
# 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)

The Nobel Prize in Physiology or Medicine 1903
Niels Ryberg Finsen

## Niels Ryberg Finsen - Facts

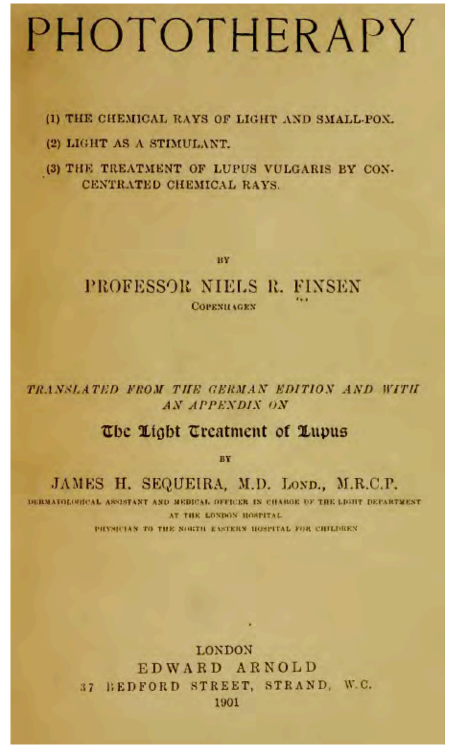
**Niels Ryberg Finsen**

**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"



PHOTOTHERAPY

(1) THE CHEMICAL RAYS OF LIGHT AND SMALL-POX.
(2) LIGHT AS A STIMULANT.
(3) THE TREATMENT OF LUPUS VULGARIS BY CONCENTRATED CHEMICAL RAYS.

BY

PROFESSOR NIELS R. FINSEN
COPENHAGEN

*TRANSLATED FROM THE GERMAN EDITION AND WITH AN APPENDIX ON*

The Light Treatment of Lupus

BY

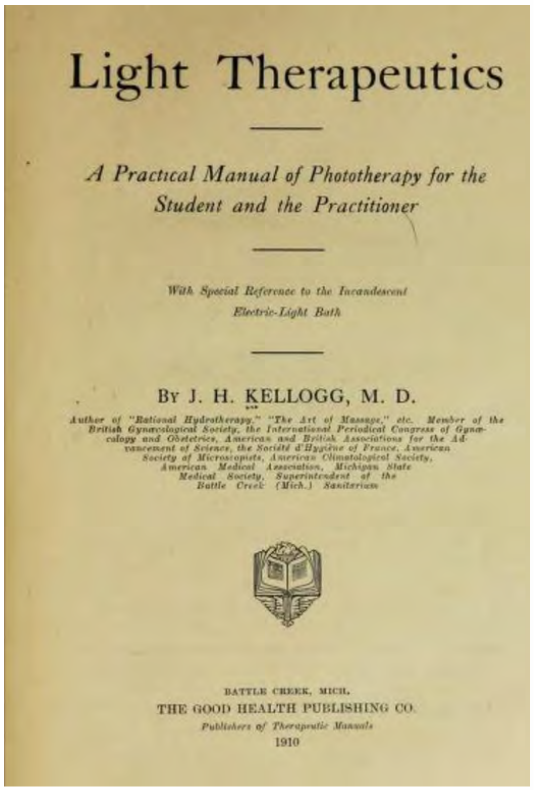
JAMES H. SEQUEIRA, M.D. LOND., M.R.C.P.
DERMATOLOGICAL ASSISTANT AND MEDICAL OFFICER IN CHARGE OF THE LIGHT DEPARTMENT AT THE LONDON HOSPITAL
PHYSICIAN TO THE NORTH EASTERN HOSPITAL FOR CHILDREN

LONDON
EDWARD ARNOLD
37 BEDFORD STREET, STRAND, W.C.
1901

## 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)


Light Therapeutics

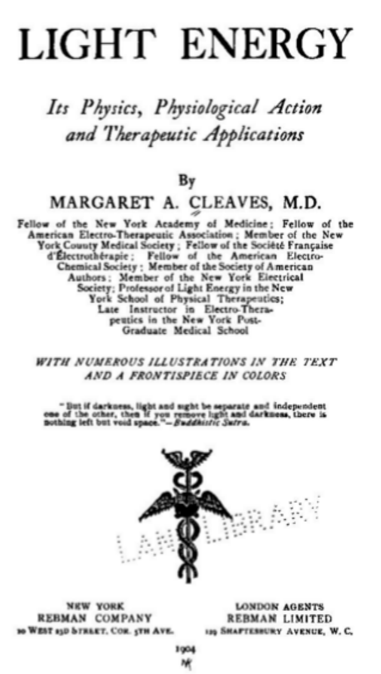
*A Practical Manual of Phototherapy for the Student and the Practitioner*

*With Special Reference to the Incandescent Electric-Light Bath*

BY J. H. KELLOGG, M. D.

*Author of "Rational Hydrotherapy," "The Art of Massage," etc. Member of the British Gynæcological Society, the International Periodical Congress of Gynæcology and Obstetrics, American and British Associations for the Advancement of Science, the Société d'Hygiène of France, American Society of Microscopists, American Climatological Society, American Medical Association, Michigan State Medical Society, Superintendent of the Battle Creek (Mich.) Sanitarium*

BATTLE CREEK, MICH.
THE GOOD HEALTH PUBLISHING CO.
*Publishers of Therapeutic Manuals*
1910


LIGHT ENERGY

*Its Physics, Physiological Action and Therapeutic Applications*

By
MARGARET A. CLEAVES, M.D.

Fellow of the New York Academy of Medicine; Fellow of the American Electro-Therapeutic Association; Member of the New York County Medical Society; Fellow of the Société Française d'Électrothérapie; Fellow of the American Electro-Chemical Society; Member of the Society of American Authors; Member of the New York Electrical Society; Professor of Light Energy in the New York School of Physical Therapeutics; Late Instructor in Electro-Therapeutics in the New York Post-Graduate Medical School

*WITH NUMEROUS ILLUSTRATIONS IN THE TEXT AND A FRONTISPIECE IN COLORS*

"But if darkness, light and sight be separate and independent one of the other, then if you remove light and darkness, there is nothing left but void space."—*Buddhistic Sutra.*

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LONDON AGENTS
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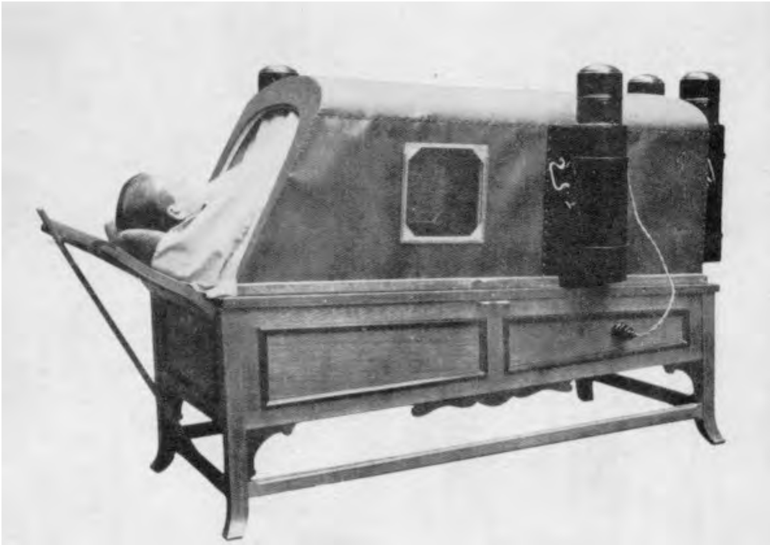
1904

Fig. 15. The Sun Bath. See page 74.

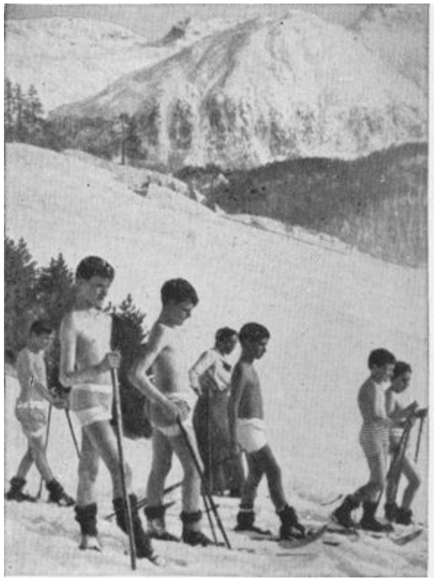
CHAPTER X.

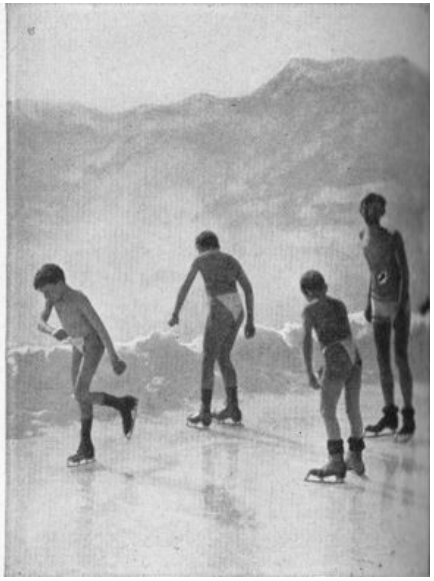
# Electric light baths – John Harvey Kellog

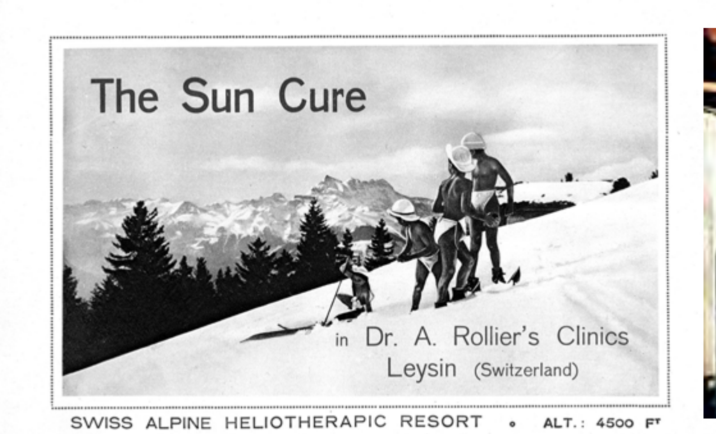




# Auguste Rollier & Heliotherapy





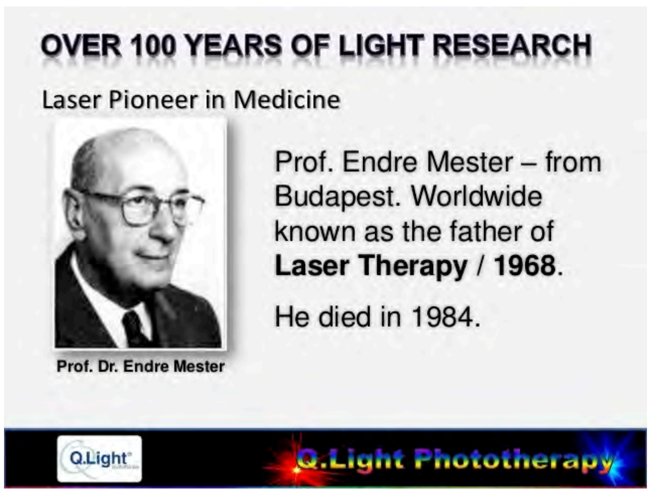




Rollier regarded exposure to the sun at temperatures above 18°C as a "hot-air bath" and not a “sunbath”

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.
McGuff PE, Deterling RA Jr, Gottlieb LS. N Engl J Med. 1965 Aug 26;273(9):490-2.

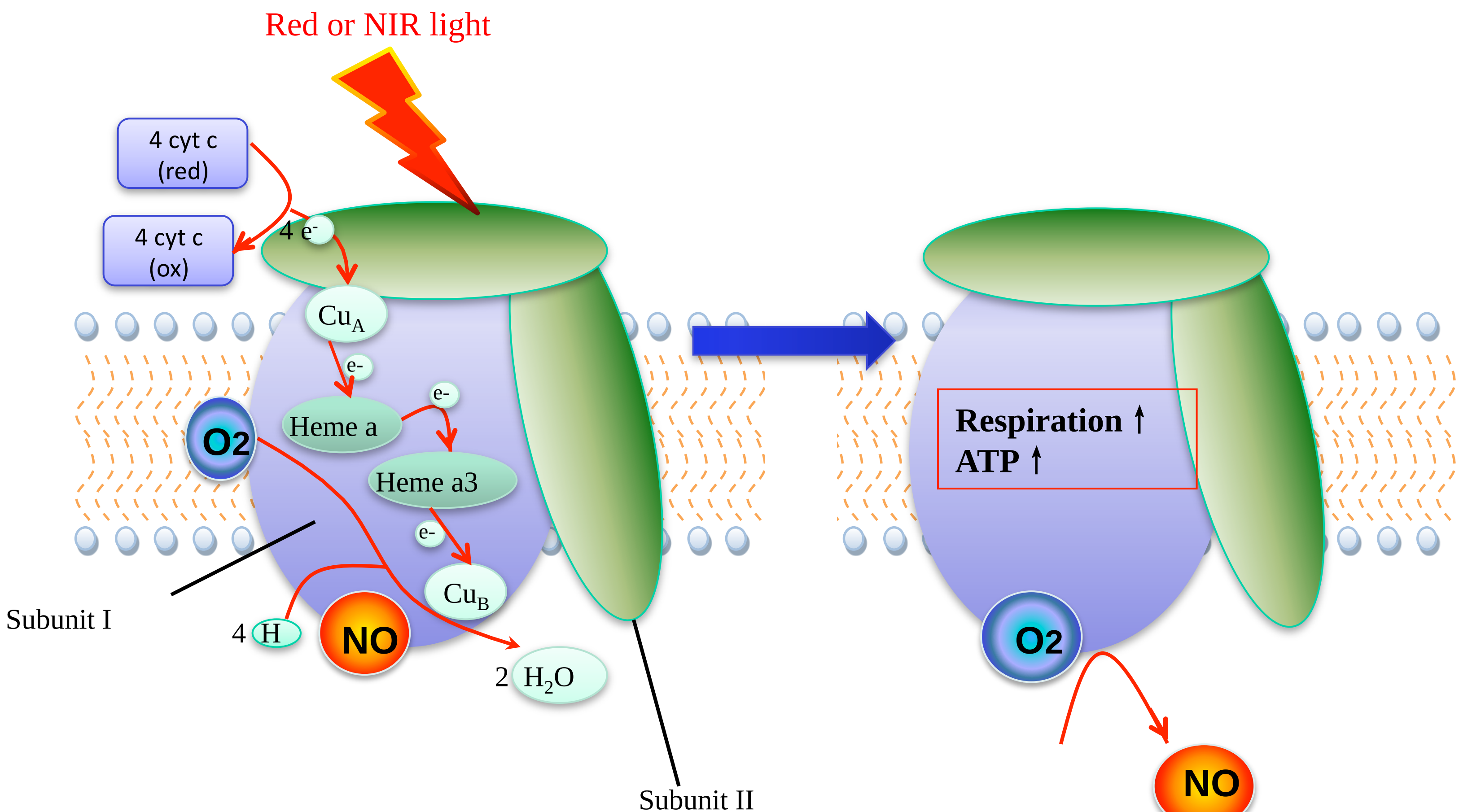

- ➢Developed an interest in laser research in 1965 and obtained a ruby laser
- ➢Attempted to repeat Paul McGuff's anti-tumor laser treatment
- ➢ When this failed, tried to see if laser treatment could cause skin cancer in mice
- ➢Observed increased hair growth and better wound healing (but no cancer)

# 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

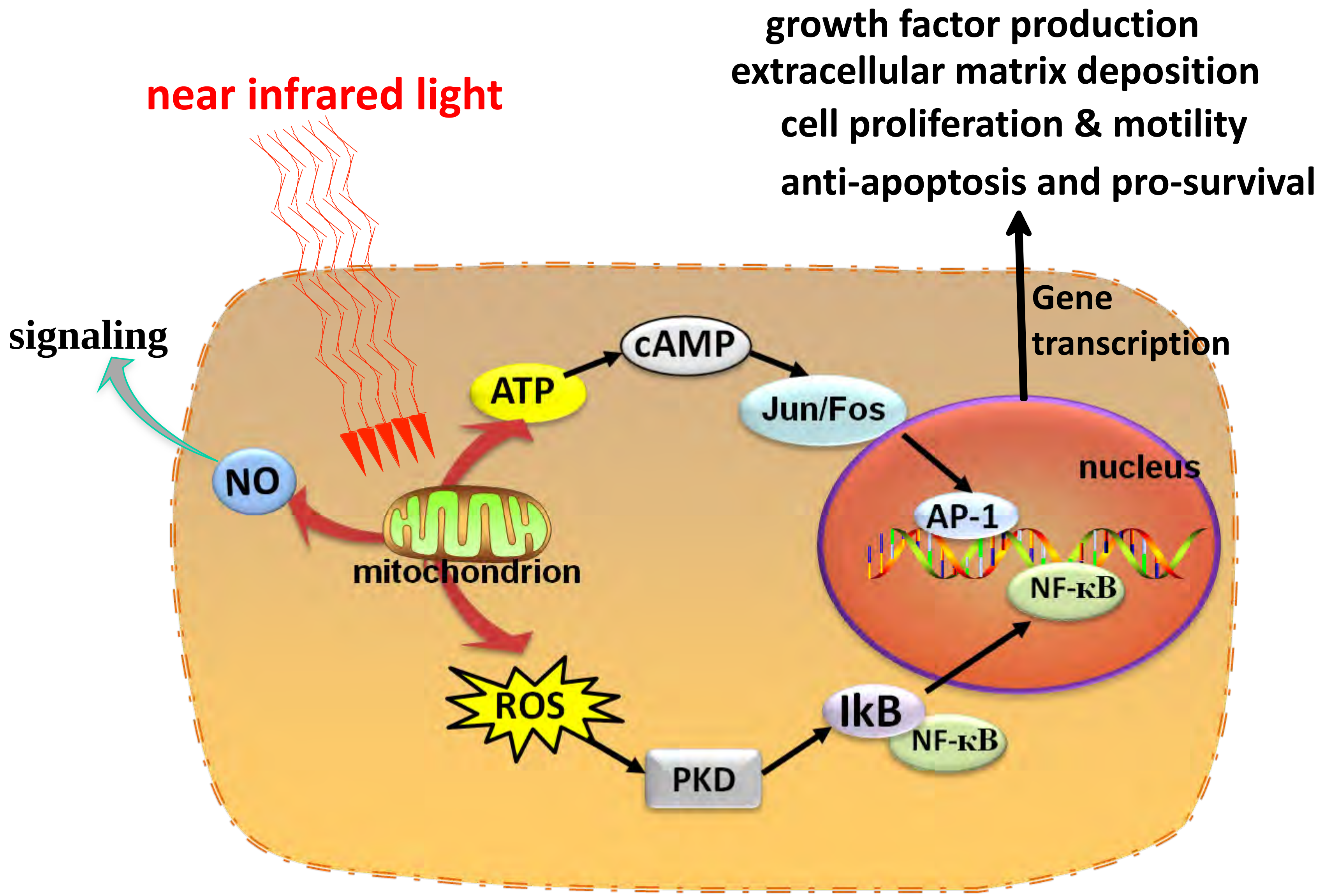
It is called "LOW" because a little light is better than a lot of light




