Scalp Application of Near-infrared Light-emitting Diode (LED) to Improve Cognition in Chronic Traumatic Brain Injury(TBI), Posttraumatic Stress Disorder (PTSD), Dementia, and Gulf War Illness (GWI)

Margaret Naeser, Ph.D.
Research Professor, Neurology
Boston University School of Medicine
Research
VA Boston Healthcare System

Yelena Bogdanova, Ph.D., Ph.D.
Principal Investigator, Neurorehabilitation Program
Physical Medicine & Rehabilitation Service
VA Boston Healthcare System
Assistant Professor, Psychiatry
Boston University School of Medicine

Presenters

Margaret Naeser, Ph.D.

Research Professor, Neurology
Boston University School of Medicine Research
Veteran Affairs (VA) Boston Healthcare System

Yelena Bogdanova, Ph.D., Ph.D.

Clinical Neuropsychologist and Principal Investigator
Neurorehabilitation Program
Physical Medicine & Rehabilitation Service
VA Boston Healthcare System

Assistant Professor of Psychiatry
Boston University School of Medicine

Margaret Naeser, Ph.D.

- VA/National Institutes of Health (NIH)-funded research, 40 years
- Since 2010: Research on effects of red/near-infrared (NIR) light-emitting diodes (LEDs) on scalp/brain for traumatic brain injury (TBI)/posttraumatic stress disorder (PTSD), dementia, Gulf War Illness (GWI), stroke/aphasia, athletes with chronic traumatic encephalopathy (CTE).
- Focus: neuroplasticity, photobiomodulation for neuromodulation and recovery.
- Editorial Board, Photomedicine and Laser Surgery (PMLS), and Fellow, American Society for Lasers in Medicine and Surgery (ASLMS)
- BA Smith College; PhD University of Wisconsin, Madison

Yelena Bogdanova, Ph.D., Ph.D.

- Dr. Bogdanova is a Clinical Neuropsychologist and a Principal Investigator at the VA Boston Healthcare System (HCS)
- She currently leads the Virtual Care, Neurorehabilitation, LED TBI Home Treatment Programs at the VA Physical Medicine & Rehabilitation Service, VA Boston HCS
- Dr. Bogdanova is an Assistant Professor of Psychiatry at the Boston University School of Medicine
- Holds a PhD in Behavioral Neurosciences and a PhD in Clinical Neuropsychology.
- Serves without compensation on the Cognitive Rehabilitation Task Force and the AP Technology Task Force of Military & Veteran Group at the American Congress of Rehabilitation Medicine

Disclosures

- Drs. Margaret Naeser and Yelena Bogdanova have no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- Some research was funded by Vielight (Hayward, CA, Toronto, Canada); and Thor Photomedicine, Inc. (Hempstead, MD, London, UK)
- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Department of Defense, nor the U.S. Government.
- This continuing education activity is managed and accredited by the Defense Health Agency J-7 Continuing Education Program Office (DHA J-7 CEPO). DHA J-7 CEPO and all accrediting organizations do not support or endorse any product or service mentioned in this activity.
- DHA J-7 CEPO staff, as well as activity planners and reviewers have no relevant financial or non-financial interest to disclose.
- Commercial support was not received for this activity.

Learning Objectives

At the end of the activity, the learners will be able to:

1. Describe the basics of low-level laser or light-emitting diode (LED) therapies - red, near-infrared wavelengths, terminology, depth of penetration.
2. Analyze results from research with scalp application of red/near-infrared LED to help treat chronic traumatic brain injury (TBI)/post traumatic stress disorder (PTSD).
3. Discuss the results from Dementia Studies, and Gulf War Illness study.

"Scalp Application of near-infrared LEDs to Improve Cognition in Chronic TBI/PTSD, Dementia, and GWI"

Three Parts to this Lecture:

1. **Terminology, Photobiomodulation (PBM); Cellular Effects**
   Low-level lasers or light-emitting diodes (LEDs)
   Wavelengths; Joules/cm^2 delivered per placement; power of device; power density, mW/cm^2

2. **Chronic, Traumatic Brain Injury (TBI) and Posttraumatic Stress Disorder (PTSD)**
   ***Spaulding Rehabilitation Hospital*, Harvard Medical School**
   Naeser, Zafonte, Krengel et al., 2014, *J. of Neurotrauma*
   VA Boston Healthcare System
   Naeser, Martin, Ho et al., 2016, *Photomedicine & Laser Surgery (PMLS)*

3. **Dementia; and Gulf War Illness**

Dementia: Saltmarche, Naeser, Ho, Hamblin, Lim, 2017, *PMLS*; Chao, 2019, *PMLS*
GWI: Chao, 2019, *Military Med.*; Martin, Chao, Krengel et al., 2021, *Frontiers Neurol.*

Part 1. Terminology and Definitions
for Photobiomodulation (PBM), with low-level lasers or LEDs

Photons

- Elementary particles of light with properties of a wave and a particle
- Electrically neutral

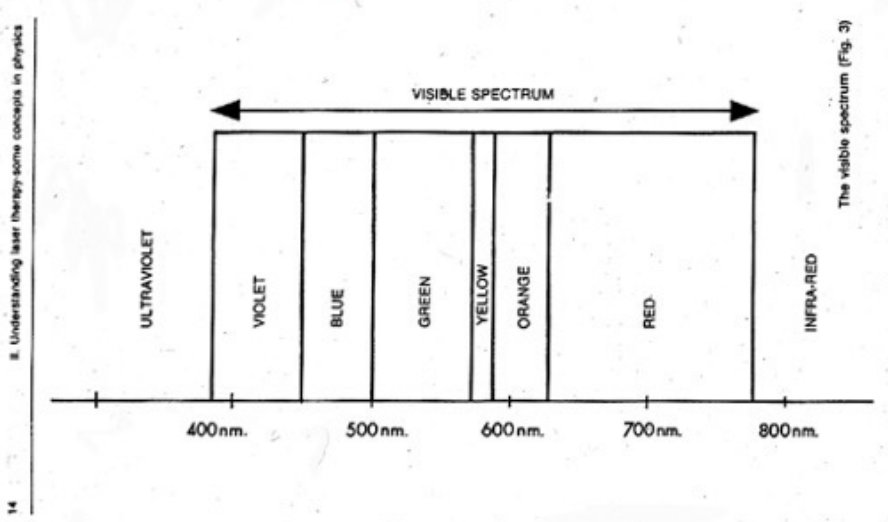
Wavelengths of Light Reported in nanometers (nm) billionth of a meter

