Transcranial Photobiomodulation for reducing autism symptoms in children.

May 1, 2022

PROTOCOL TITLE:

Transcranial photobiomodulation for reducing autism symptoms in children.

PRINCIPAL INVESTIGATOR:

Name	Yuli Fradkin, MD
Department	N/A
Phone Number	201-731-6244

RESEARCHERS:

Name	Eugenia Steingold, Ph.D
Department	N/A
Phone Number	347-779-2473

Name	Katya Sverdlov, CFA, Esq.
Department	N/A
Phone Number	917-566-8151

Name	Elizaveta Logounova
Department	N/A
Phone Number	347-866-2966

1.0 Purpose of the study:

The purpose of this 10-week feasibility study is to assess the tolerability, safety and efficacy of Transcranial LED Therapy for language learning and reducing symptoms of autism in children.

The investigators propose to enroll up to 30 participants, 2-7 years old, all of whom have recently completed the IRB approved study by JelikaLIte. They all have been previously diagnosed with moderate to severe ASD by licensed professionals according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for Autism Spectrum Disorder (ASD).

This will be an one-arm, open label study. Participants who were in the placebo condition in the previous study, will receive the treatment. Participants who were in the active condition in the previous study will repeat the course of treatment after the intermission of 3-6 months (depending on when they completed the study).

The hypothesis to be tested is that exposure to photobiomodulation will reduce children's symptoms of autism, as measured by the reduction of the Mean Scores of the Childhood Autism Rating Scales, compared to the initial baseline.

2.0 Background / Literature Review / Rationale for the study:

2.1 Background Science of Photobiomodulation and Rationale:

There are several studies that suggest that mitochondrial energy disturbance is an underlying mechanism of autism, for at least some of the children. Specifically, Weisman, Kelley, Bauman, Cohen, Murray, Mitchell and Kern (2008) looked at the medical records of 25 children diagnosed with autism and found that "Levels of blood lactate, plasma alanine, and serum ALT and/or AST were increased at least once in 76%, 36%, and 52% of patients, respectively". Furthermore, 2 out of those 25 people had rare mtDNA mutations. The authors concluded that at least for a subset of ASD children, mitochondrial disturbances in energy production could be the underlying mechanism. Furthermore, Giulilvi, Zhang, Omanska-Klusek, Ross-Intra, Hertz-Picciotto, Tasson and Pessach (2010), looked at biochemical markers of ASD kids (2-5yo), and concluded that ASD children are more likely to have Mitochondria dysfunction, mtDNA replication and mtDNA deletion than neurotypical ones.

In addition, Siddiqui, Elwell and Johnson (2016) conducted meta-analyses of the studies reporting decreased activity of mitochondrial electron transport chain (ETC) complexes and reduced gene expression of mitochondrial genes, in particular genes of respiratory chain complexes, in individuals with autism (not necessarily children). They concluded that current research supports the link between ASD and mitochondrial dysfunction. However, they also conceded that in many studies that they reviewed the sample size was small and argued for further research including near infrared spectroscopy to provide more precise information of Mitochondria dysfunction in ASD individuals. Based on these and other studies, it is reasonable to conclude that there is evidence linking ASD with mitochondria dysfunction (specifically difficulties with energy producing) in at least some ASD individuals.

Photobiomodulation has been found to be effective for treatment of other neurological conditions without any side effects. Conditions include Alzheimer's, depression, TBI and stroke, Cassano et al 2016, Hamblin 2016, Naeser et al 2011, Naeser 2010. Overall, tPBM has been shown to increase blood flow to brain as well as increase its oxidative metabolism resulting in increased brain activation and decreased inflammation. Dmochowky J & Dmoshowsky P (2018) demonstrated this process by applying tPBM to humans while simultaneously scanning brains with fMRI.

Photobiomodulation is a mechanism for general cell healing: Light photons penetrate tissue and act on the cytochrome c oxidase photoreceptor in the mitochondria of the cell. This is an enzyme that catalyzes the final step in ATP production. In a healthy cell, cytochrome c oxidase combines oxygen with NADH (a crucial coenzyme in the making of ATP) to make the hydrogen ions that drive ATP production.

When cells are damaged due to illness, stress, injury or aging, the mitochondria start making Nitric Oxide. This competes with oxygen and binds with cytochrome c oxidase stopping the production of ATP. Damaged cells also produce oxidative stress which leads to inflammation and cell death.

The light photons from PBM (photobiomodulation) devices break the bond between nitric oxide and cytochrome c oxidase, which results in the following:

- Nitric oxide (NO) is released into the bloodstream which increases circulation
- Oxygen is able to combine with NADH so that ATP can be produced
- Oxidative stress (ROS build up) is displaced

- ATP is produced at optimal levels again
- Cells can work to regenerate tissue, fight infection, or perform whatever function they are programmed to do.