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

Glycolysis >>>>> Oxidative phosphorylation

# Signaling based on mitochondrial stimulation



## Two major effects of mitochondrial switch

Glycolysis >>>>> Oxidative phosphorylation

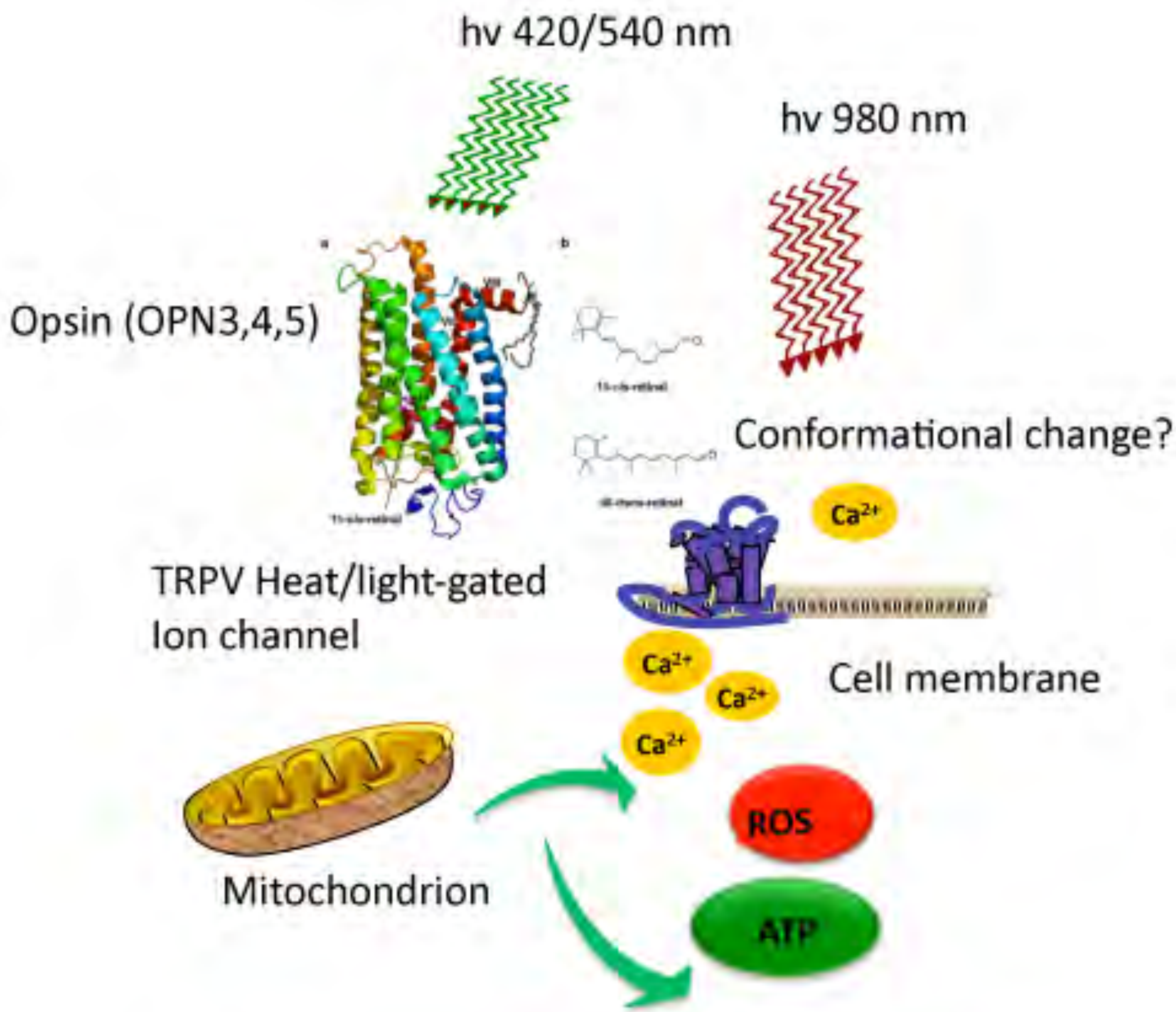
### 1. Activation of stem cells

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

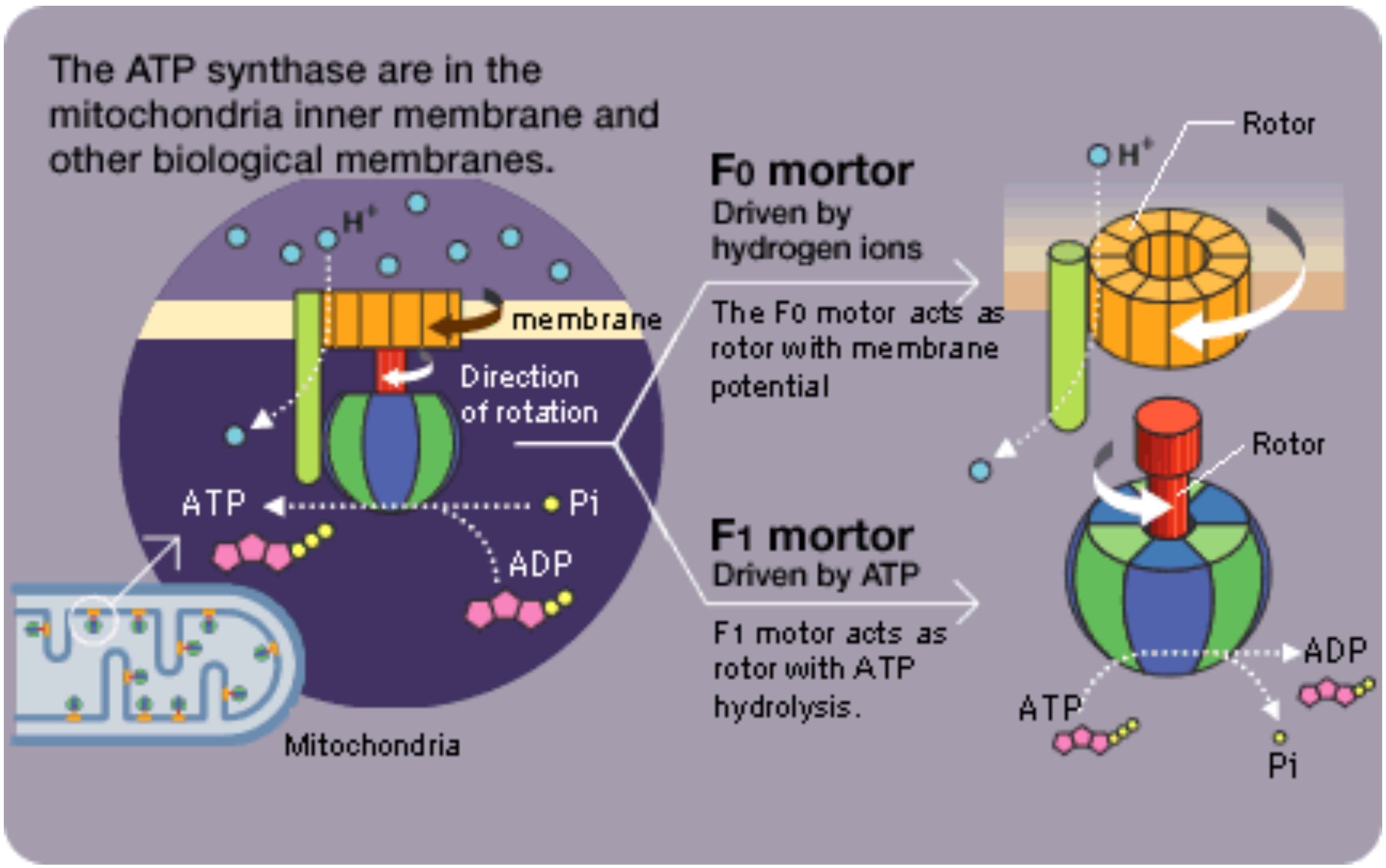
### 2. Anti-inflammatory

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



Received: 29 July 2019 | Revised: 27 November 2019 | Accepted: 29 November 2019
DOI: 10.1096/fj.201901917RR

RESEARCH ARTICLE

FASEB JOURNAL

# Blood contains circulating cell-free respiratory competent mitochondria

Zahra Al Amir Dache[1] | Amaëlle Otandault[1] | Rita Tanos[1] | Brice Pastor[1] | Romain Meddeb[1] | Cynthia Sanchez[1] | Giuseppe Arena[2] | Laurence Lasorsa[1] | Andrew Bennett[3] | Thierry Grange[3] | Safia El Messaoudi[1] | Thibault Mazard[1] | Corinne Prevostel[1] | Alain R. Thierry[1]

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.

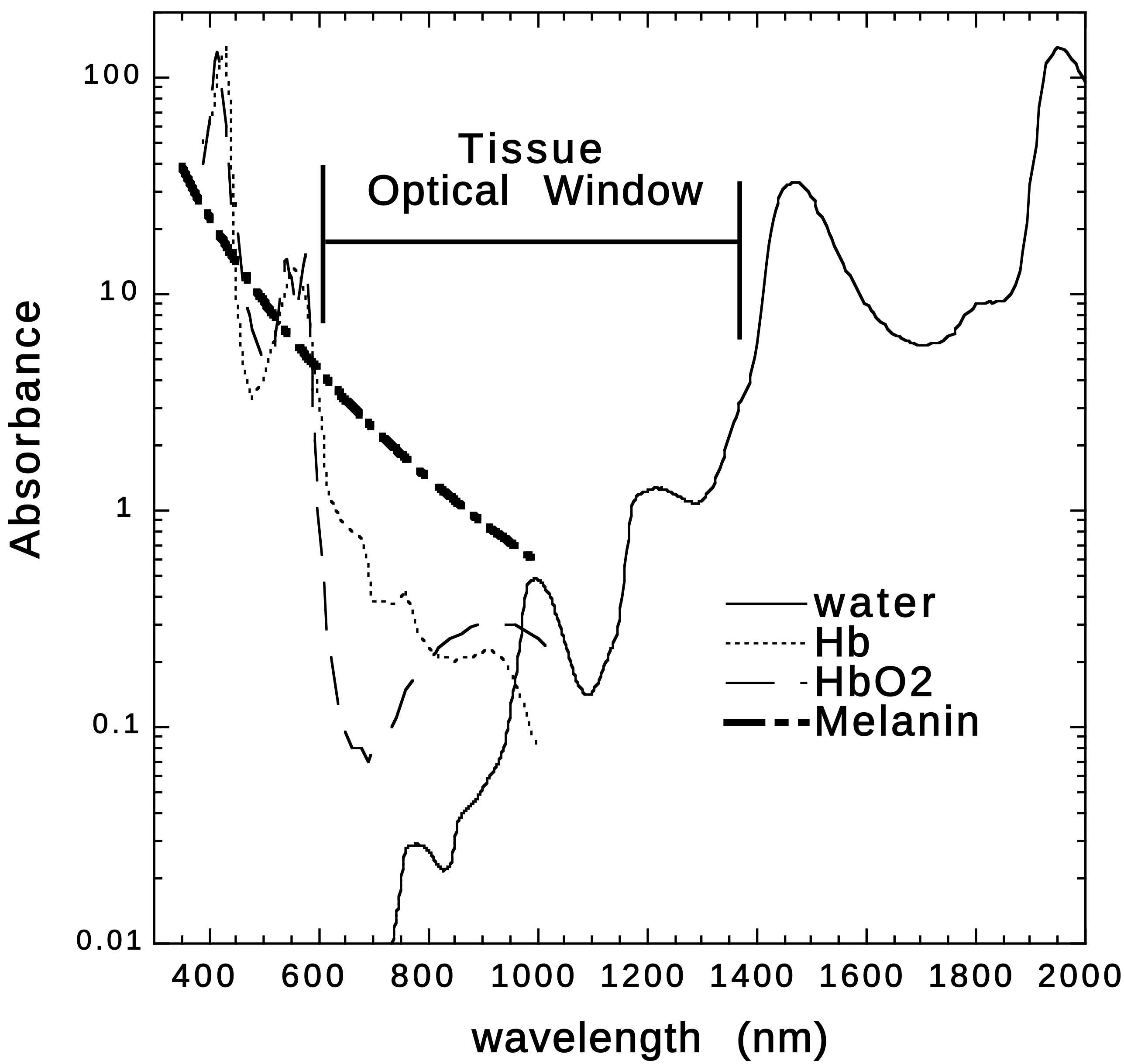
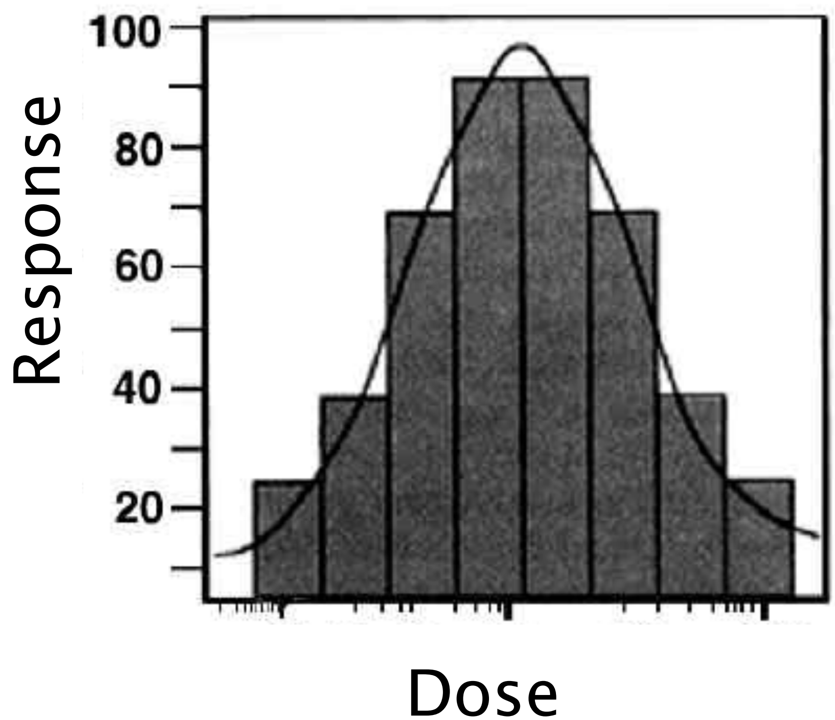

Tissue
Optical Window
water
Hb
HbO2
Melanin
100
10
1
0.1
0.01
Absorbance
400
600
800
1000
1200
1400
1600
1800
2000
wavelength (nm)

Figure 1

# Biphasic dose response?




*Dose-Response*, 7:358–383, 2009
*Formerly Nonlinearity in Biology, Toxicology, and Medicine*
Copyright © 2009 University of Massachusetts
ISSN: 1559-3258
DOI: 10.2203/dose-response.09-027.Hamblin

International Dose-Response Society

**BIPHASIC DOSE RESPONSE IN LOW LEVEL LIGHT THERAPY**

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**Aaron C.-H. Chen** □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Boston University School of Medicine, Graduate Medical Sciences, Boston, MA

**James D. Carroll** □ THOR Photomedicine Ltd, 18A East Street, Chesham, HP5 1HQ, UK

**Michael R. Hamblin** □ Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA; Department of Dermatology, Harvard Medical School, Boston, MA; Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA

# 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

STROKE
TBI

**Oxygen**
Hyperbaric oxygen
Oxygenated fluorocarbon
Oxygen supplementation

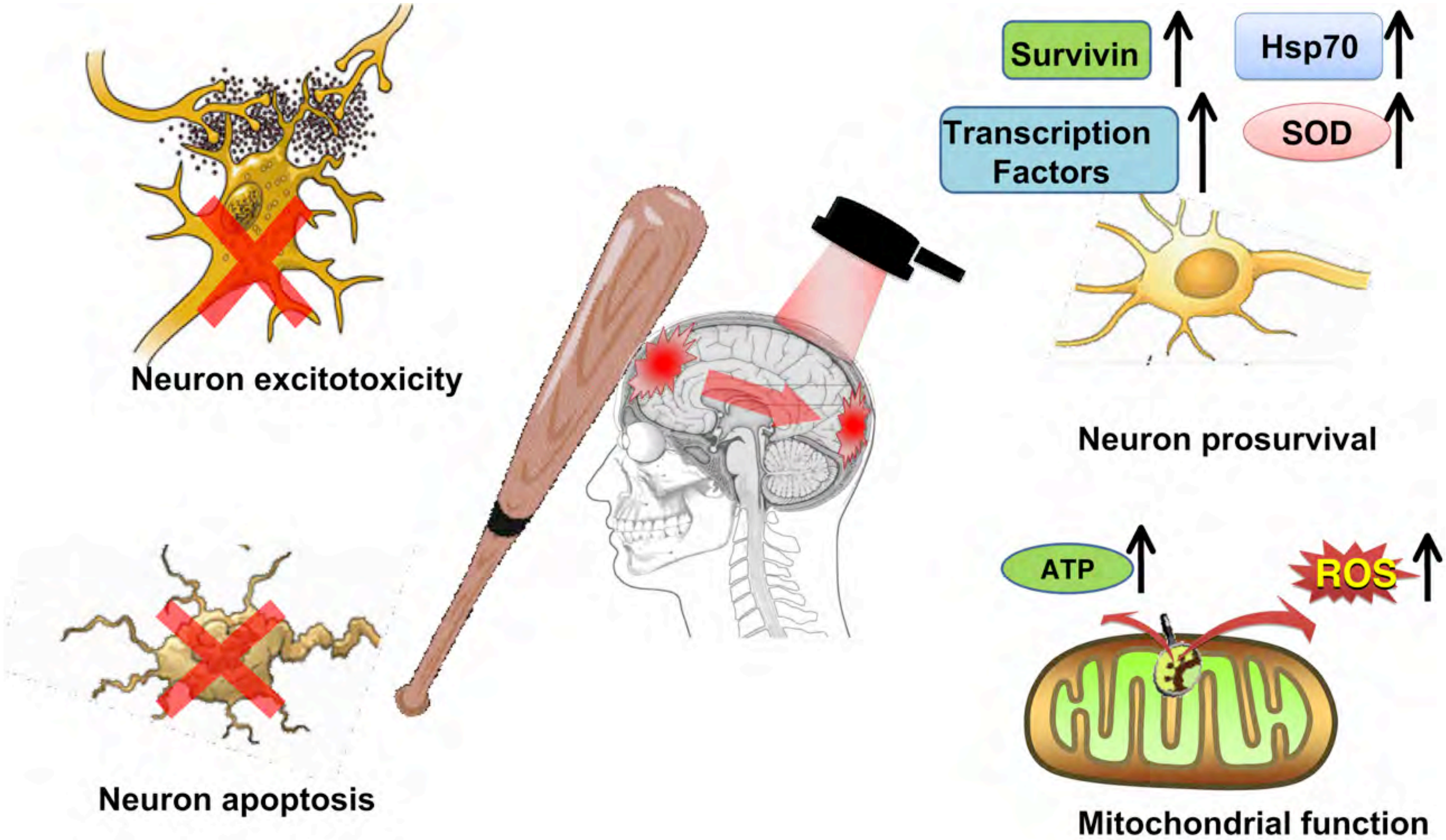
**Metabolism**
Ganglioside , Astrocyte modulator
Beta blocker,CNS stimulant
Phosphatidylcholine precursor
Fibroblast growth factor
Opioid antagonist
Prostanoid , Statin

**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

**Qiuhe Wu, MD, PhD,[1,2,3] Weijun Xuan, MD, PhD,[1,2,4] Takahiro Ando, MS,[1,5] Tao Xu, MD, PhD,[1,2,6] Liyi Huang, MD, PhD,[1,2,7] Ying-Ying Huang, MD,[1,2,8] Tianghong Dai, PhD,[1,2] Saphala Dhital, PhD,[1,9] Sulbha K. Sharma, PhD,[1] Michael J. Whalen, MD,[10] and Michael R. Hamblin, PhD[1,2,11]***

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[4]*Department of Otolaryngology, Traditional Chinese Medical University of Guangxi, Nanning, China*
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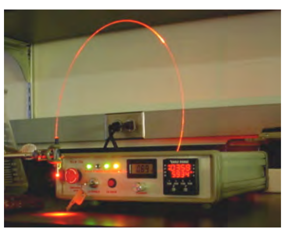
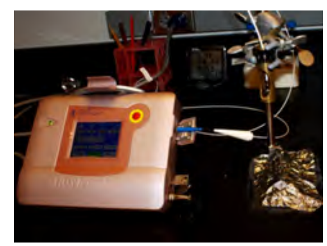
[7]*Department of Infectious Diseases, First Affiliated College & Hospital, Guangxi Medical University, Nanning, China*
[8]*Aesthetic and Plastic Center of Guangxi Medical University, Nanning, China*
[9]*Department of Microbiology, University of Tokyo, Tokyo, Japan*
[10]*Department of Pediatrics, Massachusetts General Hospital, Boston, Massachusetts*
[11]*Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts*



**665-nm laser**


**732nm Laser**


**810-nm laser**



**980-nm laser**

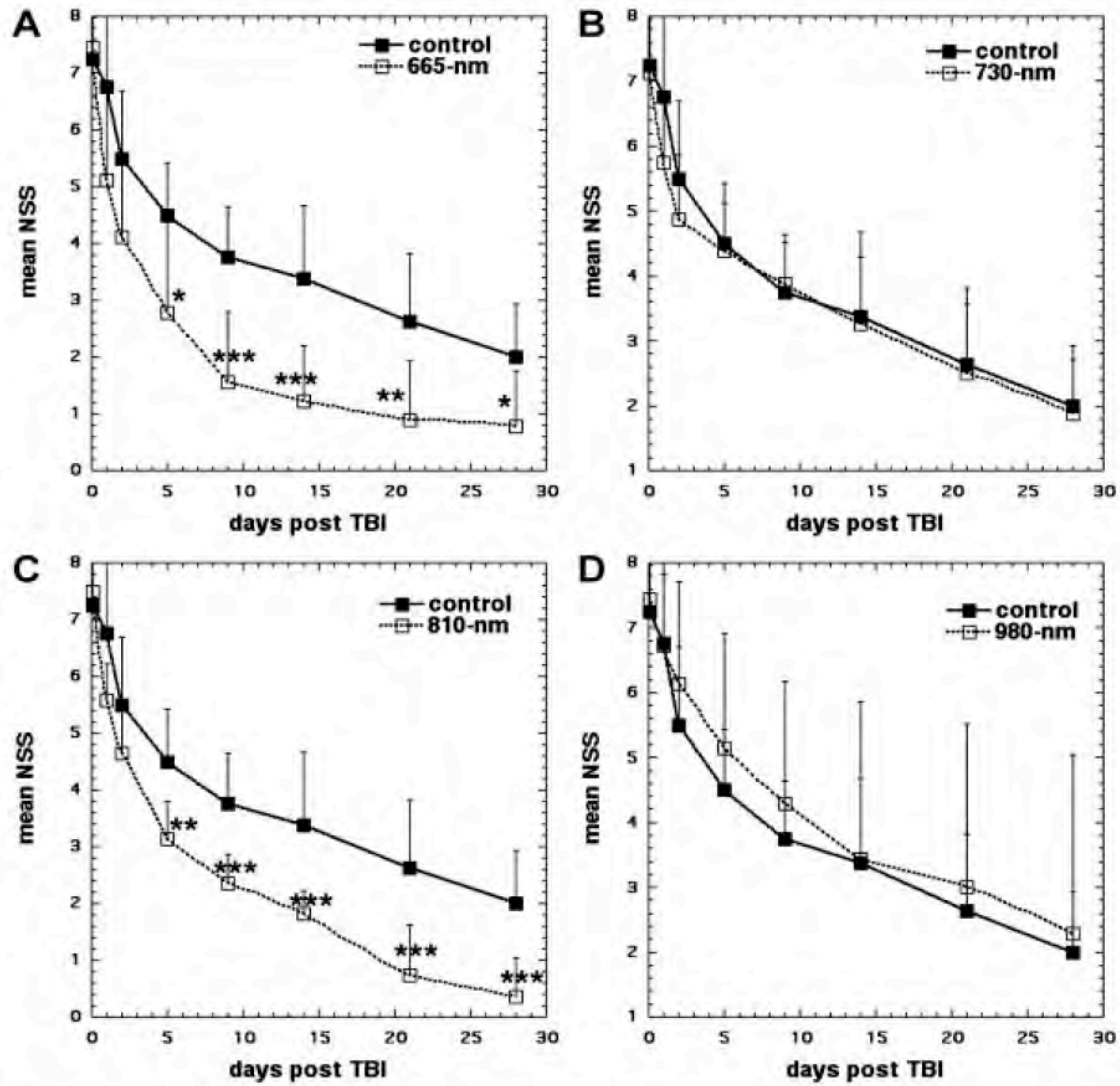


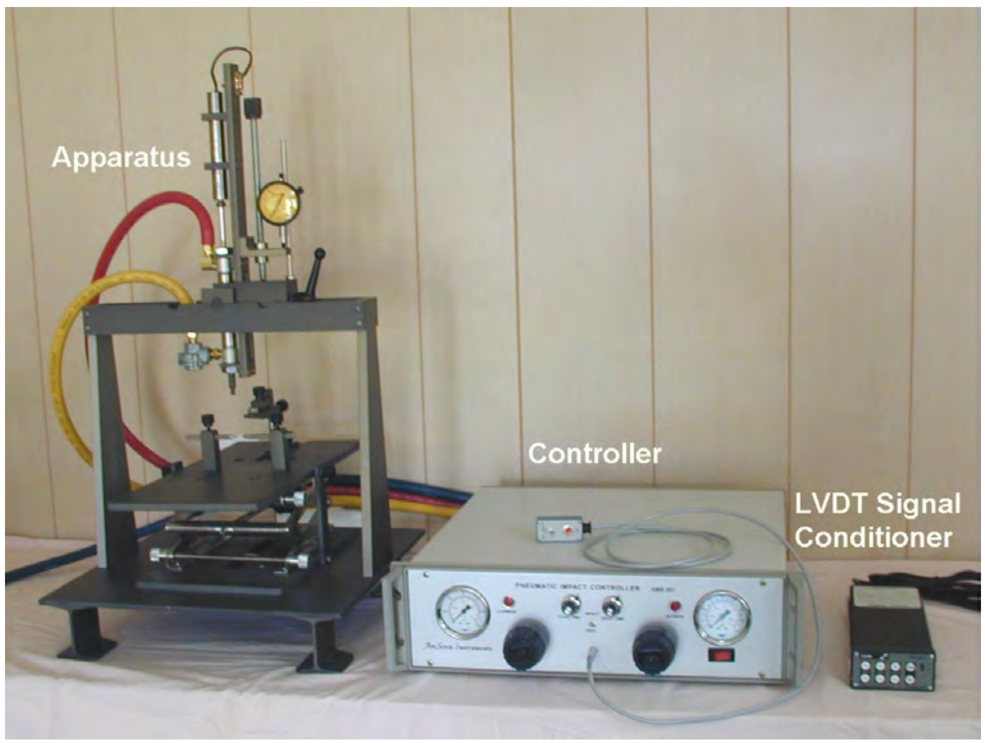

Fig. 2. Time course of NSS scores of sham and laser-treated mice. **A**: Sham-treated control versus 665 nm laser. **B**: Sham-treated control versus 730 nm laser. **C**: Sham-treated control versus 810 nm laser. **D**: Sham-treated control versus 980 nm laser. Points are means of 8–12 mice and bars are SD. $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ (one-way ANOVA).

