2 ± 0.27	$p < 0.001$
VA OI Near	0.03 ± 0.05	0.03 ± 0.05	$p > 0.05$	0.2 ± 0.25	0.14 ± 0.24	$p < 0.001$
Stereopsis	25.82 ± 12.81	25.09 ± 13.99	$p = 0.001$	128.8 ± 252.1	54.2 ± 73.31	$p < 0.001$
ET FAR	-	-	-	29.0 ± 14.84	19.13 ± 17.87	$p < 0.001$
ET Near	-	-	-	27.0 ± 17.02	18.13 ± 18.47	$p = 0.001$
XT Far	-	-	-	12.71 ± 8.3	8.14 ± 6.89	$p = 0.003$
XT Near	-	-	-	25.43 ± 12.53	16.57 ± 10.52	$p = 0.001$
HT Far	-	-	-	9.2 ± 3.03	5.17 ± 3.71	$p = 0.008$
HT Near	-	-	-	9.2 ± 3.03	5.50 ± 3.45	$p = 0.005$
XF Near	12.27 ± 5.69	14.18 ± 6.82	$p = 0.001$	-	-	-
Green OD	15.79 ± 0.6	16.05 ± 0.85	$p = 0.003$	15.38 ± 0.98	17.09 ± 0.39	$p < 0.001$
Green OI	15.94 ± 0.42	16.31 ± 0.46	$p = 0.003$	15.36 ± 0.9	17.25 ± 0.58	$p < 0.001$
Blue OD	24.82 ± 0.81	24.9 ± 1.35	$p = 0.003$	23.87 ± 0.85	25.69 ± 0.65	$p < 0.001$
Blue OI	24.54 ± 0.6	25.14 ± 0.52	$p = 0.003$	23.75 ± 1.2	25.95 ± 0.68	$p < 0.001$
Red OD	23.45 ± 1.31	24.15 ± 1.14	$p = 0.003$	23.02 ± 1.82	25.82 ± 0.67	$p < 0.001$
Red OI	23.71 ± 1.28	24.52 ± 0.65	$p = 0.003$	23.05 ± 1.48	25.98 ± 0.77	$p < 0.001$
White OD	29.55 ± 0.75	29.65 ± 1.39	$p = 0.003$	28.78 ± 1.43	31.04 ± 0.54	$p < 0.001$
White OI	29.39 ± 1.37	29.99 ± 0.97	$p = 0.003$	28.58 ± 1.73	31.09 ± 0.94	$p < 0.001$

* T-paired test and Wilcoxon test were used to detect changes between two related samples based on the normality of data distribution. Data shown as mean standard deviation or n. * Abbreviations: SA, strabismus, and amblyopia; HCs, healthy controls; OD, oculus dexter; OI, oculus sinister; ET, esotropia; XT, exotropia; HT, hypertropia.

5.3 Discussion

The present study used qEEG to collect and analyze changes in the metrics of cortical activity, such as frequencies, voltages, and coherence during the administration of LS and after the LTH program in patients with strabismus and amblyopia, and healthy controls, aged 8-30 years. LTH was administered to the control group as well, to see the effect of the filters used and document it in visually normal individuals, so that any changes found in the SA group may be considered unique. Moreover, by knowing the mechanism of its function in the control group, simulation could be specified for patients with neurodevelopment disorders such as strabismus, amblyopia, or even neurological diseases. Three EEG recordings, one at baseline, a second one during the moment of LS and a third one after the LTH program [8,9], permitted analyzing and comparing data about all parameters associated with the brain activity of the participants.

The visual performance which included clinical data such as the visual acuity, angle of deviation and phoria state, stereopsis, and dynamic visual fields across stimulation were also analyzed. The visible spectrum of light was 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 [65].

Considering that light reaches the visual cortex through the retina and the possibility to modify EEG patterns by hormonal, biochemical, and neuroelectric processes [66], it was expected LS to have an impact on the brain activity, measured in the waking-state. Four parameters were analyzed to identify the cortical activity of SA and HC groups: a) the activity and distribution of the alpha-wave, b) the interhemispheric synchronicity which represents the state of neural brain coherence (Figs 17-19), c) the unexpected discovery of the theta-wave recorded at baseline in the SA group, and d) the anteroposterior gradients which indicates low (anterior brain regions) and high (posterior brain regions) voltages in the brain.

