Photobiomodulation for Treatment of Traumatic Brain Injury and Other Brain Disorders

Michael R. Hamblin, Harvard Medical School and Wellman Center for Photomedicine at Massachusetts General Hospital
Photobiomodulation for treatment of traumatic brain injury and other brain disorders

Michael R Hamblin PhD
Outline

- History of Photobiomodulation (PBM)
- Mechanisms of PBM
- PBM in animal models of TBI
- PBM in animal models of other brain disorders
- Clinical studies
Niels Ryberg Finsen (1860-1904)

Niels Ryberg Finsen - Facts

Niels Ryberg Finsen

Born: 15 December 1860, Thorshavn, Faroe Islands (Denmark)

Died: 24 September 1904, Copenhagen, Denmark

Affiliation at the time of the award: Finsen Medical Light Institute, Copenhagen, Denmark

Prize motivation: "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science"

Nobel Lecture 1903

“My disease (later found to be Niemann–Pick disease) has played a very great role for my whole development. The disease was responsible for my starting investigations on light: I suffered from anemia and tiredness, and since I lived in a house facing the north, I began to believe that I might be helped if I received more sun. I therefore spent as much time as possible in its rays.”
History of light therapy (1904-1910)

CHAPTER X.

Electric light baths – John Harvey Kellog
Auguste Rollier & Heliotherapy

Rollier regarded exposure to the sun at temperatures above 18°C as a "hot-air bath" and not a “sunbath”
In 1960 Ted Maiman built the first working laser
In 1963 Paul McGuff treated tumors with ruby laser

Tumoricidal effect of laser energy on experimental and human malignant tumors.

➢ Developed an interest in laser research in 1965 and obtained a ruby laser
➢ Attempted to repeat Paul McGuff’s anti-tumor laser treatment
➢ When this failed, tried to see if laser treatment could cause skin cancer in mice
➢ Observed increased hair growth and better wound healing (but no cancer)
What’s in a name?

Photobiomodulation is new consensus term

Low level laser therapy
Low reactive-level laser therapy
Low intensity laser therapy
Low level light therapy
Low energy laser irradiation
Photobiostimulation
Biomodulation
Biostimulation
Cold laser
Soft laser
Laser therapy

It is called “LOW” because a little light is better than a lot of light
Respiration↑
ATP↑

Red or NIR light

4 cyt c (red)
4 cyt c (ox)

CuA
Heme a
CuB
Heme a3

4 e-
4 e-
2 H₂O

O₂
NO

Subunit I
Subunit II

Oxygen consumption UP
Mitochondrial membrane potential UP
ATP UP cAMP UP
NO released
Brief burst of ROS
Calcium modulation

Respiration↑
ATP↑

Glycolysis >>>>>> Oxidative phosphorylation
near infrared light

Signaling based on mitochondrial stimulation

growth factor production
extracellular matrix deposition

cell proliferation & motility

anti-apoptosis and pro-survival

Gene transcription

signaling

mitochondrion

NO

ATP

cAMP

Jun/Fos

AP-1

NF-κB

ROS

PKD

IκB

nucleus
Two major effects of mitochondrial switch
Glycolysis $\gg\gg\gg\gg$ Oxidative phosphorylation

1. Activation of stem cells
Stem cells in hypoxic niche carry out glycolysis
When mitochondria are activated they leave niche
in search of oxygen and activate proliferation and
differentiation programs

2. Anti-inflammatory
Macrophages with M1 phenotype are pro-inflammatory
and carry out glycolysis
When OXPHOS is activated they switch to M2 anti-
inflammatory phenotype
M2 macrophages/microglia can phagocytose (e.g.
amyloid plaque)
Signaling based on heat/light gated TRP ion channels
PBM may decrease viscosity of interfacial water allowing faster rotation of ATP synthase.
Science News from research organizations
A new blood component revealed
January 23, 2020
INSERM (Institut national de la santé et de la recherche médicale)
Summary:
Does the blood we thought to know so well contain elements that had been undetectable until now? The answer is yes, according to a team of researchers which has revealed the presence of whole functional mitochondria in the blood circulation. The discovery may deepen our knowledge of physiology and open up new avenues for treatment.
Figure 1
Biphasic dose response?
Therapeutic approaches for stroke/TBI