Visible Light

- Spectrum Range: 390nm-700nm; blue/violet to red. Some report 400nm to 650 nm.
- Penetration depth of red, is approximately 1 mm direct energy

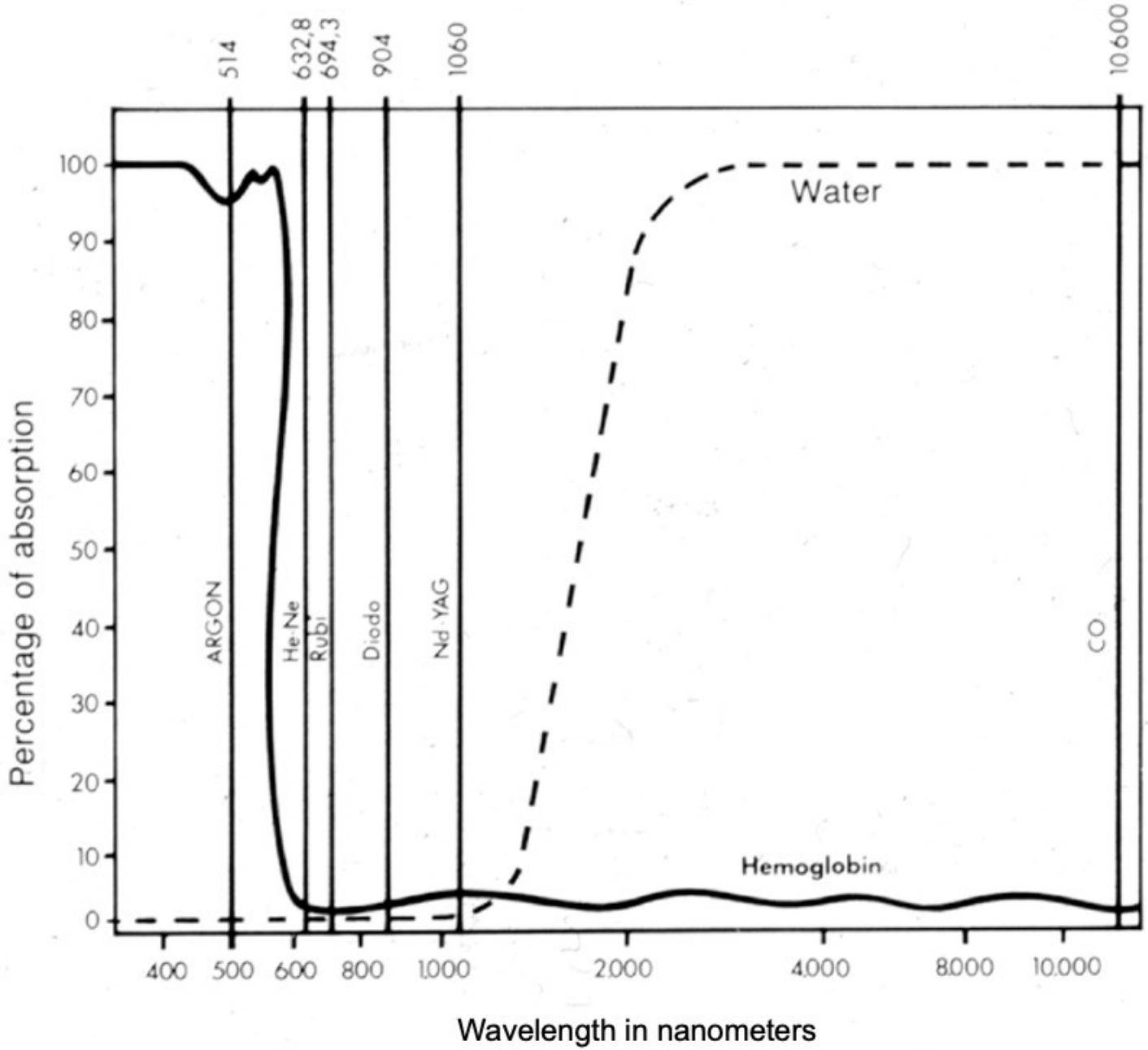
Non-visible Light, shorter or longer wavelengths

- Shorter wavelengths
  - Less than 390nm
  - ***320nm or less are cancer causing***
- Longer wavelengths
  - >700nm
  - penetrate deeper
  - Near-Infrared (810nm - 904nm)
  - *1-2 cm depth penetration*



Source: Colls Cruanes J: Laser Therapy Today, Barcelona, Laser Documentation Center, S.A, Calle Dalmau 11 - 08014, 2nd Edition, November, 1985; ISBN 84-398-6137-0. Translated by Lucie Maguire

Explains why PBM therapy primarily uses *only red or near-infrared wavelengths, 600nm to 1100nm.*



(Colls Cruanes, 1986)