OPEN ACCESS Freely available online

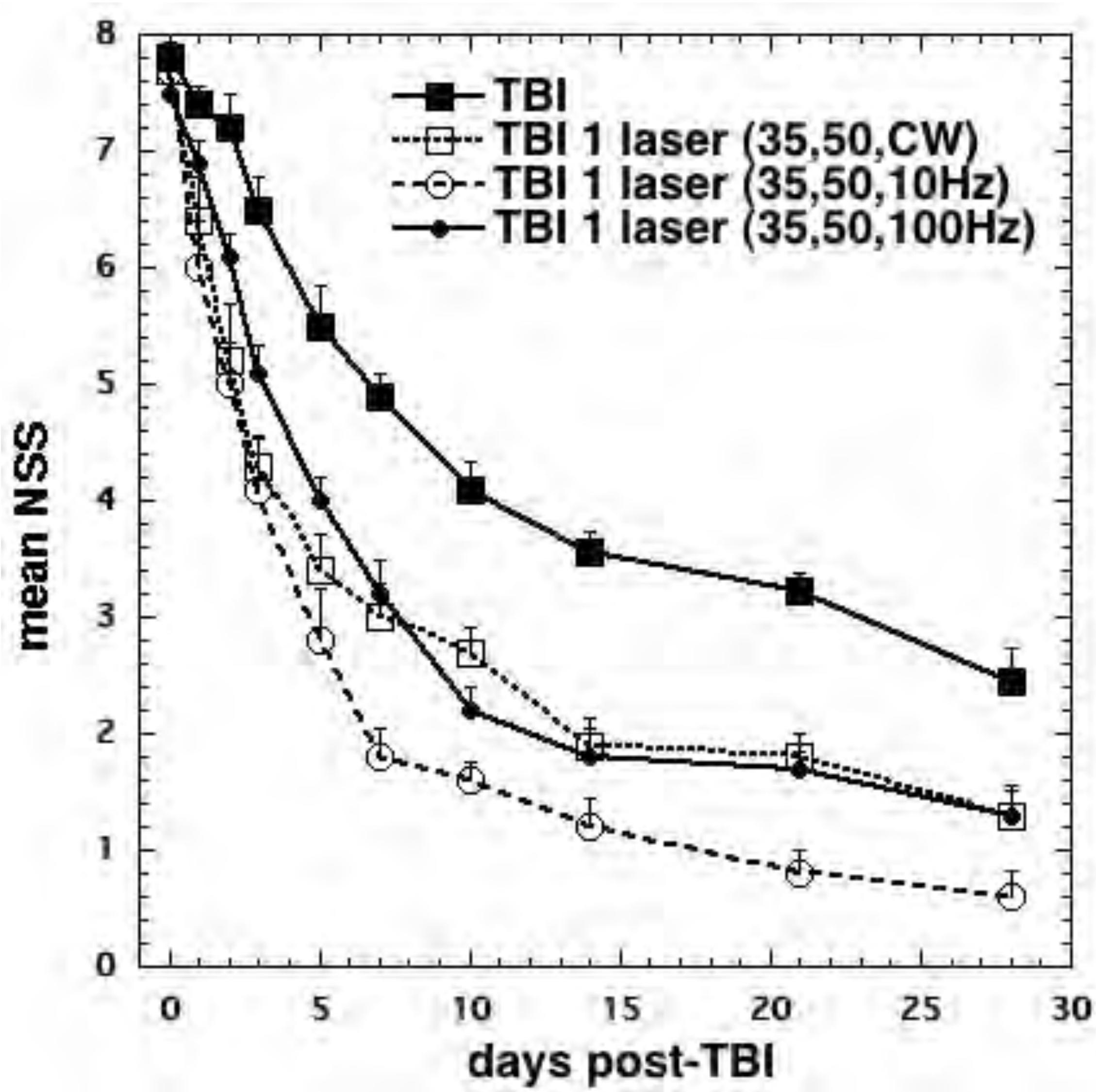
PLoS one

# Comparison of Therapeutic Effects between Pulsed and Continuous Wave 810-nm Wavelength Laser Irradiation for Traumatic Brain Injury in Mice

Takahiro Ando[1,2], Weijun Xuan[1,3,4], Tao Xu[1,3,5], Tianhong Dai[1,3], Sulbha K. Sharma[1], Gitika B. Kharkwal[1,3], Ying-Ying Huang[1,3,6], Qiuhe Wu[1,3,7], Michael J. Whalen[8], Shunichi Sato[9], Minoru Obara[2], Michael R. Hamblin[1,3,10*]



A single laser Tx of 36 J/cm$^2$ at 50 mW/cm$^2$ pulsed at 10 Hz is better than CW or 100 Hz

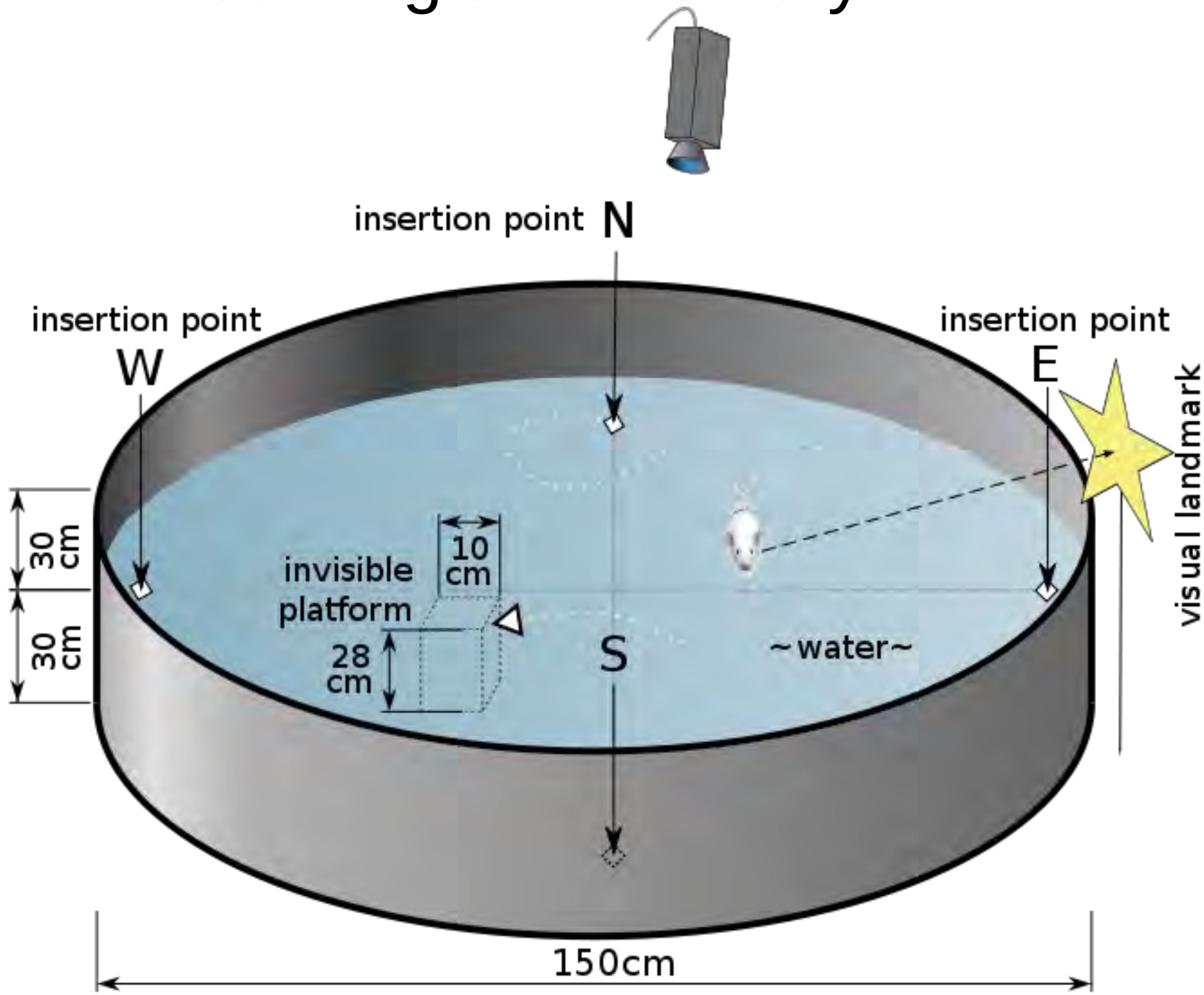


# Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice

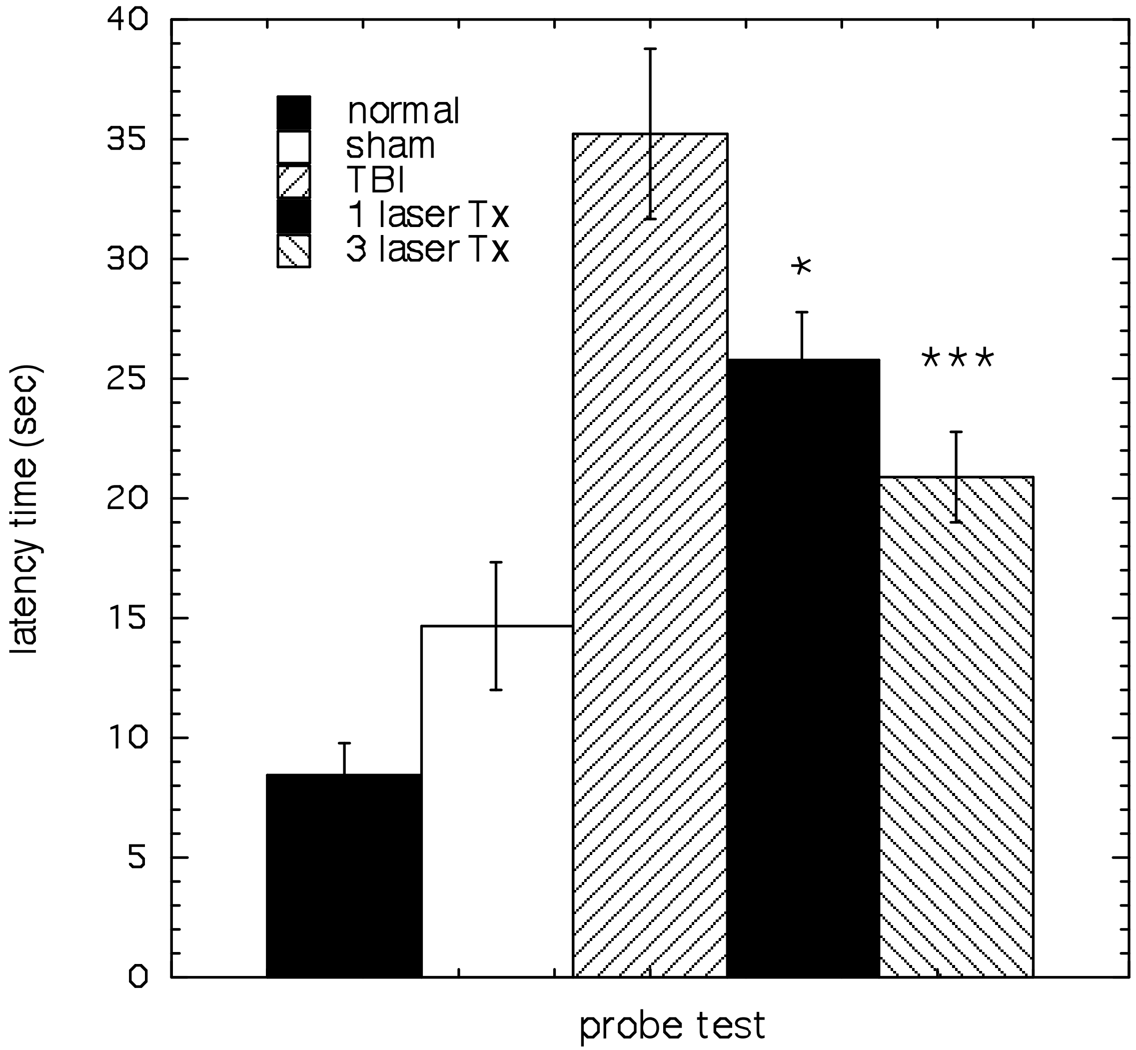
**Weijun Xuan,**[a,b,c,†] **Fatma Vatansever,**[b,c,†] **Liyi Huang,**[b,c,d] **and Michael R. Hamblin**[b,c,e,*]
[a]Ruikang Hospital Affiliated to Guangxi University of Chinese Medicine, Department of Otolaryngology, Nanning 530021, China
[b]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, Massachusetts 02114, United States
[c]Harvard Medical School, Department of Dermatology, Boston, Massachusetts 02115, United States
[d]Guangxi Medical University, First Affiliated College and Hospital, Department of Infectious Diseases, Nanning 530021, China
[e]Harvard-MIT Division of Health Sciences and Technology, Cambridge, Massachusetts 02139, United States

**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.19.10.108003]

# Morris water maze for spatial navigation, learning and memory



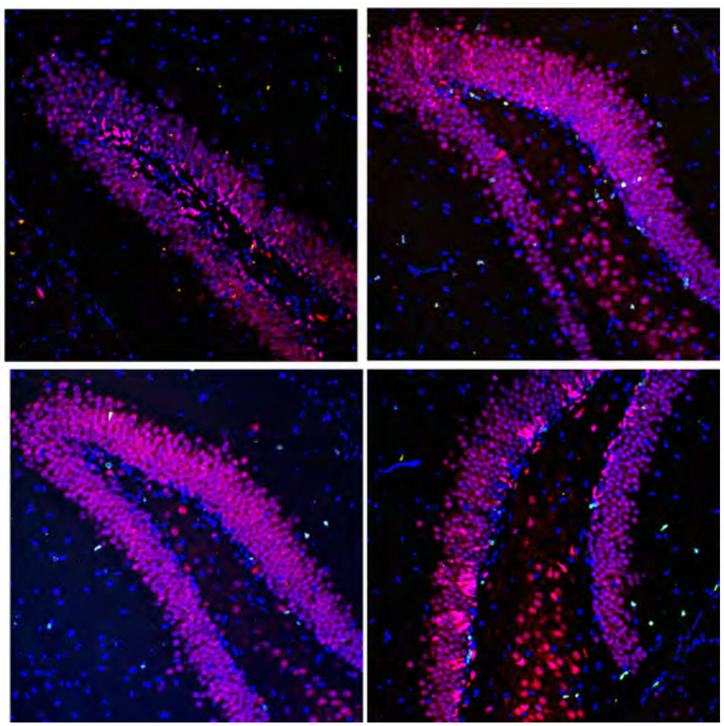
# Probe test: memory, learning



# BrdU-NeuN double staining in dentate gyrus

7 days

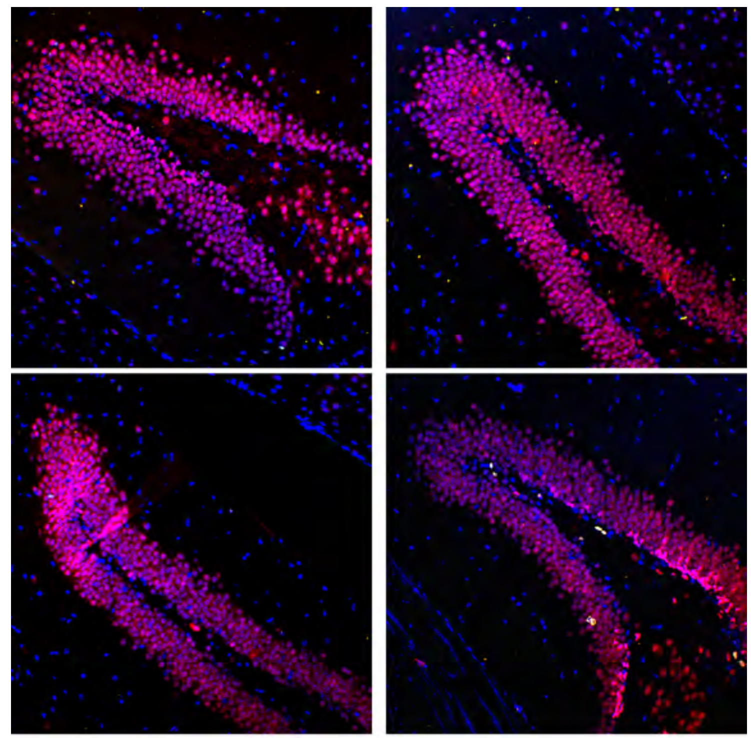
Sham TBI



1X PBM 3X PBM

28 days

Sham TBI



1X PBM 3X PBM

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citable using Digital Object Identifier – **DOI**)

