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Treatment of Neurodegeneration: Integrating Photobiomodulation and Neurofeedback in Alzheimer's Dementia, Parkinson's and TBI. A Review and Directed Magnetic Energy as a Precursor

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Abstract

Objective: The addition of Photobiomodulation (PBM) in Neurodegenerative diseases is a dual modality which is not only gaining traction but demonstrating it is safe, antiviral, and anti-inflammatory for treating neurodegeneration with photons that stimulate mitochondria increasing ATP and proteasomes increasing misfolded protein removal. Neurofeedback provides neural plasticity with increase in BDNF mRNA and the increase in dendrite production and density in the hippocampus coupled with overall growth in dendrites, density and neuronal survival.

Background: Alzheimer's disease pathophysiology is the accumulation of hyperphosphorylated tau protein neurofibrillary tangles (NFTs) and subsequently amyloid-beta (Aβ) plaques. PBM and NBF addresses the multiple gene expression and upregulation of multiple pathogenic pathways inflammation, reactive oxidative stress (ROS), mitochondrial disorders, insulin resistance, methylation defects, regulation of neuroprotective factors and regional hypoperfusion of the brain. There is no human evidence to suggest a clinical therapeutic benefit from using consistent light sources while significantly increasing safety concerns.

Method: A PBM test with early to mid-Alzheimer's was reported in 2017 consisted of double blind, placebo-controlled trial in a small pilot group of early to mid- dementia subjects under IRB approved FDA Clinical Trial. **Results:** PBM Treated subjects showed active treatment subjects tended to show greater improvement in the functioning of the executive; clock drawing, immediate recall, practical memory, visual attention and task switching (Trails A&B). A larger study using the Cerebrolite helmet in Temple Texas again of subjects in a double blind placebo controlled IRB approved FDA Clinical Trial is demonstrating not only gain in memory and cognition by increased clock drawing.

Conclusion: Next generation trials with the Cognitolite for Parkinson's disease subjects will incorporate the insights regarding significant bilateral occipital hypocoherence deficits gained from the QEEG analyses. When applying PBM to many biological systems, the pulsed wave (PW) mode was reported to be more effective than the continuous wave (CW) mode. Future applications will integrate non-invasive stimulation delivery including full-body and transcranial and infrared light with pulsed electromagnetic frequencies.

Background; Alzheimer's dementia

Pathophysiology: The current pathophysiology of Alzheimer's disease is the accumulation of neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein and subsequently amyloid-beta (Aβ) plaques that clogs neurosynaptic connections with memory loss and eventual neurodegeneration and eventually brain atrophy. However, this concept is slowly being taken one step back to preceding chronic brain inflammation. Further evidence for this will be presented throughout this manuscript and why that this concept of *directed energy* is not only gaining traction but demonstrating that this approach works, is efficacious, relatively inexpensive, and safe!

A common characteristic in many neurodegenerative disorders, including Alzheimer's, is this accumulation in misfolded protein aggregates. Most of the protein degradation is attributed to the ubiquitin proteasome pathway. Ubiquitin-proteasome function is affected by AB accumulation. [1] Myeku et al. demonstrated that by activating cAMP-PKA signals in 2016, Tau-driven 26S proteasome deficiency and cognitive dysfunction in a mouse model can be avoided early in illness. [2] This underlies the photobiomodulation mechanism (PBM) used to increase mitochondrial ATP and proteasomal clearance of Tau and β Amyloid in the development of Alzheimer's disease in mouse models and now in humans!

Alzheimer's etiology and pathogenesis is complex, with many genetic and environmental risk factors including stress and insulin resistance. The expression of many genes, and upregulation of multiple pathogenic pathways result in amyloid β peptide (Aβ) deposition, tau hyperphosphorylation, inflammation, reactive oxidative stress (ROS), mitochondrial disorders, insulin resistance, methylation defects and down regulation of neuroprotective factors. [3]

Antibody therapy of Tau and Amyloid beta, vaccines and other methods to decrease Tau and or Amyloid have not been successful after considerable pharmaceutical and biotech efforts. [4]

In Indianapolis, Eli Lilly revealed a significant improvement to his closely watched clinical trial for the drug solanezumab of the Alzheimer, which failed to achieve statistical significance. "How to quantify the effects of the medication is a major challenge in these trials," says Dennis Selkoe, a neurologist at Brigham and Women's Hospital in Boston who was not involved in the Lilly study. "While people with early Alzheimer's may have mild memory loss and concentration and focus issues, they may still follow the recipes, make a cup of coffee, or drive a car," Selkoe reiterates. Those skills over the course of an 18-month clinical trial are unlikely to improve much."[5]

Therefore, animal trials often demonstrate improvement in a therapy long before human clinical trials show any benefit! A report on animal models using photomodulation with near infrared light to treat AD pathology in K369I tau transgenic model (K3)l engineered to develop neurofibrillary tangles, and the APPs/PSEN1dE9 transgenic model (APP/PS1) to develop amyloid plaques was published in Alzheimers Research and Therapy. 2014. [6]

History of Photobiomodulation in Alzheimer's dementia:

A group of researchers at the University of Sunderland in Northern England began in the late 1990s with Gordon Rex Dougal, an electrical engineer and physician who published online in 2008 using a 1072 nm LED-built NIR helmet to treat AD. Something oddly, up until recently no peer-reviewed publications described this approach. [7] For a picture of this early prototype NIR Helmet see Figure 1 below.

Figure 1. Gordon Dougal and Collaborators at University of Sunderland NIR Helmet. "Medical experts in the North-East of England believe they could have found the key to turning back the brain's biological clock and reverse the effects of dementia and memory loss!

Using this as a background, Marvin Berman PhD in the Philadelphia area at the Quietmind foundation contacted Douglas Rex Dougal, a medical practitioner in the UK and obtained several of his helmets. See Figure 2 below for the next version of this helmet looking at its inside.

The experimental device used 1100 LEDs set in 15 arrays of 70LEDs/array with all matched to 1060-1080nm and pulsed at 10hz with a 50% duty cycle. Stimulation was administered for 6 minutes daily over 28 consecutive days. (Figure 2 is inside view of the current version of Cognitolite Transcranial Photomodulation System. As contrasted with the original NIR helmet used in the study.)