Laser Wavelengths (nm), and Depth of Laser Penetration

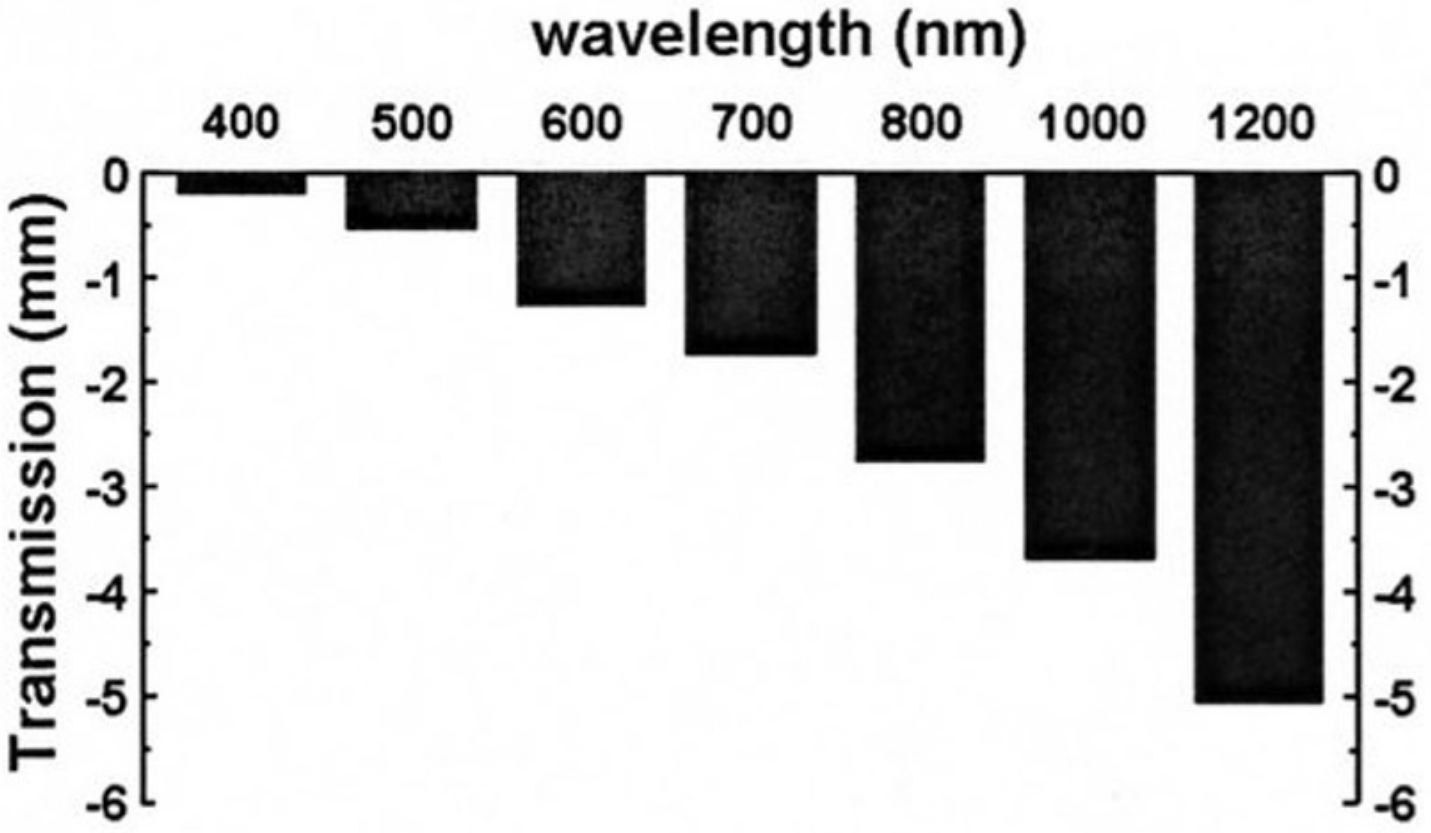
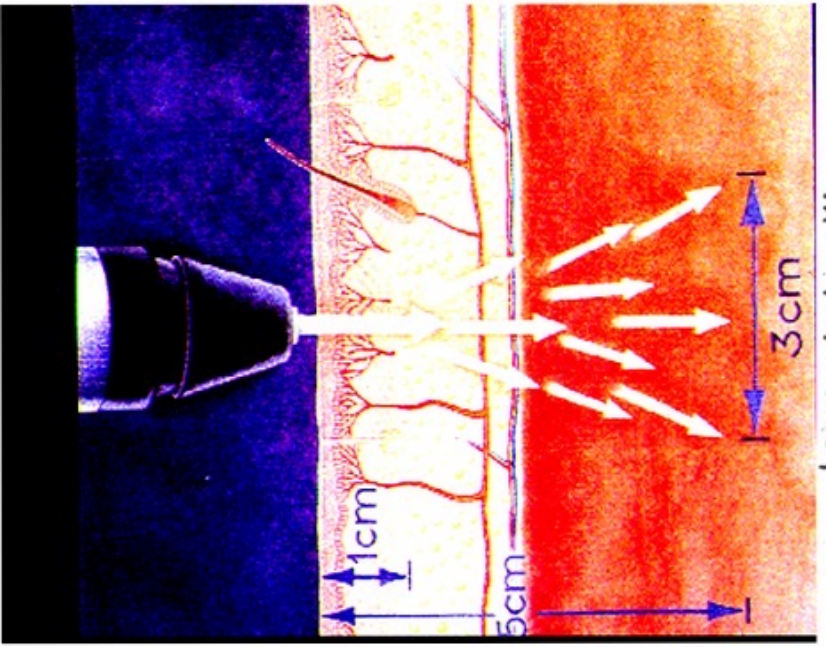
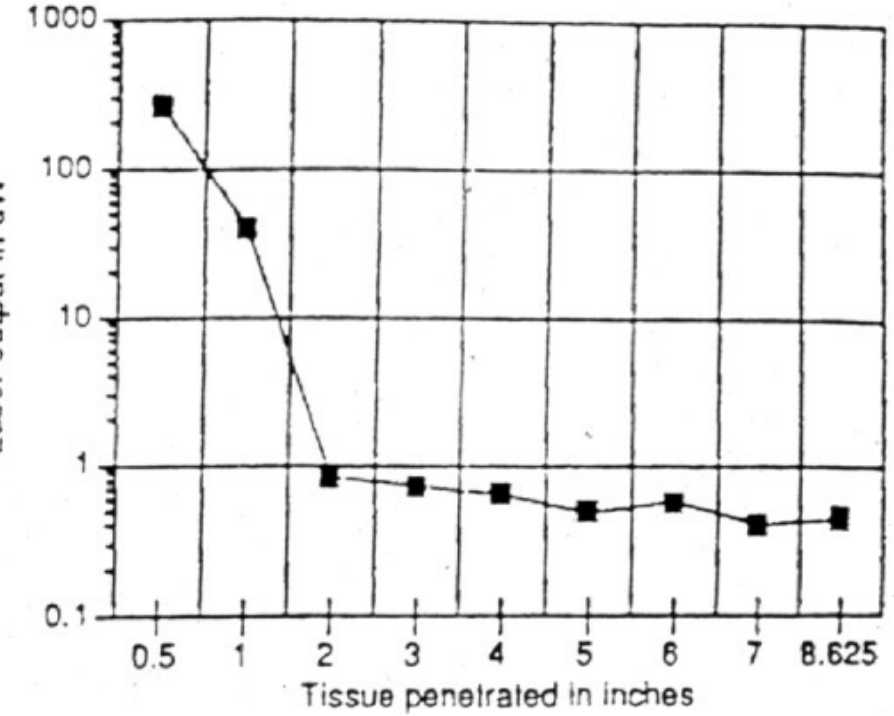