J. Biophotonics 1–10 (2014) / **DOI** 10.1002/jbio.201400069

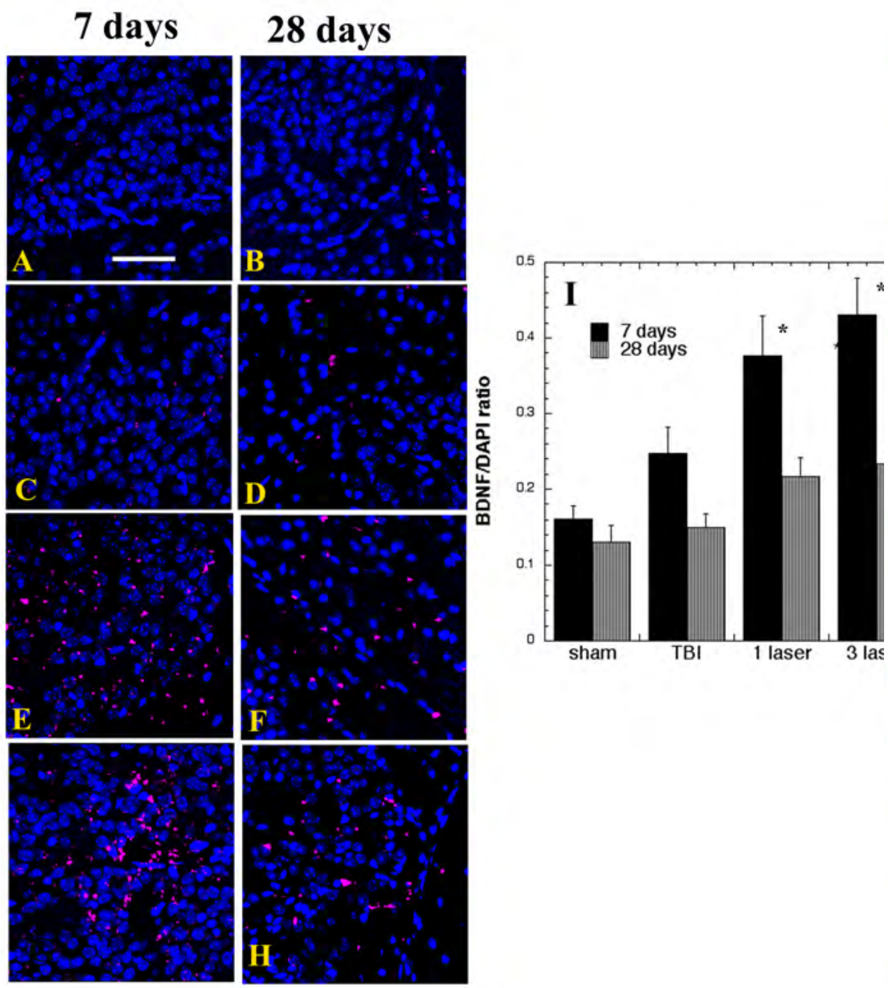
Journal of
BIOPHOTONICS

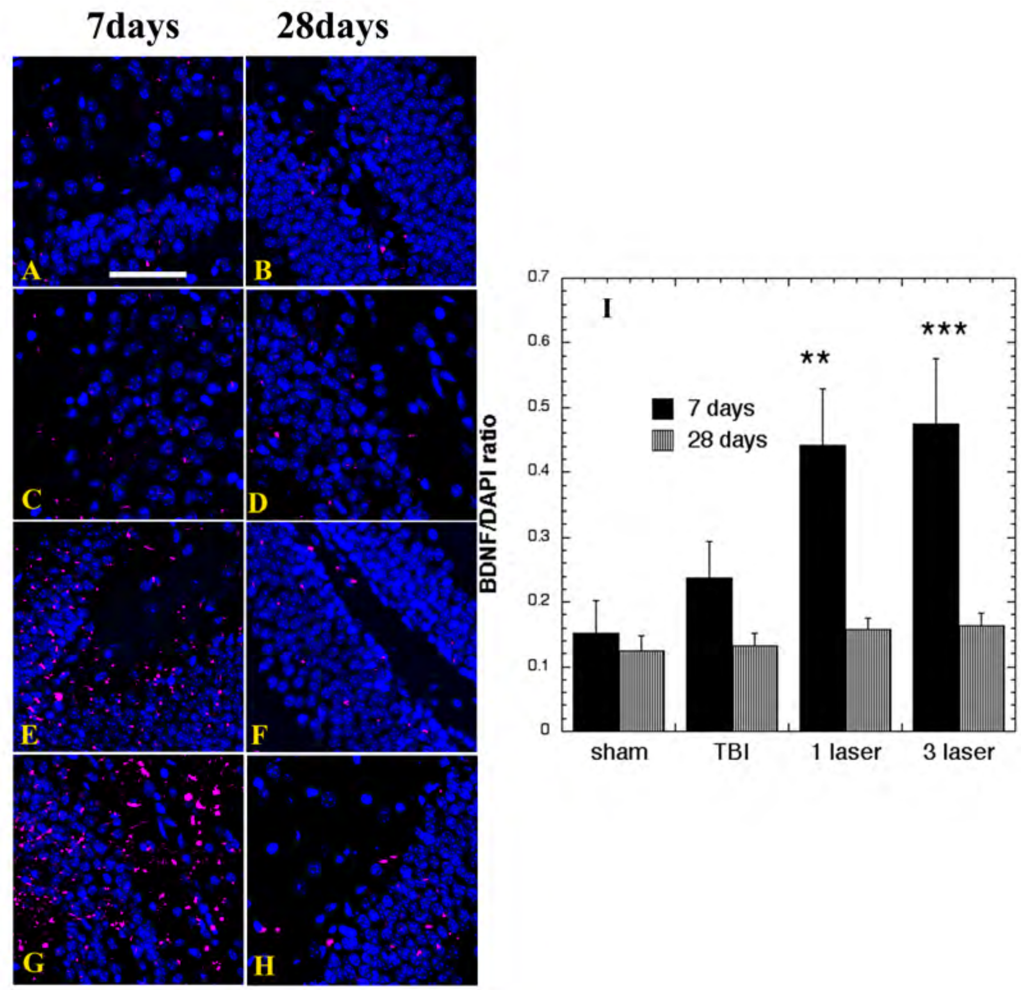
FULL ARTICLE

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

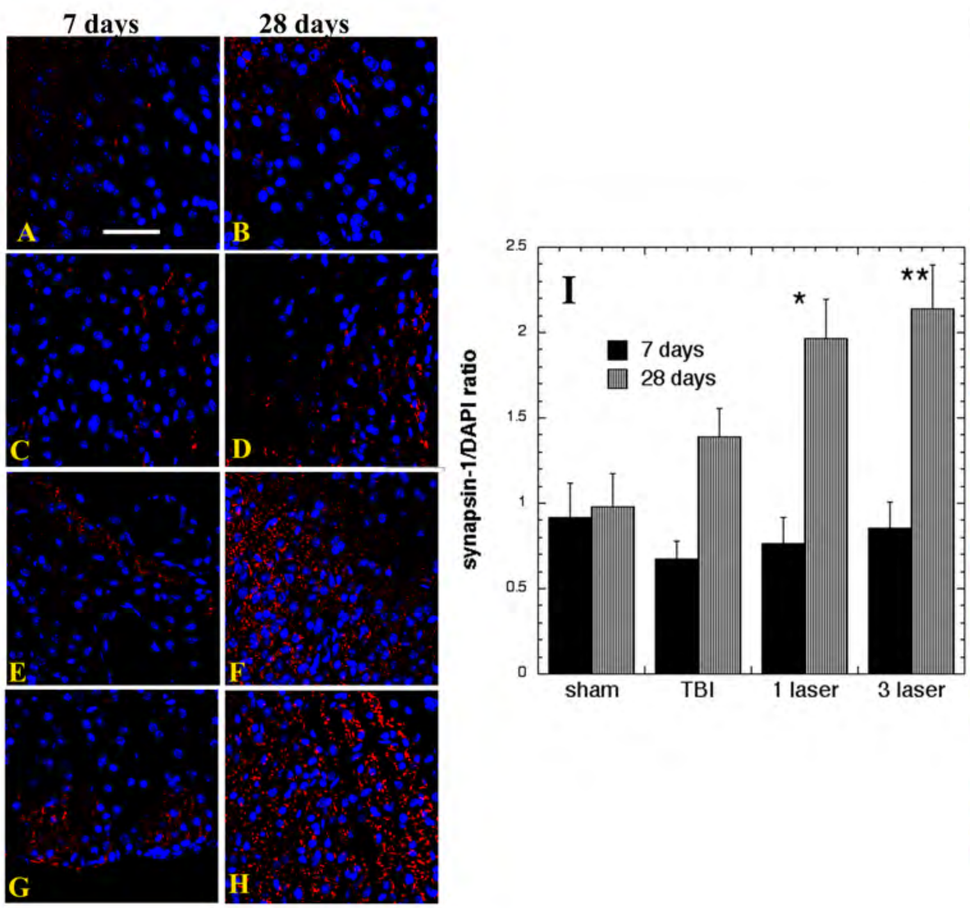
*Weijun Xuan*[†,1,2,3], *Tanupriya Agrawal*[†,1,2], *Liyi Huang*[2,4], *Gaurav K. Gupta*[2,5], *and Michael R. Hamblin*[*,1,2,6,7]

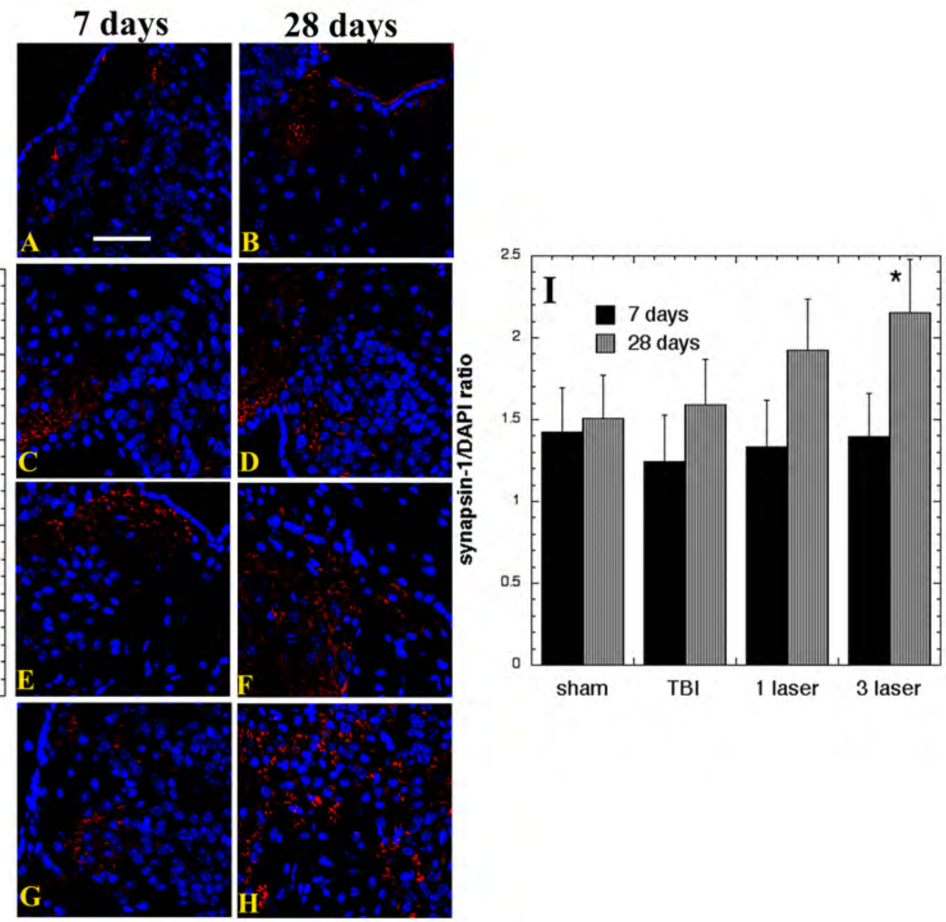
# Brain derived neurotrophic factor (BDNF) in SVZ and DG



# Synapsin-1 in perilesional cortex and SVZ



Journal of Cerebral Blood Flow & Metabolism (2014) 34, 1391–1401
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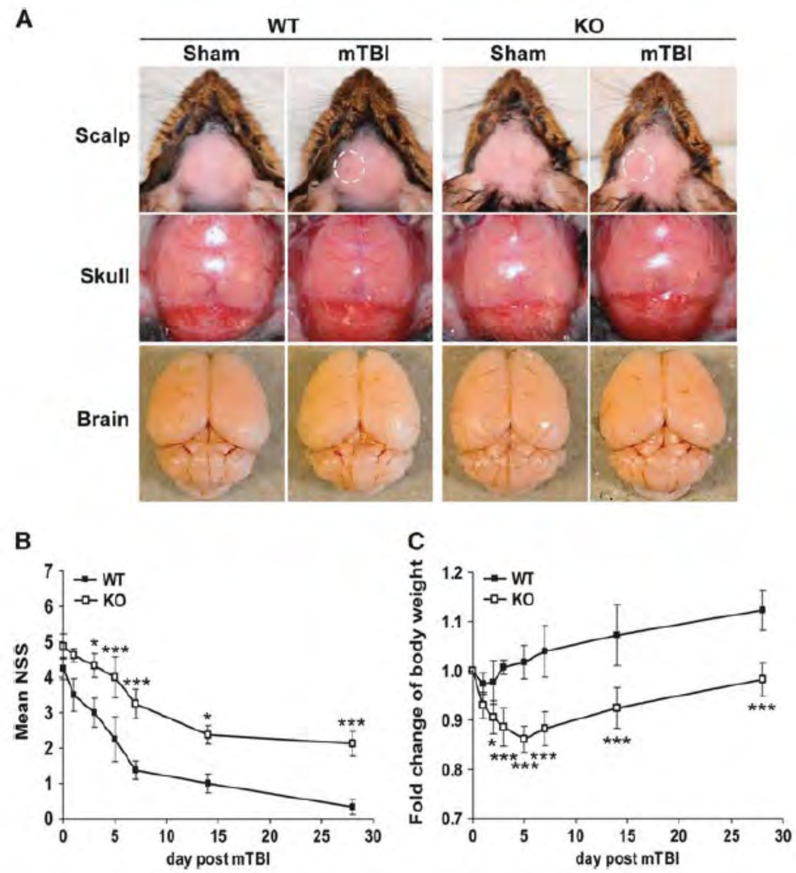
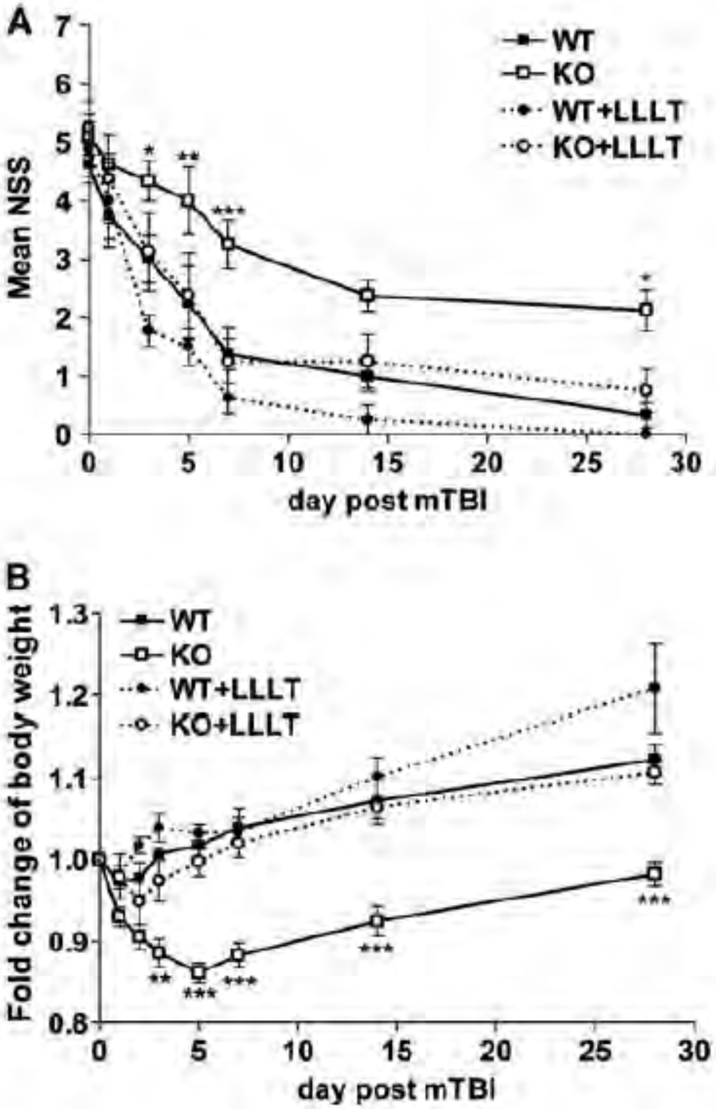
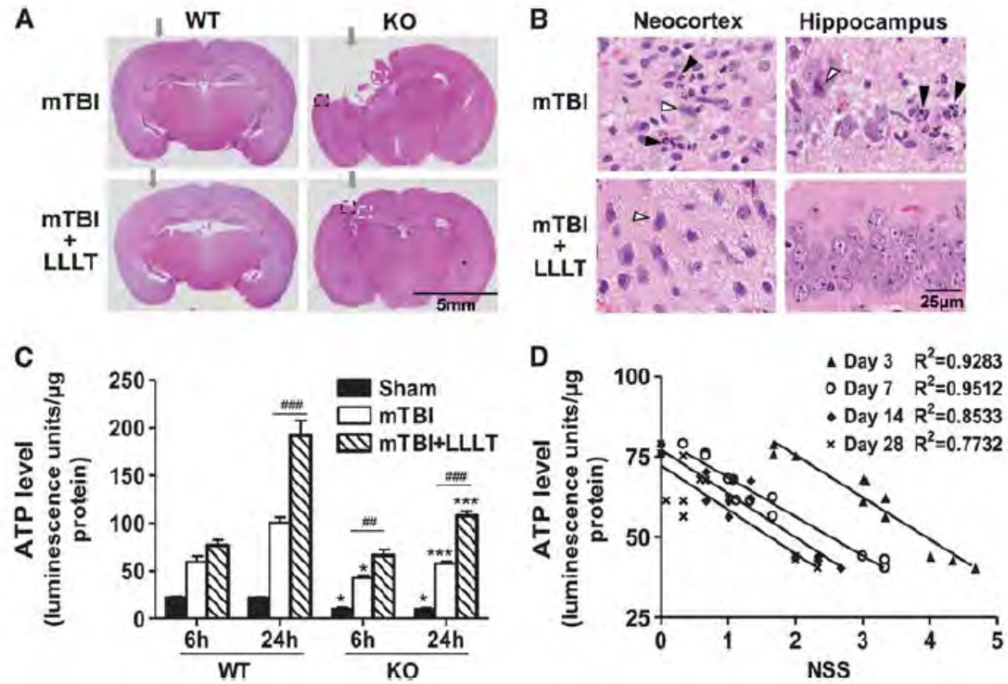
ORIGINAL ARTICLE

# Low-level laser therapy effectively prevents secondary brain injury induced by immediate early responsive gene X-1 deficiency

Qi Zhang[1,2], Chang Zhou[1,2], Michael R Hamblin[1,2,3] and Mei X Wu[1,2,3]




A
Mean NSS
day post mTBI
WT
KO
WT+LLLT
KO+LLLT
B
Fold change of body weight
day post mTBI
WT
KO
WT+LLLT
KO+LLLT


A
WT
KO
mTBI
mTBI + LLLT
5mm
B
Neocortex
Hippocampus
mTBI
mTBI + LLLT
25μm
C
ATP level (luminescence units/μg protein)
Sham
mTBI
mTBI+LLLT
6h
24h
WT
KO
D
ATP level (luminescence units/μg protein)
Day 3 R2=0.9283
Day 7 R2=0.9512
Day 14 R2=0.8533
Day 28 R2=0.7732
NSS

Journal of Cerebral Blood Flow & Metabolism (2015) 35, 1435–1444
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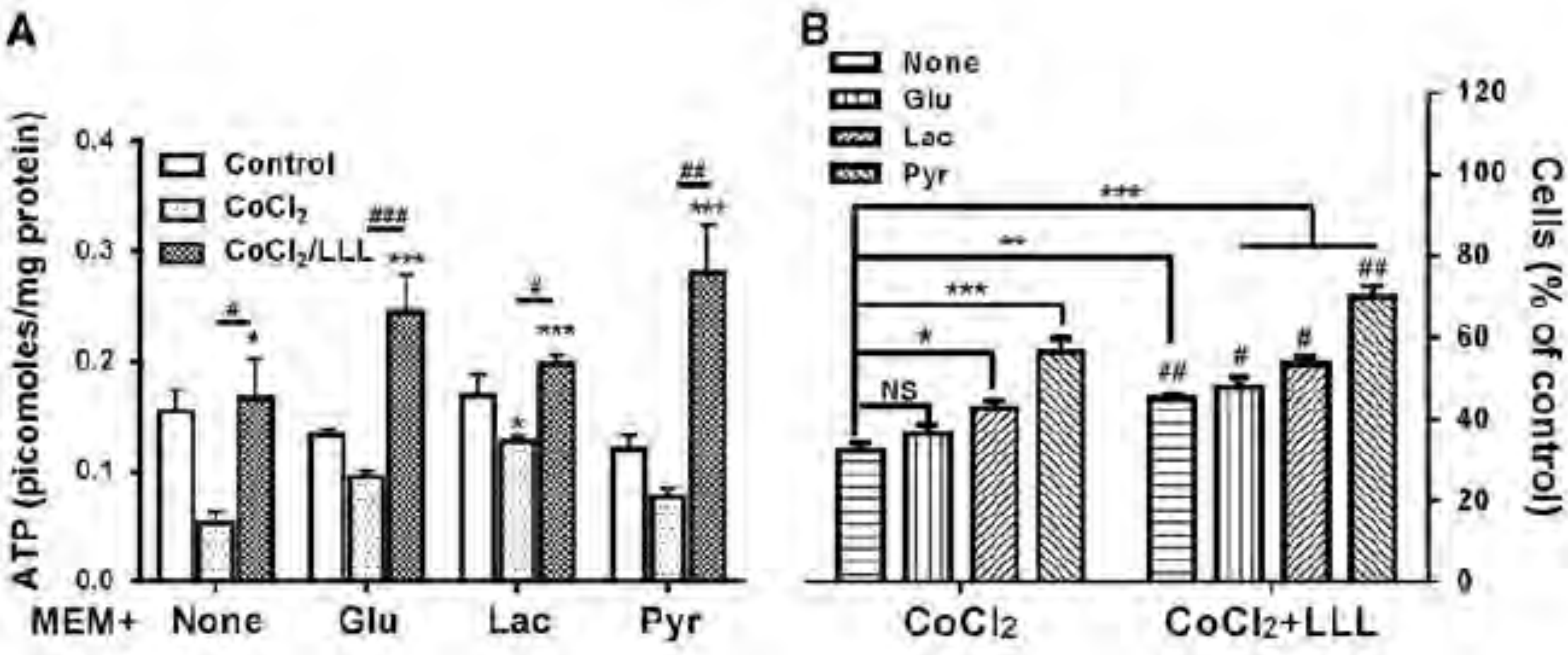
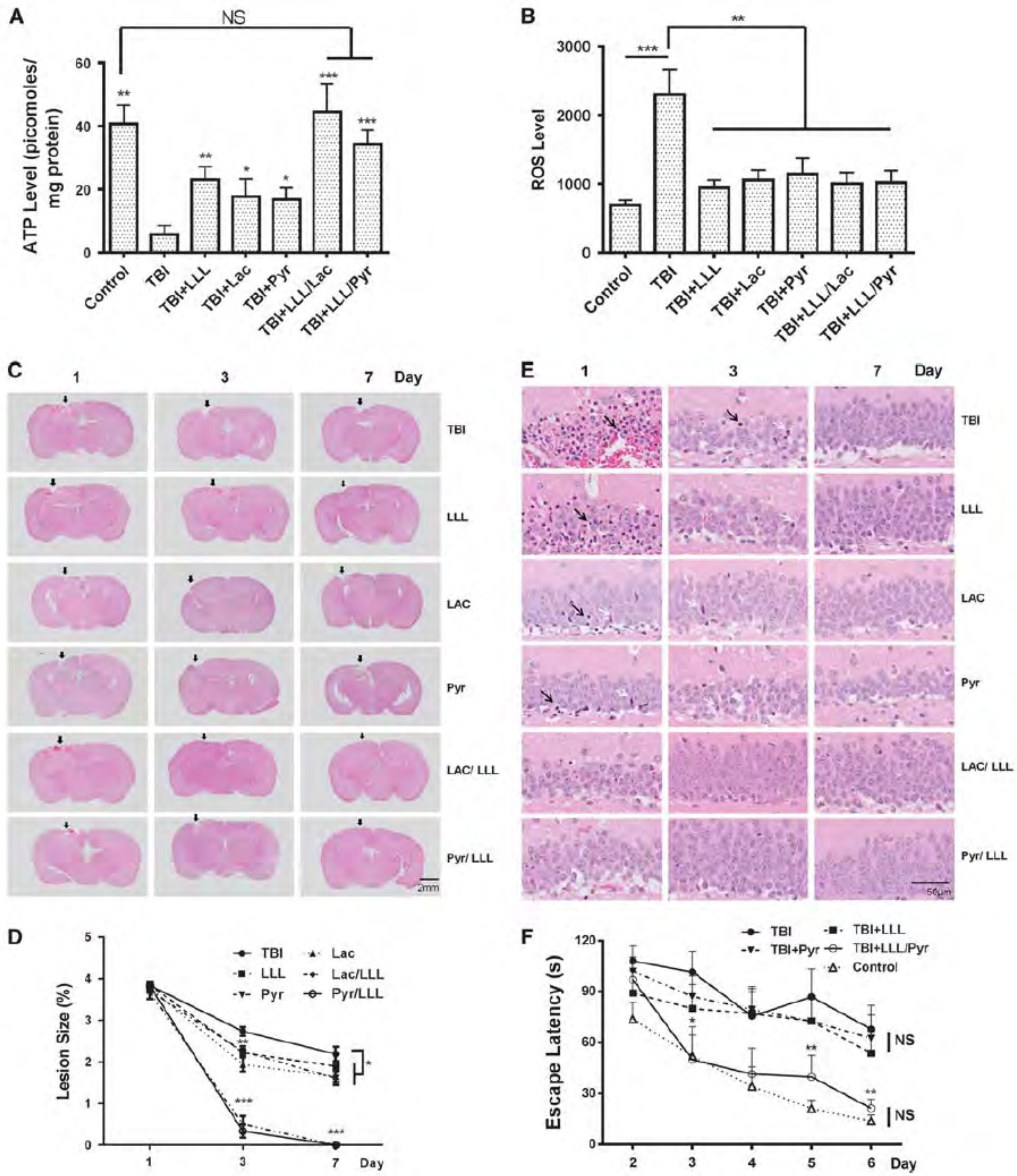
ORIGINAL ARTICLE