This is how PBM works to reduce inflammation and pain, increase circulation and restore normal cell function in general, and there are multiple FDA approved photobiomodulation devices for wound healing, pain and inflammation (e.g., from Erchonia). Since this mechanism works for all types of cells (e.g, including glial cells and neurons), this technology could potentially treat many conditions, including neurological conditions via tPBM (transcranial photobiomodulation), such as Depression, Stroke, TBI, Dementia, and Autism.

There are several clinical trials that are ongoing regarding the efficacy of tPBM in treating neurological submissions. Shiffer (2020) showed with 22 participants that tPBM could also be effective for treating opioid cravings (NSF SBIR funded research). There are also several new ongoing clinical trials with larger number of participants: Dan Iosifescu started (partially funded by NIMH) research in NYU Langone and Mass General Hospitals investigating how tPBM affects depression (with 30 participants, randomized, placebo-controlled study, https://clinicaltrials.gov/ct2/show/NCT04366258). In addition, Iosifesku, Cassano and Ozorio started a Phase II clinical trial (with 125 participants, partially funded by NIH), investigating the effect of tPBM on Dementia and Alzheimer Disorder. (https://clinicaltrials.gov/ct2/show/NCT04784416). Cerganoglu started investigating how tPBM affects depression in a randomized controlled placebo controlled trial with 60 participants (https://clinicaltrials.gov/ct2/show/NCT04569058). Furthermore, Cassano is starting studies on 23 individuals with Down Syndrome (https://clinicaltrials.gov/ct2/show/NCT04668001) and on 60 children with ADD and Autistic traits (https://clinicaltrials.gov/ct2/show/NCT04569058).

Transcranial photobiomodulation (tPBM) could be the solution to Mitochondrial Disturbances in ASD individuals (resulting in functional brain connectivity): Michael Hamblin (2016) argued that Transcranial Photobiomodulation ("tPBM") could be helpful in addressing various neurological disorders (including ASD) because Nitric Oxide could be dissociated by photons of light. When Nitric Oxide is dissociated, the mitochondrial membrane potential is increased, more oxygen is consumed, more glucose is metabolized and more Adenosine Triphosphate (ATP) is produced by the mitochondria. In another paper, Dr. Hamblin discusses research on the effect of light stimulation on mitochondria, specifically he discusses in vitro studies with isolated mitochondria (isolated rat livers), where increased ATP synthesis was detected. Furthermore, tPBM has been found to be effective in treating several neurological conditions and disorders, including Stroke (Naeser and Hamblin, 2011), Traumatic Brain Injury (Naeser and Hamblin, 2015; Naeser et al, 2016) and Alzheimer's Disease (Johnston et al, 2015).

Transcranial photobiomodulation is likely to be especially effective for ASD (autism spectrum disorder), as recent research has shown that ASD is associated with the inflammation of non-neuronal glial cells (astrocyte and oligodendrocyte). Furthermore, Nassir et al, 2021, identified multiple single-cell clusters from three distinct developmental human brain regions (anterior cingulate cortex, middle temporal gyrus and primary visual cortex) with high concentration of inflamed glial cells. Cognilum stimulates targeted brain areas including those areas (e.g., occipital lobe and middle temporal gyrus) with high concentration of the inflamed glial cells. In addition, stimulating targeted brain areas simultaneously improves their functional brain connectivity (which is also crucial for ASD). Overall, many researchers seem to agree that ASD could be a result of Mitochondrial disturbances, which leads

to brain disconnectedness and tPBM could be beneficial for increasing ATP, promoting brain connectivity and reducing symptoms of ASD.

There is preliminary data that transcranial photobiomodulation reduces symptoms of autism (e.g. improvement of speech, improvement of responsiveness, reduction of tantrums, and abberant behaviors, improvement of sleep, and improvement of eye contact). Leisman et al (2018) administered tPBM to children (5-18 years old) diagnosed with autism and found significant reduction in symptoms (after only 2 months of applications, two sessions a week). Leisman et al stimulated brain's temporal lobe (to reach Broca and Wernike areas) as well as occipital lobe. Leisman et al (2018) specifically argued that administration of tPBM increases brain connectivity. Leisman et al used ERCHONIA laser for their study).

It should be noticed that even though the same technology (tPBM) is used for different condition, the devices are different (they irradiate different brain areas, the pulsing is different, the wavelength of the light and the power). JelikaLite's Cognilum device specifically irradiates brain areas affected by autism.Therefore, even though this technology is used for various conditions, our device is specifically designed to reduce symptoms of Autism. Please see section 2.4 below – for the description of the results of our recent IRB-approved study.