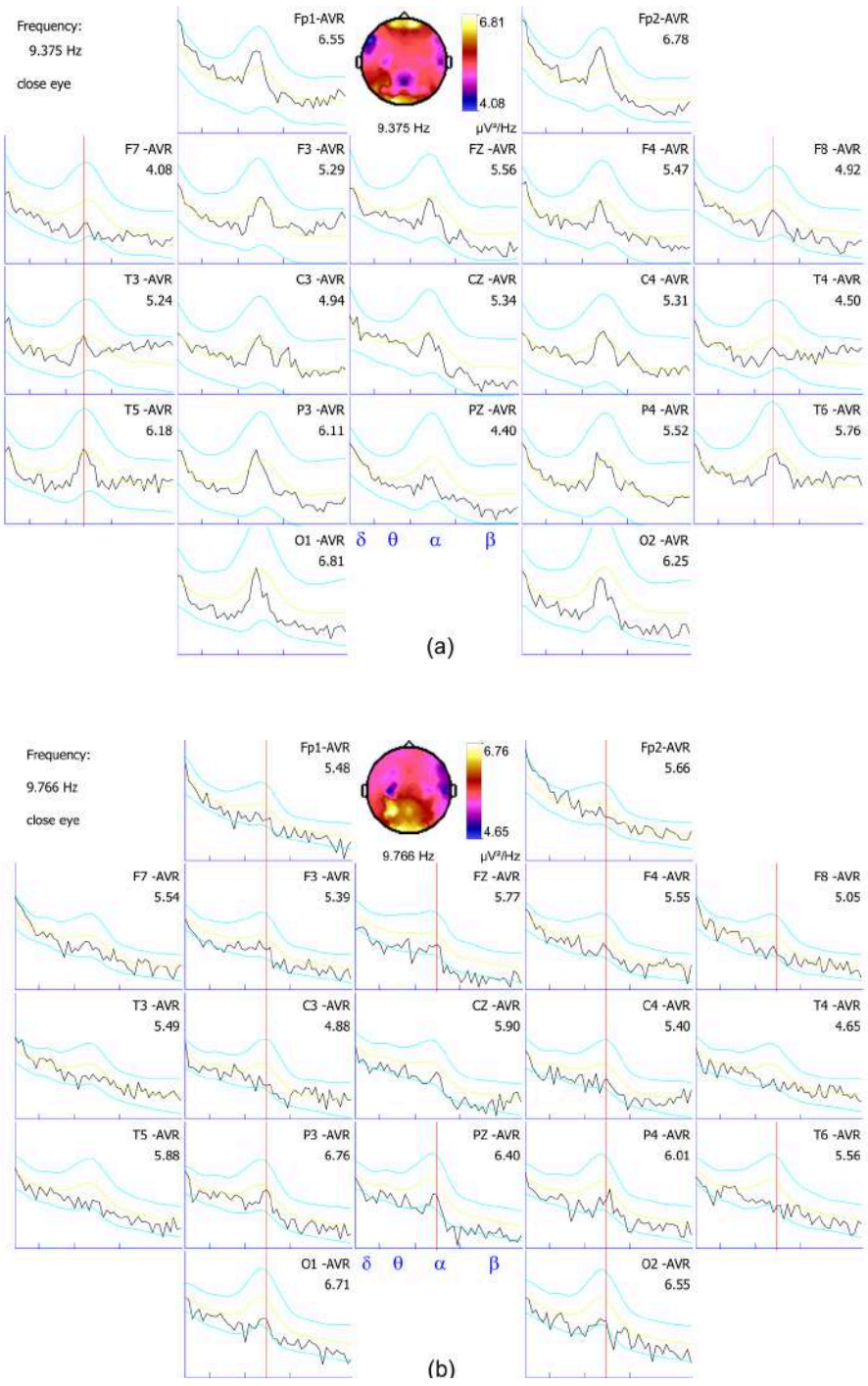

Figure 18. The distribution and frequency of alpha-wave activity at baseline (a) and during (b) light stimulation through digital brain mapping.