# 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




A
NS
ATP Level (picomoles/ mg protein)
Control
TBI
TBI+LLL
TBI+Lac
TBI+Pyr
TBI+LLL/Lac
TBI+LLL/Pyr
B
ROS Level
C
1
3
7
Day
TBI
LLL
LAC
Pyr
LAC/ LLL
Pyr/ LLL
2mm
E
50μm
D
Lesion Size (%)
Lac
Lac/LLL
Pyr/LLL
F
TBI+Pyr
TBI+LLL/Pyr
Escape Latency (s)

Contents lists available at ScienceDirect

Brain Research

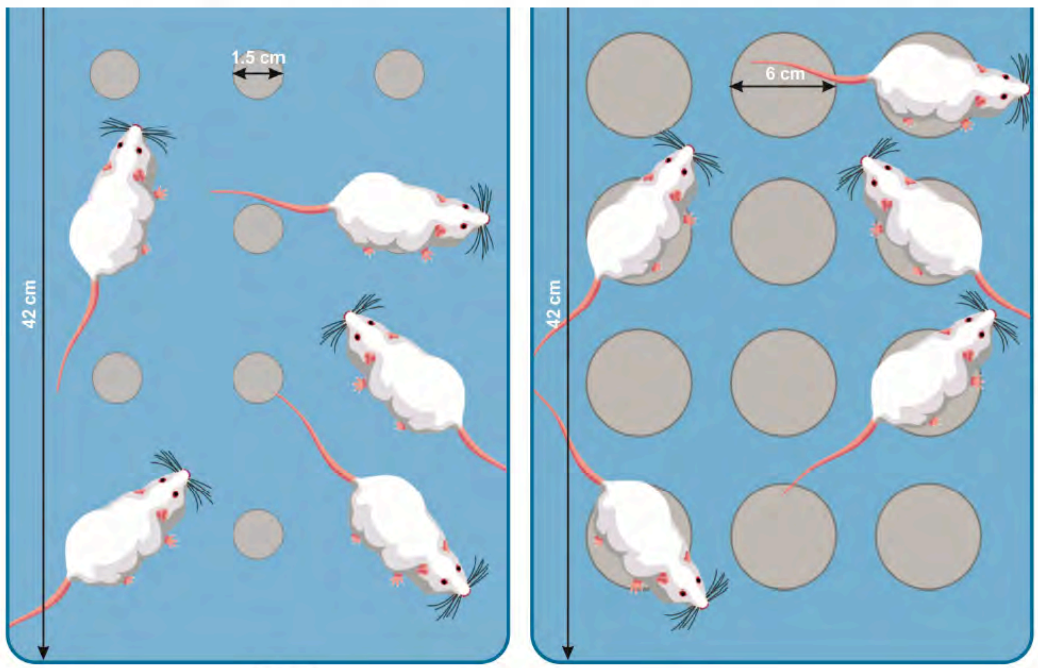
journal homepage: www.elsevier.com/locate/bres

Research report

# Transcranial near-infrared photobiomodulation attenuates memory impairment and hippocampal oxidative stress in sleep-deprived mice

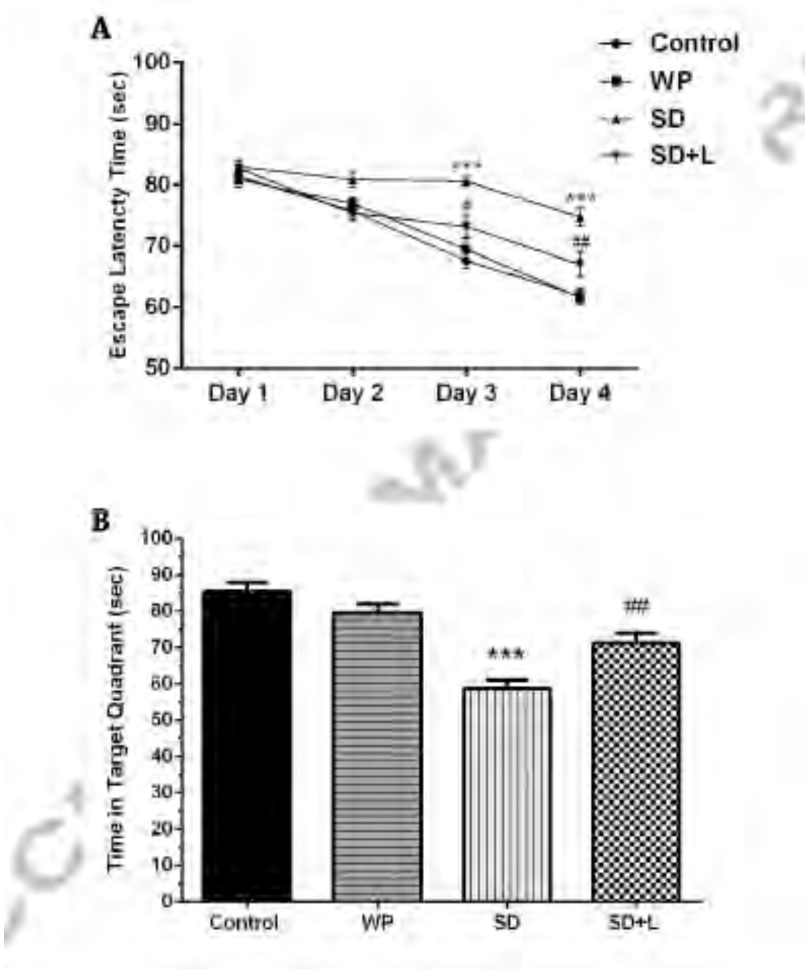
Farzad Salehpour [a,b], Fereshteh Farajdokht [a], Marjan Erfani [a,c], Saeed Sadigh-Eteghad [a], Siamak Sandoghchian Shotorbani [d], Michael R. Hamblin [e,f,g], Pouran Karimi [a], Seyed Hossein Rasta [b,h,i], Javad Mahmoudi [a,*]

Sleep Deprived SD

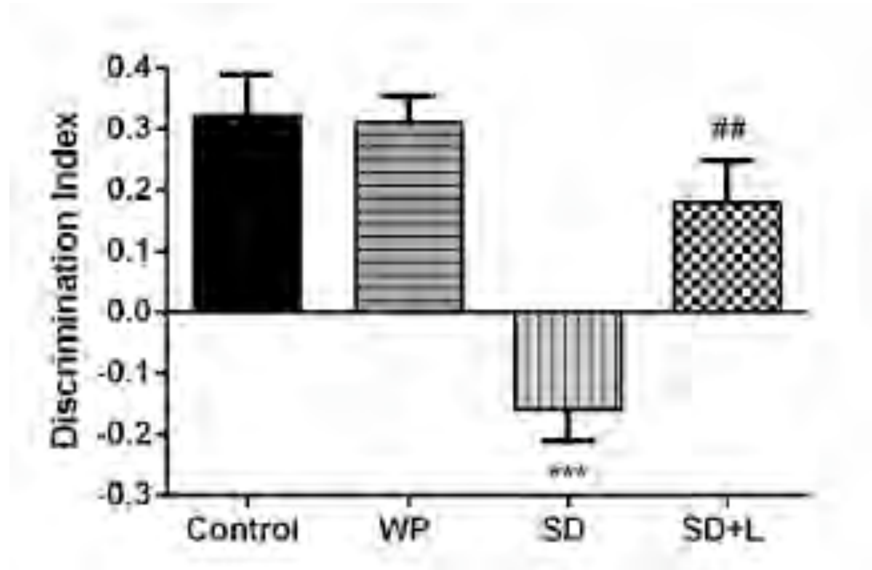



Wide Platform WP

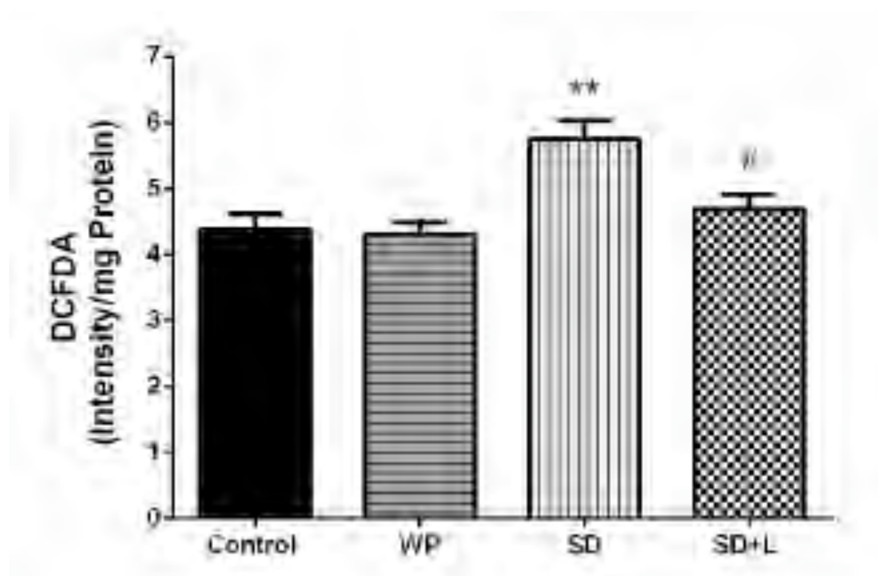
810 nm, 10 Hz,
8 J/cm2 to brain surface
1X day for 3 days




Barnes maze task




What-Where-Which task

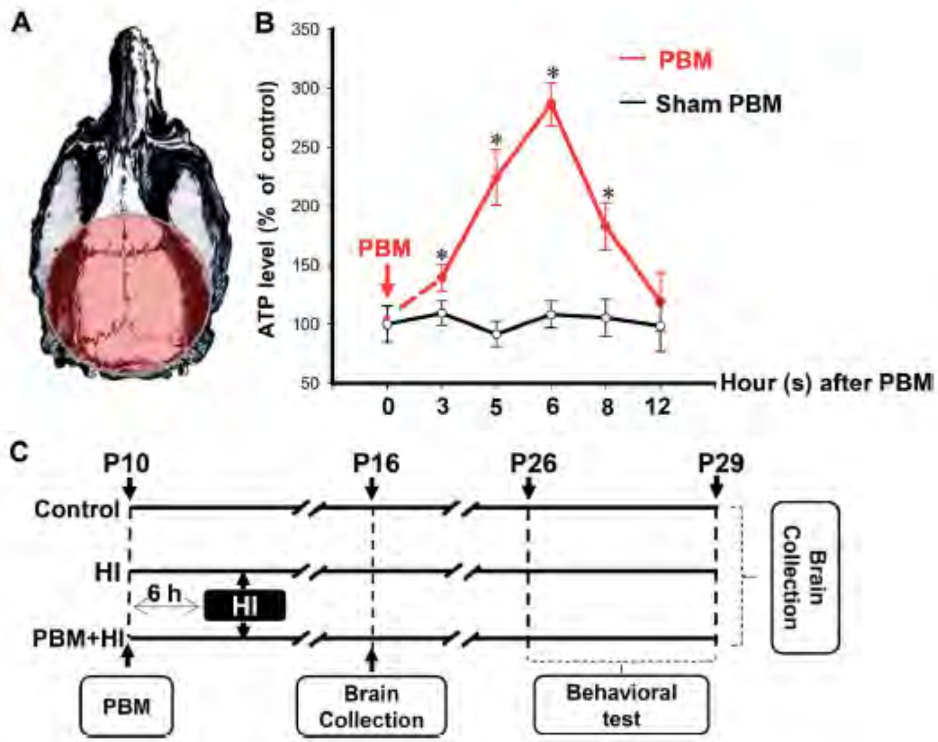



Oxidative stress in Hippocampus

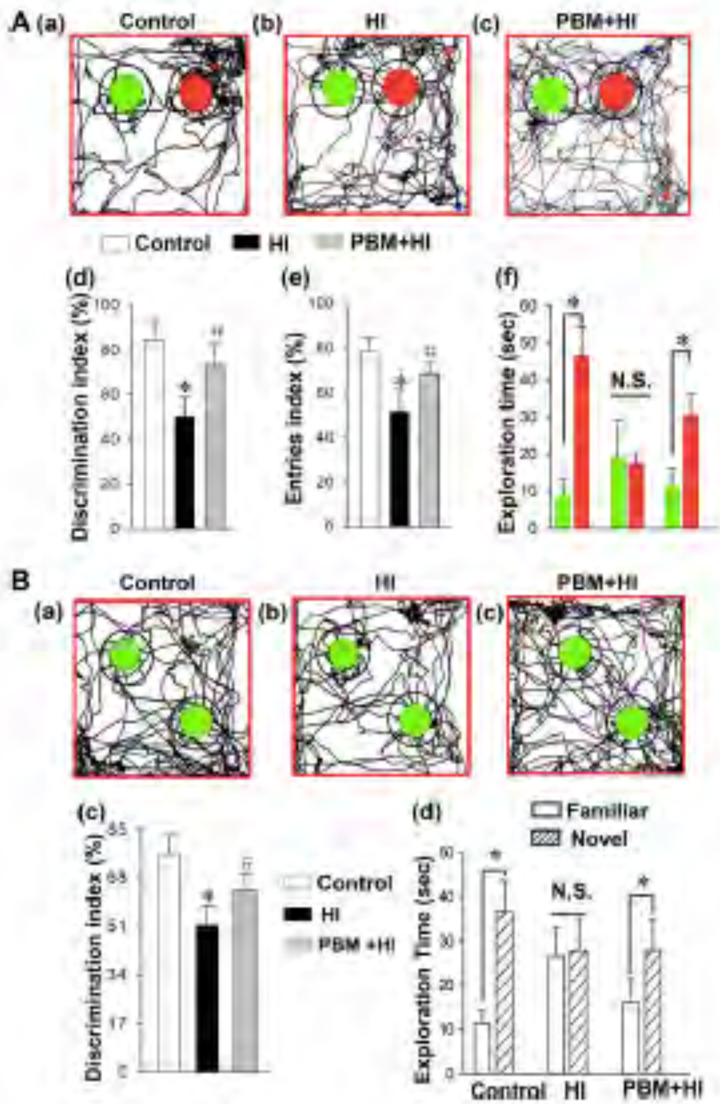
*J Biophotonics*. 2019 June ; 12(6): e201800359. doi:10.1002/jbio.201800359.

# Photobiomodulation Preconditioning Prevents Cognitive Impairment in a Neonatal Rat Model of Hypoxia-ischemia

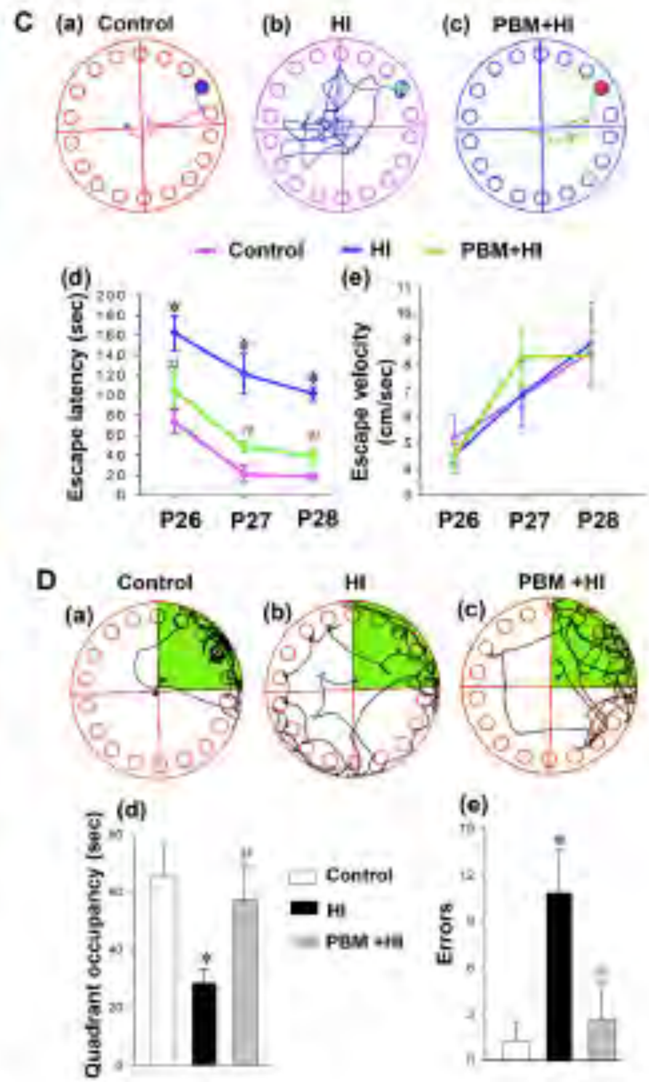
Luodan Yang[1,2,a], Yan Dong[2,a], Chongyun Wu[1], Yong Li[2], Yichen Guo[2], Baocheng Yang[2], Xuemei Zong[2], Michael R. Hamblin[3,4,5], Timon Cheng-Yi Liu[1], and Quanguang Zhang[1,*]