**Antioxidants**
- Ebselen
- NXY-059 a nitrone spin-trap agent
- Tirilazad
- Edaravone
- Iron chelator
- Traditional Chinese medicine

**Anti-inflammatory**
- Anti-neutrophil adhesion molecule
- Nitric oxide signal transduction down-regulator: lubeluzole
- Corticosteroid
- Interleukin-1 receptor antagonist

**Circulation**
- Volume expansion
- Flow enhancer
- Vasodilator
- Hemodilution
- Blood pressure-related strategy

**Neurochemical**
- Serotonin antagonist
- Serotonin receptor agonist
- Serotonin uptake inhibitor

**Oxygen**
- Hyperbaric oxygen
- Oxygenated fluorocarbon
- Oxygen supplementation

**Metabolism**
- Ganglioside, Astrocyte modulator
- Beta blocker, CNS stimulant
- Phosphatidylcholine precursor
- Fibroblast growth factor
- Opioid antagonist
- Prostanoid, Statin

**Excitotoxicity**
- Potassium channel opener
- Sodium channel blocker
- Calcium chelator
- Magnesium
- GABA agonist
- Glutamate/AMPA antagonist
- NMDA receptor/polyamine blocker

**Physical intervention**
- Hypothermia (brain cooling)
- Hemicraniectomy
- Osmotic agent

Clinical trials of pharmacological and physical therapies for stroke/TBI
Transcranial PBM may improve TBI
Animal studies
Low-Level Laser Therapy for Closed-Head Traumatic Brain Injury in Mice: Effect of Different Wavelengths

Qiuheng Wu, MD, PhD, Weijun Xuan, MD, PhD, Takahiro Ando, MS, Tao Xu, MD, PhD, Liyi Huang, MD, PhD, Ying-Ying Huang, MD, Tianghong Dai, PhD, Saphala Dhital, PhD, Sulbha K. Sharma, PhD, Michael J. Whalen, MD, and Michael R. Hamblin, PhD

1 Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, Massachusetts
2 Department of Dermatology, Harvard Medical School, Boston, Massachusetts
3 Department of Burns and Plastic Surgery, Jinan Central Hospital Affiliated to Shandong University, Jinan, China
4 Department of Otolaryngology, Traditional Chinese Medical University of Guangxi, Nanning, China
5 Department of Electronics and Electrical Engineering, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan
6 Laboratory of Anesthesiology, Shanghai Jiaotong University, Shanghai, China
7 Department of Infectious Diseases, First Affiliated College & Hospital, Guangxi Medical University, Nanning, China
8 Aesthetic and Plastic Center of Guangxi Medical University, Nanning, China
9 Department of Microbiology, University of Tokyo, Tokyo, Japan
10 Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts
11 Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts
Fig. 2. Time course of NSS scores of sham and laser-treated mice. **A**: Sham-treated control versus 665 nm laser. **B**: Sham-treated control versus 730 nm laser. **C**: Sham-treated control versus 810 nm laser. **D**: Sham-treated control versus 980 nm laser. Points are means of 8–12 mice and bars are SD. *P < 0.05; **P < 0.01; ***P < 0.001 (one-way ANOVA).
Comparison of Therapeutic Effects between Pulsed and Continuous Wave 810-nm Wavelength Laser Irradiation for Traumatic Brain Injury in Mice

Takahiro Ando¹,², Weijun Xuan¹,³,⁴, Tao Xu¹,³,⁵, Tianhong Dai¹,³, Sulbha K. Sharma¹, Gitika B. Kharkwal¹,³, Ying-Ying Huang¹,³,⁶, Qiuhe Wu¹,³,⁷, Michael J. Whalen⁸, Shunichi Sato⁹, Minoru Obara², Michael R. Hamblin¹,³,¹⁰*
A single laser Tx of 36 J/cm² at 50 mW/cm² pulsed at 10 Hz is better than CW or 100 Hz.
Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice