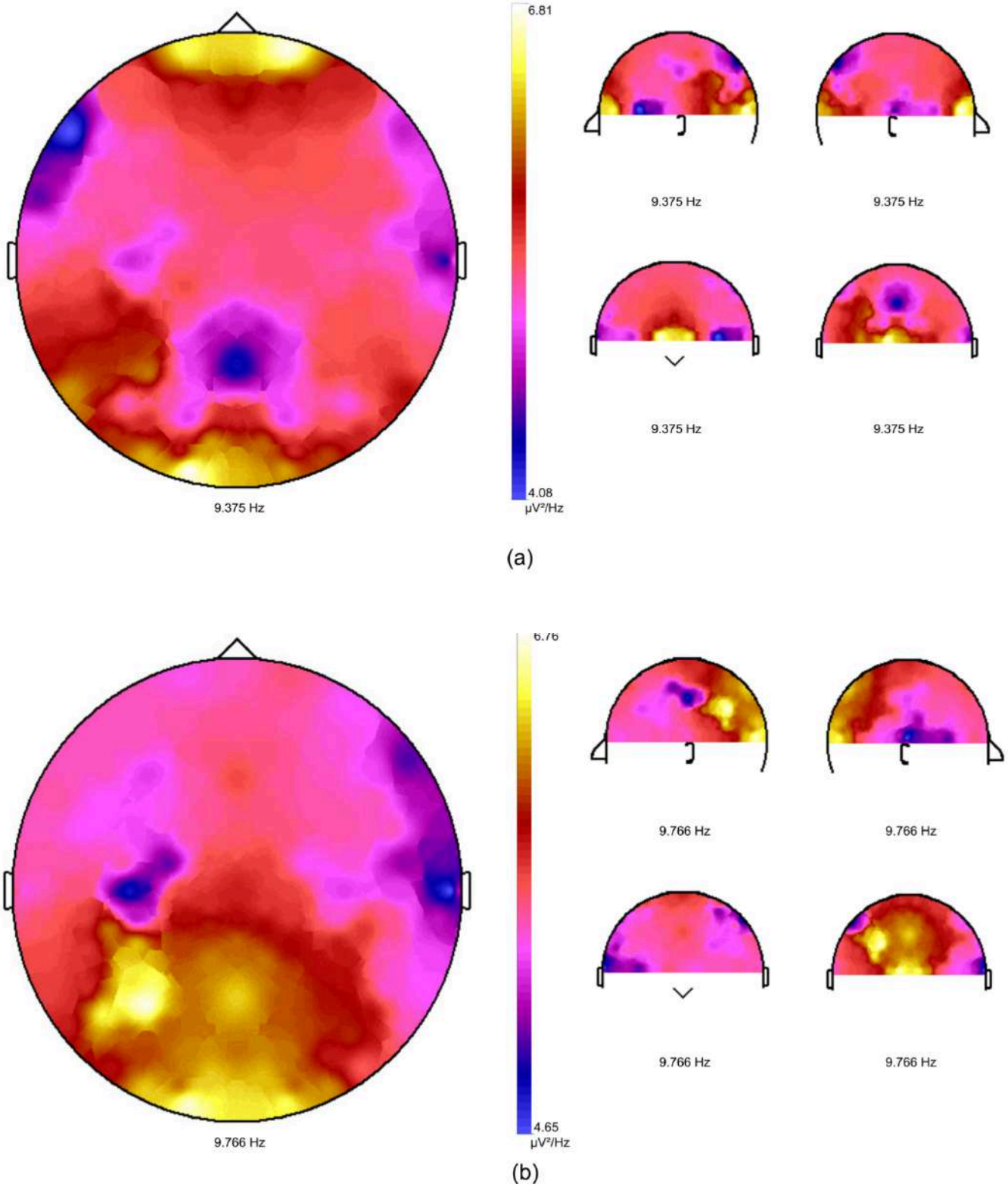

Figure 19. The anteroposterior gradient at baseline (a) and during light stimulation (b), as measured in µV2/Hz, through digital brain mapping. Lower voltage is represented in blue-pink, while higher voltage is indicated by bright yellow red