# Object recognition




# Barnes maze

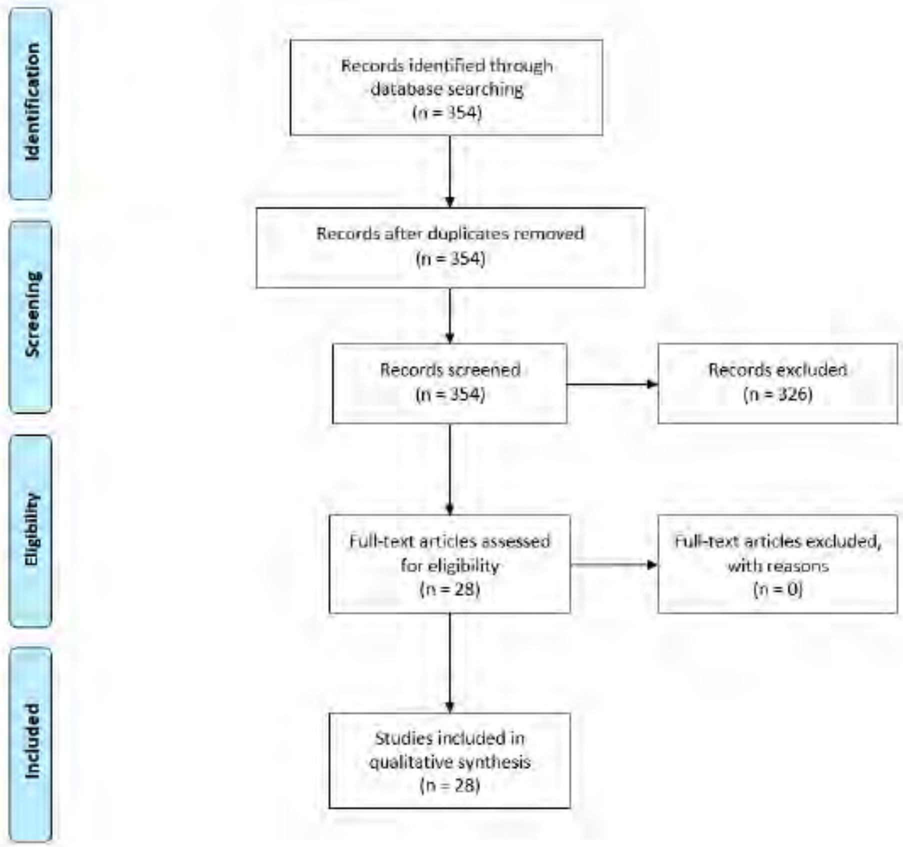


*biomolecules*

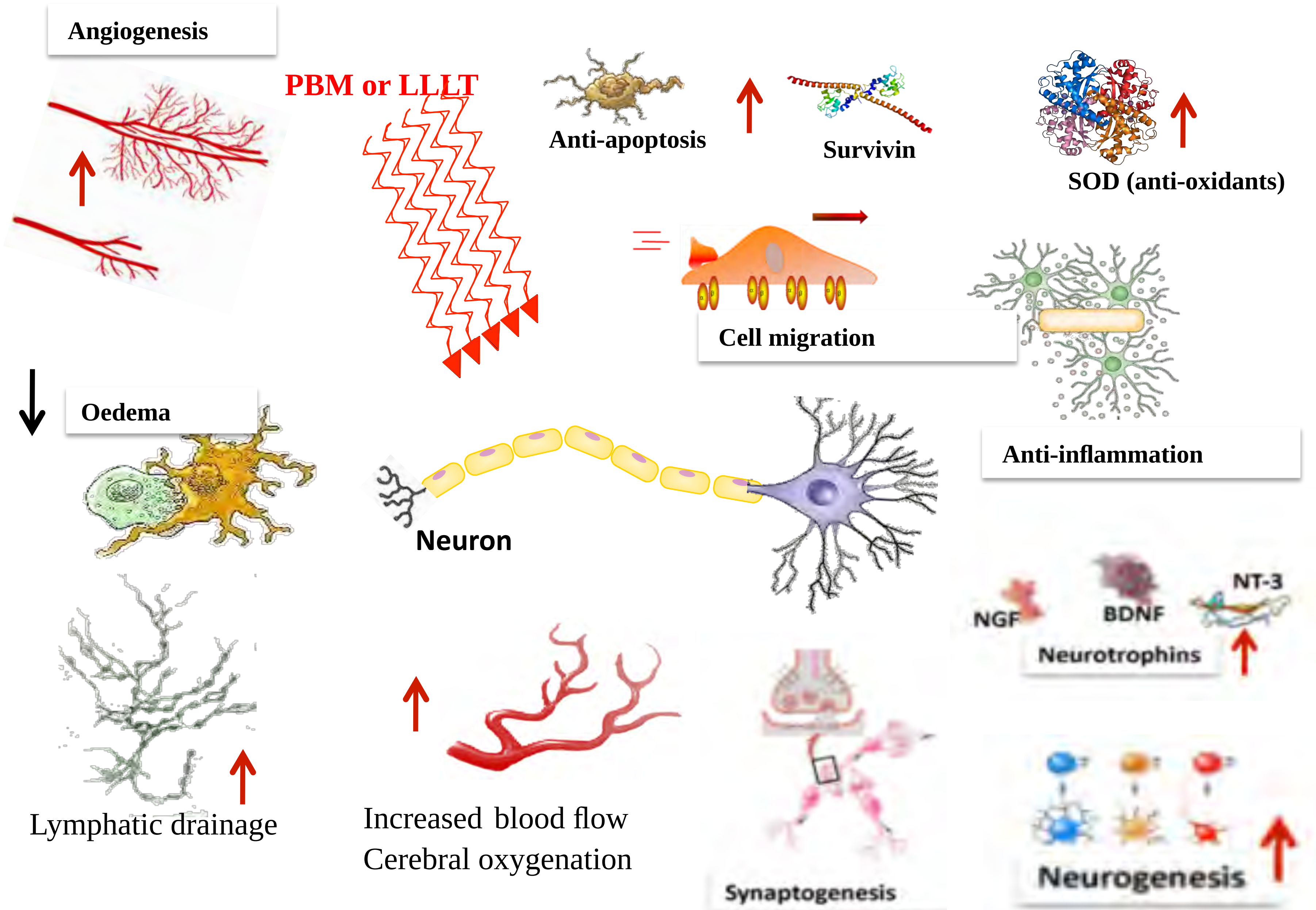
*Review*

# Photobiomodulation for Parkinson's Disease in Animal Models: A Systematic Review

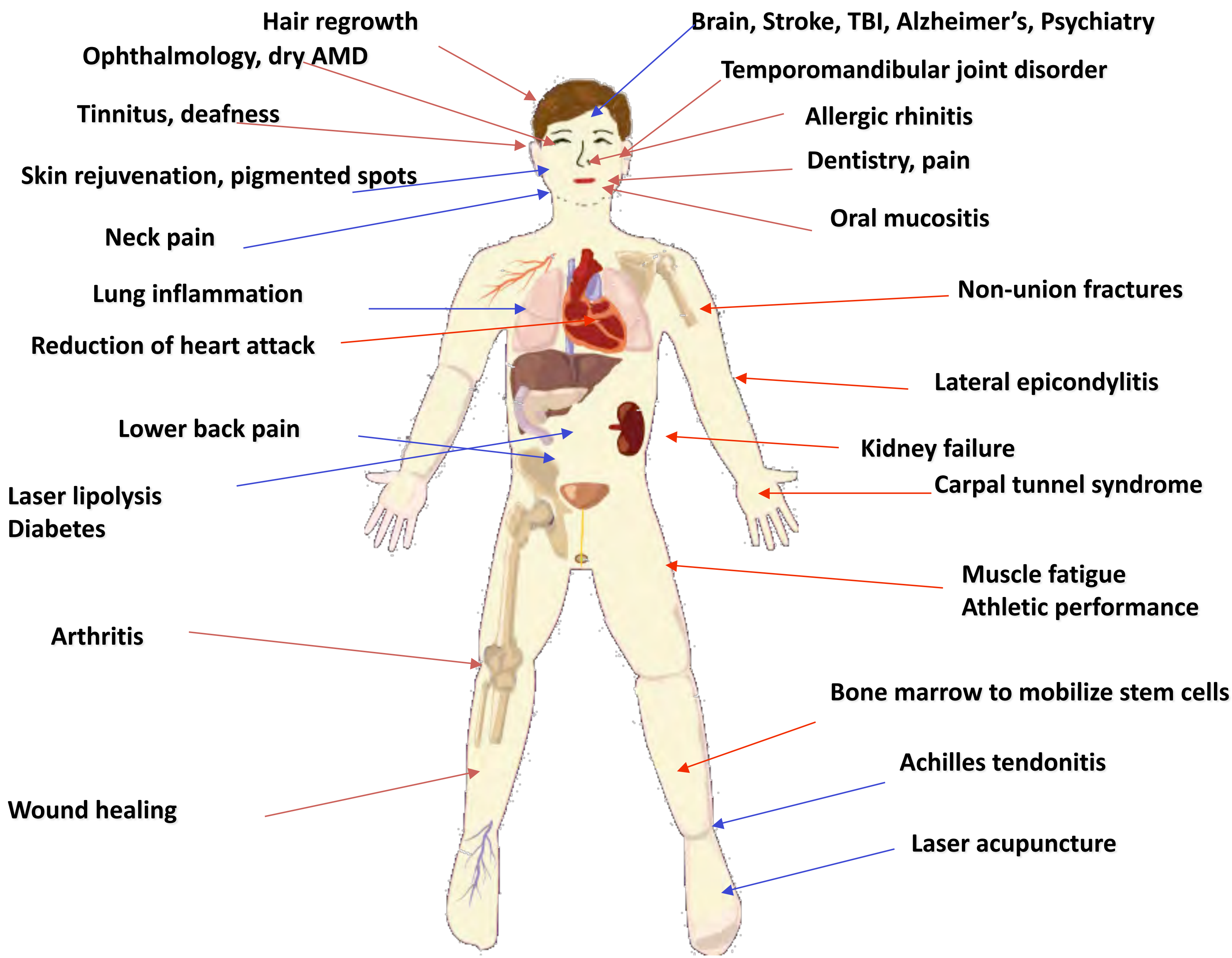
**Farzad Salehpour [1,2,3] and Michael R Hamblin [4,5,*]**



# Multiple mechanisms for PBM in brain



# 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

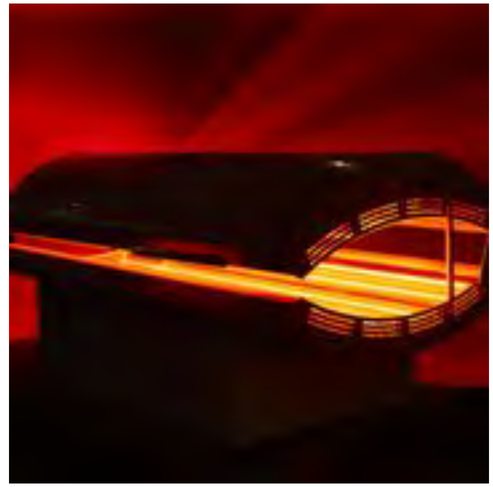
Light Cure


K Laser

Multiradiance

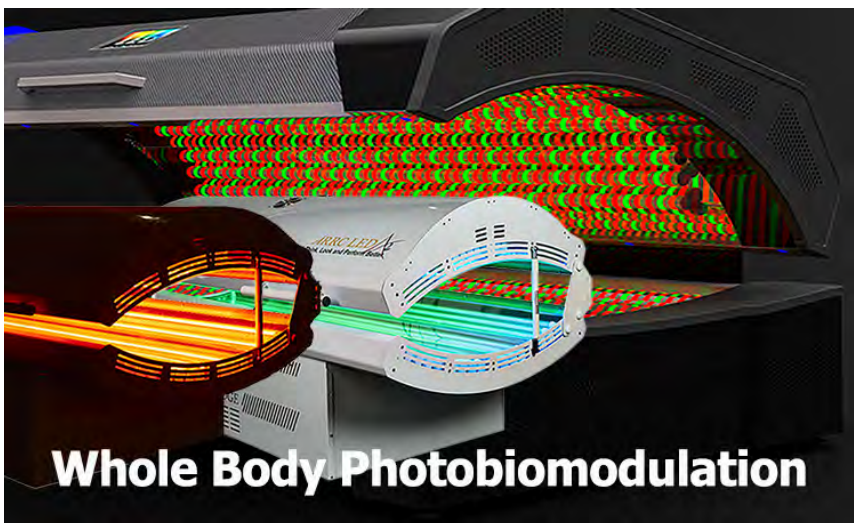
# Whole body photobiomodulation


Novo-THOR



Rejuvalight

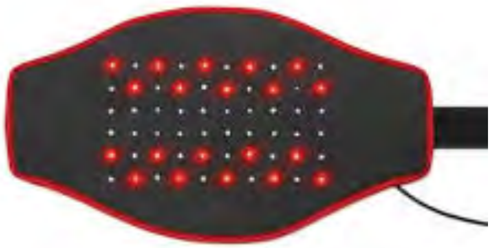

Planet fitness

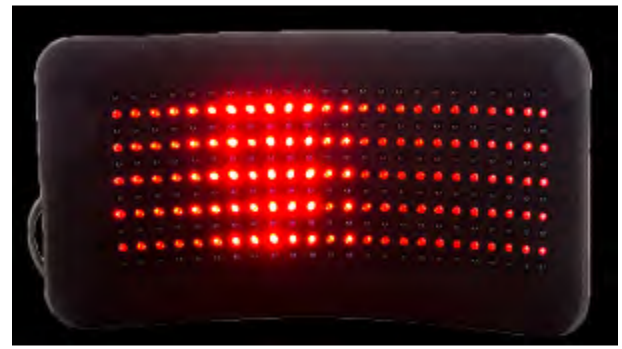


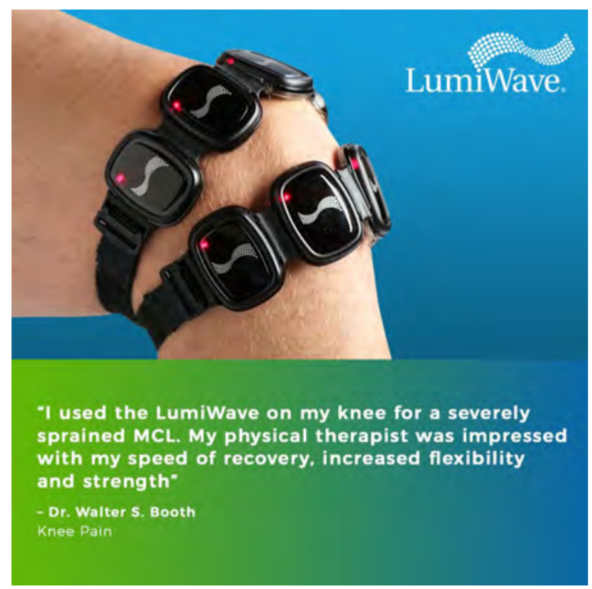

ARRC LED


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 Saltmarche[c], Maxine H. Krengel[a,b], Michael R. Hamblin[d,e,f], Jeffrey A. Knight[a,b,g]

[a]VA Boston Healthcare System (12-A), 150 So. Huntington Ave., Boston, MA, USA 02130
[b]Dept. of Neurology, Boston Univ. School of Medicine, 85 E. Concord St., Boston, MA, USA 02118
[c]MedX Health Inc., 220 Superior Blvd., Mississauga, ON L5L 2L2, Canada
[d]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston MA 02114
[e]Dept of Dermatology, Harvard Medical School, Boston MA 02115
[f]Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA
[g]National Center for PTSD - Behavioral Sciences Division, VA Boston Healthcare System

MedX LED cluster
870-nm & 633-nm

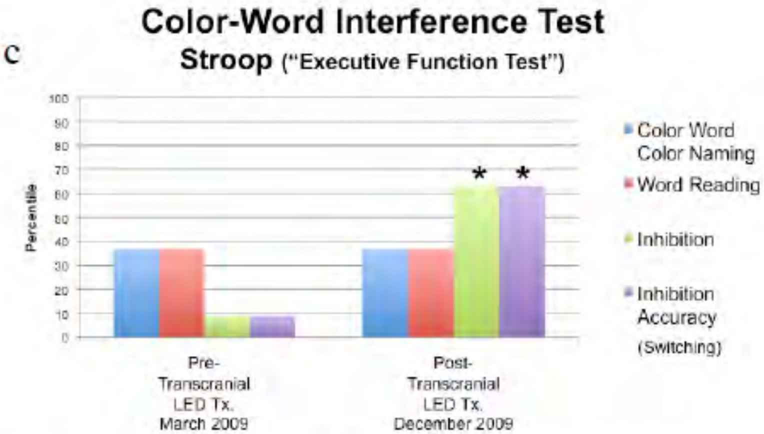
Case1. 59 yo F, 7 yr. post-MVA after 8 weekly Tx.'s, ability to do computer work had improved 10-fold, obtained home unit and has used daily for 5 years.

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.

a


b

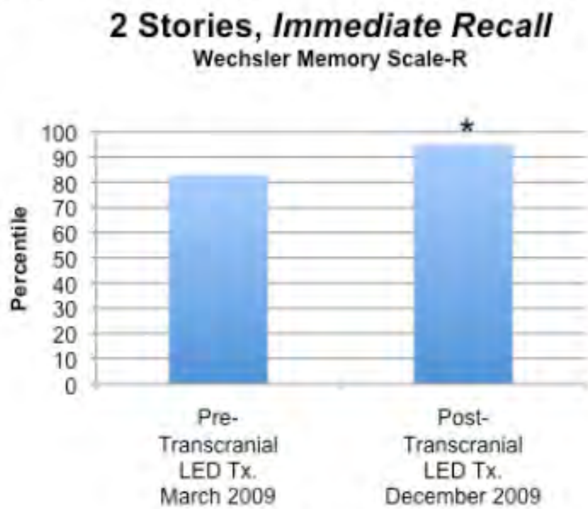
c




* +2 SD Improvement, inhibition, inhibition accuracy

**P2, Pre- and Post- LED Tx., *Neuropsychological Test Results***
**Post- LED Testing,Post- 9 months, nightly, transcranial LED Tx.**

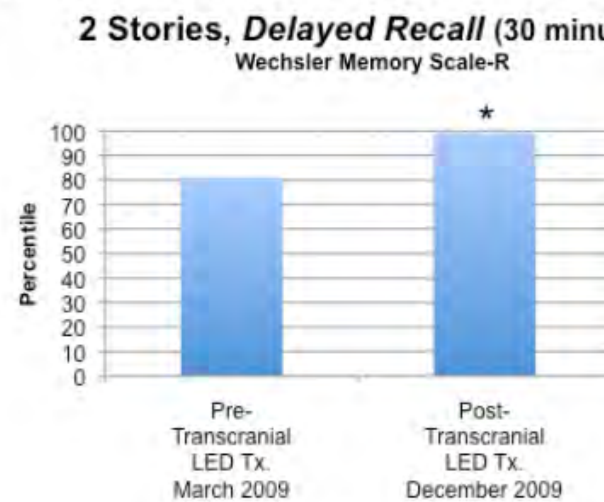
c




* Significant Improvement, +1 SD: Memory

**P2, Pre- and Post- LED Tx., *Neuropsychological Test Results***
**Post- LED Test, Post- 9 months, nightly, transcranial LED Tx.**

c




* Significant Improvement, +2 SD: Memory

JOURNAL OF NEUROTRAUMA 31:1–10 (XXXX 2014)
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DOI: 10.1089/neu.2013.3244

# 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. Krengel,[1] Paula I. Martin,[3] Judith Frazier,[4]
Michael R. Hamblin,[5] Jeffrey A. Knight,[3] William P. Meehan III,[6] Errol H. Baker,[3]

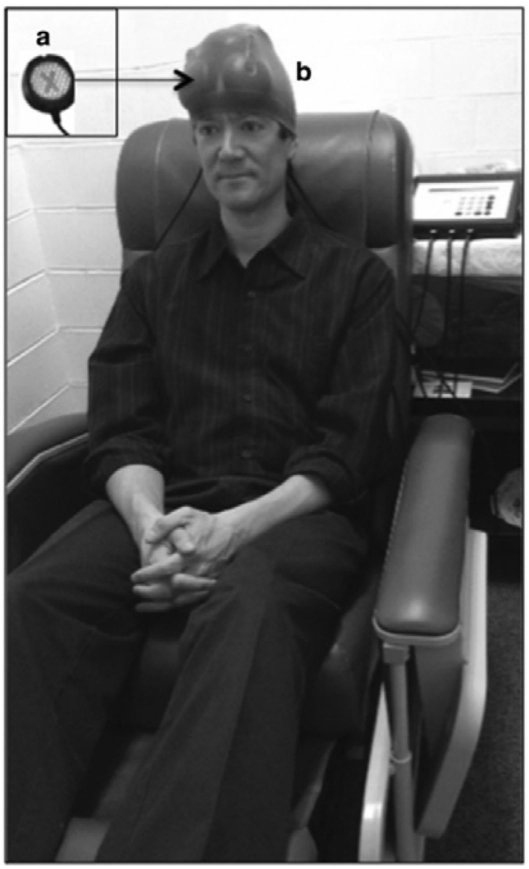



TABLE 3. PSYCHOSOCIAL CHANGES AFTER LIGHT-EMITTING DIODE (LED), REPORTED BY PARTICIPANTS AND FAMILIES

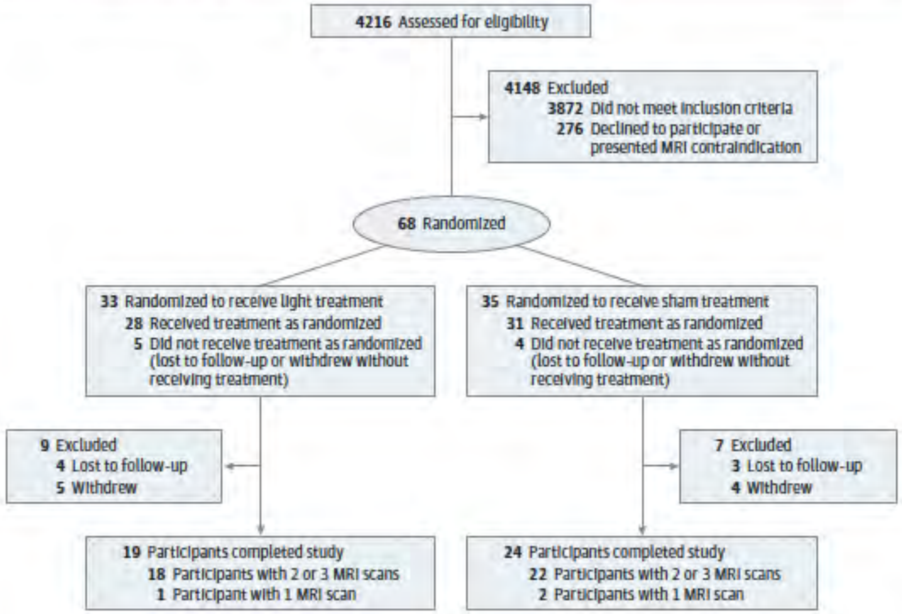
| *ID number* | *Psychosocial changes post-LED* |
|---|---|
| P1 | Able to sort bills, write checks and read essays, tasks he had been unable to perform for 5 years, since the MVA. |
| P2 | Able to continue work 22 hours/week, and later, full-time. Headache pain was reduced; no longer required medication for headache pain. |
| P3 | 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. |
| P4 | Clinically meaningful decrease in post-traumatic stress disorder (PTSD). |
| P5 | 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. |
| P6 | Remained disabled. |
| P7[a] | Remained disabled. |
| P8[a] | Post- LED treatment series, able to return to the military for further evaluation. |
| P9[a] | Remained disabled. |
| P10 | 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. |
| P11[a] | 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. |

JAMA Network Open.
Original Investigation | Neurology

# Effect of Transcranial Low-Level Light Therapy vs Sham Therapy Among Patients With Moderate Traumatic Brain Injury
## A Randomized Clinical Trial

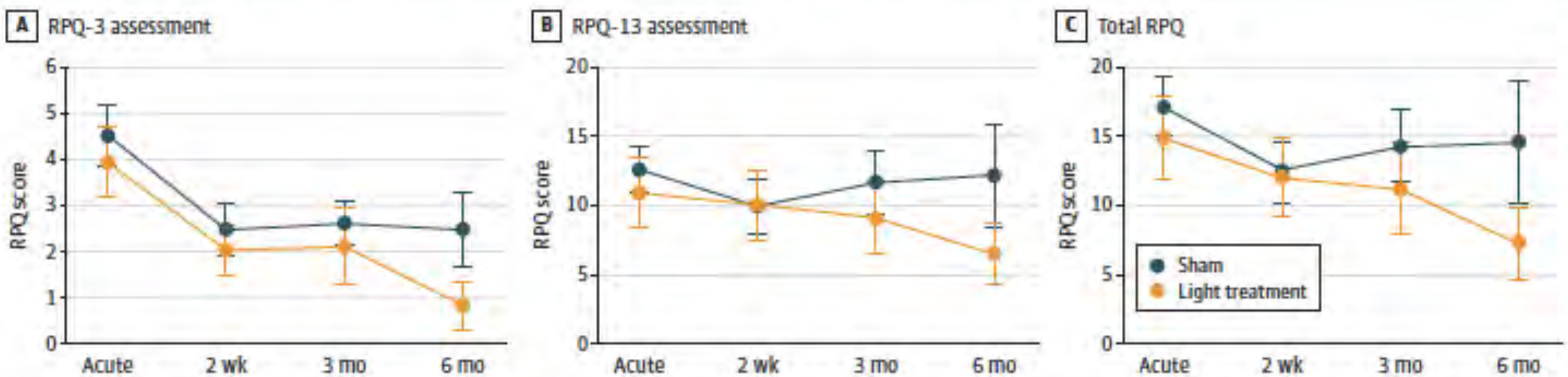
Maria Gabriela Figueiro Longo, MD, MSc; Can Ozan Tan, PhD; Suk-tak Chan, PhD; Jonathan Welt, BS; Arman Avesta, MD; Eva Ratai, PhD; Nathaniel David Mercaldo, PhD; Anastasia Yendiki, PhD; Jacqueline Namati, PhD; Isabel Chico-Calero, PhD; Blair A. Parry, BA; Lynn Drake, MD; Rox Anderson, MD; Terry Rauch, 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




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




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 × treatment: $P = .97$. B, Scores from RPQ-13 assessment, including later, more cognitive and behavioral symptoms. Time: $P = .91$, treatment: $P = .67$, and time × treatment: $P = .89$. C, Total RPQ scores. Time: $P = .39$, treatment: $P = .61$, and time × treatment: $P = .91$.

