THE EFFICACY OF GREEN LIGHT THERAPY TREATMENT FOR MIGRAINES

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Abstract:

Migraines affect over a billion people worldwide and are characterized by acute head pain, light sensitivity, and sometimes nausea. As migraines can be very debilitating, many pharmaceutical treatment options are available. However, for some people, these treatments may be ineffective and inconvenient. This study seeks to explore the underlying physiological mechanisms underlying Green Light Diode therapy and its connection to oculomotor control and neuron activation. Employing a completely randomized double-blind crossover experimental design allows researchers to examine the effects of GLED exposure daily, over a period of 14 days. Near-Infrared Spectroscopy, Electroencephalography, and Right Eye system's eye-tracking technology, are all employed to detect changes in blood flow, pressure, and electrical activity through alpha waves. Previous data collected within our laboratory indicated that those suffering from migraines, when compared directly to healthy controls, tend to express decreased blood flow within the temporal lobes and impaired oculomotor control. We hypothesize that the introduction of GLED therapy to chronic and episodic migraine sufferers will assist in correcting deficits in blood flow and effectively lower migraine frequency as a whole. This study aims to support a safe and non-invasive treatment of migraines while explaining the mechanism of photo biomodulation within the human brain.

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Introduction:

Green Light Diode Therapy has recently emerged as an alternative non-pharmacological intervention for migraines, offering a safe substitute for failing traditional methods. In a 2021 study by the University of Arizona Health Sciences, researchers found that both episodic and chronic migraine patients had found significant relief from GLED exposure (Martin et. al 2021). Certain wavelengths of light were also found to amplify the pain associated with migraines, yet green light proved to be more comfortable. Unlike certain migraine medications, no adverse effects related to GLED were found. The term antinociceptive explains how the brain processes blocking pain within the sensory neurons. This mechanism functions by reducing the excitability of sensory neurons and suppressing pain signal transmission within central pathways. This is what ultimately leads to a lesser perception of pain. Given the evidence from this previous study, functional near-infrared spectroscopy, electroencephalography, and eye-tracking technology can assist in further investigation to better understand what changes in blood oxygenation and neural activity in the brain to indicate an antinociceptive effect is taking place.

Research Questions:

This study attempts to answer multiple research questions: what is the neurological response within the brain when exposed to GLED, how are blood flow patterns and neural activity directly influenced by GLED, and how do these changes in blood flow and neural activity connect to an antinociceptive effect? Knowing that green light diode treatment is already effective, the goal is to tie all of these questions together and understand "why" it's effective. Given that the analysis of data from fNIR and EEG presents noticeable differences in brain activity before and after exposure to green light, it will highlight the process by which the brain blocks migraines.

The purpose of this research study is to determine the efficacy of green light diode treatment for migraines while explaining the physiological response of the brain in response to it. Utilizing East Carolina's Visual Motor Lab, technology such as fNIR (functional near-infrared spectroscopy) and EEG (electroencephalogram) and eye-tracking (RightEye), will be used to assess neurological responses to GLED (green light-emitting diodes). Preliminary research revealed that exposure to certain wavelengths of green light can reduce the intensity and how often migraines occur (Martin et al.). The goal is to understand what the brain does in response to green light and how these neurological responses mitigate migraine symptoms. In doing so, setting the investigation up as a crossover design will allow for the comparison of brain activity between GLED and placebo effects

Literature Review

The purpose of this section is to examine relevant and current research literature to provide an accurate explanation regarding the pathophysiological foundation for this proposed study. Essentially, through previous findings related to migraine physiology, neuronal activity, and GLED treatment, we can integrate these to build a clearer understanding of their influence within the brain.

Migraine Pathophysiology

Migraines can be commonly misunderstood as a subset of severe headaches. This isn't entirely true though, as migraines are events involving the delicate balance of nerves, sensory pathways, and blood flow. A migraine state can be defined as the brain becoming extremely sensitive to external stimuli (Goadsby et al 2017.). This suggests that the root issue can be derived from dysfunction within the central nervous system as opposed to solely blood flow circulation. Upon activation of the main pathway related to head pain,

the trigeminovascular pathway, nerves tasked with sensing pain within the meninges become overstimulated. Neurons start to relay strong pain signals within the brain even in response to normal stimuli (Bernstein and Burstein 2012).