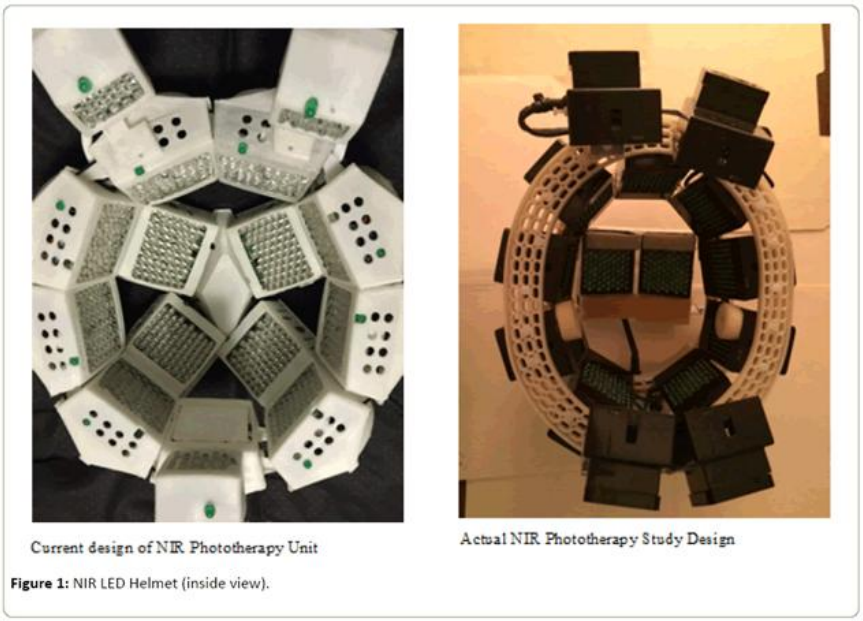
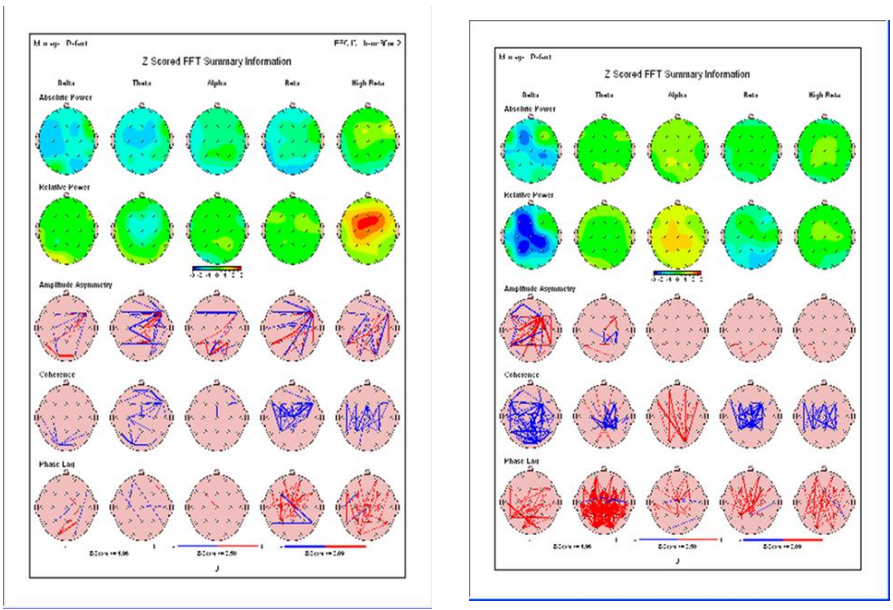


Figure 2. On right, NIR Helmet used in treatment of Alzheimer's and Parkinson's dementia Clinical Trial at Quietmind Foundation and Baylor Scott White, on left, NIR Helmet used first in Pilot Study of Alzheimer's dementia by Dr Marvin Berman.

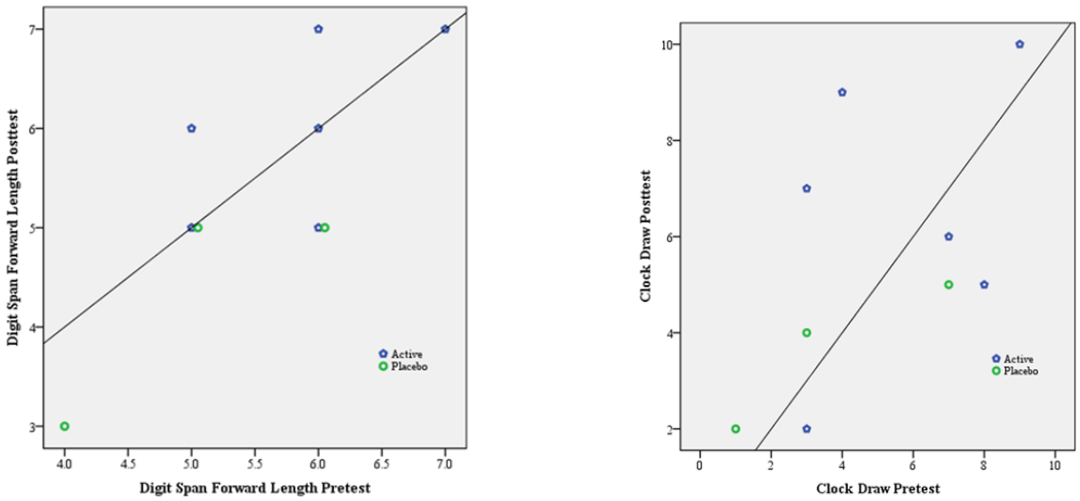
Alzheimer's Pilot Placebo Controlled Clinical Trials;

A small pilot trial was performed in early to mid-Alzheimer's and we recently stated in 2017 that pilot double blind, placebo-controlled study (n=11) 6 involved, 3 controls and 2 dropouts assessed the impact of 28 consecutive, six-minute Near Infrared (NIR) stimulation transcranial sessions. Patients were drawn from many local areas in continuing care, using both print and electronic media. All participants were independently diagnosed by a neurologist with possibly Alzheimer's dementia, using the NIA-OA criterion. Testing included Mini Mental State Test MMSE, Quantitative EEG (QEEG), Alzheimer's Scale-Cognitive Disorder Assessment (ADAS-Cog) that was performed on the first day of treatment and within3 days of completing 28 consecutive exposure sessions, Surface cortical perfusion was measured before and after each treatment session using infrared spectroscopy. A two -minute baseline was recorded using the Biocomp Research Hemoencephalography recording and Bioexplorer software. Quantitative EEG changes before NIR helmet and after as seen below.



A. Before NIR intervention **B. After NIR therapy**

Figure 3. Delta power increase = improved alertness, attention. Alpha decrease = less anxiety



Results showed changes in executive functioning; clock drawing, immediate recalls, praxis memory, visual attention and task switching (Trails A&B) as well as improved EEG amplitude and connectivity measures. Although there was no statistical improvement in this small pilot study, improvement in clock drawing in some patients over controls demonstrated its moderate sensitivity and specificity for detecting executive cognitive dysfunction in people even with normal MMSE. [8]

Photobiomodulation and Neurofeedback:

The addition of photobiomodulation and neurofeedback in Neurodegenerative diseases is a dual method that is gaining traction at this very moment. Photobiomodulation (PBM) is safe and Photobiomodulation (PBM) is a safe and active anti-inflammatory antiviral agent for the treatment of functional neurodegenerative, inflammatory and infection-based diseases. [9]. [18]. Research efforts have expanded globally and evidence regarding the efficacy of the PBM continues to mount in an ever-widening range of conditions in support of use. This analysis shows how PBM is used as a tool in the multimodal treatment of neurodegenerative disorders, such as dementia and Parkinson's disease, for example. PBM is seen as an important therapy at the tissue level to minimize cortical inflammation and to improve cellular oxygenation and perfusion. Quantitative biofeedback preparation focused on electroencephalography, often called neurofeedback, facilitates renormalization of the neural communication. The combination of the two approaches shows promise as a tool to safely and effectively stop the progression of disease, prevent further neuronal damage, promote the removal of neurofibrillary plaques and tangles while training in intra- and interhemispheric communication renormalization

Berman previously described the historical background and action mechanisms underlying the effects of PBM and EEG biofeedback (neurofeedback) training. [10] Near-infrared light has been shown to support healing and improved functioning of the motor, cognitive, behavioral and metabolism. [11] Combining the two approaches with functional and integrative biomedical treatments, e.g. stem cell therapy, gene therapy, optogenetically delivered chemotherapy, constitutes a systemic intervention strategy that can add further enhance the effective delivery of precision medicine. See Figure 1 below for Images of Brain treated by PBM and QEEF Neurofeedback.