# **Vielight Neuro** Combined Transcranial And Intranasal Therapy


Small clinical trial for Alzheimer's disease in Toronto, canada

Photomedicine and Laser Surgery
Volume XX, Number XX, 2017
Mary Ann Liebert, Inc.
Pp. 1–10
DOI: 10.1089/pho.2016.4227

**Original Research**

# 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,[1] Margaret A. Naeser, PhD,[2,3] Kai Fai Ho, PhD,[4]
Michael R Hamblin, PhD,[5,6] and Lew Lim, PhD, DNM, MBA[7]

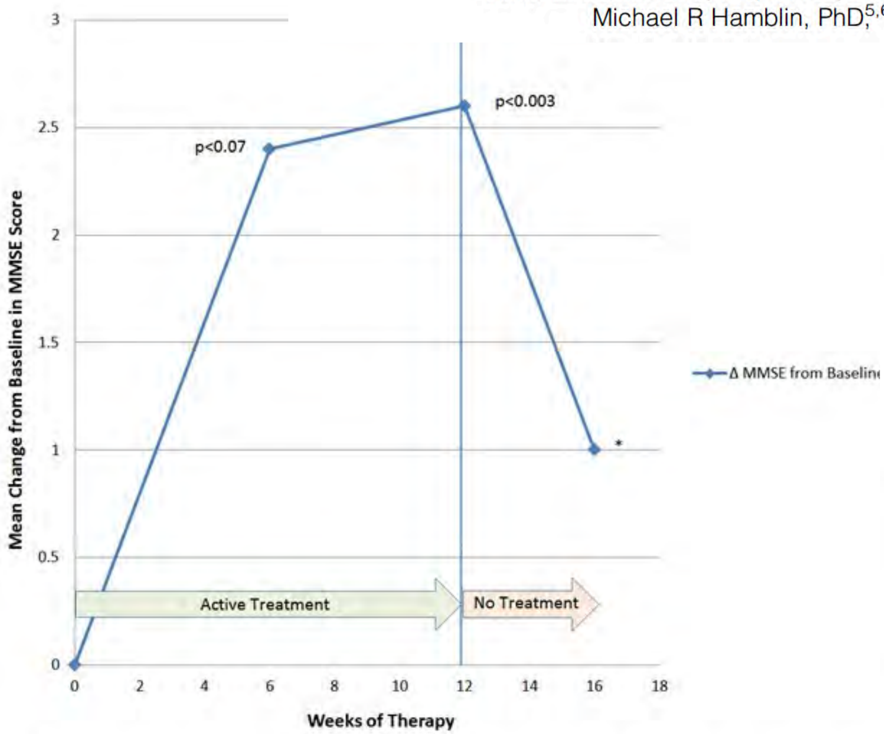



**FIG.2.** Mean change from baseline in MMSE scores. Higher numbers indicate better cognition on this test.

*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".

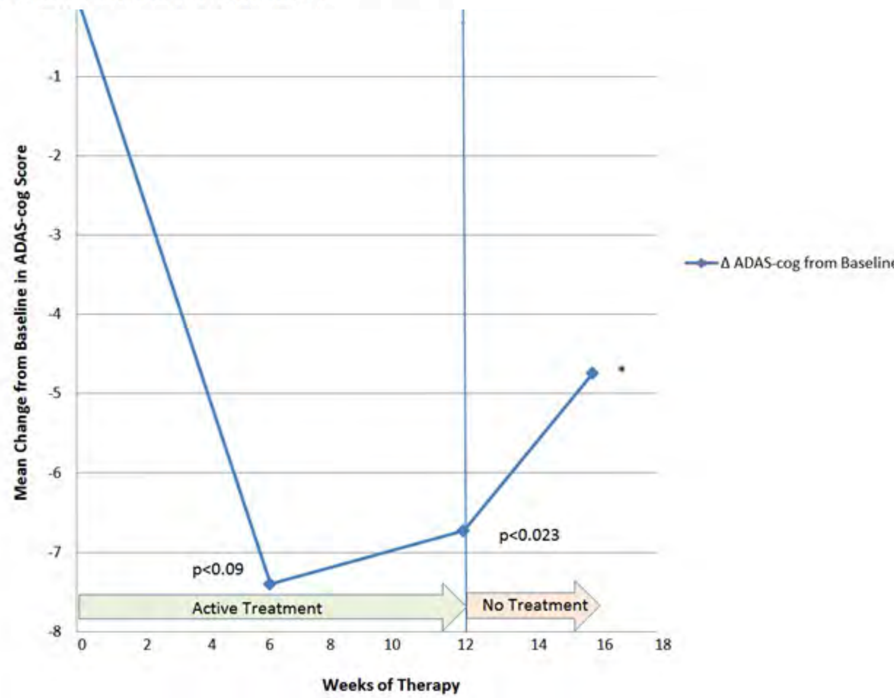



**FIG.3.** Mean change from baseline in ADAS-cog scores. Lower numbers indicate better cognition on this test.

*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".

Photobiomodulation, Photomedicine, and Laser Surgery
Volume 37, Number 3, 2019
© Mary Ann Liebert, Inc.
Pp. 159–167
DOI: 10.1089/photob.2018.4569

**Photobiomodulation—Case Report**

# 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, DABCN[3,7]

***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.

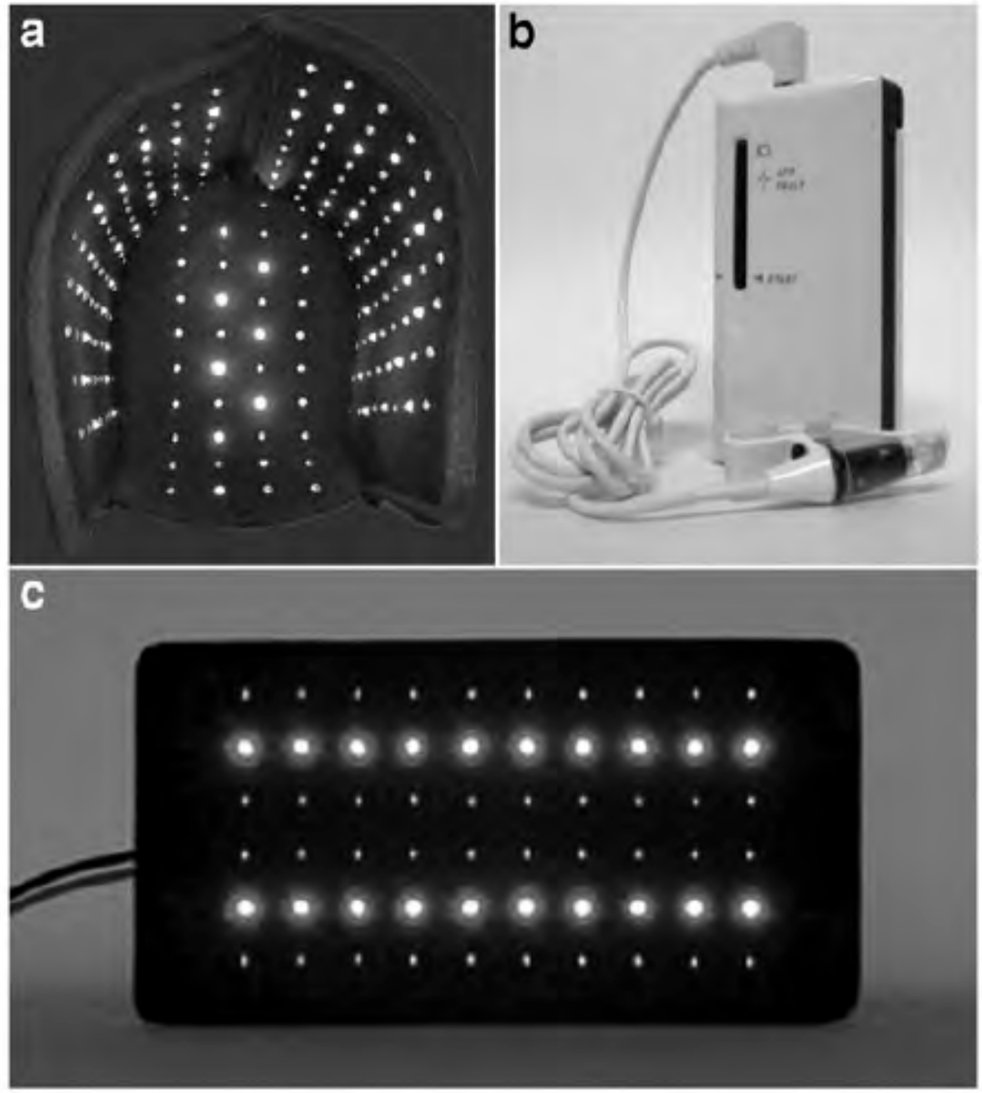

a
b
c

Table 2. Descriptive Data of Patients' and Caregivers' Assessments

| | *Pre-treatment* | *Post-treatment* |
|---|---|---|
| Patient-related assessments | | |
| Montreal Cognitive Assessment[a] | 18 | 24 |
| WMQ[b] | | |
| Storage domain | 20 | 6 |
| Attention domain | 15 | 2 |
| Executive domain | 18 | 2 |
| Total | 53 | 10 |
| Alberta Smell Test[c] | 0 (R)/0 (L) | 2 (R)/2 (L) |
| Peanut butter test | 0 cm (R)/(L) | 18 cm (R)/10 cm (L) |
| Caregiver-rated patient self-care assessments (Lawton–Brody scales)[d] | | |
| IADL | 5 | 8 |
| PSM | 6 | 6 |
| Caregiver burden self-assessment questionnaire | | |
| Caregiver stress level[e] | 6 | 4 |
| Current health[f] | 3 | 2 |

[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.

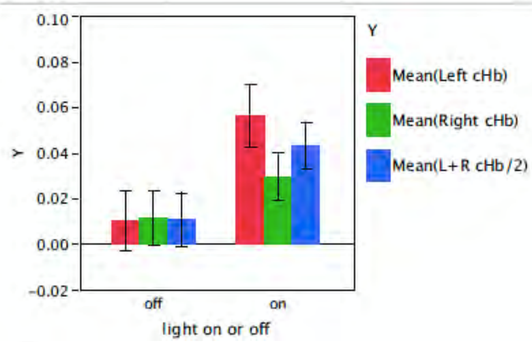
# PBM for Depression and PTSD

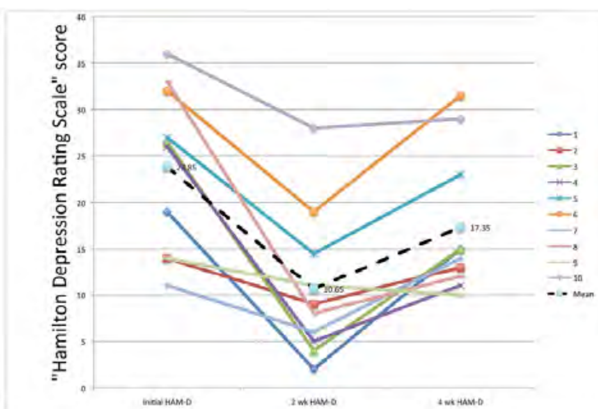
**Behavioral and Brain Functions** BioMed Central

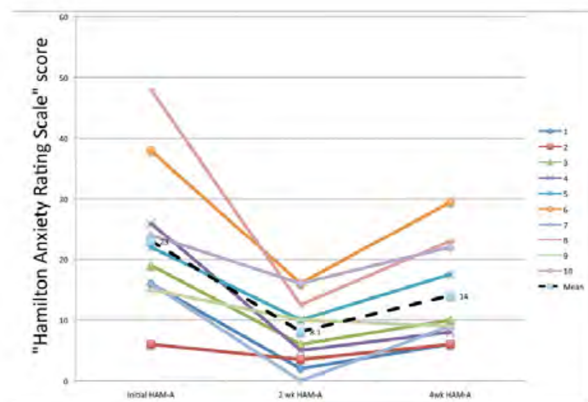
Research **Open Access**

**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 Johnston[3], Caitlin Ravichandran[2], Ann Polcari[1], Martin H Teicher[1], Robert H Webb[3,4] and Michael R Hamblin[3,4,5]



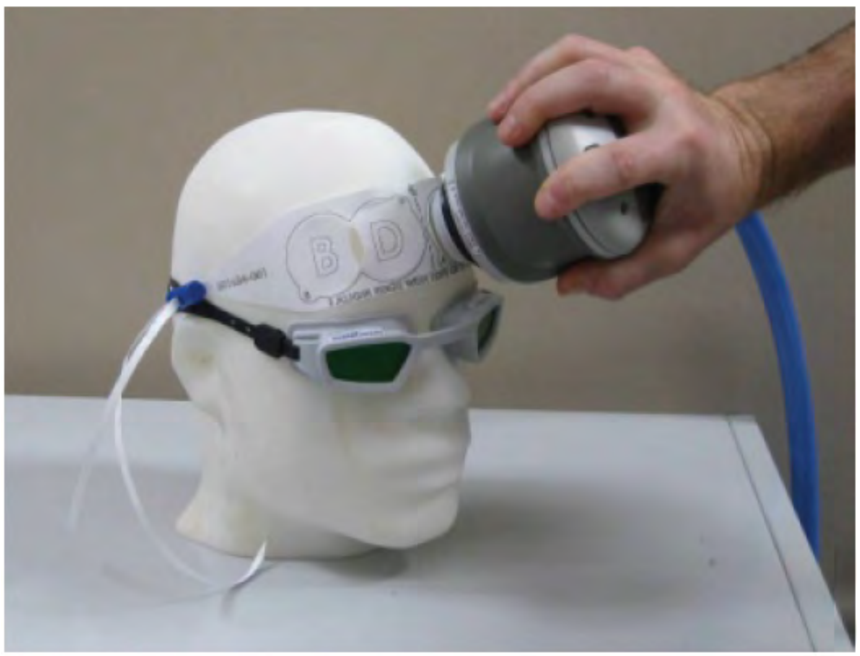



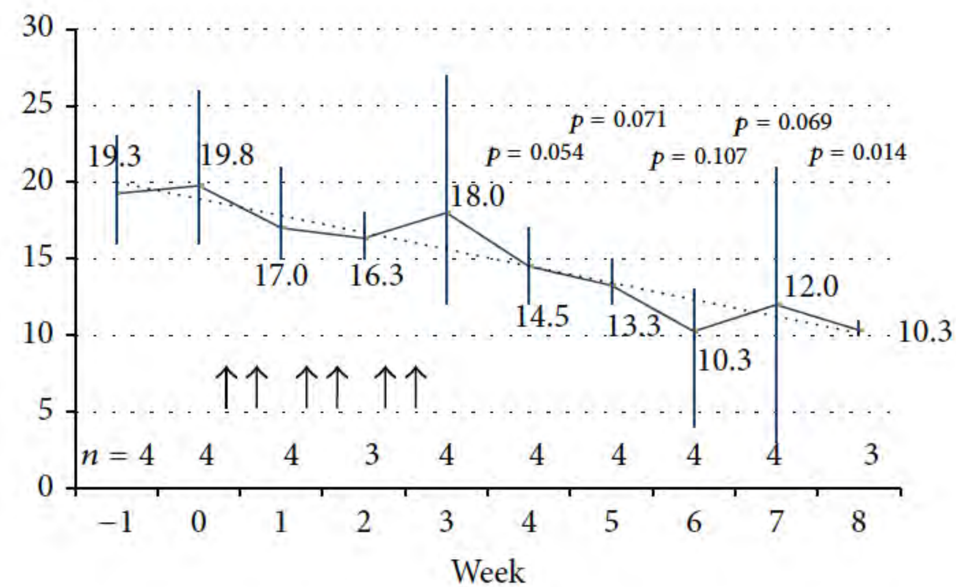
Hindawi Publishing Corporation
Psychiatry Journal
Volume 2015, Article ID 352979, 8 pages
http://dx.doi.org/10.1155/2015/352979

*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] Luis 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. Iosifescu[1,4]**





# A Novel Treatment of Opioid Cravings with an Effect Size of .73 for Unilateral Transcranial Photobiomodulation over Sham

Fredric Schiffer[1*], William Reichmann[2], Edward Flynn[3], Michael R. Hamblin[4], Hannah Mccormack[3]

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

| – | Active (n=17) | Sham (n=17) | P-value |
|---|---|---|---|
| Patients with decrease in OCS of | 9 (52.9%) | 3 (17.6%) | 0.0289 |

# Devices for transcranial PBM (published)

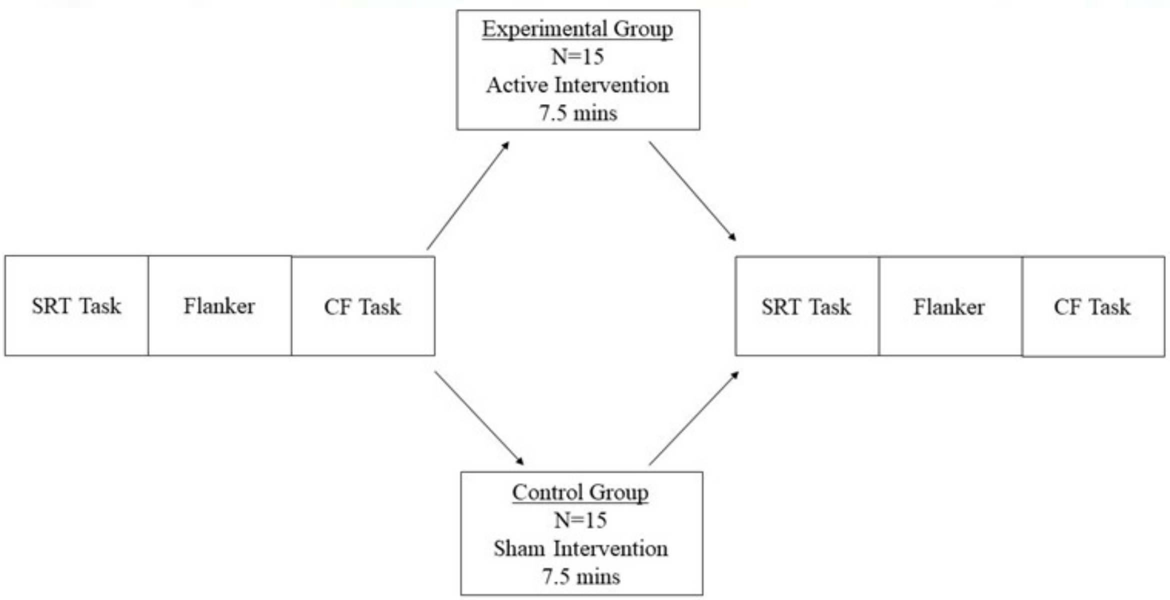
Received: 17 May 2018 | Accepted: 14 November 2018
DOI: 10.1002/gps.5039