The heightened excitability of these neurons contributes to a phenomenon known as Cortical Spreading Depression. CSD for short, this mechanism is related to the observed increased sensitivity of neurons. This is the core explanation supporting the underlying events resulting in the sensory symptoms surrounding a migraine event. CSD is described as a wave of electrical activity that moves slowly across the brain, leading to an intermittent activity shutdown. In terms of brain pathophysiology, this activity shutdown can be explained by the visual disruption and heightened sensitivity of individuals with migraines (Dodick, 2018). In the referenced study, Dodick's depictions of visual processing connecting CSD's depolarizing wave and suppressed brain activity, provide a justification for this study to emphasize focus on the occipital and temporal lobes' involvement. These regions are important to visual and sensory processing, so it is imperative that we investigate them.

EEG and Migraines

According to a review by Zhang et al. in 2023, electroencephalography research and application on migraine patients now offer a powerful and inexpensive method to investigate the neurological mechanisms of a migraine. Migraines are extremely prevalent and still aren't a validated neurological disorder due to a lack of suitable diagnostic markers. Despite the contradictory findings of previous EEG studies on migraine patients based on the analysis of EEG signal patterns, recent EEG solutions and processing methods enable a more comprehensive investigation of the brain and its

disruptions during a migraine. In quantitative studies using EEG on migraine patients, abnormally high levels of EEG band power were seen in the alpha, theta, and delta frequency bands. These correspond to abnormally high levels of alpha band slowing and asymmetry within many migraine patients which is indicative of high levels of band power across low frequency bands. Current advanced EEG methods and solutions now identify abnormally high cortical functional coherence in patients with migraines to conclude disruptions in sensory processing. Cortical excitation also occurs and corresponds with migraines with aura as well as migraines without aura present.

Dysfunctional Eye-Movement and Blood Flow

Prior evidence from McKendrick et al. (2001) suggests that the brain experiences impairment even in the interictal phase. The term, interictal phase, describes the period between migraine episodes. This research study focusing on the interictal stage also uncovered that visual dysfunction resulting from migraines can last up to seven days following an event. This ongoing dysfunction suggests temporal processing impairment and a lack of inhibitory control, meaning the visual cortex is unable to effectively sort through and adjust to ongoing stimuli after the migraine attack happens. Nystagmus and reduced pursuit accuracy, both abnormalities related to eye movement, were reported in people with migraines as well (Wilkinson et al.,2006). Compiling these two closely related sources together reinforces the use of oculomotor testing, RightEye, as a testing measure for the study.

Moving on to a blood-flow examination, it's clear that the migraine brain has problems effectively regulating oxygen levels. A study done using fNIR technology revealed that healthy individuals naturally contain up to five times more oxyhemoglobin quantity than

migraine patients when actively involved in cognitive tasks (Pourshoghi et al., 2015) This indicates migraine patients' brains have a naturally diminished ability to adjust and regulate blood flow. This notion is further supported by EEG research; researchers found, within migraine patients, power output in the occipital lobes was noticeable asymmetrical, further advancing the point of reduced neuronal activity due to cortical inhibition. The design of this study is shaped by these profound results, and employing fNIR assessment is the most effective approach to assess alterations in blood flow. EEG will serve to specifically monitor O1/O2 electrodes so we can evaluate deficits in the occipital lobe's alpha activity and determine if GLED can fill these gaps.

Mechanism of GLED

One of the most prevalent migraine symptoms presented is light sensitivity, in other words photophobia, yet research explains that wavelength is the centerpiece of this symptom. Certain wavelengths of light are more strenuous on a person's vision and can create an increased chance of provoking a migraine. Noseda et al (2013) found a visual pathway where specialized neurons within the thalamus barely produced a response to green light exposure but energetically reacted to the presence of blue and red light. This leaves researchers suggesting the presence of one extraordinarily unique pathway in which the brain processes green light in a manner that allows it to engage the visual system without activating the pain-related pathways of the thalamus.

Martin et al. continued to build on this idea through showing that a narrow range of green light frequences, specifically 525 nm for 1-2 hours daily over 10 weeks, can reduce the frequency of migraines. As a result, those suffering from chronic and episodic migraines saw an overall improved quality of life throughout the duration of the study. Focusing on

photosensitive retinal ganglion cells (ipRGCs), research found that targeted wavelength exposure can lead to decreased pain signals transmitted to the brain. Our study attempts to connect the behavioral outcomes uncovered by Martin and the physiological findings of Noseda and Pourshoghi to test whether green light therapy reduces pain through correcting neurovascular coupling.