Fig. 1 Transmission in skin. Approximate skin transmission depth at which the incident radiant exposure has decreased by 90%. The transmission depth for a 99% decrease can be calculated by doubling the corresponding 90% depth. Data shown are for fair Caucasian skin. Graph drawn from data presented in [29]

(Anderson et al., 1981; Whittaker, 2004)





Infrared laser, 904 nm

10 Watt peak power pulsed (3,500 pps), gallium arsenide diodes

Four laser diodes placed in a horizontal strip 5.6 cm long

Pulse width, 157 ns for pulses generated

Hudson DE. Preliminary study to measure laser light and LED penetration through tissue. Respond Systems (Branford, CT) Technical Report;1997:1-4.

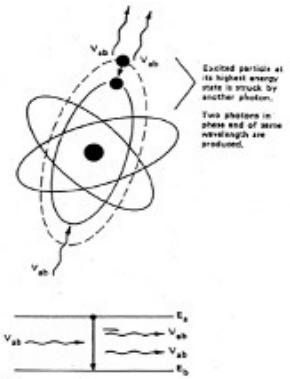
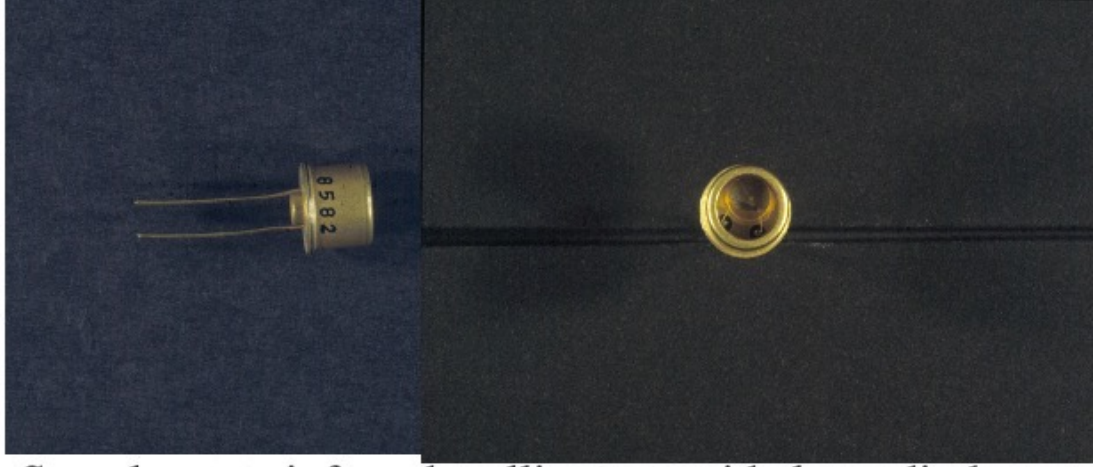


FIGURE 9–1
The principle of stimulated emission. Two photons are emitted from orbit when another photon strikes. E_a, E_b = electrons; V_{ab} = energy of photons.

Source: Seitz LM, Kleinkort JA: Low-Power Laser: Its Applications in Physical Therapy. Chapter 9, in Thermal Agents in Rehabilitation. Michlovitz SL, Editor and Wolf SL, Editor-in-Chief. Philadelphia, F.A. Davis Co., 1986, pp. 217-238.



Sample, near-infrared, gallium arsenide laser diode, 904nm.

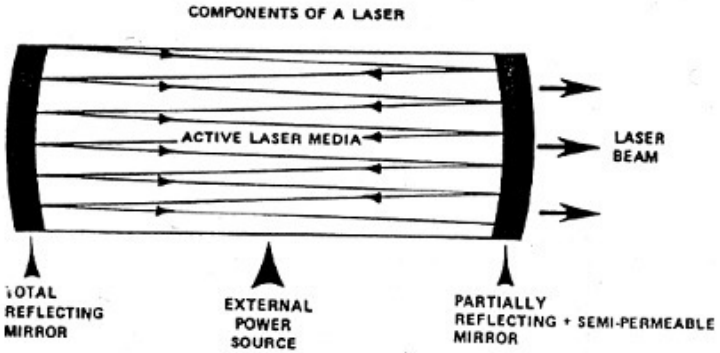


FIGURE 9–3
Basic components of laser.