Figure 1. Images of Brain PBM and QEEG Neurofeedback. (Images; Internet)

The latest practical medical approach for assessing and treating dementia has been discussed by Bredesen and colleagues, and this emphasis will be on latest measuring techniques such as quantitative EEG (QEEG) and near-infrared spectroscopies. There is an growing movement towards neurophysiologic incorporation with non-invasive neurotherapeutic approaches to positively affect healthy functioning. Neurodegenerative diseases are good candidates for these therapeutic approaches. Bredesen conducted work on the multidetermined origins of mental, neurocognitive, and behavioral problems. [12]

The following list represents Bredesen's main diagnostic components for assessing and treating dementia patients. Biomarkers with an X also respond to transcranial photobiomodulation (TPBM) positively. Since 2020, peer reviewed published manuscripts now demonstrate that all of the 35 diagnostic components are met with PBM Positive Effects. See Table 1 below!

Table 1; Diagnostic components of Bredesen assessing and treating dementia patients. Functional and inflammatory biomarkers associated with neurodegenerative disorders with indicators that respond positively to transcranial near - infrared photobiomodulation.

Biomarker/Functional Mechanisms **PBM Positive Effect (X)**
1. Decrease Aβ production **X**
2. Increase Aβ degradation & clearance **X**
3. Decrease Aβ oligomerization X (Comerta,Krishnan,Taglialetela 2017)
4. Increase BDNF (Brain Derived Nerve Factor) **X**
5. Increase NGF (Nerve Growth Factor) X (Gomes 2012)
6. Increase G-CSF X (Hamblin,Yang 2019)
7. Increase ADNP X
8. Decrease p-tau **X**
9. Decrease homocysteine X (Hamblin 2019)
10. Build synapses X (Berman , Nichols 2019)
11. Decrease 4/2

X
12. Increase A/G Ratio (Albumin/Globulin) X (Hamblin 2019)
13. Decrease Inflammation **X**
14. Inhibit NF-kBX X (de Freitas, Hamblin 2017)
15. Increase GSH (glutathione) X
16. Increase antioxidants (SOD) X (de Freitas, Hamblin 2017)
17. Decrease Iron, copper, increase zinc–target of Zn X (Hamblin 2017)
18. Increase CBF X
19. Increase Ach X (Hamblin, Huang 2019)
20. Increase nAChR α 7 signaling X (Hamblin, Huang 2019
21. Increase Aβ transport X (Eneng, Dungel 2019)
22. Decrease ApoE4 effect X (Hamblin, Huang 2019)
23. Increase GABA X (de Freitas, Hamblin 2017)
24. Decrease NMDA glutamate receptors X (Hamblin, Huang 2019)
25. Optimize hormones X (de Freitas, Hamblin 2017
26. Increase vitamin D X (Anju, 2019)
27. Decrease pro-NGF X (Berman, Nichols 2019)
28. Decrease caspase-6 X (de Freitas, Hamblin 2017)
29. Decrease N-APP X (Zhang, Shen et al 2020)
31. Increase Memory **X**
32. Increase Energy **X**
33. Increase Mitochondrial function **X**
34. Increase Mitochondrial protection **X**
35. Increase chaperone expression **X*** (Chazot,2018) (de Freitas 2017) (Heo 2019)

Neurodegeneration Pathophysiology;

Although the predominant Alzheimer's disease pathophysiology is thought to be the accumulation of hyperphosphorylated tau protein neurofibrillary tangles (NFTs) and subsequently amyloid-beta (Aβ) plaques, chronic inflammation in the brain is now becoming more evident The role of emerging pathogens such as dental spirochetes, Borrelia Bd the pathogen of chronic Lyme disease with biofilms and fungal and viral infections have been implicated.. A common feature of many neurodegenerative diseases,

including Alzheimer's, is this accumulation of misfolded protein aggregates. [13] Most protein degradation is caused by the ubiquitin proteasome pathway. AB accumulation affects the system of ubiquitin-proteasome. [14]

To model the NFTs seen in human AD it has been necessary to develop transgenic mice that express further gene alterations in addition to mutated APP such as mutated human tau as reported by Lewis et al. 2001; Oddo et al. 2003b) or removal of nitric oxide synthase 2 as shown by Wilcock et al. 2008. These multigenic AD transgenic models do develop NFTs similar to those seen in human brain and have aided the explication of the relationship between Aβ and tau 6) with Aβ pathology seeming to precede the onset of tau pathology , consistent with the amyloid cascade hypothesis. [15] [16] [17]

DNA methyltransferase 3A (DNMT3A) is one of two essential human de novo DNA methyltransferases for cellular development and differentiation transcription regulation. There is growing evidence that RNA plays a role in directing DNA methylation within mammalian cells to specific genomic locations. Two modes of DNMT3A in vitro RNA regulation have been described here. A single-stranded molecule of RNA that is antisense to the promoter of E-cadherin binds in a structurally dependent fashion tightly to the catalytic domain causing a powerful inhibition of DNMT3A activity. Two other RNA molecules bind specifically in vitro modulation of RNA DNMT3A activity supports in vivo data interacting with DNMT3A for transcription regulation. [18] This mechanism can be used to observe that NIR light regulates transcription. DNMT3A outside the catalytic domain at an allosteric site, causing no catalytic change.

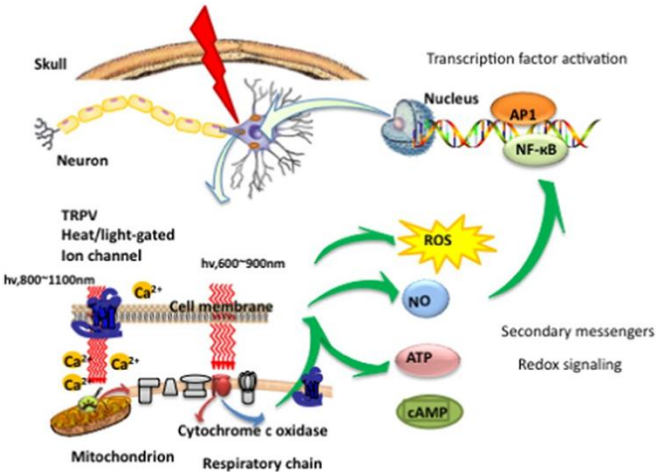


Figure 2. Transcription factor activation molecular and intracellular mechanisms of transcranial low-level laser (light) or photobiomodulation. Ca2+, calcium ions; cAMP, cyclic adenosine monophosphate; NF-kB, nuclear factor kappa B; NO, nitric oxide; ROS, reactive oxygen species; TRPV, transient vanilloid potential receptor. (Hamblin Ref.11]

There is currently no evidence that site-specific NIR light control of subtelomeric DNA methylation can affect DNA methylation, but optokenically, blue light has been shown to selectively increase methylation at subtelomeric CpG sites at the six ends of the chromosome examined by SR Choudhury and Purdue associates. This blue-light activation resulted in a progressive increase of the length of telomeres over three generations of HeLa cell replications. They concluded that targeting DNMT3A at subtelometric DNA sites increases methylation at different genomic sites within a HeLa cell model. [19]

Materials and Methods;

Photobiomodulation Therapy: Initially, low-level laser therapy was the term used to describe the therapeutic use of intensive monochromatic light energy with photobiomodulation becoming the more comprehensive laser and LED light energy terminology. There is no human evidence to suggest a clinical therapeutic benefit from using consistent light sources while significantly increasing safety concerns, e.g. tissue-heating related damage, are increasing. Look at the Table. 2.