Weijun Xuan, Fatma Vatansever, Liyi Huang and Michael R. Hamblin

Abstract. The use of transcranial low-level laser (light) therapy (tLLLT) to treat stroke and traumatic brain injury (TBI) is attracting increasing attention. We previously showed that LLLT using an 810-nm laser 4 h after controlled cortical impact (CCI)-TBI in mice could significantly improve the neurological severity score, decrease lesion volume, and reduce Fluoro-Jade staining for degenerating neurons. We obtained some evidence for neurogenesis in the region of the lesion. We now tested the hypothesis that tLLLT can improve performance on the Morris water maze (MWM, learning, and memory) and increase neurogenesis in the hippocampus and subventricular zone (SVZ) after CCI-TBI in mice. One and (to a greater extent) three daily laser treatments commencing 4-h post-TBI improved neurological performance as measured by wire grip and motion test especially at 3 and 4 weeks post-TBI. Improvements in visible and hidden platform latency and probe tests in MWM were seen at 4 weeks. Caspase-3 expression was lower in the lesion region at 4 days post-TBI. Double-stained BrdU-NeuN (neuroprogenitor cells) was increased in the dentate gyrus and SVZ. Increases in double-cortin (DCX) and TUJ-1 were also seen. Our study results suggest that tLLLT may improve TBI both by reducing cell death in the lesion and by stimulating neurogenesis. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.19.10.08003]
Morris water maze for spatial navigation, learning and memory
Probe test: memory, learning
BrdU-NeuN double staining in dentate gyrus

7 days
Sham      TBI

1X PBM  3X PBM

28 days
Sham      TBI

1X PBM  3X PBM
FULL ARTICLE

Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis

Weijun Xuan†, 1, 2, 3, Tanupriya Agrawal†, 1, 2, Liyi Huang2, 4, Gaurav K. Gupta2, 5, and Michael R. Hamblin*, 1, 2, 6, 7
Brain derived neurotrophic factor (BDNF) in SVZ and DG
Synapsin-1 in perilesional cortex and SVZ
Low-level laser therapy effectively prevents secondary brain injury induced by immediate early responsive gene X-1 deficiency

Qi Zhang\textsuperscript{1,2}, Chang Zhou\textsuperscript{1,2}, Michael R Hamblin\textsuperscript{1,2,3} and Mei X Wu\textsuperscript{1,2,3}
Low-level light in combination with metabolic modulators for effective therapy of injured brain

Tingting Dong, Qi Zhang, Michael R Hamblin and Mei X Wu
Transcranial near-infrared photobiomodulation attenuates memory impairment and hippocampal oxidative stress in sleep-deprived mice

Farzad Salehpour a,b, Fereshteh Farajdokht a, Marjan Erfani a,c, Saeed Sadigh-Eteghad a, Siamak Sandoghchian Shotorbani d, Michael R. Hamblin e,f,g, Pouran Karimi a, Seyed Hossein Rasta b,h,i, Javad Mahmoudi a,*

Sleep Deprived SD

Wide Platform WP

810 nm, 10 Hz, 8 J/cm² to brain surface 1X day for 3 days
Barnes maze task

What-Where-Which task

Oxidative stress in Hippocampus
Photobiomodulation Preconditioning Prevents Cognitive Impairment in a Neonatal Rat Model of Hypoxia-ischemia

Luodan Yang\textsuperscript{1,2,a}, Yan Dong\textsuperscript{2,a}, Chongyun Wu\textsuperscript{1}, Yong Li\textsuperscript{2}, Yichen Guo\textsuperscript{2}, Baocheng Yang\textsuperscript{2}, Xuemei Zong\textsuperscript{2}, Michael R. Hamblin\textsuperscript{3,4,5}, Timon Cheng-Yi Liu\textsuperscript{1}, and Quanguang Zhang\textsuperscript{1,*}
Object recognition

Barnes maze
Photobiomodulation for Parkinson’s Disease in Animal Models: A Systematic Review

Farzad Salehpour\(^1,2,3\) and Michael R Hamblin\(^4,5,*\)
Multiple mechanisms for PBM in brain