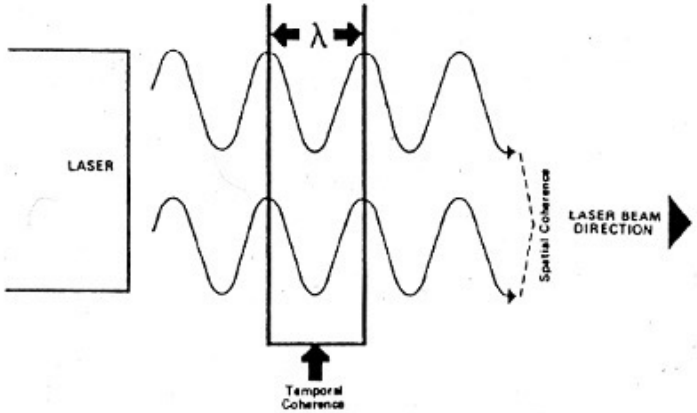


FIGURE 9–4
Coherence—The laser is highly coherent in temporal and spatial planes.

Laser light has photons that are *monochromatic and coherent*.

Source: Seitz LM, Kleinkort JA: Low-Power Laser: Its Applications in Physical Therapy. Chapter 9, in Thermal Agents in Rehabilitation. Michlovitz SL, Editor and Wolf SL, Editor-in-Chief. Philadelphia, F.A. Davis Co., 1986, pp. 217-238.

Higher Power Lasers

Class IV (>500 mW or even 100 W)

Coherent, and monochromatic light

Hazardous to eyes, requires goggles

Lens of the eye would further intensify the laser beam

Need U.S. Food and Drug Administration (FDA) approval

Used in surgery and for tissue ablation

Lower Power Lasers = Low-Level Laser Therapy (LLLT)

Class IIIb (5-500mW)

Coherent, and monochromatic light

'cold lasers' (do not heat up)

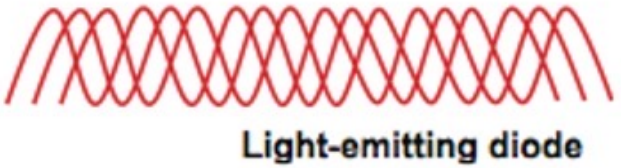
Only hazard if pointed directly into cornea/lens/r

Light-emitting Diodes (LEDs)

Most of the therapeutic ones are 500-1000mW

Noncoherent, but are monochromatic light

Not required to wear goggles; no ocular hazard



MeSH Term Now: Photobiomodulation, PBM, since 2015. Formerly, LLLT

How to Calculate the Number of Sec. Required to Produce 1 Joule of Energy

Three variables are listed below which you must know about a specific laser, before using it. You will also need to know the beam spot size in cm2, which is explained later.

1. The Wavelength, in nanometers (nm, one billionth of a meter). For "laser acupuncture," the wavelength is usually in the red-to-infrared range of 600-1,000 nm. Otherwise, the hemoglobin or water may block the laser beam. The laser manufacturer supplies information on the nm wavelength for each laser.

2. The Power, number of watts, or milliwatts (mw). Usually only 5 or 500 mw (always less than 500 mw). If the laser is greater than 500 mw, it will cause an "ouch" response, and will burn the skin. The laser manufacturer supplies information on the number of milliwatts for each laser.

3. The number of seconds exposure = 1 joule of energy A "joule" is a *unit of work energy* - for example, the energy expended by a current of 1 ampere flowing for 1 second through a resistance of 1 ohm.

Some low-level laser research or clinical papers are published showing only the number of Joules (J) used, per point on the skin. ***It is better, however, to know treatment protocols in J/cm², per point,*** or per cm² on the skin, as is explained on additional pages in this handout. When J/cm² is calculated for a specific laser, the beam spot size must also be known (in cm²). It is important, however, to understand the basic concept of Joule, or unit of work energy.

Energy Density Dosages (Joules/cm^2) *per Point* for Various Treatment Effects

These are also generally used with LED Therapies.

- Analgesic effect: Muscular pain ---------- 2 to 4 joules/cm^2
  Joint pain ---------- 4 to 8 joules/cm^2
- Anti-inflammatory effect: Acute and subacute 1 to 6 joules/cm^2
  Chronic ---------- 4 to 8 joules/cm^2
- Eutrophic effect: ---------- 3 to 6 joules/cm^2
- Circulatory effect: ---------- 1 to 3 joules/cm^2

Note: The World Association for Laser Therapy, WALT, also has a list of Dosages, but only in Joules, not Joules/cm^2

(Colls Cruanes, 1986)

How to Calculate Number of *Seconds* Required to Produce *1 J/cm²* from a laser or LED

Formula: $1\ J/cm^2$ **in seconds =** $\frac{\text{Beam Spot Size in } cm^2}{\text{Power Output of Laser in Watts}}$ $(\pi \times r^2)$

With a *500 mW Laser*, with a 1.14 cm diameter aperture:

Power Output, in Watts: 500 mW (milliwatts) = .500 W (Watts)

Beam Diameter, in cm: *1.14 cm* ***Beam Radius, in cm:*** 0.57 cm

Beam Spot Size in cm^2: $\pi \times r^2$ $3.14 \times .57 \times .57 = 1.02\ cm^2$

$$1\ J/cm^2 \text{ in seconds} = \frac{\text{Beam Spot Size in } cm^2}{\text{Power Output of Laser in Watts}}$$

$$1\ J/cm^2 \text{ in seconds} = \frac{1.02\ cm^2}{.500\ W}$$

$1\ J/cm^2 =$ ***2.04 Seconds***

How to Calculate Number of *Seconds* Required to Produce *1 J/cm²* from a laser or LED

Formula: $1\ J/cm^2$ **in seconds =** $\frac{\text{Beam Spot Size in } cm^2}{\text{Power Output of Laser in Watts}}$ $(\pi \times r^2)$

With a *5 mW* Laser Lecture Pointer, with a 1.14 cm diameter aperture:

Power Output, in Watts: 5 mW (milliwatts) = .005 W (Watts)