Table 2; Wavelength and pathological effect of Low Level Light (LLL).

Wavelength range	Pathological effect
180–315 nm (UV-B, UV-C)	photokeratitis (inflammation of the cornea, equivalent to sunburn)
315–400 nm (UV-A)	photochemical cataract (clouding of the eye lens)

400–780 nm (visible)	photochemical damage to the retina, retinal burn
780–1400 nm (near-IR)	cataract, retinal burn (Wikipedia,2018)

In particular in the marketing of PBM applications and devices, there are numerous instances of laser and LED-based treatment conflating. Therefore, we advocate exclusively the development of LED-based technology for transcranial and intraocular self-administered applications. Our advocacy is also in response to the growing recognition that a significant proportion of modern healthcare assessment and intervention service delivery is shifting from face-to-face office-based structure to telemedicine and cloud-based applications. [20]

A search for the world's medical literature (250 + trials) of pharmacotherapeutic agents for Alzheimer's treatment does not provide any long-term improvements published. [21] Naesar and Hamblin previously published PBM studies using low-level Near-Infrared (NIR) stimulation in the treatment of traumatic brain injury (TBI) in 2015. NIR light passes readily through the scalp and skull and arrive at the upper 1-5cm of the brain. The primary photoreceptors for (600-950nm) red and NIR light are in the terminal link of the mitochondrial respiratory chain. [22]

Cortical neurons, which are abundant in mitochondria, have increased biochemical pathways such as increased ATP and signaling pathways triggered by ROS. Photobiomodulation (PBM) is dependent on the ability of light to alter the metabolism of cells, as it is especially absorbed by general hemoproteins and cytochrome c oxidase (COX)[27]. Regulating gene expression and neurotransmitter activity in the hippocampus and other brain regions usually associated with memory disorders is showing to be successful targets for PBM. Most notable was the increase in BDNF mRNA and the increase in hippocampal dendrite output and density coupled with overall growth in dendrites, density and neuronal survival in Meng, 2013 and further supported by Grillo in 2013, Ojha, in 2011, Bradford in 2007, and increasing production of molecular chaperones by Doggett and finally by Chazot in 2013. [24] [25] [26] [27] [28] [29]

Near Infrared photobiomodulation decreases synaptic vulnerability to Aβ.

Comerta and researchers at Galveston University of Texas worked on synaptic dysfunction due to disruption of the binding of amyloid beta and tau oligomers that are one of the earliest impairments in AD. They reported that a group of people called Non-Demented with Alzheimer's Neuropathology (NDAN) who had Alpha Beta (Aβ) oligomer at the synapses but had cognitive function retention differentiated from a group of demented AD subjects. They showed that these non-demented individuals displayed similar levels of soluble Aβ oligomers throughout their central nervous system, but their synapses were devoid of Aβ oligomers, suggesting that NDAN subjects are somehow resistant to Aβ oligomers. They investigated NIR light's ability to decrease synaptic susceptibility to Aβ oligomer binding, thus increasing synaptic functioning. They used wild type (Wt) mice in the hippocampus of PBM-treated mice in the presence and absence of Aβ oligomers to determine the impact of NIR light treatment on the binding of Aβ oligomers to isolated synaptosomes and long-term potentiation (LTP). Findings included significantly reduced Aβ1–42 at the synapses of the 6-month-old Tg2576 mice that overexpressed human amyloid precursor protein (APP). [21]

These changes coincided with post-PBM synaptic mitochondrial health retention and increase in both Wt and Tg2576 and CD-1 mouse models. [22][23] .This study provides additional evidence to support NIR light therapy as a viable treatment for AD by Camerota in,2017 that specific PBM protocols can effectively reduce synaptic vulnerability to damaging Aβ oligomers.[23] These and other findings, particularly work by Chazot and colleagues at Sunderland University and Durham University, helped further clarify the mechanism of action underlying PBM's biochemistry. See the figure. 2. [24]

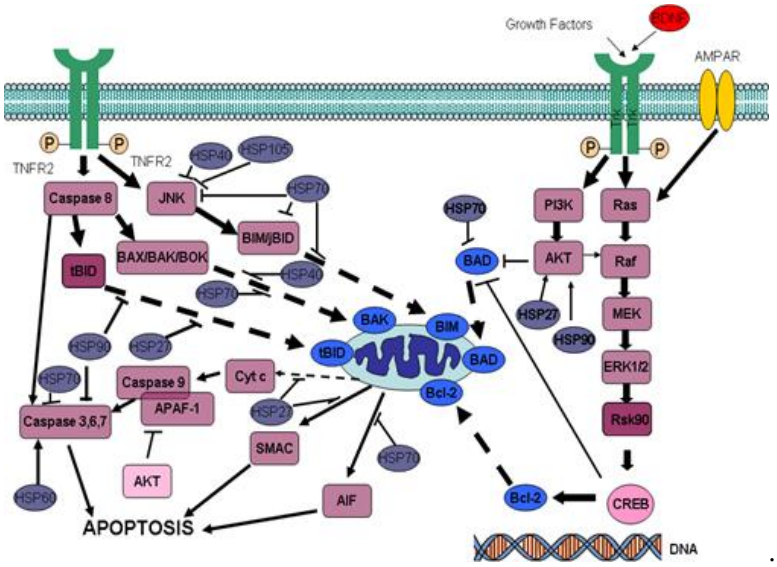


Figure 3. Photobiomodulation mechanism of action (unpublished and published material from Grillos S., Duggett, N., Ennaceur, A., Chazot, PL). A range of selective HSPs have been shown to be upregulated following in vivo treatment of Alzheimer's mice (HSP27, 60, 70, 90, 105) (Grillo et al., 2013; Grillo & Chazot; Duggett & Chazot, unpublished; Schirmera (2016, in press); highlighting the role of these proteins in mitochondrial function, apoptosis and protein folding mediated by chaperon.

Photobiomodulation Treatment in Chronic TBI.

Human photobiomodulation trials started by Naesar in 2015 reported eleven chronic TBI patients whose cognition improved after treatment with red and NIR light emitting diodes (LEDs) applied transcranially to the forehead and scalp at 10 minutes per area and nasally red light at 18 outpatient sessions. Neuropsychological testing for Executive Function at 1, 2 and after 18 LED treatment treatments showed improvement in the Stroop test.[25]

Researchers at the University of Sunderland by Grillo in 2013 reported using non-invasive 1072 nm pulsed (10hz) stimulation on an animal model of dementia (TASTPM mice). This was the first peer-reviewed publication that described the use of this higher wavelength as a potential method of treatment. Here we see a decrease in the number of placebo (no light) small plaques vs active6-minute exposures over two consecutive days, twice a week over five months. [26]