Jelikalite recently completed a study with the same group of participants who are proposed to enroll in this follow-up study. There was a statistically significant reduction in CARS scores in the Active Condition, but not in the Placebo Condition (Fradking et al, 2021).

2.2 Publications:

Published research on the benefit of photobiomodulation in neurological conditions:

- Cassano P., Petrie S.R., Hamblin M.R., Henderson T.A., Iosifescu D.V. Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. Neurophotonics. 2016;3:031404.
- Hamblin, M. R. (2016). Shining Light on the Head. BBA Clinical, 6, 113-124
- Leisman, Machado, Machado (2018) Effects of Low-Level Laser Therapy in Autism Spectrum Disorder. Clinical Medicine Research, 111-130.
- Naeser M.A., Saltmarche A., Krengel M.H., Hamblin M.R., Knight J.A. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. Photomed. Laser Surg. 2011;29:351–358.
- Naeser M.A., Martin P.I., Lundgren K., Klein R., Kaplan J., Treglia E., Ho M., Nicholas M., Alonso M., Pascual-Leone A. Improved language in a chronic nonfluent aphasia patient after treatment with CPAP and TMS. Cogn. Behav. Neurol. 2010;23:29–38.
- Saltmarche A.E., Naeser M.A., Ho K.F., Hamblin M.R., Lim L. Alzheimer's Association International Conference, Toronto, Canada. 2016. Significant Improvement in Cognition after Transcranial and Intranasal Photobiomodulation: A Controlled, Single-Blind Pilot Study in Participants with Dementia
- WE NEED TO INCLUDE FRADKIN (from Rucares).

2.3 Background of the Cognilum Physical Device:

We are developing a safe and effective protocol for administering tPBM via a wearable device. This physical device is getting developed by JelikaLite Corp. The parameters are developed by Dr. Eugenia Steingold (the researcher of this study), Dr. Michael Hamblin (leading photobiomodulation expert from Harvard Medical School and an advisor to JelikaLite), Dr. Margaret Naeser (leading neuroscientist who is studying photobiomodulation at Boston Medical University and an advisor to JelikaLite), and David Conroy (an industrial product designer with over 30 years of expertise in designing medical devices). The purpose of this feasibility study is to evaluate the safety and comfort of the product, as well as preliminary efficacy of the treatment effect. The device will stimulate Default Mode Network (to increase brain connectiveness) as well as Broca and Wernike areas (to facilitate speech comprehension and production) and Occipital lobe (as many ASD children rely on visual information for language learning). The device is physically light, comfortable to wear for children and could eventually be used at home as frequently as necessary.

The reason why the device may be helpful to children is because of the science of photobiomodulation. The device will have embedded LED lights in it, which will shine red light and near infra red lights. The children will wear the device for approximately 5-10 minutes, twice a week (closely replicating the protocol of Leisman et al as well as the clinical study at MGH). The light stimulates mitochondrial ATP production. Only about 2% of the light penetrates the skull. However, because brain is the largest energy consuming organ of the body, even those 2% result in significant improvement of the symptoms (even small boost in ATP production results in significant improvement). Having more energy enables the brain cells to heal, grow and form new neural connections. Other benefits of tPBM is increased blood flow to the brain, which increase brain oxygen supply and reduce inflammation.

There have been two clinical studies done already that show that photobiomodulation reduces symptoms of autism. The major difference between our device and those used before is that we will be using LED instead of lasers and we will specifically target Default Mode Network (DMN) and language areas. Massachusetts General Hospital study (quoted above) targeted DMN. Leisman et all targeted broca and wernike areas and occipital lobe. We will target both DMN (to increase connectivity) and Language areas (broca and wernike) to facilitate language learning.

Previous studies (Naeser et al) found that targeting DMN reduces symptoms of Alzheimer, TBI and Stroke. Dr. Naeser also shared with us her tPBM language production protocol, which she used with her Stroke patient who also suffered from Aphasia. Therefore, there are preliminary findings suggesting that using our protocol will be beneficial for children with autism, because it is expected to improve their language abilities and reduce other symptoms. Because our device uses LED lights instead of laser, it is light, wearable, easy to use by young children. We are specifically using soft, soothing materials, which will be comfortable even for children with sensory-integration difficulties (exhibited by ma**ny children with ASD).**

This device received a Non-Significant Risk Designation from the FDA and it was used in the completed, IRB approved study by Jelikalite.