Methods

This study aims to recruit between 12-20 participants in total. Each participant is required to be at least 18 years of age and must have a clinical diagnosis of chronic or episodic migraines. As for exclusion criteria, any potential participant possessing a history of neurological disorders will not be allowed to participate in the study. Participants will be recruited through student flyers and surveys.

Research Design

This research is set up as a randomized, double-blind crossover study. Two groups of participants are created at random, and the participants will be assigned.

Group 1: Given green-tinted (GLED) glasses first.

Group 2: Given red-tinted (placebo control) glasses first.

Research Instrumentation

FNIR (Functional Near-Infrared Spectroscopy): We'll use fNIR technology to measure and observe changes in blood flow, specifically in oxyhemoglobin and deoxyhemoglobin, within the temporal and frontal lobes. After collecting this data, Matlab toolbox will process the information through a 0.1 Hz filter.

EEG (Electroencephalography): EEG will be utilized to monitor the brain's electrical activity. We will specifically focus on the occipital and parietal regions'

alpha power output through recordings from the O1, O2, P3, and P4 electrodes. Combining both the occipital and parietal region allows us to assess visual and spatial processing along with visual control. This examines the occipital and parietal power produced, in Hz, recorded from the EEG electrodes. The reasoning for this is because these areas tend to see irregular alpha modulation patterns during the interictal migraine stage. From there, alpha activity changes will be closely followed throughout the participant's experience with GLED therapy with the tinted glasses, participants undergoing the placebo (control) intervention, and the participant's initial baseline activity.

RightEye Tracking: This technology uses infrared sensors to track eye movement, and we'll use this during testing to assess participants' saccade and smooth pursuit when tracking a virtual object.

Procedure and Interventions

1. **Baseline Testing (Day 1):** Each participant will undergo 30 total minutes of neurological monitoring with EEG, fNIR, and RightEye tracking. This will take place in a non-stimulating environment, and participants will be tasked with tracking a moving virtual image during this time. The first day will serve as a comparative baseline for neural activity.
2. **First Intervention Phase (Day 1-14):** After splitting the participants into two groups, one will receive GLED glasses and the other will receive red glasses as a placebo. Participants will be instructed to wear these glasses 2-3 hours daily for 14 straight days. However, since it's unlikely that all participants will be able to fully comply with this, we ask that they keep a tracking log along the way. This

log tracks compliance, average daily usage, migraine frequency, and overall experience.

3. **Mid-Point Reassessment (Day 15):** Following the conclusion of the two-week period, participants from the green-tinted glasses group will return to the lab to undergo the same neurological testing as before. It will be the same half hour virtual reality task with the same technology as well.
4. **Crossover/Phase 2 (Days 16-30):** Groups 1 and 2 will switch glasses with one another. Now, group 2 which possesses the green-light glasses will complete the same two-week protocol that group 1 just completed.

Preliminary Data and Expected Outcomes

The purpose of this section is to outline the preliminary laboratory data and explain how this justifies the study's design. On top of that, we'll discuss the expected results of this study.

Hemodynamics-Preliminary Findings

The Visual Motor Lab previously collected data from 43 migraine suffering participants and confirmed that there are obvious decreases in cerebral blood flow without any treatment. One group labeled MA, meaning migraines with visual aura, displayed abnormally low neurovascular coupling, compared to healthy controls, in their temporal and frontal lobe regions when assessed with fNIR and eye-tracking (Nelson et al.). This previous study did not employ the use of GLED therapy; instead, it established a respectable profile of migraines that this study aims to correct.

Neurovascular Uncoupling: Group MA exhibited a clear disruption in the sync between neurons and blood vessels, resulting in reduced blood flow in the temporal

lobes. This comparison is drawn from healthy controls. Both the right and left temporal lobe in participants with migraines presented with significantly lower levels of total hemoglobin (p =0.045, p =0.043).

Oculomotor Findings

Oculomotor Deficit: The MA group had some issues with maintaining smooth visual tracking when completing the tasks. This is most likely due to CSD, cortical spreading depression, exerting negative influence within visual processing. For testing and data processing purposes, a participant's gaze failing to fall within seven millimeters or more from the target was considered gaze deviation. The p value indicates deficits in efficient eye-tracking.