Cell line (lymphocytes exposed to UVA) and pretreated neurons in culture were then exposed to varying concentrations of nitric oxide research in the original bench studies by Bradford, in 2005. [27] Subsequent media attention by Derbyshire in 2008 caught the attention of Quietmind Foundation researchers who studied the effect of non-invasive brainwave biofeedback training on cognitive and behavioral symptoms in subjects with early to mid-stage dementia. [28] Berman & Frederick in 2009 and 2011, the current first author and colleagues at the Quietmind Foundation started a collaboration with the inventor of the Cerebrolite, Gordon Dougal, MD, BSEE, a physician and electronic engineer in the UK who conduct the first PBM treatment for cognitive and behavioral symptoms of dementia in human clinical trials. The transcranial and intraocular Cerebrolite PBM system provides approximately 600mw of 1065-1075 nm of 10hz pulsed photic stimulation. The current experimental protocol for dementia and Parkinson's called for two, daily, five-minute stimulation sessions at 5-6 hour AM/PM intervals. Treatment protocols now employ the 5th generation device design, collaboratively developed with Dr. Dougal at Maculume Ltd. since 2008, tested by the research group at QMF with the goal of integrating neurofeedback training and PBM into a neurotherapeutic application that can simultaneously improve tissue-level pathology and abnormal neural connectivity. [29]

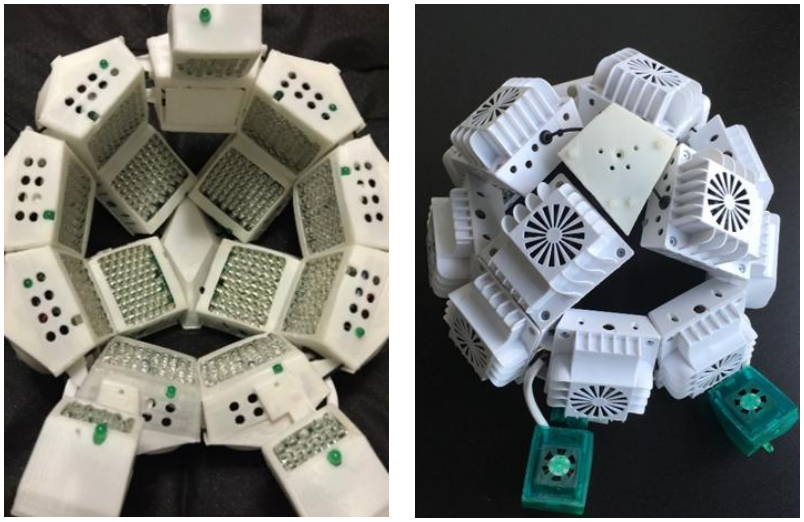
Results;

Pilot Clinical Trials of NIR Helmet in Alzheimer. Berman MH, Halper JP, Nichols TW, et al,

A pilot PBM test with early to mid-Alzheimer's was reported in 2017 consisted of double blind, placebo-controlled trial (n=11) 6 active, 3 controls and 2 dropouts evaluating the effect of 28 consecutive, six-minute Near Infrared (NIR) stimulation transcranial

sessions. Several local continuing care communities recruited patients using print and online media. All subjects were independently diagnosed with probable Alzheimer's dementia by a neurologist by means of the criteria of NIA-OA. Testing included Mini Mental Status Exam MMSE, Quantitative EEG (QEEG), Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) on the first day of treatment and within 3 days of completing the 28 consecutive six-minute daily exposure sessions required. Surface cortical perfusion was measured before and after each transcranial and intraocular exposure using near-infrared spectroscopy (FP1 & FP2) in which a two-minute baseline was recorded using near-surface infrared spectroscopy developed with Biocomp Research Hemoencephalography by Toomim in 2000 and Bioexplorer software in Janow's lab in 2002. After each session, QEEG changes were recorded and described in greater detail elsewhere. [30] [31]

The most significant changes in transcortical electrical activity have been the normalization of central Alpha (8-12 Hz) amplitudes and Delta (0-4Hz) and Theta (4-8 Hz) hypocoherence and phase lag, i.e. internodal correlation. Improved delta and theta are associated with improved alertness and attention in the sleep architecture, and reduced alpha may result in reduced anxiety. John Nash, PhD recently commented that, "Delta waves are wide geographically and raise wide neuronal regions closer to the threshold, with the rapid waves riding on the delta's large ocean swells. This widespread integration of frontal systems is caused by a lack of delta; it also prevents effective sleep start and restoration of sleep." [32] [33]

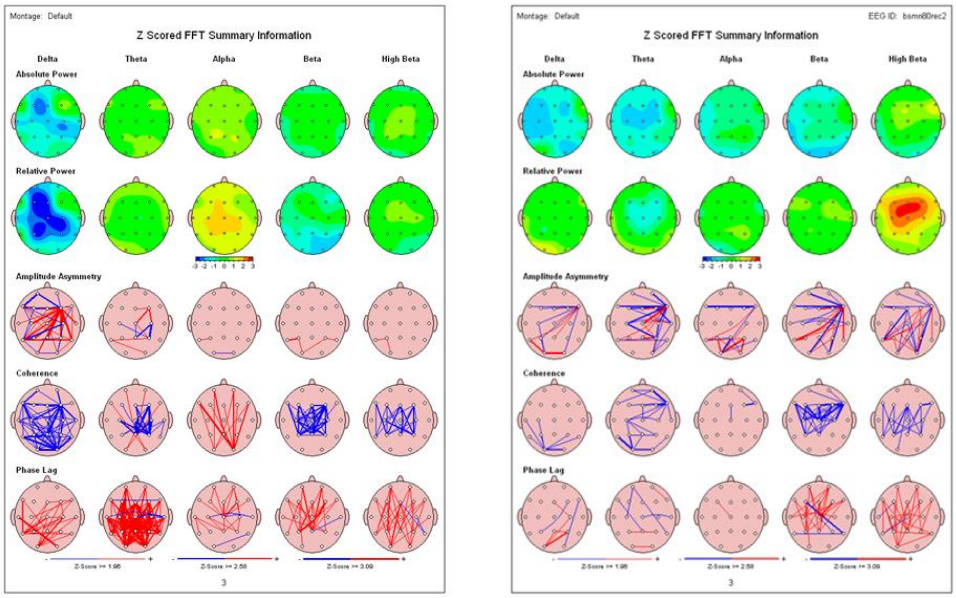


Inside view Top View

Figure 4. NIR LED helmet; *Cerebrolite transcranial-intraocular 1068nm photobiomodulation system*

The substantial impact PBM can have on both power and coherence aspects of electrophysiological activity is quite apparent and this can serve as noninvasively determined biomarkers discriminating between various neurodegenerative disorders including Parkinson's.

Figure 5. Quantitative EEG changes before 1065-75nm transcranial and intraocular Stimulation



Clock Draw Pretest and Digit span measure.