2.4 Results of the Previous Pilot Study using the same device

Our recently concluded pilot study collaborates these predictions. We enrolled 30 participants who were 2-6 year old (16 in active and 14 in sham-control condition). Participants in the active condition have improved significantly (as measured by Childhood Autism Rating Scale). Participants in the sham condition showed no such improvement (see Chart 1). Furthermore, EEG data showed reduction of Delta waves over the course of the study for the participants of Active condition only (see Chart 2). Frolich et al (2021) reported that high amplitude Delta waves in the wakeful state are associated with neurological disorders and mitochondria disorders. Therefore, this reduction of Delta waves is a signature of the brain healing process (see attached presentation by Naviaux, 2021). Lastly, the change in Delta correlated significantly with the change in CARS showing that the kids whose CARS scores reduced (reflecting their reduction of symptoms) also experienced reduction in their Delta waves (see Chart 3). Lastly, we also found an increase in Theta waves in the children, whose CARS score decreased (inverse correlation between intensity of Theta and CARS scores, see Chart 4). Recent research has shown that there is an insufficient intensity of Theta waves in the children diagnosed of ASD (e.g., Ortiz-Mantilla et al, 2019). This redistribution of brain waves from Delta to Theta in the active condition is signaling of the healing that's happening as a result of treatment with tPBM.

(See attached Charts 1-4 with exact statistics below).

Chart 1: There was a significant reduction in CARS score in the Active Condition only ($F=6.47$, $p<.05$).

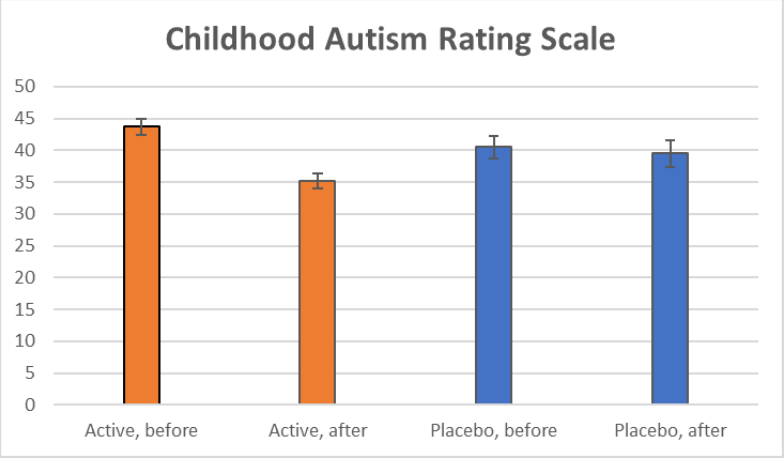


Chart 2: Delta Waves reduced in the Active Condition: Pearson's R squared -.45,($p<.05$, $n=9$) However, this correlation was not significant for the Placebo Condition, Pearson's R squared is -.1, ($p>.1$, $n=8$).

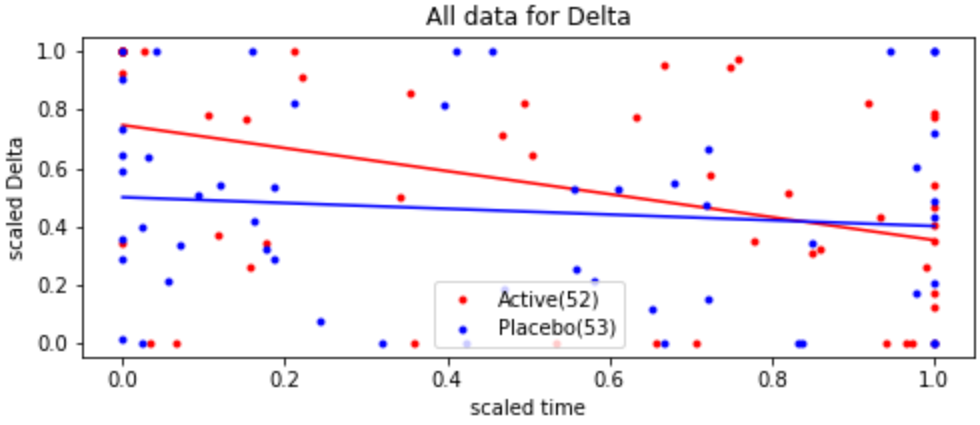


Chart 3: The study revealed a statistically significant correlation between the change in CARSII scores and Change in Delta waves (n=15). Specifically, children (mostly in Active condition), who experienced reduction in CARSII also experienced reduction in Delta waves.