- Angiogenesis
- PBM or LLLT
- Anti-apoptosis
- Survivin
- SOD (anti-oxidants)
- Cell migration
- Oedema
- Lymphatic drainage
- Increased blood flow
- Cerebral oxygenation
- Anti-inflammation

Neuron

NGF, BDNF, NT-3
Neurotrophins

Synaptogenesis

Neurogenesis
Clinical studies
Hair regrowth
Ophthalmology, dry AMD
Tinnitus, deafness
Skin rejuvenation, pigmented spots
Neck pain
Lung inflammation
Reduction of heart attack
Lower back pain
Laser lipolysis
Diabetes
Arthritis
Wound healing

Brain, Stroke, TBI, Alzheimer’s, Psychiatry
Temporomandibular joint disorder
Allergic rhinitis
Dentistry, pain
Oral mucositis
Non-union fractures
Lateral epicondylitis
Kidney failure
Carpal tunnel syndrome
Muscle fatigue
Athletic performance
Bone marrow to mobilize stem cells
Achilles tendonitis
Laser acupuncture
Laser Therapy devices for Photobiomodulation

Light Force

Aspen

THOR laser/LED

Light Cure

K Laser

Multiradiance
Whole body photobiomodulation

Novo-THOR

Rejuvalight

Planet fitness

ARRC LED

JOOVV maxi
Home use LED devices for photobiomodulation
Transcranial LED therapy for cognitive dysfunction in chronic, mild traumatic brain injury: Two case reports

Margaret A. Naeser*a,b, Anita Saltmarchec, Maxine H. Krengel*a,b, Michael R. Hamblindi,ef, Jeffrey A. Knight*a,b,g

aVA Boston Healthcare System (12-A), 150 So. Huntington Ave., Boston, MA, USA 02130
bDept. of Neurology, Boston Univ. School of Medicine, 85 E. Concord St., Boston, MA, USA 02118
cMedX Health Inc., 220 Superior Blvd., Mississauga, ON L5L 2L2, Canada
dWellman Center for Photomedicine, Massachusetts General Hospital, Boston MA 02114
eDept of Dermatology, Harvard Medical School, Boston MA 02115
fHarvard-MIT Division of Health Sciences and Technology, Cambridge, MA
gNational Center for PTSD - Behavioral Sciences Division, VA Boston Healthcare System

Case 1. 59 yo F, 7 yr. post-MVA after 8 weekly Tx.’s, ability to do computer work had improved 10-fold, obtained home unit and has used daily for 5 years.

Case 2. 52 yo F, multiple concussions and PTSD, Tx.’d daily with home unit, memory and “executive function” tests improved >2 SD, after 9 months. Off “Medical Disability” status after 4 months of home treatments; returned to full-time work.
P2, Pre- and Post- LED Tx., Neuropsychological Test Results. Post- LED Testing, Post- 9 months, nightly, transcranial LED Tx.

2 Stories, Immediate Recall
Wechsler Memory Scale-R

2 Stories, Delayed Recall (30 minutes)
Wechsler Memory Scale-R

* Significant Improvement, +1 SD: Memory
Significant Improvements in Cognitive Performance Post-Transcranial, Red/Near-Infrared Light-Emitting Diode Treatments in Chronic, Mild Traumatic Brain Injury: Open-Protocol Study

Margaret A. Naeser,1 Ross Zafonte,2 Maxine H. Krenge,1 Paula I. Martin,3 Judith Frazier,4 Michael R. Hamblin,5 Jeffrey A. Knight,9 William P. Meehan III,5 Errol H. Baker,3