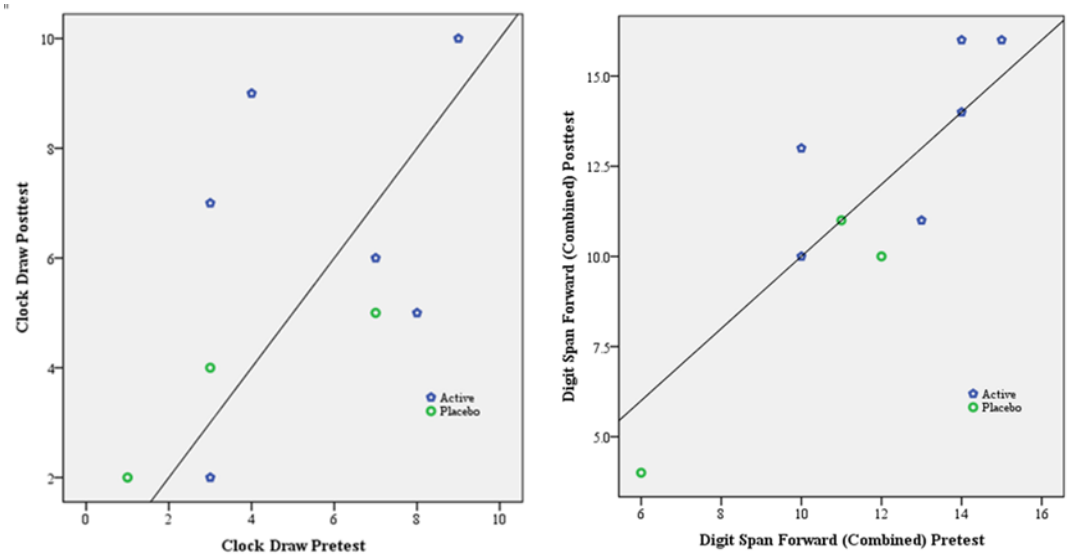


Figure 6. Graphs Comparing Active and Placebo Clock Drawing and Digit Span Forward Scores

Results showed active treatment subjects tended to show greater improvement in the functioning of the executive; clock drawing, immediate recall, practical memory, visual attention and task switching (Trails A&B). Because of the sample size, statistical significance could not be achieved. Clock drawing improvements showed moderate sensitivity and specificity to detect executive cognitive dysfunction even with normal MMSE in people by the present authors in 2017.[16]

Dr. Jason Huang, chairman, Department of Neurosurgery, Baylor Scott & White Health (BSWH) Temple, TX, conducted a recently completed replication study. A Texas A&M Health Science Center affiliate and post-doctoral fellow and study coordinator Damir Nizamutdinov, PhD, approved the 1068 nm Cerebrolite device as a safety trial. Ethics approval was obtained and recruitment began in June 2017 as a single-center, double-blind, randomized, placebo-controlled trial in April 2018. Subjects (N=12, 4 active placebo 8) all from the Plummer Movement Disorders Center of BSWH, Temple, TX. The study stated that "to determine the effectiveness of this new light stimulation helmet on executive functioning (attention, working memory, learning and remembering strategies,

planning, organizing, self-monitoring, inhibition and flexible thinking) in subjects diagnosed with early-stage dementia." Therefore, since all subjects were drawn from the patient pool of the Movement Disorders Center, all subjects were doubly diagnosed with Parkinson's disease so that they could serendipitously evaluate the PBM treatment on memory and cognitive functions of subjects, motor planning, coordination and expressiveness of behavior.[34]

Pilot PBM Study Results: PRE/POST Active and Placebo Quantitative EEG Analysis

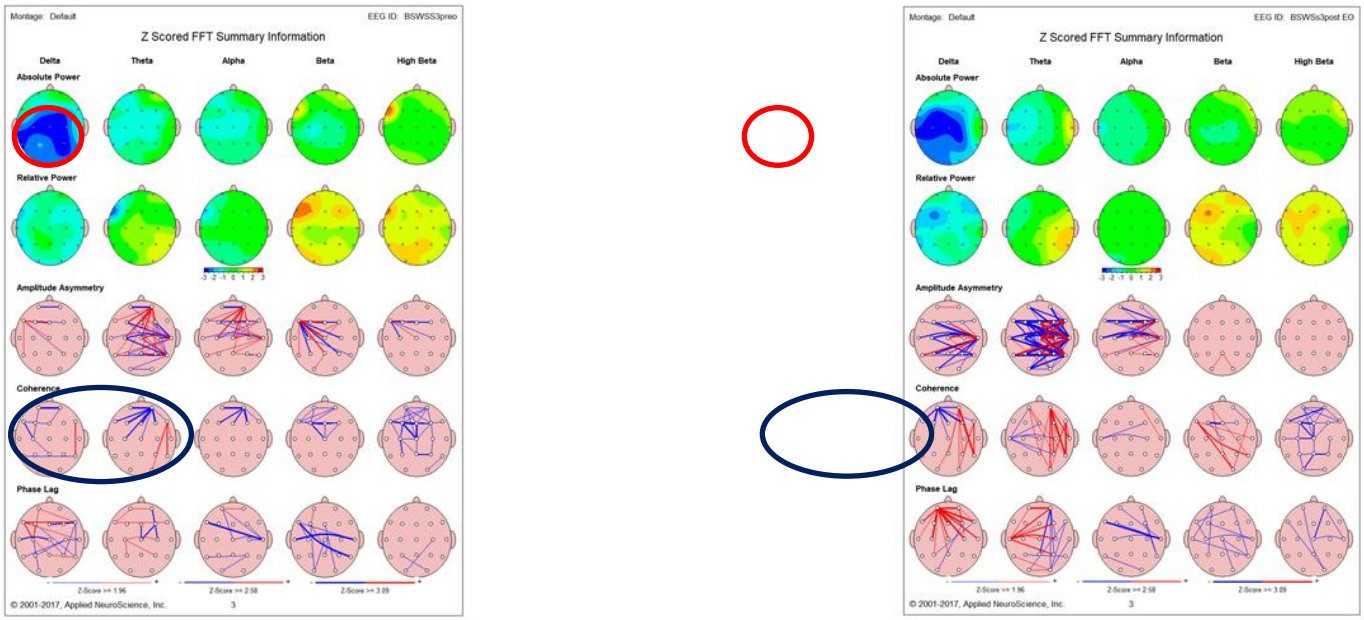


Figure 7. Baylor Scott & White Pilot PBM study results: Pre/Post Active and Placebo QEEGs. Note no difference in absolute power in central delta and left prefrontal and parietal beta relative power and more abnormality in coherence.