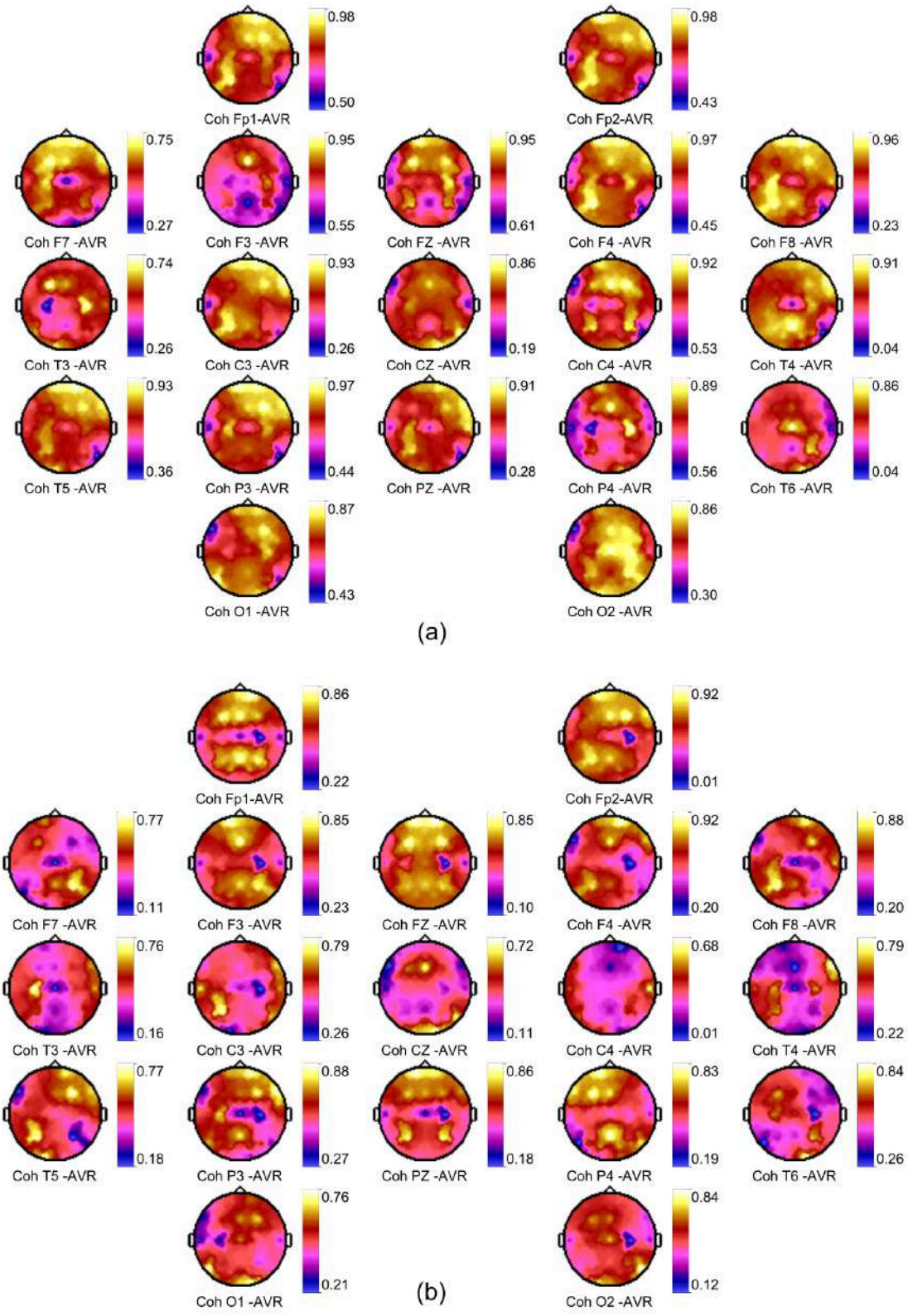

Figure 20. The interhemispheric coherence at baseline (a) and during light stimulation (b) measured through digital brain mapping. Fz, Cz, and Pz are situated along the midline of the scalp and thus divide the hemispheres.

Let´s remind us that light can give life to a cell (photobiomodulation therapy) or destroy it (photodynamic therapy). The first one uses low irradiance to regenerate but the second one uses light in tandem with a non-toxic photosensitizing dye to destroy cancerous cells. Additionally, bright light therapy targets photosensitive retinal ganglion cells to treat patients with seasonal affective disorders (SAD) and the direct application of infrared light to the head in photobiomodulation therapy can enhance the cognition of patients who have undergone traumatic events.

Modulations by light happens at cortical level which are not only detected in areas involved in the top-down regulation of attention but also in regions involved in bottom-up feedback associated with the reorientation of attention as seen in the enhancement of the neural activity of participants engaged in auditory tasks during its exposure and several minutes afterwards.

Since the use of devices such as tablets, cellphones, videogames etc., neuroscience has already demonstrated that the sleep-awake cycle can be altered. Changes in the human circadian rhythmicity have a big influence on the cognitive processes, which improve across the day and declines throughout the night and exposure to bright light impacts deeply alertness, sleep, and psychometric measures. To summarize, being life on earth a dependent variable of light itself, the visual system wouldn´t resist to its power, which we came to demonstrate through this research.

The Alpha-Wave Activity and Interhemispheric Synchronicity

The alpha rhythm (8–12 Hz) as the crucial component of the EEG signal is mostly found in the occipital regions, followed by parietal and posteriors ones. The V1 cortex connects with other areas of the brain through association areas so that the information it has received can have a deeper and more detailed connotation. Connections between areas are made through axons, (white matter), and can connect nearby and distant intrahemispheric cortical areas, as well as interhemispheric brain areas.

Alpha-rhythm reflects a significant thinking information of the human body, representing its cortical functionality [67]. Alpha rhythm is normally present when a subject is mentally inactive, yet alert, with eyes closed and can be easily disrupted by visual attentiveness, where beta-waves show up [68]. The alpha-wave activity, which is defined by its frequency and spatial topography, has been shown to be reactive to stimuli and decreases

when eyes are open and during drowsiness and sleep [69]. Its activity is translated into a good or bad cortical functionality. For this reason, our interest was focused on measuring and monitoring its symmetry, activity, and distribution within hemispheres. By contrast, the beta-wave activity, which is found in frontal lobes under a cognitive task, was not considered for the statistical analysis, as not being directly related to the electrical functionality of the brain [70]. Additionally, patients were in a relaxed state and not under cognitive stimulation.