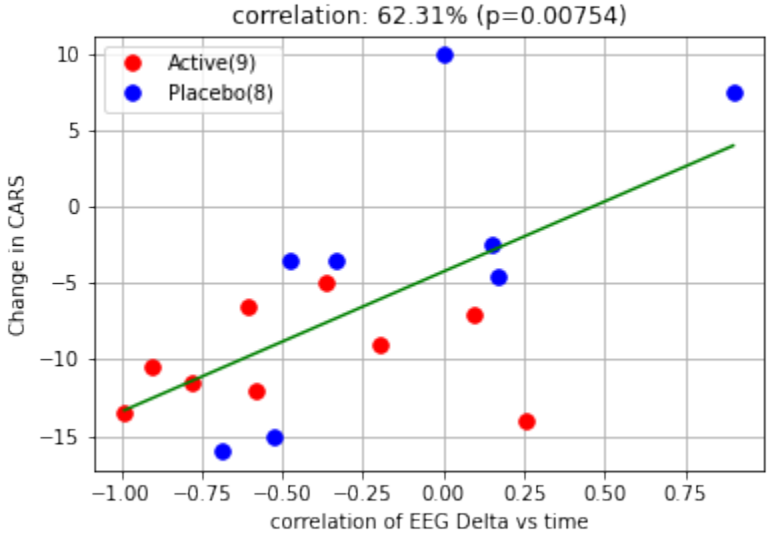
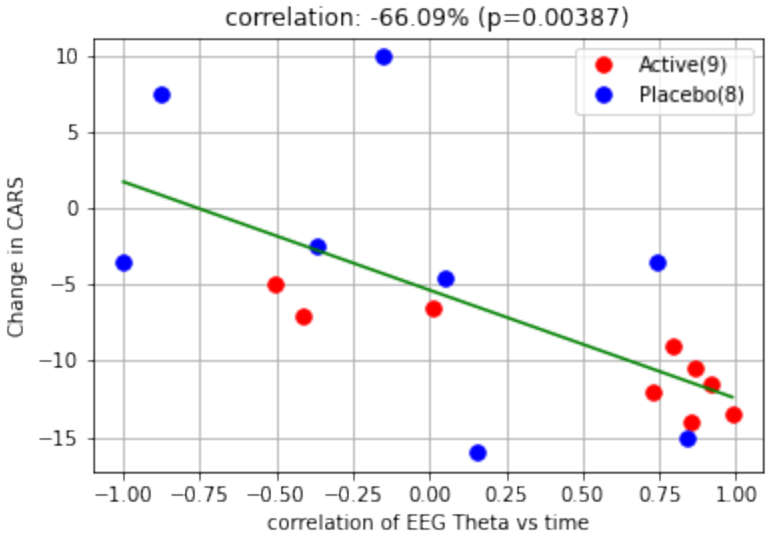


Chart 4: Increase in Theta waves correlated with Decrease in CARSII.



3.0 Safety of the Device

The device has been designated as "Non-Significant Risk" by the FDA in November 2020.

The device is not approved or marketed.

The device does not pose a risk to participants under 21 CFR 812.3(m).

This investigational device is not:

- Intended as an implant and presents a potential for serious risk to the health, safety or welfare of a participant;
- Purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety or welfare of a participant
- For a use of substantial importance in diagnosing, curing, mitigating or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a participant or
- Otherwise presents a potential for serious risk to the health, safety or welfare of a participant.

4.0 Inclusion and Exclusion Criteria:

Inclusion Criteria:

1. Male or female participants between 2 years and 7 years of age (inclusive), of all races.
2. Previously diagnosed with moderate or severe ASD by a licensed professional.
3. Participants may be receiving any behavioral intervention therapy (e.g., ABA, Floor Time) during the course of the treatment. The final statistical analysis will control for the participants receiving behavioral therapies in control and experimental conditions. We expect the majority of the participants in both

control and experimental conditions to be receiving behavioral therapies. There is no known interactions or complications of tPBM with behavioral therapy.
4. Parents of participants must understand the nature of the study.
5. Parents of participants must sign an IRB- approved informed consent form before initiation of any study procedures.
6. Parents of participants must have a level of understanding sufficient to communicate with the investigator and study coordinator, and to cooperate with all tests and examinations required by the protocol.
7. Participant child experiencing a major psychiatric disorder will be allowed to participate in the study provided they do not meet any exclusionary criteria.
8. The participant child is willing to participate in this study.
9. Participant previously participated in the JelikaLite pivotal clinical trial that took place in 2021, either in the active or placebo conditions.

Exclusion Criteria:
1. Participant child is experiencing severe self-injurious behavior or severe aggressive behavior to self or others (within past 7 days).
2. Participant has been diagnosed with another psychiatric or neurological disorder (e.g. epilepsy) or have exhibited symptoms of major psychiatric disorders within the last 30 days.
3. Participant has an unstable medical condition (that requires clinical attention).
4. Participant has a significant skin condition at the procedure sites (i.e., hemangioma, scleroderma, psoriasis, rash, open wound or tattoo).
5. Participant has an implant of any kind in the head (e.g. stent, clipped aneurysm, embolised AVM, implantable shunt - Hakim valve).
6. Any use of light-activated drugs (photodynamic therapy) within 14 days prior to study enrollment (in US: Visudine (verteporfin) - for age related macular degeneration; Aminolevulinic Acid- for actinic keratoses; Photofrin (porfimer sodium) - for esophageal cancer, non-small cell lung cancer; Levulan Kerastick (aminolevulinic acid HCl) - for actinic keratosis; 5-aminolevulinic acid (ALA)- for non-melanoma skin cancer).
7. Current treatment with a psychotropic medication.
8. Investigator and his/her immediate family, defined as the investigator's child or grandchild.