Beam Diameter, in cm: *1.14 cm* ***Beam Radius, in cm:*** 0.57 cm

Beam Spot Size in cm^2: $\pi \times r^2$ $3.14 \times .57 \times .57 = 1.02\ cm^2$

$$1\ J/cm^2 \text{ in seconds} = \frac{\text{Beam Spot Size in } cm^2}{\text{Power Output of Laser in Watts}}$$

$$1\ J/cm^2 \text{ in seconds} = \frac{1.02\ cm^2}{.005\ W}$$

$1\ J/cm^2$ = *204 Seconds* (3 Min, 24 Sec)

Thus, **POWER IS IMPORTANT**

IN TERMS OF **TIME NECESSARY TO PRODUCE 1 J/cm^2**,

AND ***TIME TO TREAT***:

With the ***500 mW laser*** (approximately 1 cm diameter aperture): **1 J/cm^2 = 2.04 Seconds**

With the ***5 mW laser pointer*** (approximately 1 cm diameter aperture): **1 J/cm^2 = 3 Min, 24 Sec**

Sample Spec.'s for a Light-Emitting Diode (LED) Cluster head Device

FDA-Cleared, Non-significant risk, since 2003

Circular-shaped. Cluster-head diameter: 5.345 cm (2.1 inches)
Treatment Area ("Beam" spot size): 22.48 cm^2

Single cluster head contained ***61 diodes***:

9** red **633 nm diodes

52** near-infrared **870 nm diodes

Total optical output *Power*: 500 mW (±20%) CW

1 J/cm^2 = 45 sec

***Power Density*: 22.2 mW/cm^2** (±20%)

10 min per area; 13.3 J/cm^2 per area (0.4 J/cm^2 to brain cortex).

Estimate: 2-3% of NIR photons from extra-cranial placement will reach 1 cm deep, to reach surface brain cortex. (Wan,Parrish, et al., 1981; Tedford et al., 2015)

LED device used to improve cognition in chronic, mTBI (Naeser et al., 2011; 2014; 2016)

Review Terminology: Low-Level Laser, or LED parameters

Photons

- Elementary particles of light with properties of a wave and a particle

Wavelengths of Light Reported in nanometers (nm) billionth of a meter

Primarily work with Photons in *Red (600's nm)*, and *Near-infrared (NIR) (800's nm)*

Red, 1 mm direct penetration; Near-infrared, 1-2 cm, or up to 4-5 cm

Joule

- Unit of Work Energy

Energy Density, Joules per cm^2 = J/cm^2 delivered to a spot or cm^2 area on a wound, or to a painful area, or to the scalp/brain, etc.

Beam Spot Size in cm^2 (π x r^2). Calculated by the user.

Formula: 1 J/cm^2 in seconds = Beam Spot Size in cm^2 (π x r^2)
Power Output of Laser in Watts

Power Density, Power per cm^2 = mW/cm^2 e.g., 22 mW/cm^2 or 150 to 300 mW/cm^2

Provided by the Manufacturer of that specific laser or LED device.

Range is often 20 mW/cm^2 to 150 mW/cm^2 or more, with LED cluster heads.

Cellular Effects of Red/NIR Low-Level Lasers or LEDs.

Collagen and protein Synthesis (Wound healing)

Increased Adenosine Triphosphate (ATP) synthesis
Especially in hypoxic/compromised cells

Promote Vasodilation
Blood and Lymphatic vessels

Neurotransmitter release **(Serotonin)**

Increase in stem cell proliferation;
Brain-derived neurotrophic factor (BDNF);
Synapsin-1 synaptogenesis;
Neurogenesis (mice studies)

Anti-oxidant and **Anti-inflammatory** effects

Table 1. Cellular Effects of Low-Energy Laser Irradiation (Basford, 1989)