During LS, the alpha-wave activity measured at baseline was higher in the HC group compared to the SA group. Same results were obtained after the LTH program. Considering the physiology of the visual system, this could indicate higher levels of visual engagement [71] and enhancement of the integrity and functionality of visual pathways. Under normal circumstances, alpha-wave activity should decrease when eyes are open as recorded at baseline, 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. Additionally, an increase in its frequency after the complete cycle (twenty sessions) of LTH was found in both groups.

Although this incrementation wasn't statistically significant [72], clinically, EEG oscillations in the alpha band reflect cognitive and memory performance [67,73], and it can derive in an enhanced visual system and its components as well [74]. As different brain areas are associated with specific motor, sensorial or learning and rational cortical activities [75] (e.g., Cz, C3, and C4 have been associated with sensory and motor functions; Pz, P3, and P4 with perception and differentiation; F7 with rational activities; T5 and T6 with memory; T3 and T4 with emotional situations; and O1 and O2 with visual processes), the spatial distribution of the alpha-wave activity could be related to a detailed cognitive process [75,76]. 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 [72,75]. By contrast, LS altered the distribution of alpha waves within hemispheres, and the state of synchronicity in HCs, acting as a balance disrupter.

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. Considering the visual

development and its functionality, dysfunction visual pathways that need to be rehabilitated react positively to an adequate stimulus [76]. Using LS, we provide the visual system with a stimulus to react and overcome its status "quo." The above-mentioned 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 [74], changes can be produced to the visual system as the rest of the sensory and motor modalities. After the LTH program, alpha rhythm was prompted towards the occipital and parietals regions, as it is expected in a normal and functional brain. Such a change is associated with a heightened synchronization and communication between hemispheres, as well as a balanced activity of whole brain [76,78]. An interesting fact is that defined interhemispheric synchronicity was seen in all patients stimulated with filters transmitting light in the blue spectrum. By contrast, an irregular pattern of interhemispheric synchronization and alpha-wave distribution was seen in patients where filters transmitting light in the red spectrum were used. The statistical analysis showed that after LTH, synchronicity was obtained in 62.5% of SA patients stimulated with filters transmitting light in the red spectrum. However, 37.5% of them remained asynchronic [79].

Literature suggests that esotropic patients present deeper and worse sensory-motor visual adaptations than exotropic ones, accompanied by significant changes in the brain network to compensate for their visual deficiencies [4,80]. Therefore, the reaction to the LTH could be proportional to the amount of the adaptations reached at the visual and cortical level of each patient [15,16]. The results obtained after the LTH program showed that exotropic patients activate interhemispheric synchrony more often than esotropic ones and brain coherence is more probable to be reached in patients with exotropia than patients with esotropia. Therefore, light therapy can be a promising classifier between esotropic and exotropic patients [81].

Research on the monochromatic light of 460 nm, has already shown its impact on alertness, sleep, and psychometric measures [51]-[53], which could explain the positive effect of light in the blue spectrum in the brain activity of SA patients.

No significant changes were seen in the distribution of alpha-wave activity and the state of the brain coherence in HCs. These results lead us to the hypothesis that only a dysfunctional visual pathway in need of rehabilitation reacts to a stimulus such as light, to overcome its status “quo”. HCs possess already a functional visual system with no clinical manifestation, as well as strong brain network connections. Consequently, once the light

stimulus is off, the brain returns to its previous cortical network organization and functionality. On the contrary, a perfect state of synchronization was established in all SA patients when the light stimulus was on, and alpha-wave was distributed to the occipital lobes in all of them, regardless of the wavelength of filters used during the process of stimulation [42].

These results suggest that when the stimulus is on, the brain awakes and becomes active, looking forward to being stimulated. Nonetheless, in this research, it was shown that after the LTH program and once the stimulus is off, such a perfect state of synchronization cannot be achieved in all patients, even though important changes and new patterns of organization are recorded in most of them [82]. These results hypothesize that by repeating the LTH program depending on the patient's necessity and introduce new light equipment's in the whole treatment program, we could accelerate the process of cortical changes.