5.0 Sample Size:

Up to 30 children will be included in the study. All the screening has been done already, as we anticipate bringing back the children who already participated in the previous study, described in 2.4 above.

6.0 Research Locations:

1720 East 14th Street, Brooklyn NY 11229
This is a private professional office, with a waiting room and a receptionist. There are several private rooms within the office.

The child will led to a private room, which will have toys and books inside it. The caregiver and one of the researchers will be present in the room at all times.

315 West 57th Street, Suite 401, New York, NY 10006
This is a private professional office, with a waiting room and a receptionist. There are several private rooms within the office.
The child will led to a private room, which will have toys and books inside it. The caregiver and one of the researchers will be present in the room at all times.

7.0 Procedures Involved:

7.1 Location: The study will use pre-test and post-test design. The entire study on the children will be done in the office. The weekly interview with the parent may be done either in office or by phone, as preferred by the parent.

7.2 Conditions: There will be only one active condition.

7.3 Participants: The participants will be 2 to 7 years old children previously diagnosed with moderate or severe ASD. Children of all genders and races will be included in this study.

7.4 Treatment: The treatment will take place twice a week for up to 30 minutes at a time.

During the study, while participants will be wearing the photobiomodulation device, they may be playing with their parent or the experimenter, using the toys of their choice (out of the many available in the experimenter's office). The caregivers will be present during the experiment at all times. When the child and the parent arrive, they will be welcomed to the office, and introduced to the toys.

The child will be encouraged to play with toys and interact with the parent (or the experimenter).

If the child becomes uncomfortable, the parents will be able to leave the experiment without any punishment. No coercion or deception is involved in this study.

7.5 Pre and Post-Testing:

The following measurements will be used for pretest and post-test.

- Childhood Autism Rating Scale (CARS2)

CARS 2 scores will be compared for analyses.

In addition, EEG will be collected from the participants pre and post -treatment in each session. Mobile FDA cleared EEG device from Brain Scientific will be used to collect children's pre and post test EEG.

There is no known danger of EEG collecting. In this study it will be using for measuring the efficacy treatment only.

7.6 On-going Data Collection: Parents will be asked to keep a daily diary of the child's behavior, specifically – words spoken, comprehension of instructions, eye contact, his sleep pattern, number of tantrums, anxiety, social interaction and eating. Qualitative data will be collected through short weekly interviews with the parents. These interviews can take place either in Dr. Steingold's office during the child's treatment or by phone. During those weekly interviews, the parents will be asked questions about their children's responsiveness to language, number of words they can produce, eye-contact, anxiety, frequency of tantrums, eating, and difficulties falling asleep and sleeping through the night. Please see attached proposed script for the weekly call. The qualitative data will be used to further inform and supplement quantitative data.

The study will collect qualitative and quantitative data. The quantitative data will be the total CARS2 scores of the participants, obtained before and after the study is done. Repeated-measure t-tests will be used to analyze quantitative data. In addition, we will collect Before and After Prefrontal cortex EEG from the control and experimental treatment groups to measure electrophysiological changes in Prefrontal cortex. after treatment. EEG data will be analyzed (using Time-Frequency analysis), and after baseline normalization, the data will be used in aggregate to compare conditions numerically. In addition, we will obtain qualitative data from weekly parental interviews, during which we will ask participants' parents about their children's behavior (see attached protocol). Qualitative data will be used for information purposes and will supplement quantitative data.

The PI will analyze quantitative and qualitative data. An independent contractor (a neuroscientist) will be analyzing the collected EEG data at the end of the study, however, the individuals conducting the analysis will not have access to the private identifiable information.

7.8 Confidentiality: Participants' confidentiality will be protected by assigning them Study ID. The quantitative data will be analyzed and reported only as aggregate (averages and F scores). The qualitative data will be studied only by the researchers and, if reported for illustrative purposes only, it will be attached to the Study ID (not the identifying information). The participants will be asked for consent to report qualitative data with the Study ID.

-

8.0 Recruitment Methods:

We will contact via phone call the parents of children who have participated in our previous study, approved by the WCG IRB under IRB Tracking ID 120200004.

Once a prospective parent contacts the researchers, they will be re-screened for eligibility. They will be asked questions regarding the Inclusion and Exclusion criteria. If the child is determined eligible, we will schedule their first session, which will start with debriefing about the purposes of the study, benefits and risks. After debriefing, participants will sign the Informed Consent (if they are still willing to

participate),and proceed to the study. (Please see attached script for eligibility screening and obtaining Informed Consent).