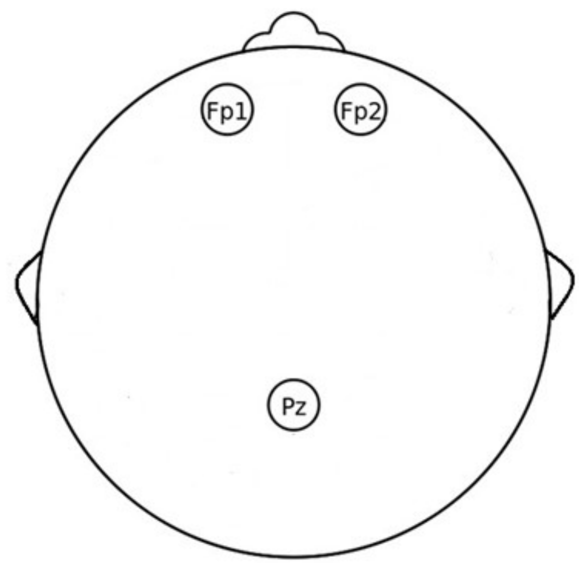
RESEARCH ARTICLE

WILEY International Journal of Geriatric Psychiatry

# Photobiomodulation improves the frontal cognitive function of older adults

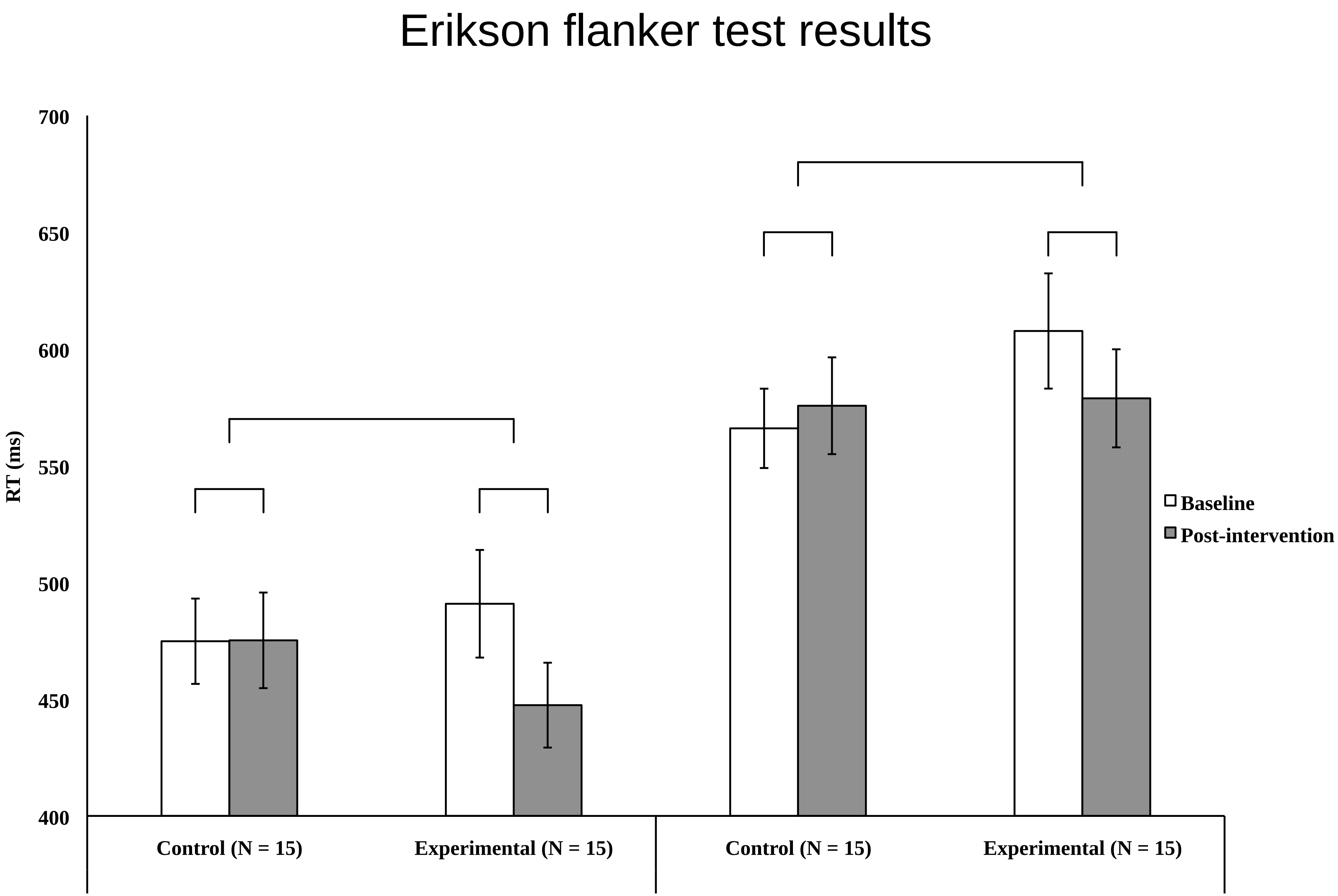
Agnes S. Chan[1,2] | Tsz Lok Lee[1] | Michael K. Yeung[1] | Michael R. Hamblin[3,4,5]



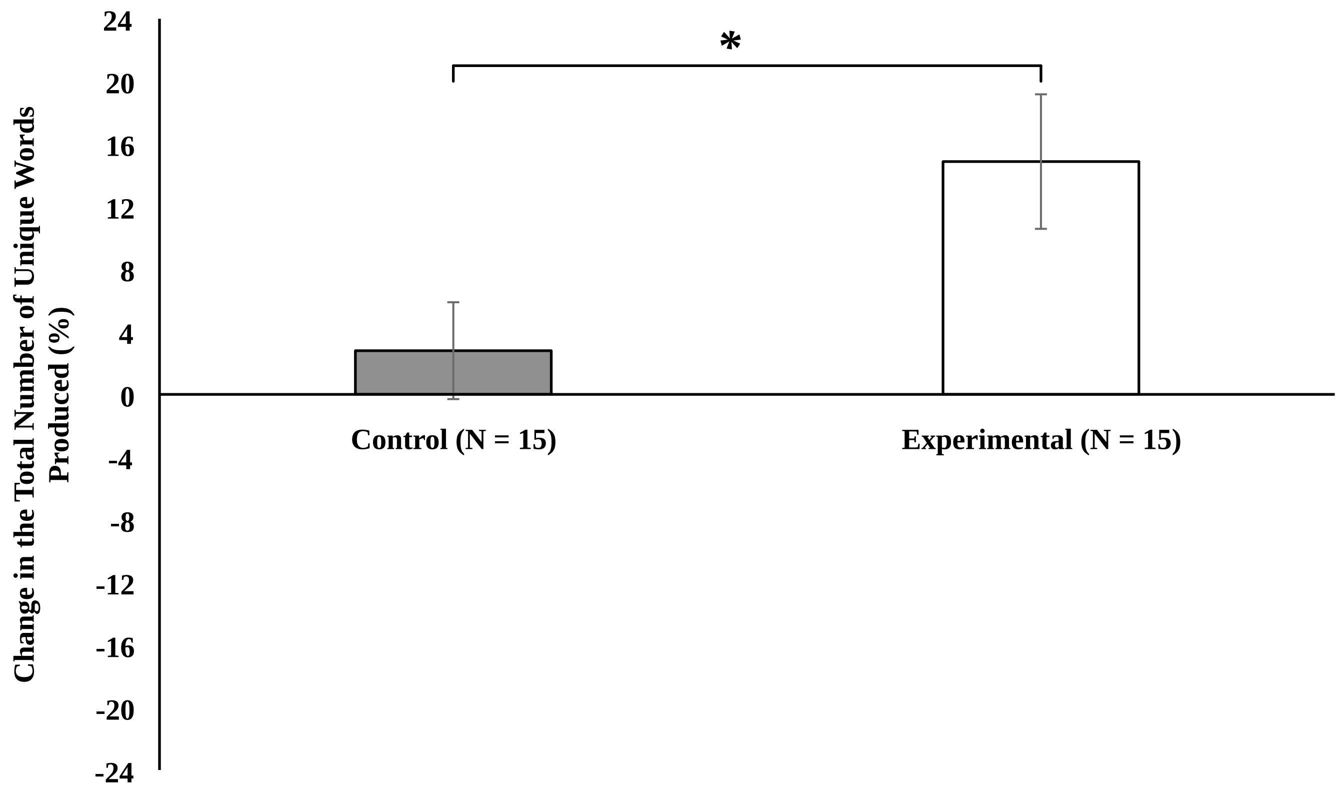

SRT = Simple Reaction Time Task
CF Task = Category Fluency Task
Flanker = Erikson flanker test

| Congruent | Incongruent |
|---|---|
| >> >> > >> >> | >> >> < >> >> |
| << << < << << | << << > << << |



Erikson flanker test results
RT (ms)
700
650
600
550
500
450
400
Baseline
Post-intervention
Control (N = 15)
Experimental (N = 15)
Control (N = 15)
Experimental (N = 15)

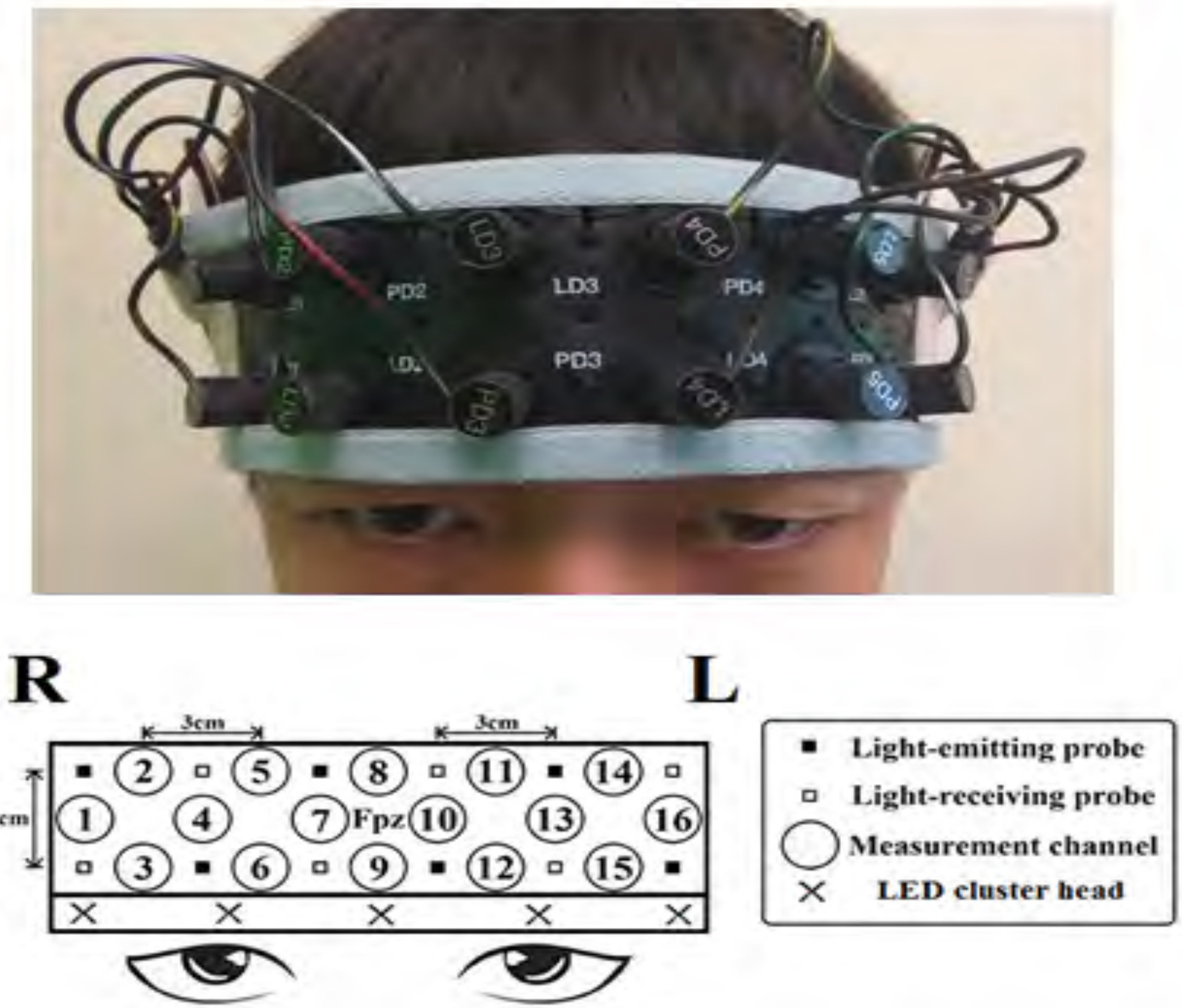
# Category fluency test results



Photoneuromodulation makes a difficult cognitive task less arduous

Agnes S. Chan[1,2], Tsz Lok Lee[1] & Michael R. Hamblin[3,4]

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.


PD2
LD3
PD4
PD3
R
L
3cm
3cm
3cm
1
2
3
4
5
6
7
Fpz
8
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14
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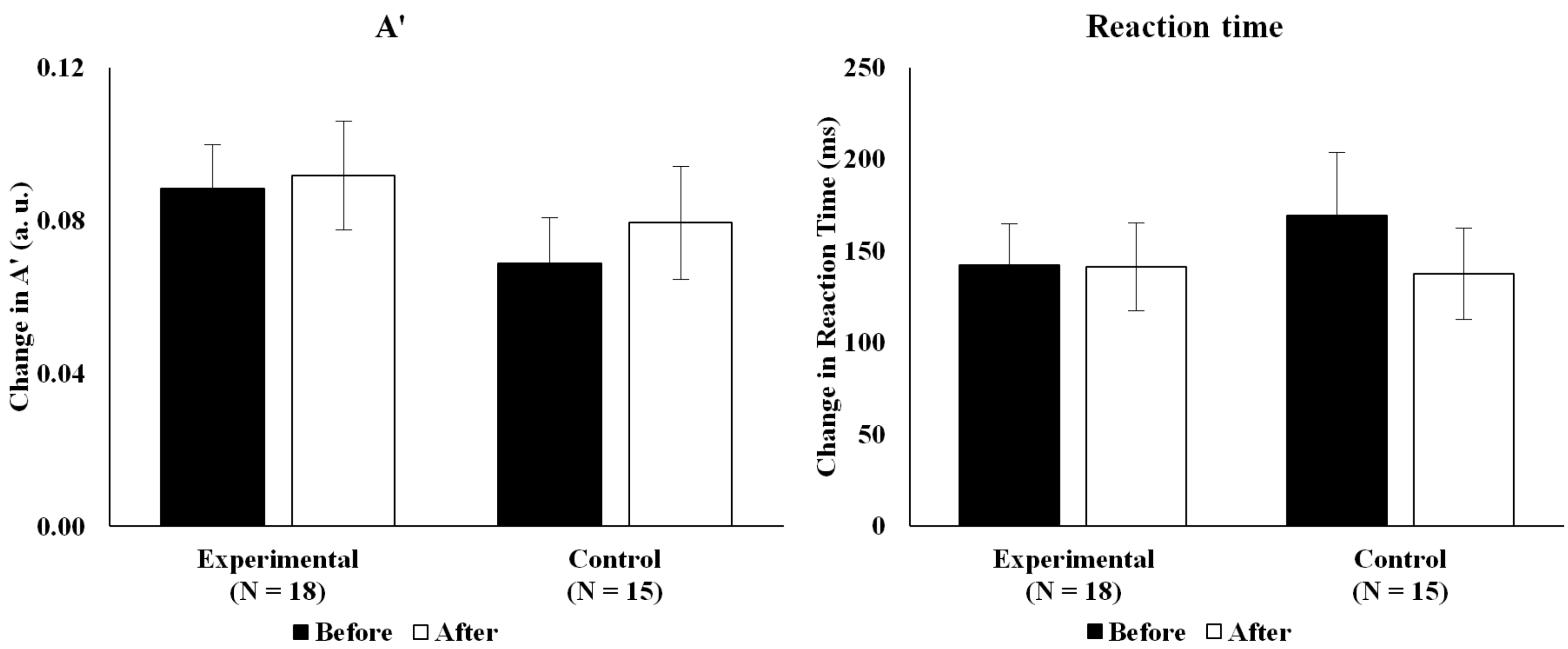
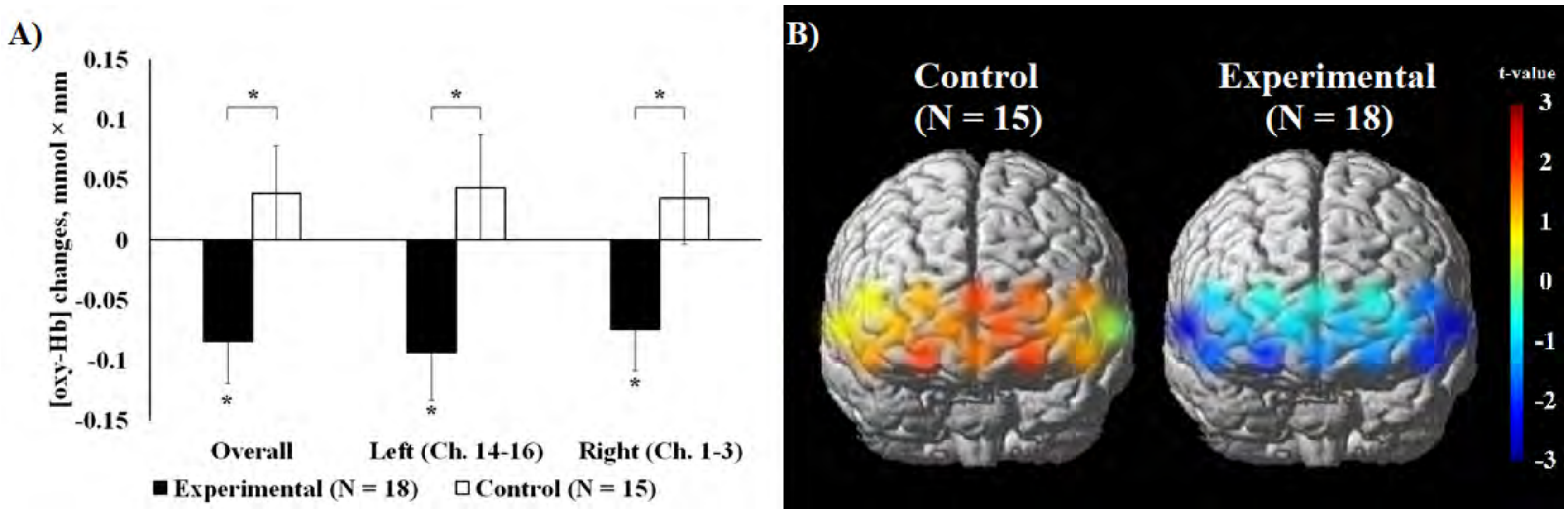
16
Light-emitting probe
Light-receiving probe
Measurement channel
LED cluster head

# Only minor changes in memory performance



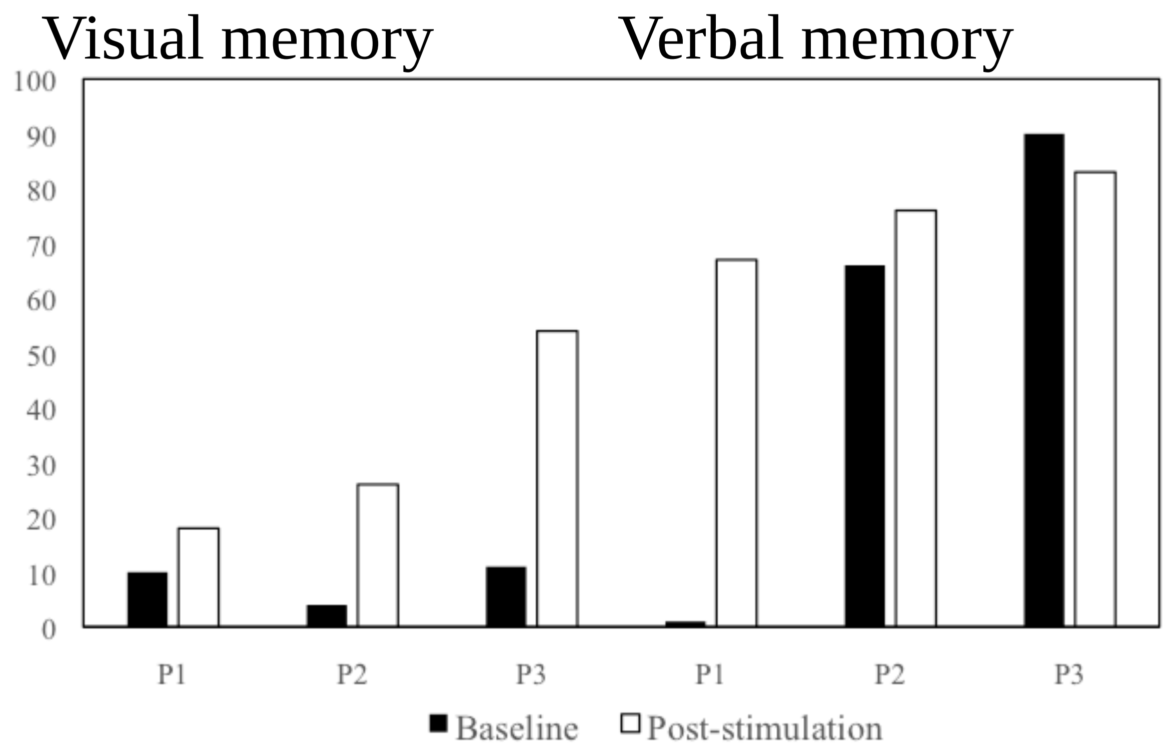
Significantly lower blood flow



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.



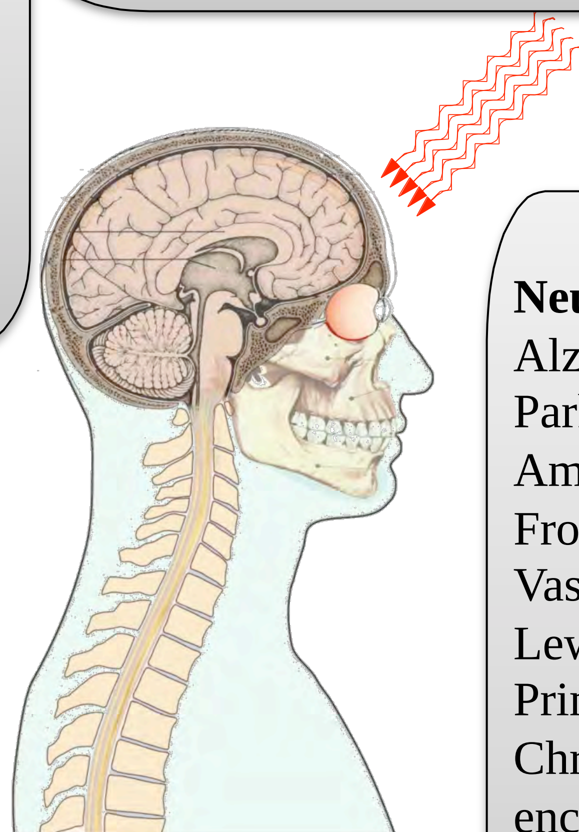
# Common pathways in neurodegenerative and psychiatric disease

| | | |
|---|---|---|
| Neuroinflammation | Low BDNF | Alzheimer’s |
| Oxidative Stress | Impaired Neurogenesis | Parkinson’s |
| Excitotoxicity | Hippocampal Shrinkage | Depression |
| Mitochondrial Dysfunction | Impaired Synaptogenesis | Post traumatic stress disorder |
| Neuronal Apoptosis | Cortical Shrinkage | Bipolar Disorder |

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

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

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



**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

# 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

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