The Theta-Wave Activity and Its Distribution

An unexpected scientific finding of the qEEG analysis, was the recording of a second spectral peak (theta-wave, 4–8 Hz), solely in SA patients, at both conditions; baseline, and after the administration of LTH program, featuring a frontal predominance in most of them. Even though theta-waves activity favored the frontal lobe, its distribution through hemispheres became more homogeneous after LTH. Theta waves do not typically present in the waking-state [68]. Normally, theta-waves appears when drowsiness or the central nervous system is in the state of inhibition. Its presence in the waking-state except for indicating a slower neural processing, is also an indirect marker of age evolution [68]. Although there was a non-statistically significant increase in its value after the LTH program, clinically it can be translated into a different cognitive and memory performance [67,73].

Event-related changes indicate that the extent of theta-wave synchronization is positively correlated with the ability to encode new-information, and oscillations in the alpha and theta band are associated with differences in cognitive and memory performance [67,73]. It should be highlighted that the permanence of theta-waves even after the administration of LTH, suggesting that the brain of SA patients maintain the same organization pattern of networks, despite the stimulation provided. 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 attributable to an aberrant neurodevelopment or dysfunctional cortical maturation, persisting 20 sessions of LTH

program. Likewise, theta waves were also present in parietal and temporal lobes. Parietal lobes have a fundamental role in body map awareness and spatiotemporal relationships, while temporal lobes store visual patterns and nonverbal memory. The presence of theta waves is a sign of slowness at the cortical level, meaning that neuronal immaturity is likely to be present in patients with congenital endotropia. These data are important when rehabilitating a strabismic child, to direct therapy towards the needed areas.

Further, the depression of the brain activity in a specific region may indicate aberrations in functions associated with this brain area [69], such as a focal, regional, or generalized cerebral dysfunction. In [42], no theta-wave was recorded when the light stimulus was on, whereas after twenty consecutive sessions of LTH and once the stimulus is off, theta-wave activity emerges in all patients, suggesting that light could be an activating stimulus for the brain.

The Anteroposterior Gradient

The anteroposterior gradient is defined by the values of high and low voltages. 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. Significant differences in its value were observed when comparing the two groups. The most peculiar finding was the negative value of low voltage measured in HCs, and the positive one seen in SA patients, under all conditions. Additionally, the difference between the two values (high voltage - low voltage value) during the administration of LS and after the LTH program, was higher in HCs when compared to SA patients.

Finally, low, and high voltage values increased significantly during LS in SA patients, without statistically significant changes in HCs. On the other hand, after the LTH program, while high voltage values increased from Time 1 to Time 2 in SA patients, they decreased in HCs, suggesting that by subjecting HCs to a twenty-day program of unnecessary LTH, instability is provoked to the brain network. Another scientific data to be distinguished, is the increment of high voltages in SA patients, but its decrease in HCs after the LTH program. In a healthy brain, high voltage is indicative of a greater neural activation and can be an indirect measure of the number of synapses [74], which in turn defines the neural networks and cortical plasticity [82].

The conclusion drawn then is that in SA patients, LTH promotes a defined anteroposterior voltage gradient, and increases the cortical activity which helps 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, resulting in an increased cortical activity and functionality [74]. This phenomenon accounts for why each new experience or event can help the brain to re-wire its physical structure [82]. On the other hand, the decrease in its value in HCs, could indicate that LTH acts as a destabilizing stimulus on the brain activity of a healthy person, as recorded by the qEEG. Based on the above, it can be suggested that when a specific pattern of light stimulation is offered to a dysfunctional visual pathway, it could trigger new responses in the benefit of brain's re-wiring process.

Undoubtedly, light can be a significant brain modulator for SA patients and should be the first step before any other treatment, as it brings the brain to a better state of interhemispheric synchronicity. An enhanced state of brain coherence, improves the learning process of new patterns, as required in SA patients. qEEG was 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 [74]. Nevertheless, other techniques have been used to study the brain's functionality of strabismic patients. [36]-[38],[80]. Through this research, new information about the cortical activity in the waking-state of strabismic and amblyopic patients at baseline, during the administration of light stimulation and after the LTH program, is provided. Its impact on the visual performance on the participants was measured as well.

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 [75,77]. Our results are going to 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, these results come to complement what other neuroimaging studies have shown; that strabismus comes with changes in the whole brain [82,83], reflected in the cortical electrical activity of these patients and that LTH should be introduced as a powerful and non-invasive treatment for patients with neurodevelopment disorders.

Spearman Correlations

Another impressive data of this analysis, were the correlations found between the qEEG metrics, being exclusively to SA patients. A strong positive correlation for the alpha-wave activity before and after the treatment was showed. Low and high voltages were positively related at baseline and after the administration of LTH as well. These results make us hypothesize that the brain organization and activity of patients with strabismus and amblyopia is governed by his own laws. Considering that all patients had primary strabismus, adaptations to their sensorimotor imbalance have already been made to overcome this sensory deficit. We believe that there must be reached such a level of organization to compensate for any kind of visual deficiencies that strabismus may cause [85].