<table>
<thead>
<tr>
<th>ID number</th>
<th>Psychosocial changes post-LED</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Able to sort bills, write checks and read essays, tasks he had been unable to perform for 5 years, since the MVA.</td>
</tr>
<tr>
<td>P2</td>
<td>Able to continue work 22 hours/week, and later, full-time. Headache pain was reduced; no longer required medication for headache pain.</td>
</tr>
<tr>
<td>P3</td>
<td>Non-talkative at entry, but became quite verbal and talkative after LED Tx. Husband reported that she was “better adjusted” at home. Beck Depression Index (BDI) remained at moderate level.</td>
</tr>
<tr>
<td>P4</td>
<td>Clinically meaningful decrease in post-traumatic stress disorder (PTSD).</td>
</tr>
<tr>
<td>P5</td>
<td>Clinically meaningful decrease in PTSD. Wife reported that he was more active around the home and was able to perform errands. Went on a job interview.</td>
</tr>
<tr>
<td>P6</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P7a</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P8a</td>
<td>Post-LED treatment series, able to return to the military for further evaluation.</td>
</tr>
<tr>
<td>P9a</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P10</td>
<td>Clinically meaningful decrease in PTSD. Pre-LED treatment, the patient reported recurrent nightmares of the mTBI event. After a few weeks of LED treatments, he reported that the nightmares had stopped.</td>
</tr>
<tr>
<td>P11a</td>
<td>Prior to the post-testing at 1 week, she was promoted to a new position, causing distress. PTSD and BDI were minimal at pre-Tx., and at 2 months post-LED. She reported better sleep.</td>
</tr>
</tbody>
</table>
Effect of Transcranial Low-Level Light Therapy vs Sham Therapy Among Patients With Moderate Traumatic Brain Injury
A Randomized Clinical Trial

Maria Gabriela Figueiro Longo, MD, MSc; Can Ozan Tan, PhD; Suk-tak Chan, PhD; Jonathan Welt, BS; Arman Avesta, MD; Eva Ratai, PhD; Nathaniel David Mercaldo, PhD; Anastasia Yendiki, PhD; Jacqueline Namati, PhD; Isabel Chico-Calero, PhD; Blair A. Parry, BA; Lynn Drake, MD; Rox Anderson, MD; Terry Rauch, PhD; Ramon Diaz-Arrastia, MD, PhD; Michael Lev, MD; Jarone Lee, MD; Michael Hamblin, PhD; Benjamin Vakoc, PhD; Rajiv Gupta, MD, PhD
Figure 1. Patient Flow Diagram

4716 Assessed for eligibility

4148 Excluded
3872 Did not meet inclusion criteria
576 Declined to participate or presented MRI contraindication

68 Randomized

33 Randomized to receive light treatment
21 Received treatment as randomized
5 Did not receive treatment as randomized (lost to follow-up or withdrew without receiving treatment)

28 Randomized to receive sham treatment
31 Received treatment as randomized
4 Did not receive treatment as randomized (lost to follow-up or withdrew without receiving treatment)

9 Excluded
4 Lost to follow-up
5 Withdrew

19 Participants completed study
18 Participants with 2 or 3 MRI scans
1 Participant with 1 MRI scan

24 Participants completed study
22 Participants with 2 or 3 MRI scans
2 Participants with 1 MRI scan

MRI indicates magnetic resonance imaging.

Figure 2. Evolution of Clinical Symptoms of Traumatic Brain Injury (TBI) in the Low-Level Light Therapy and Sham Groups

A. RPQ-3 assessment

Scores on the Rivermead Post-Concussion Symptoms Questionnaire, a 16-item self-assessment questionnaire. Each item in the questionnaire is assessed on a 5-point scale ranging from 0 (no problem) to 4 (severe problem). Bars show the standard error of the mean. A. Scores from RPQ-3 assessment, including early, objective, and physical symptoms of TBI. Time: \( P < .001 \), treatment: \( P = .40 \), and time \( \times \) treatment: \( P = .97 \). B. Scores from RPQ-13 assessment, including later, more cognitive and behavioral symptoms. Time: \( P = .91 \), treatment: \( P = .67 \), and time \( \times \) treatment: \( P = .89 \). C. Total RPQ scores. Time: \( P = .39 \), treatment: \( P = .61 \), and time \( \times \) treatment: \( P = .91 \).
Vielight Neuro Combined Transcranial And Intranasal Therapy

Small clinical trial for Alzheimer’s disease in Toronto, Canada
Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report

Anita E. Saltmarche, RN, MHSc, Margaret A. Naeser, PhD, Kai Fai Ho, PhD, Michael R Hamblin, PhD, and Lew Lim, PhD, DNM, MBA

**FIG. 2.** Mean change from baseline in MMSE score. Higher numbers indicate better cognition on this test.

*The p-value for Week 16 is omitted due to missing data from a patient who dropped out during the “4-Week No-Treatment Period”.