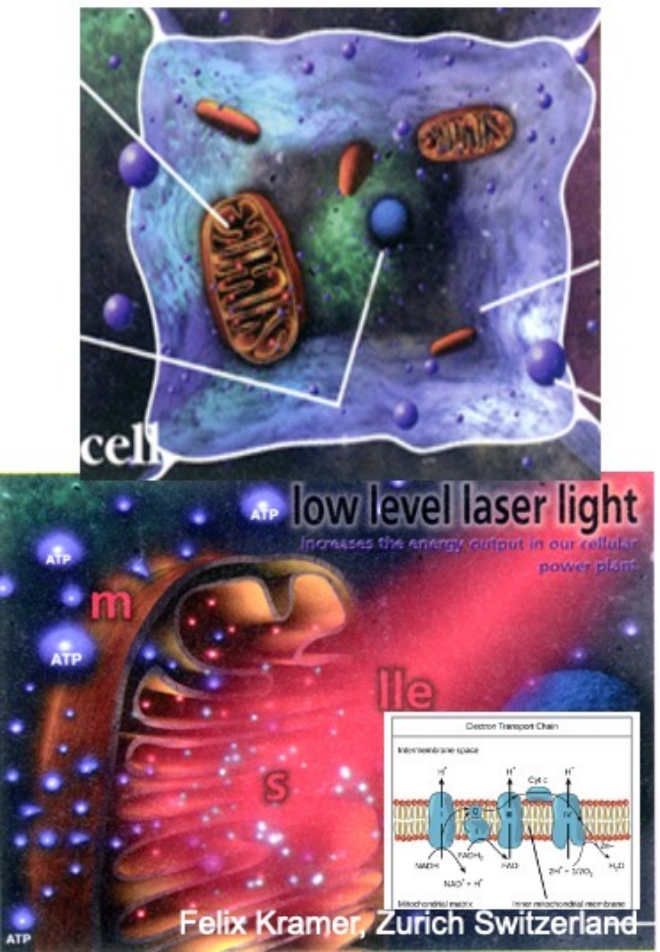
Phenomenon	Change and reported	Model	Laser
Collagen and protein synthesis Glassberg, Lask, Uitto, 1988 Simunovic, Ivankovich, 1988 Barabas, Bakos, Szabo, et al, 1988 Mester, Toth, Mester, 1982 Lyons, Abergel, White, Dwyer, Castel, Uitto, 1987 Hermah, Khosla, 1987	Increase & decrease	Human fibroblasts, rabbit skin, human synovium, bovine cartilage	HeNe HeNe + GaAs Nd:PO, glass Nd:YAG
RNA synthesis Glassberg, Lask, Uitto, 1988 Simunovic, Ivankovich, 1988 Barabas, Bakos, Szabo, et al, 1988 Mester, Toth, Mester, 1982 Lyons, Abergel, White, Dwyer, Castel, Uitto, 1987 Herman, Khosla, 1987 Karu, 1987	Increase	Mouse skin	HeNe
Cell proliferation Hardy, Hardy, Fine, Sokal, 1967 Abergel, Dwyer, Meeker, lask, Kelly, Uitto, 1984	Increase & decrease	Mouse fibroblasts, human lymphocytes	Ruby HeNe GaAs
Cell granule release Trelles, Mayayo, Miro, Rigau, Baudin, 1988	Increase	Mouse mast cells	HeNe
Cell Motility Sato, Landthaler, Haina, Schill, 1984	Increase	Human sperm	Kr
Membrane potential Passarella, Casamassima, Molinari, Pastore, Quagliariello, Catalano, Cingolani, 1984 Passarella, 1988 Kubasova, Kovacs, Somosy, Unk, Kokai, 1984	Increase	Rat liver mitochondria, human fibroblasts	HeNe
Cell binding affinities Kubasova, Kovacs, Somosy, Unk, Kokai, 1984 Passarella, Casamassima, Quagliariello, Caretto, Jirillo, 1985	Increase	Human lymphocytes and fibroblasts	HeNe
Neurotransmitter release Vizi, Mester, Tizba, Mester, 1977 Oxyhemoglobin dissociation Itzkan, Tang, Bourgelais, 1988	Increase Increase	Acetylcholine (guinea pigs)	Ruby
Phagocytosis Mester, Mester, Mester, 1985	Increase	Human leukocytes	Ruby
ATP syntheses Passarella, Casamassima, Molinari, Pastore, Quagliariello, Catalano, Cingolani, 1984 Passarella, 1988	Increase	Rat liver mitochondria	HeNe
Intercellular matrix Yew, Wong, Chang, 1982	Increase	Mouse retina	HeNe
Prostaglandin synthesis Mester, Toth, Mester, 1982	Increase	Rat skin	HeNe

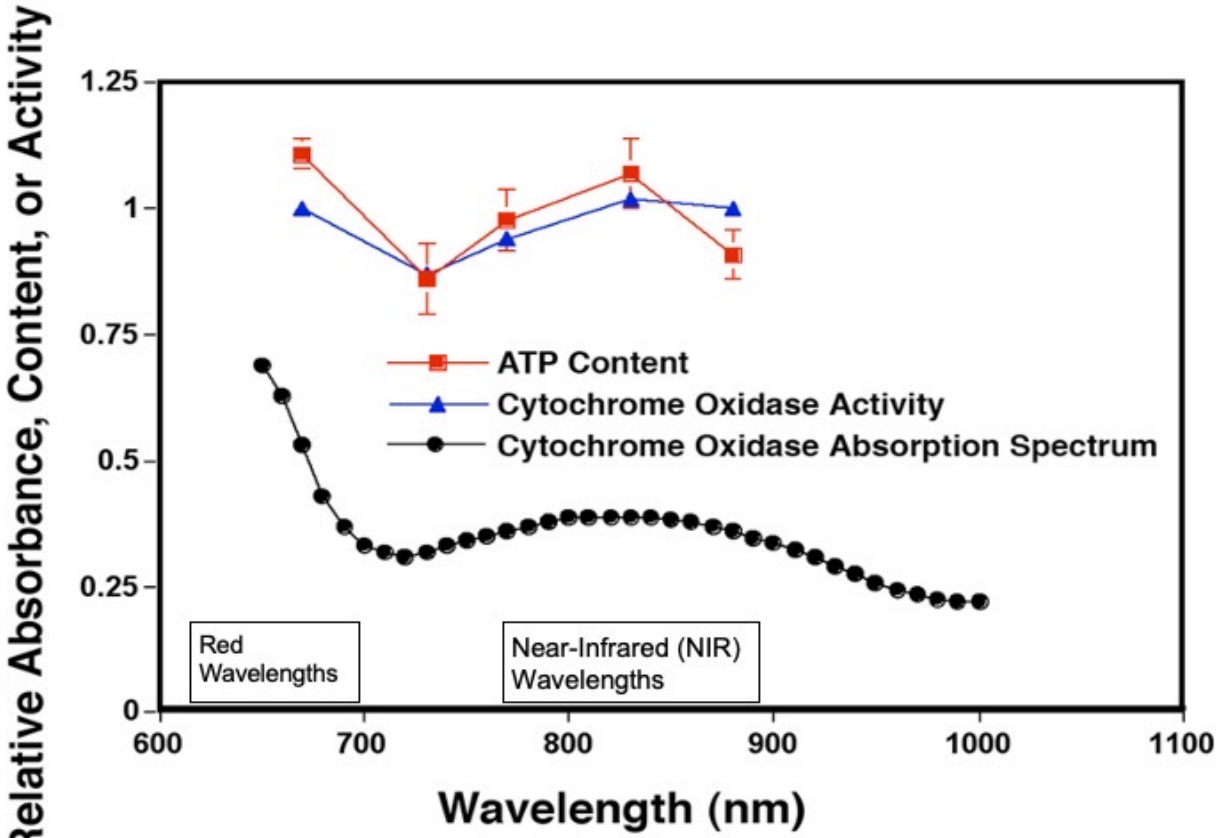
Rationale for Low-Level Laser Therapy (LLLT) and Light-emitting Diode (LED) Therapy:

Cytochrome c oxidase, in last complex of the electron transport chain in **mitochondria** maximally absorbs light in wavelengths of ***red and near-infrared (NIR)***.