Changes in Visual Metrics

Based on the knowledge that absorption of light by the visual pigments in photoreceptors triggers a cascade of chemical events that increases electrical neural activity, changes in the visual performance of participants were expected to be found after the LTH program. Specifically, significant improvements were seen in all evaluated areas in SA patients, while in HCs, the amount of stereopsis decreased, and the phoria state deteriorated, without affecting visual acuity. Larger dynamic visual fields were measured after light therapy in all participants, being those more evident in SA patients. These results confirm our hypothesis that when an adequate stimulus is provided to a suffering visual system, positive results are obtained, as shown in SA patients. On the contrary, a well-organized and functional system can be destabilized when an unnecessary stimulus is given, as seen in HCs.

The development of the visual system is the result of the interaction of several dynamic processes. Genetic information designs the appropriate structures and functional capabilities to develop optimal vision; however, experience enriches it and keeps it functional. Vision in children undergoes very important changes during their cortical maturation, progressing from a very coarse perception to the finest and most detailed perception in adulthood. When a child is born the visual system and visual receptors are immature. Fovea is not fully developed until the age of four, when the number of cones in the retina represent half of the adult value, while the functionality of the peripheral retina starts up immediately upon contact with light. The optic pathways are partially myelinated, which is enhanced experiencing the benefits of light,

movement, and object shapes [19,54].

On the other hand, the immature visual cortex requires visual experience to acquire structural maturity, which allows data integration. Functional development and cortical maturity increase with the passage of information through the neural circuits. A very important part of the first visual pathway is the lateral geniculate body, already present at birth, reaching adult size at six months. Its development and functioning are fundamental as here the nerve cells of the visual system divide into magno, parvo and coniocellular, each one in charge of processing in a specific way the information captured by the visual system [19,54].

The maturation of the visual system is followed by the formation of multiple synapses, (connections between nerve cells through the synaptic button), with maximum density at eight months. As the child grows and gains visual experience there is a synaptic organization and unused connections are progressively lost, until the age of eleven years, (known as the final period of deep plasticity). However, neuroscience has made it broadly known that cortical plasticity continues throughout life if the brain is constantly stimulated with stimuli of different intensities and patterns. It can be said that during the first three months of life there is a maturation of the functionality of the visual system that allows moving from a vague to an expressive gaze, from tracking movements replaced by micro-saccades to a uniform and symmetrical movement, from an involuntary saccadic movement, controlled by the subcortical parts to a desired saccadic movement, controlled by the motor cortex [20-22].

The crucial point to achieve binocularity is foveal alignment and fixation, which allow directing the eyes to the same focal point. This phenomenon starts monocularly and then binocularly. Binocular vision and sensory fusion consist of the union of two similar images coming from each eye into a single perception at the cortical level. The fused images are localized in space according to the retinal area they stimulate [11].

When processing the stimulus, the cerebral cortex relates it to the surrounding environment, establishing its relative location in space and its egocentric location with respect to the individual. The stimulus is further analyzed according to brightness, shape, color, motion, direction, etc. Children with visual problems such as amblyopia and strabismus, do not develop binocular vision, because of the cortical suppression of one of the stimuli to avoid diplopia and visual confusion. This, in turn, is associated with difficulties in interpreting space, locating stimuli, correctly perceiving the speed and exact direction of the object, measuring, and calculating distances, unevenness in the ground, etc. Spatial-temporal problems hinder motor play and correct contralateral coordination, resulting in difficulties in academic

performance [16,19].

One of the most important functions of the visual system and the connections established with other areas of sensory integration is the mental representation of objects, which aids memory and learning. The mental representation or visualization of an object starts from the perceptual experience reached through the sensory modalities. These are sensory organs which allow us to obtain direct stimuli that provoke the necessary amount of afferences so that the brain starts constructing the reality that surrounds us based on this information, which is why, when we are exposed to an external stimulus, the CNS processes reality as virtual [16]. When we evoke an image without direct stimulus, we do it from the data stored in our memory. In the end, the reality we live is not the same for everyone because it is not perceived directly, but we process, analyze, and compose the data that reaches the CNS. All the information that bombards the child in the first months of life and in the years that follow, is stored, integrated, compared, and related thanks to the maturation of different brain areas which can differentiate between known and new stimuli [37].

More than any other sense, vision allows us to navigate through our environment and act based on what we see. Gross and fine motor efficiency can be attributed to the fact that some of our actions, such as reaching for an object, are based, in part, on a repertoire of movements derived directly from vision. Perception of objects results in the generation of both visual and motor signals in the brain, whether there is an intention to act on the object or not [19]. The properties of an object affect an observer's reaction time to judge its orientation, thus providing evidence that directed visual attention is responsible for the automatic generation of motor signals associated with the spatial characteristics of perceived objects. Attentional shifts to locate objects perceived by the visual system automatically generate some motor response codes that mimic the way oculomotor systems are recruited to make postural adjustments essential for survival [64].