Smooth Pursuit (Vertical): Higher efficiency error of p=0.034 indicates strong gaze deviation.

Smooth Pursuit (Circular): Efficiency error of p=0.012 indicates a similar pattern.

Hypothesizing GLED's Effects

This study stands for the hypothesis that GLED therapy can initiate antinociceptive effects while reducing the hyperexcited neurons within the brain. From what we've learned through the research outlined above, we'd expect to see the following outcomes materialize if everything goes according to plan.

1st Prediction: Temporal Blood Flow Improves

Rationale: In the study *Exploring the Relationship Between Migraines, Hemoglobin, and Oculomotor Dysfunction* by Nelson et al, data supported that

people with migraines have consistent reductions in hypoperfusion within the temporal lobes.

Expected Result: Following 14 consecutive days of green light intervention, we'd expect to see this deficit in blood flow start to correct itself. Screening from fNIR scans should reveal significant increases in the overall oxyhemoglobin contained in the temporal lobes when directly compared to their own control (red light) group. Preferably, the group that underwent green-light therapy will disperse from the previously established migraine profile and trend towards similarity with the healthy control groups mentioned earlier.

2nd Prediction: Oculomotor Efficiency Restores

Rationale: The preexisting research claims that GLED works to reduce unintended fluctuations in neural networks and the hyperexcitability seen in the occipital lobe. Therefore, migraine sufferers should see an improvement in eye control as a cascading impact.

Expected Result: We'd expect to observe a measurable decrease in eye-tracking errors when testing both vertical and circular smooth pursuit. More specifically, the obvious gaze deviation (>7mm) from participants with migraines should drop within the cutoff range after the introduction of GLED. When comparing results to the self-control group, this exemplifies the visual cortex's improvement in processing movement because of green light.

3rd Prediction: Bridging Physiology and Real-World Signs

Rationale: The research produced by Martin et al relied-on participants reporting their own pain levels and failed to investigate the underlying causes.

Expected Result: The correlation between blood flow in the temporal lobes and migraine frequency should present an extremely strong negative correlation. Fundamentally, as fNIR testing reveals neurovascular coupling is improving, then the frequency of reported migraine episodes among participants should decrease proportionally. This would validate the claim from previous research that improvements in cerebral hypoperfusion lead to reductions in pain.

Discussion:

The migraine brain is naturally distinct from a healthy brain even without an occurrence of an attack; preliminary research supports this as well. Individuals diagnosed with chronic and episodic migraines experience chronic neurovascular uncoupling (NVU) as a result of reduced hemoglobin levels in the temporal lobes. The entire goal of this proposed research study is to uncover how humans can correct this deficiency through the use of GLED. Green light therapy is already proven to induce an antinociceptive reaction in the brain, so our study helps clarify the physiological explanation of this through showing measurable changes in blood flow and improved oculomotor performance. Evidence of this connection would be the first of its kind, and a major step towards restoring balance within the brain to eliminate pain, rather than masking it through prescriptions and other interventions that primarily focus on treating symptoms.

Significance/Impact:

In the near future, I hope to apply to, and attend, the Brody School of Medicine here at East Carolina. I aspire to become an orthopedic surgeon someday as this is something I've always wanted to do. Without a doubt, pain management is something a medical student will

need a deep understanding of, and this research will greatly expand my understanding of that. Chronic pain is often a common problem within the field of orthopedics as well. Researching non-invasive interventions like green light diode therapy will introduce me to brain-related research and allow me to gain insight into strategies to reduce pain after operation. EEGs are very commonly used in orthopedics to monitor pain perception, anesthesia effectiveness during surgery, as well as assessing recovery. Becoming very effective at operating an EEG would also be a huge advantage in medical school, as they're used to assess patients with brain injuries, seizure disorders, and sleep disorders. As someone with Irlen's syndrome, a defective signaling pathway from the eyes to the brain causing visual irregularities, understanding brain signaling has always fascinated me. One day, I hope to research this as well and use my skills developed from this research project to assist others like me. Throughout this project, I'll develop skills like critical thinking, communicating with participants, data analysis, time management, and collaboration. All of which are necessary in medical school. I plan to present my completed research to the ECU Kinesiology Department.

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