**FIG. 3.** Mean change from baseline in ADAS-cog scores. Lower numbers indicate better cognition on this test.

*The p-value for Week 16 is omitted due to missing data from a patient who dropped out during the “4-Week No-Treatment Period”.
Rapid Reversal of Cognitive Decline, Olfactory Dysfunction, and Quality of Life Using Multi-Modality Photobiomodulation Therapy: Case Report

Farzad Salehpour, MSc,1-3 Michael R. Hamblin, PhD,4-6 and Joseph O. DiDuro, DC, MS, DABCN3,7

Materials and methods: Patient received twice-daily PBM therapy at home using three different wearable light-emitting diode (LED) devices. For the first week containing a mixture of continuous wave mode red (635 nm) and NIR (810 nm) LEDs, a prototype transcranial light helmet and a body pad were used. The body pad was placed on various areas on the lower back and the helmet was worn while seated. After the first week of treatment, an intranasal LED device, 10-Hz pulsed wave mode NIR (810 nm), was initiated in the left nostril twice daily. All three devices were applied simultaneously for an irradiation time of 25 min per session.
<table>
<thead>
<tr>
<th>Table 2. Descriptive Data of Patients’ and Caregivers’ Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment</strong></td>
</tr>
<tr>
<td>Patient-related assessments</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment(^a)</td>
</tr>
<tr>
<td>WMQ(^b)</td>
</tr>
<tr>
<td>Storage domain</td>
</tr>
<tr>
<td>Attention domain</td>
</tr>
<tr>
<td>Executive domain</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Alberta Smell Test(^c)</td>
</tr>
<tr>
<td>Peanut butter test</td>
</tr>
<tr>
<td>Caregiver-rated patient self-care assessments (Lawton–Brody scales)(^d)</td>
</tr>
<tr>
<td>IADL</td>
</tr>
<tr>
<td>PSM</td>
</tr>
<tr>
<td>Caregiver burden self-assessment questionnaire</td>
</tr>
<tr>
<td>Caregiver stress level(^e)</td>
</tr>
<tr>
<td>Current health(^f)</td>
</tr>
</tbody>
</table>

\(^a\)Scores range from zero to 30, with 26 and higher considered normal. 22 indicates MCI, and 16 or below indicates dementia.

\(^b\)Total score is out of 120, higher scores indicating more complaints.

\(^c\)Cutoff score for impairment in neurodegenerative diseases is 2 out of 10 trials in either nostril.

\(^d\)14 is normal.

\(^e\)1 = not stressful; 10 = extremely stressful.

\(^f\)1 = very healthy; 10 very ill.

IADL, instrumental activities of daily living; L, left; MCI, mild cognitive impairment; PSM, Physical Self-Maintenance Scale; R, right; WMQ, Working Memory Questionnaire.
PBM for Depression and PTSD

Behavioral and Brain Functions

Research

Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety

Fredric Schiffer*1, Andrea L Johnston3, Caitlin Ravichandran2, Ann Polcari1, Martin H Teicher1, Robert H Webb3,4 and Michael R Hamblin3,4,5
Clinical Study

Near-Infrared Transcranial Radiation for Major Depressive Disorder: Proof of Concept Study

Paolo Cassano,¹ Cristina Cusin,¹ David Mischoulon,¹ Michael R. Hamblin,² Luís De Taboada,³ Angela Pisoni,¹ Trina Chang,¹ Albert Yeung,¹ Dawn F. Ionescu,¹ Samuel R. Petrie,¹ Andrew A. Nierenberg,¹ Maurizio Fava,¹ and Dan V. Iosifescu¹,⁴
A Novel Treatment of Opioid Cravings with an Effect Size of .73 for Unilateral Transcranial Photobiomodulation over Sham

Fredric Schiffer1*, William Reichmann2, Edward Flynn3, Michael R. Hamblin4, Hannah Mccormack3