When light reaches the brain, its impact becomes obvious on the brain connectome and its functionality. Depending on the wavelength used, we have the power to redistribute the alpha rhythm towards the occipitoparietal regions and bring the lost balance between hemispheres. The visual system showed a great reaction the light stimulation, which does not have to come as a surprise when we consider that the retina becomes functional thanks to the light experience, as life in earth depends on the light cycle. The clinical findings obtained in the present study suggest that when needed, the visual process can be actively changed through LTH, fostering new visual abilities and improving old ones, otherwise, the

same stimulation can work as a destabilizer. Considering the presence of neuroplasticity throughout life, with different responses according to age [82], changes can be produced to the visual system as the rest of the sensory and motor modalities. Light therapy should then be implemented as a complementary tool in the treatment of patients with strabismus and amblyopia or those receiving conventional active visual therapy. Furthermore, based on the results obtained during and after a complete cycle of LTH, we strongly believe that more therapies focused on the use of light should be implemented to accelerate the treatment process. Complementing previous studies on light exposure, our research provides new information about the brain activity and the visual performance of strabismic and amblyopic patients at baseline and after a complete cycle of LTH. This research showed that light is an adequate stimulus to enhance the brain activity and visual abilities of SA patients. The synchronization reached 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 [77,78]. LTH provoked 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. Nonetheless, LTH can only benefit a suffering brain and a visual pathway which needs to be enabled. Its use in healthy population can destabilize the visual system.

Our results can 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 therapy should be considered in the context of treating SA patients and other neurodevelopmental disorders as well. Finally, this research comes to complement what other neuroimaging studies have shown; that strabismus and amblyopia come with changes in the whole brain, which are reflected in the brain activity and visual performance as well; a reason why, LTH should be implemented as an effective, non-invasive treatment in these patients, and other neurodevelopment disorders.

5.4 Significance/Impact

This research is a breakthrough in the field of strabismus and amblyopia, as for the first time the brain activity of SA patients under the effect of the light is measured in real time, and its impact on the visual system is confirmed. The new scientific information generated promises to finally shield light not only in the cortical electrical activity of SA patients, as well as open paths towards a better understanding of other neurodevelopment disorders. New therapies based on the power of light as a brain modulator can be proposed, helping the whole treatment process of patients with cortical dysfunctions.

5.5 Future Works

Visually-evoked potentials can be used to broaden our knowledge on the effect of monochromatic light in SA patients so peculiar specificities about each wavelength could be clarified to create a new range of filter combination to enhance the brain response during and after its use in patients in need of rehabilitation. Our research opens pathways to new collaboration with different fields of neuroscience in benefit on patients with different cortical dysfunctions.

5. Publications

1. Ibrahimi, D.; Mendiola-Santibañez, J.D.; Cruz Martínez, E.; Rodríguez-Reséndiz, J.; Pacheco, I.T. Cortical Activity at Baseline and During Light Stimulation in Patients with Strabismus and Amblyopia. IEEE Access 2021, 9, 22430–22446.
2. Ibrahimi, D; Mendiola-Santibañez, J.D.; Cruz-Martínez, E.; Gómez-Espinosa A.; and Torres-Pacheco, I. Changes in the Brain Activity and Visual Performance of Patients with Strabismus and Amblyopia after a Compete Cycle of Light Therapy. Sci. 2021, 11(5), 657.

6. Appendix/Abbreviations

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-uncover and Krimsky tests. While the cover test is considered the most reliable means of measuring the angle of strabismus, the Krimsky test better suited for children who have difficulty collaborating.

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 based on 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.

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.

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. 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 stereo blindness.

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.

Once fixation was determined, 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 20/80 or better. The test was conducted in a dimly lit room, and the patients wore correction glasses. An after-image was used for this purpose according to the proposal advanced by Bielchowsky [15,16].

Abbreviations

The following abbreviations are used in this manuscript: LTH, light therapy; SA, strabismus and amblyopia; HCs, healthy controls; qEEG, quantitative electroencephalogram; DBM, digital brain mapping; FFT, fast Fourier transform; CNS, central nervous system; VA, visual acuity; FCFT, functional color field tester; CSO, College of Syntonic Optometry; CI, confidence level; OD, oculus dexter; OI, oculus sinister; R, right; L, left; ET, esotropia; XT, exotropia; HT, hypertropia; (α), alpha-wave; (θ), theta-wave.

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