Withdrawal from the Study

Each participant (and their parents) has a right to withdraw from the study at any time. If a participant decides to withdraw from all components of a research study, we will discontinue interacting or intervening with the participant in order to obtain data about his or her participation in the study, we will not obtain additional identifiable private information about the participant for the research study from any source, and we will not obtain identifiable private information about the participant for the research study by observing or recording private behavior without interacting with the participant.

When a participant will inform us that he / she decides to withdraw, we will ask the participant to clarify whether the participant wishes to withdraw from all components of the trial or only from the primary interventional component of the trial. If the participant wishes to withdraw only from the primary interventional component, we may ask for permission to contact the participant to collect follow-up data about the child's behavior.

9.0 Recommendation for Only One Parent Consent

Both this proposed study and the investigational device do not involve greater than minimal risk.

Rationale for the device:

Safety of Photobiomodulation: Photobiomodulation has been extensively studied on humans for more than 30 years, including its use for neurological conditions. There are several photobiomodulation products (for neurological conditions) that are on currently on the market (using both LED and Lasers). The consumers report no side-effects.

After more than three decades of research there are no known major side effects attached to photobiomodulation therapy.

The device has been designated as "Non-Significant Risk" by the FDA.

Rare Minor Side effects for first time users only include: Tiredness (temporary) – probably due to the release of metabolites but the majority report a resurgence of energy. Headaches (temporary) – from the reactivation of neural connections and increased microcirculation.

Safety Issues of our product specifically: Our product emits non-laser based irradiation (incoherent light) with a low level energy intensity. Infrared emits non-laser based irradiation (incoherent light) with a low level energy intensity. We use 850 nm. The participants might perceive slight warm. No other perceptions will be produced by wearing the device. No feelings of discomfort are anticipated (the device is especially made for children, it's very comfortable and soothing to wear). There are no known side-effects of photobiomodulation (with 30 years of research and studies, including research on 5 year old children diagnosed with ASD).

Rationale for the study:
The study activities include: 1) wearing the device and / or r 2) free play. In addition, the parents will be interviewed about the child's behavior on a weekly basis.
None of these activities present greater than minimal risk to the health and well-being of the participants.

10.0 Consent Process

Parents of child participants will be debriefed about the purposes of the study. They will be explained risks and benefits. The researcher will answer all their questions. The participants will review the Informed Consent form. Parents will be given an opportunity to ask questions about the consent. The parents will be explained that they do not have any obligation to participate in the study and their refusal to participate will not affect any current treatment or benefits that they or their child currently receives. This explanation will take place in person, in Dr. Steingold's office, in a private room.

During the conversation, we will ask questions to ensure that the parent understands that the participation is voluntary, that the child may be placed in the placebo group, the time commitment required, the possible risks of being in the study and possible benefits.

Prior to enrolling a child in the study, we will collect the signed Informed Consent from the parents of every participant.

We will not be obtaining consent from the child participants. The reason is as follows: children between the ages 2 to 7 years, especially those diagnosed with ASD, have limited mental capacity and cannot be reasonably consulted about the risks and benefits of the study. Children will be asked to wear a device on their head. Due to their limited level of comprehension and responsiveness, they may not be able to give an affirmative verbal assent.

Nonetheless, if children demonstrate a visible discomfort, or verbally say that they do not want to wear the device, they will not be forced to do it.

-

11.0 Financial Compensation:

No financial compensation will be provided.
Parents of participants will be responsible for the cost of transportation to the research facilities. This is minimal risk to the participants.

12.0 Potential Benefits to Participants:

The possible benefit for the participant child may be improvement of speech, improvement of responsiveness, reduction of tantrums, reduction of anxiety, improvement of sleep, and improvement of eye contact.

13.0 Risks to Participants:

Potential Risks	Mitigating Factors
Some questions may be very personal or upsetting to the parents	Parents may skip any questions that they do not want to answer.
The child may feel uncomfortable wearing the headband and may want to take it off early	If the child wants to take off the headband, we will first encourage him to wear it, by attempting to divert his attention to other things, such as toys and music. If, however, the child insists on taking off the headband, he / she will not be forced to wear it and he / she may be able to take it off before the conclusion of the session.
Breach of confidentiality (child's data being seen by someone who shouldn't have access to it)	We'll keep all children identifying information separate from the research data, but we'll be able to link it by using a study ID. We will destroy this link after we finish collecting and analyzing the data.
The child maybe receiving concomitant medical treatment	Even though there are no interaction of the tPBM with any medications, children currently receiving any psychotropic medications on a regular basis, will be excluded from participating in this pilot-study. This will be determined during initial screening.
The child might be receiving behavioral Intervention such as ABA simultaneously with participating in the study.	There is no known negative interaction of this treatment with any behavioral treatment. The children should be able to receive their regular behavioral therapies while being enrolled in this study. Clinicians will monitor (based on parental and therapists' interviews) each child's progress.
There may be risks that we do not know about yet. Exposure to LED lights is not known to have any negative side effects.	After years of study, there are no known negative side effects of photobiomodulation. Throughout the study, we'll tell parents if we learn anything that might affect their decision to let their child participate. Minor transient side effects may include headaches, agitation, and hyper-activity. These side effects are sometimes observed in the beginning of the treatment and usually resolve on their own. Parents will be informed of these potential minor side-effects in the Consent form.
Some participants may have to be withdrawn from the study	If the child is not able to attend all the required sessions and the caregiver is not able to reschedule a cancelled session within a 7-day window, then the child may have to be withdrawn from the study.