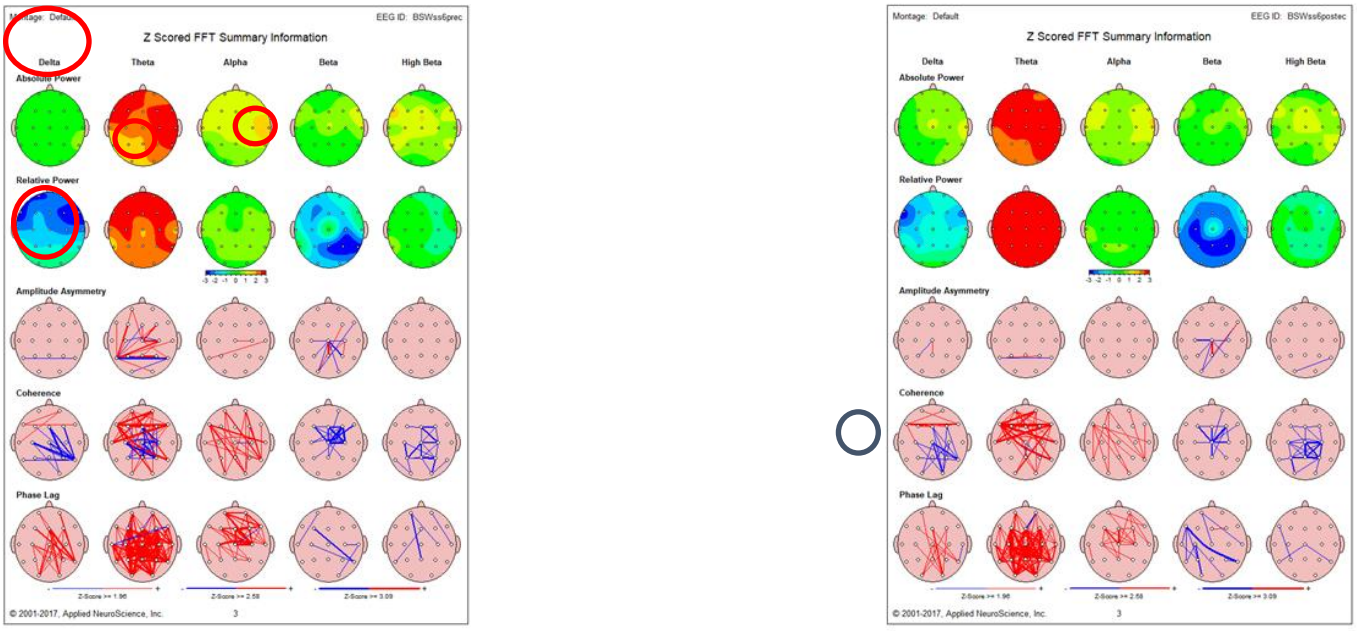


Figure 8. Post Active 28 consecutive twice daily, 5-minute treatment shows normalized Delta relative power (red circle) and absolute Alpha amplitude (blue circle) and decreased theta, alpha & beta coherence.

These findings, which highlight the impact of PBM on amplitude reduction but little to no effect on neural connectivity, underline the need for an intervention strategy to reduce inflammation, enhance regional cerebral perfusion and ATP and interhemispheric and higher-order network connectivity that is directly affected by neurofeedback training.

Neuropsychological Testing Results:

In addition to the QEEG, Mini Mental Status Exam (MMSE), Alzheimer's Disease Assessment Scale (ADAS-Cog), Auditory Verbal Learning Test (AVLT), Category Fluency Test, Trail Making, Boston Naming and WAIS-R digital symbol substitution , Clock Drawing Test is a standard tool for procedural and practical memory evaluation.

Examples of two active treatment subjects below show significant improvement!

Pretreatment; **Post Treatment**

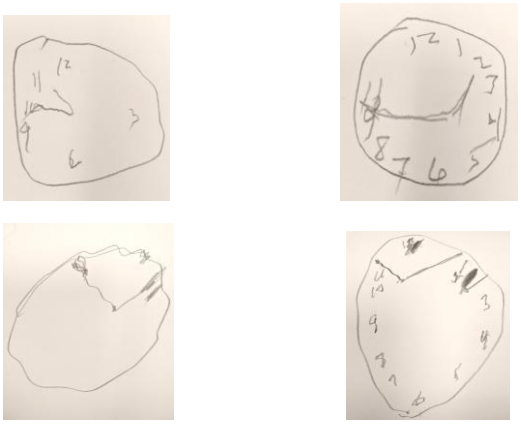


Figure 9. Clock Drawings. The value of clock drawing has been found to be moderately sensitive and specific for detecting executive cognitive dysfunction in people even with normal MMSE. Angela J et al.

Next generation trials with the Cognitolite for Parkinson's disease subjects will incorporate the insights regarding significant bilateral occipital hypocoherence deficits gained from the QEEG analyses. Stimulation protocols will focus more stimulation toward the occiput by reversing the ocular device's ocular arrays to stimulate the foramen and thereby increasing the level of PBM stimulation to the substantia nigra where it is shown that large numbers of dopamine neurons are negatively affected. [11]) Use of this technique has improved gait, bradykinesia and cognitive-behavioral responsiveness in clinical practice especially in combination with intensive neurofeedback training to correct bilateral occipital hypocoherence.

Similar results were obtained using the transcranial and intranasal 810nm 10Hz pulsed PBM technology developed by Vielight's Neuro Alpha. In a randomized placebo-controlled trial, Saltmarche (2016) studied 19 subjects with varying degrees of dementia using a combination of transcranial (PBM) and intranasal (PBM) to investigate the effect of the Vielight Neuro system (see Fig.) on subjects with dementia and mild cognitive impairment. To investigate the effects of PBM on memory and cognition, this was a single blind study. With a follow-up period of 4 weeks, subjects with impaired memory / cognition were randomized to active and sham treatments over 12 weeks. They were evaluated with scales of MMSE and ADAS-cog. The protocol involved in-clinical use of a combined transcranial-intranasal PBM device and in-home use of an intranasal device-only PBM device and daily experiences were noted in a journal by participants / caregivers. Researchers noted that active participants with moderate to severe impairment (MMSE scores 5–24) showed substantial improvements after 12 weeks (5-point MMSE score). A significant improvement in ADAS-cog scores has also been observed. They also reported better sleep, less angry outbursts and wandering, decreasing anxiety. During the 4-week follow-up period of no-treatment, symptom declines were noted. Participants with mild to normal impairment (MMSE scores 25 to 30) in both active and sham subgroups showed improvements, demonstrating that may reflect the phenomena of passive sensory stimulation that may occur in clinically controlled trials. [35]

Applying Magnetic Directed Energy in Alzheimer's Treatment;

Photobiomodulation is one of several non-invasive methods of influencing core biological functions including transcranial magnetic and pulsed electro-magnetic fields, by Pena-Philippides in 2014 and transcranial ultrasound and Tufail in 2010 that are being employed in studying and treating a wide range of functional and metabolic disorders. [36] [37] The application of neuromodulation

in Alzheimer's was first reported by Nichols & Pearce in 2006 using moderate magnetic field therapy to treat AD. Their report in the Society for Neuroscience involved magnetic therapy of 0.5 Tesla employing two large and strong non-pulsing DC electromagnet fields (EMF) stimulation with the subject lying in a between two large electromagnets. The treatment produced a temporary increase in the magnetic force on the atoms of the body resulting in a higher velocity and precession of certain orbiting electrons thereby increasing electron transfer and chemical reactions.[38] Alzheimer's disease (AD) is a neurodegenerative disease secondary to oxidative stress, associated with genetic and environmental factors such as exposure to pesticides and heavy metals with subsequent depletion of mitochondrial protective enzymes, superoxide dismutase and glutathione via free radical toxicity.[39].

This along with gene expression demonstrated by Wang, Che, Du, Ha and Yarema at Hopkins has shown that by modulating cell signaling and differentiation, thousands of genes could be regulated up and down by moderate magnetic fields in 2 human embryonic stem cell lines. [40] NASA researchers have also shown that picoTesla magnetic fields in human neuronal cells results vary in similar molecular genetic changes regarding growth potential as measured by gene chip analysis of 10,000 genes.[41]

Pulsed Frequency Significance in Photobiomodulation;

When applying PBM to many biological systems, the pulsed wave (PW) mode was reported to be more effective than the continuous wave (CW) mode. The reason for PW-PBM's higher efficiency is poorly understood, however. Here, after treatment with PBM, Kim and associates recently suggest using delayed luminescence (DL) as a reporter for mitochondrial activity. DL originates primarily from reactive oxygen species (ROS) and adenosine triphosphate (ATP) transmission chain systems with mitochondrial electron. DL's decline time depends on the pulse frequencies of applied light that correlate with human dental pulp stem cells (discs)'s biological responses. Using low power light, the wavelength of which is 810 nm and 38 mJ / cm2 of energy density, a pulse frequency of 300-Hz prolonged the DL pattern and increased alkaline phosphatase activity. They also analyzed morphological mitochondrial changes and their volume density and found evidence to support physiological mitochondrial changes with an increase in length not number from PBM treatment. Their data suggest a new methodology to determine the efficacy of PBM in differentiating hDPSCs and the specific pulse frequency.[42]