Table 4. Comparison of Clinically Meaningful Improvement in Mean OCS Between Active and Sham Treatment One Week After Treatment. All Randomized Patients with Complete Data

<table>
<thead>
<tr>
<th></th>
<th>Active (n=17)</th>
<th>Sham (n=17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with decrease in OCS of</td>
<td>9 (52.9%)</td>
<td>3 (17.6%)</td>
<td>0.0289</td>
</tr>
</tbody>
</table>
Devices for transcranial PBM (published)
Photobiomodulation improves the frontal cognitive function of older adults

Agnes S. Chan¹,² | Tsz Lok Lee¹ | Michael K. Yeung¹ | Michael R. Hamblin³,⁴,⁵

SRT = Simple Reaction Time Task
CF Task = Category Fluency Task
Flanker = Erikson flanker test

Congruent
Incongruent
Erikson flanker test results

Control (N = 15)          Experimental (N = 15)          Control (N = 15)          Experimental (N = 15)

Congruent

Incongruent

RT (ms)

Baseline

Post-intervention
Category fluency test results

Change in the Total Number of Unique Words Produced (%)

Control (N = 15)  Experimental (N = 15)
Photoneuromodulation makes a difficult cognitive task less arduous

Agnes S. Chan1,2, Tsz Lok Lee1 & Michael R. Hamblin3,4

A real (or sham) single PBM session (810 nm, CW LED, 8 min, 28.8 J/cm2, 144 J) was administered to the forehead in the experimental (or control) group. Before and after the stimulation, all participants performed an n-back task with 0- and 3-back conditions, and their hemodynamic responses during the tasks were measured using NIRS.
Only minor changes in memory performance
Significantly lower blood flow
Photoneuromodulation Improves Memory, Mental State and Functional Abilities in Amnesic Mild Cognitive Impairment: Three Case Reports

Agnes S. Chan, Ph.D.,*1,2 , Sophia Sze, Ph.D.,1,2 , Tsz Lok Lee, Ph.D.,1 , Michael R. Hamblin, Ph.D. 3,4,5

Three patients (mean age = 62) received 18-sessions of PNM stimulation, twice per week for nine weeks. PNM (810 nm, CW LED, 8 min, 28.8 J/cm², 144 J) was delivered using a device placed across the forehead of the patients.

![Graph showing improvement in visual and verbal memory before and after PNM stimulation for patients P1, P2, and P3.](image-url)
Common pathways in neurodegenerative and psychiatric disease

- Neuroinflammation
- Oxidative Stress
- Excitotoxicity
- Mitochondrial Dysfunction
- Neuronal Apoptosis
- Low BDNF
- Impaired Neurogenesis
- Hippocampal Shrinkage
- Impaired Synaptogenesis
- Cortical Shrinkage
- Alzheimer’s
- Parkinson’s
- Depression
- Post traumatic stress disorder
- Bipolar Disorder
Neurodegenerative diseases
Alzheimer’s disease
Parkinson’s disease
Amyotrophic lateral sclerosis
Frontotemporal dementia
Vascular dementia
Lewy body dementia
Primary progressive aphasia
Chronic traumatic encephalopathy
Creutzfeldt–Jakob disease
Huntington's disease

Neurodevelopmental disorders
Autism (autism spectrum disorder)
Attention deficit hyperactivity disorder (ADHD)

Traumatic brain disorders
Acute stroke
Chronic stroke
Acute traumatic brain injury
Chronic traumatic brain injury
Global ischaemia (heart attack)
Birth trauma
Coma (vegetative state)

Psychiatric diseases
Major depressive disorder
Suicidal ideation
Major anxiety
Post traumatic stress disorder
Addiction
Insomnia

Neurodevelopmental disorders
Autism (autism spectrum disorder)
Attention deficit hyperactivity disorder (ADHD)
Conclusions

• Photobiomodulation has a history of over 100 years
• Mechanisms of PBM are becoming understood
• Animal studies of TBI
• Clinical studies – acute & chronic TBI, Alzheimer’s disease, depression, opioid addiction
• Clinical studies - cognitive enhancement
Acknowledgments