	1. If the child has completed at least 8 weeks, we will ask them to do final assessments and this data will be included in the final analysis. 2. If the child has completed less than 8 weeks and missed a week due to sickness, the family will be offered to restart the 12-week course. Regardless of the outcome, we will ask the child's parents for permission to contact them in the future with follow up questions regarding the child's behavior.

14.0 Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data:

Participants will be only interacting with Dr. Steingold, Ms. Sverdlov, Esq, or Ms. Logounova (researcher). Participants and their parents will be tested individually, in a quiet room, and their confidentiality will be protected, as they won't be interacting with each other or with anybody else outside of the researchers.

The participants will be explained that they can refuse to answer any question. They can also refuse to participate in the study at any time. We do not anticipate uncomfortable questions, however, we will assure the participants that their level of comfort is of utmost importance, and we will explain to them that there is no penalty involved for their refusal to answer any specific question.

Only Dr. Steingold and Ms. Sverdlov will be able to access individual information. The participants will be immediately assigned Study ID number and only STUDY ID will be used for data analysis and reporting. Only aggregated data will be used for further reporting to the scientific community or to the business community. Individual data will be reported for illustrative purposes only with STUDY ID (not identifying personal information).

The following information will be included as data: Signed consent form (immediately scanned and stored in a cloud). Pre and Post-test Cars2 scores (with STUDY ID assigned). Weekly interview data (with STUDY ID assigned).

Identifying information will include Name and Age, Gender and number of therapy hours of the participant, Name and phone number of the parent. Children's age, gender and number of therapy hours will be used for matching purposes (for assigning to the control or treatment condition). Neither names of the participants nor names and phone numbers of their parents will be used for data analysis or reporting. Their names and phone numbers will be stored separately, in encrypted (password protected) file, in a secure cloud. Secure clouds as well as encryption and password protection will be used to protect identifying information.

The raw research data will be stored for 6 years. The identifying parental information will be kept for a year, for potential follow up interviews. The consent form will include their permission to keep identifying data for a year.

Although we do not plan to re-contact the participants after the study is complete, a follow up interview in 6 months or a year could be useful to assess the sustainability of the benefits of photobiomodulation. In this case, we will be applying for a separate IRB (minimal risks) to conduct the follow up interview. Presently, we do not plan to do it (although we recognize that it could potentially be useful for research purposes).

The data will be stored in encrypted, password protected files in a secure cloud.

15.0 Data Monitoring Plan to Ensure the Safety of Participants:

We will conduct weekly interviews with the parents, asking them questions about child's behavior and functioning to collect both safety and efficacy data. The interviews will be conducted either by telephone or in person (per parental choice). Please attached interview protocol. Dr Steingold, a licensed clinical psychologist will review the data. The detailed qualitative data will be collected. No statistical analysis is necessary.

If a participant shows sudden developmental regress, we will recommend immediate neurological evaluation and his/her participation will be discontinued (unless this participant has been manifesting regress prior the start of the study). If two participants suddenly manifest signs of regress (not anticipated, not seen before in prior photobiomodulation studies), we will immediately discontinue the study.

16.0 Data, and if applicable, Specimen Banking:

The raw research data will be stored for 6 years. The identifying parental information will be kept for a year, for potential follow up interviews. The consent form will include their permission to keep identifying data for a year.

Although we do not plan to re-contact the participants after the study is complete, a follow up interview in 6 months or a year could be useful to assess the sustainability of the benefits of photobiomodulation. In this case, we will be applying for a separate IRB (minimal risks) to conduct the follow up interview. Presently, we do not plan to do it (although we recognize that it could potentially be useful for research purposes).

The data will be stored in encrypted, password protected files in a secure cloud.

17.0 Data Sharing:

Only aggregated data will be shared with scientific community (via publications). Only aggregated data will be shared with potential investors. If individual data (e.g., from an interview) is shared for illustrative purposes, identifying information will NOT be shared (STUDY ID will be assigned to each participant).