One of the most important findings in this study is that pulsing PBM brings differential biological consequences according to the pulsing frequency. The DL lifetime was longer after PW-PBM irradiation, and the effects of rotenone, AMA, and NAC depended on the pulse frequency. Whereas cells treated with 30–300-Hz PW-PBM had higher and longer-lasting DL in all cases, cells treated with lower or higher frequency PW-PBM showed big changes when a complex III blocking agent AMA and N Acetylcysteine (NAC) were added. DL signals were more affected by a complex III blocking agent (AMA) than by a complex I blocking agent (rotenone). The authors assumed that the different wavelengths of light originated from this difference. Many studies used UV-VIS light and flavins or nicotinamide adenine dinucleotide (NADH) were their target molecules. The target molecules should be different because they used NIR light in this study. Cytochrome c and cytochrome c oxidase are known to absorb longer wavelength light, including NIR, which supports the role of complex III in NIR-induced DL25. Excited or metastable-state-cytochrome c could bind with complex III forwards or backwards depending on the environ-mental conditions, as observed. [42]

In a study reported in Cell April 4, 2019 MIT researchers further explored the effects of gamma wave stimulation using sound in Alzheimer's mouse models. Previous research by Tsai and colleagues at MIT in 2016 in mouse model of Alzheimer's used light at 40 Hz over 1 hour a day for a week and found reduced levels of amyloidβ an phosphorylated Tau but the results were transitory. This time the group played clicks at 40 Hz an hour a day for a week reduced levels of beta-amyloid in the auditory cortex and nearby hippocampus, a part of the brain responsible for learning and memory. Stimulated mice performed better on memory tasks, including recognizing objects and navigating a water maze to find a hidden platform. Researchers also saw changes in activation responses in microglia and astrocytes, cells involved in clearing debris, and in blood vessels. Researchers then exposed mice to a combination of light and sound stimulation, which expanded the effects beyond the visual and auditory cortex to the prefrontal cortex, an area of the brain important for planning and completing tasks. Using imaging analysis, the scientists found a unique clustering effect of microglia around amyloid deposits in stimulated mice and reduced amyloid pathology. The effects were short-lived, however, diminishing a week after stimulation. In a repeat study published May 2 ,2019 in Neuron, MIT researchers tested the effects of longer-term treatment by exposing mouse models with more advanced Alzheimer's disease to up to 6 weeks of gamma entrainment by visual stimulation. Results showed stimulation increased gamma brain waves in the visual cortex and higher-order brain areas, including the hippocampus and prefrontal cortex. Continuing stimulation also preserved neuronal and synaptic density in these brain regions, improved performance on memory tasks, and reduced inflammation. Findings point to an overall neuroprotective effect, even in the later stages of neurodegeneration, the researchers reported.[43] [44]

However, when applied to human studies of Alzheimer's dementia using the same stimulus of flickering light and auditory 40 Hz according to Rudi Tanzi at Harvard," it didn't work." What was missing was not the frequency but the wave length 1078 to 1080nm and the Near Infra-Red Light from the LED helmet that penetrates through the skull to excite the mitochondria of the brain tissue. [45]

However, next generation Cerebrolite Helmets will also have auditory stimulus of 40 HZ.

Conclusions;

As evidence of its effectiveness continues to appear in peer-reviewed literature, PBM applications continue to evolve. Approximately 5300 to 6300 studies containing the search term ' photobiomodulation therapy," low level laser therapy," low level light therapy' are shown in the PubMed database. Clinical applications will continue to evolve from the clinical research focus of the Quietmind Foundation on the design and development of at-home and day treatment programs for neurodegenerative and neuropsychiatric disorders treatment. The integration of PBM tissue level treatment and neurofeedback for neural connectivity renormalization is rooted in the understanding that, "in the final analysis, the only part of our being that holds a relationship with the external world is the nervous system." (Feldenkrais, 1949) The benefits of a more efficient (robustly adaptive) functioning central nervous system that interacts within a healthier biochemical ecosystem can be leveraged in this way. It is hoped that by adopting a systems-centered approach, we are enhancing our ability to address the etiological complexities inherent in neurodegenerative disorders and to design direct clinical service models within our health delivery systems more successfully that can support the development of neurodegenerative treatment and prevention strategy. [46][47]

Collective efforts within and between the relevant disciplines are now focused on design, engineering and development of algorithms to integrate neurophysiological (LORETA z-score neurofeedback), cardio-diagnostic (Heart Rate Variability) and frequency-specific, targeted energy and PBM to deliver scalable, safe, reliable and effective, home-based, affordable neurotherapeutic treatment solutions. Such programs would increase health at the tissue level, thereby enhancing neurophysiological sensitivity, i.e. enhancing the ability to discriminate similarities and differences and functional health, resulting in improved neurocognitive functioning. HRV consistency and EEG consistency and phases related activity can then be used as a measure of broad systemic flexibility and, as such, a neuro marker that relates to our capacity for adaptive responsiveness. [48]

Neurotherapeutic techniques that measure evoked EEG dominant frequency activity can be used to guide treatment, first by introducing pulsed electromagnetic stimulation below conscious awareness level and monitoring changes in dominant frequency activity. Operationally understood as its approximation of randomness, this real-time dominant frequency variability can then be evaluated and combined with the normalization of EEG amplitude, consistency, phase lock and phase reset. [49] [50].

The theory of chronic inflammation also would explain one of the biggest mysteries about Alzheimer's: why some people can have brains clogged with amyloid plaques and tau tangles and still think and behave perfectly normally. "What made those people resilient was lack of neuroinflammation," states Rudi Tanzi, a professor of neurology at Harvard Medical School and one of the leaders behind this new view of Alzheimer's. Their immune systems kept functioning normally, so although the spark was lit, the forest fire never took off, he says. In Tanzi's fire analogy, the infection or insult sparks the amyloid match, triggering a brush fire. As amyloid and tau accumulate, they start interfering with the brain's activities and killing neurons, leading to a raging inflammatory state that impairs memory and other cognitive capacities. The implication, here he reiterates, "that it is not enough to just treat the amyloid plaques, as most previous drug trials have done. If you try to just treat plaques in those people, it's like trying to put out forest fire by blowing out a match." [51]

This is another reason to start therapy with NIR LED helmet therapy earlier before when there is already marked inflammation and brain damage.

Finally, all recent and past additions of scientific studies confirming of Bredesen functional and inflammatory biomarkers associated with neurodegenerative disorders with indicators that respond positively to transcranial near - infrared photobiomodulation that have now been published. Older studies such as Gomes et al in 2012, to more recent reviews in Hamblin M, Huang YY in "Photobiomodulation in the Brain "in 2019 have been reviewed. [52][53]

Future applications will integrate non-invasive stimulation delivery including full-body and transcranial and infrared light with pulsed electromagnetic frequencies. Ultrasound, microcurrent, pulsed electromagnetic fields, infra-low electromagnetic energy and digitally transformed analog sound may be added as new research demonstrates their additional uses and power to the therapeutic enterprise.

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