This will ***increase ATP production*** **(and improve cellular respiration and oxygenation).**

(Karu, 1995; 2005)

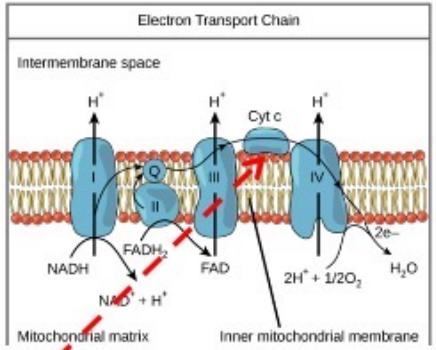




(Wong-Riley et al., 2005)

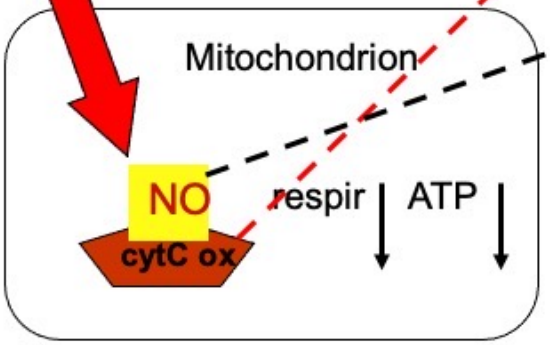
Hypothesis for Hypoxic/compromised cells

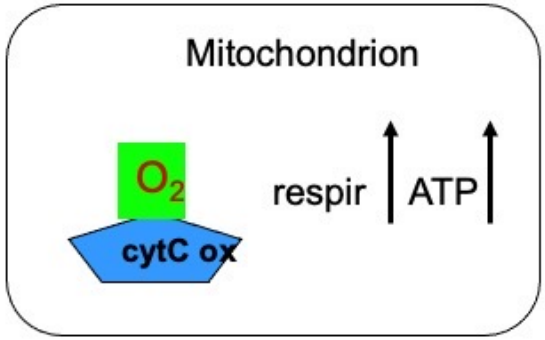
Red or NIR light



In a stressed, hypoxic cell

NO





Hypothesis regarding effect of red or near-infrared (NIR) light on the **primary photo-acceptor, Cytochrome C Oxidase (cytC ox), dotted red line** in this diagram, located in the mitochondrial membrane. Before red/NIR LLLT/LED application, the **CytC ox appears "saturated" with nitric oxide (NO), yellow box.** After application of red/NIR photons, the **mitochondria will increase ATP production** and improve cell respiration.

The **NO is *pushed outside the cell wall,* *dotted black line;* this will promote local vasodilation.**

M. Hamblin, R. Anderson, Wellman Center for Photomedicine, MGH

Explains why:

Normal cells and tissue generally do not respond

Hypoxic cells, damaged cells, and tissue at risk of death respond well

Effects continue for long time after light is switched off

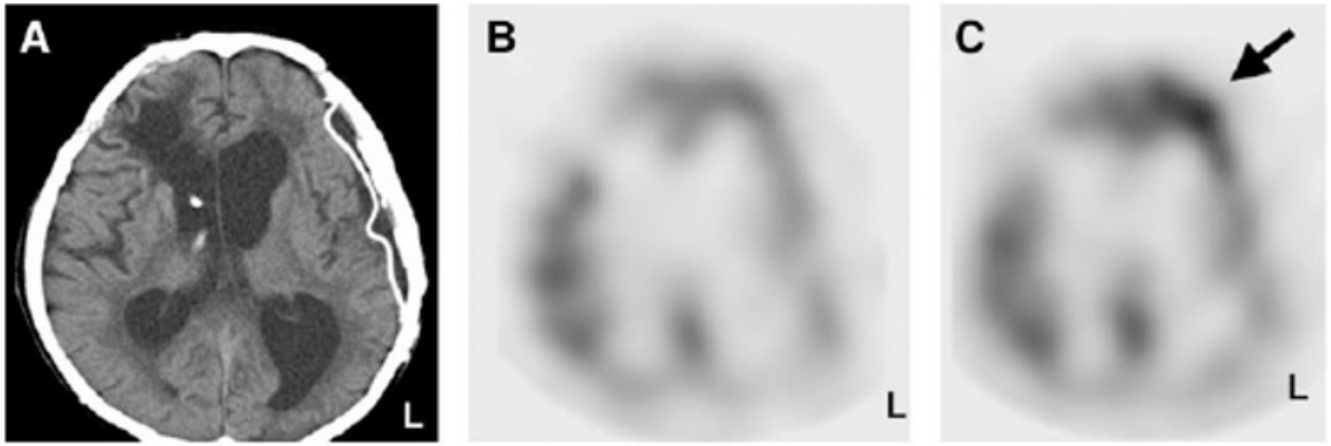
Released nitric oxide temporarily ***increases blood flow in illuminated area***

Released nitric oxide ***reduces swelling by dilating lymphatic vessels and increasing drainage***

(Hamblin et al., 2005; Ayuk et al., 2018)

Promotion of Vasodilation after series of LED treatments:

Transcranial LED to treat Severe TBI, Persistent Vegetative State



A) Computed Tomography (CT) scan for persistent vegetative state case, at 7 Mo. post-severe TBI.

B) Single-photon emission computed tomography (SPECT) scan also at 7 Mo.; ***pre- transcranial LED (tLED) therapy.***

C) SPECT scan at **30min after last tLED treatment, after 3 Mo. of LED therapy,** showing ***focal increase of 20%*** (vs. pre-LED) for ***Regional cerebral blood flow (rCBF)*** in the left anterior frontal cortex (black arrow).

(Nawashiro et al., 2012)

Mitochondria travel along the axons.

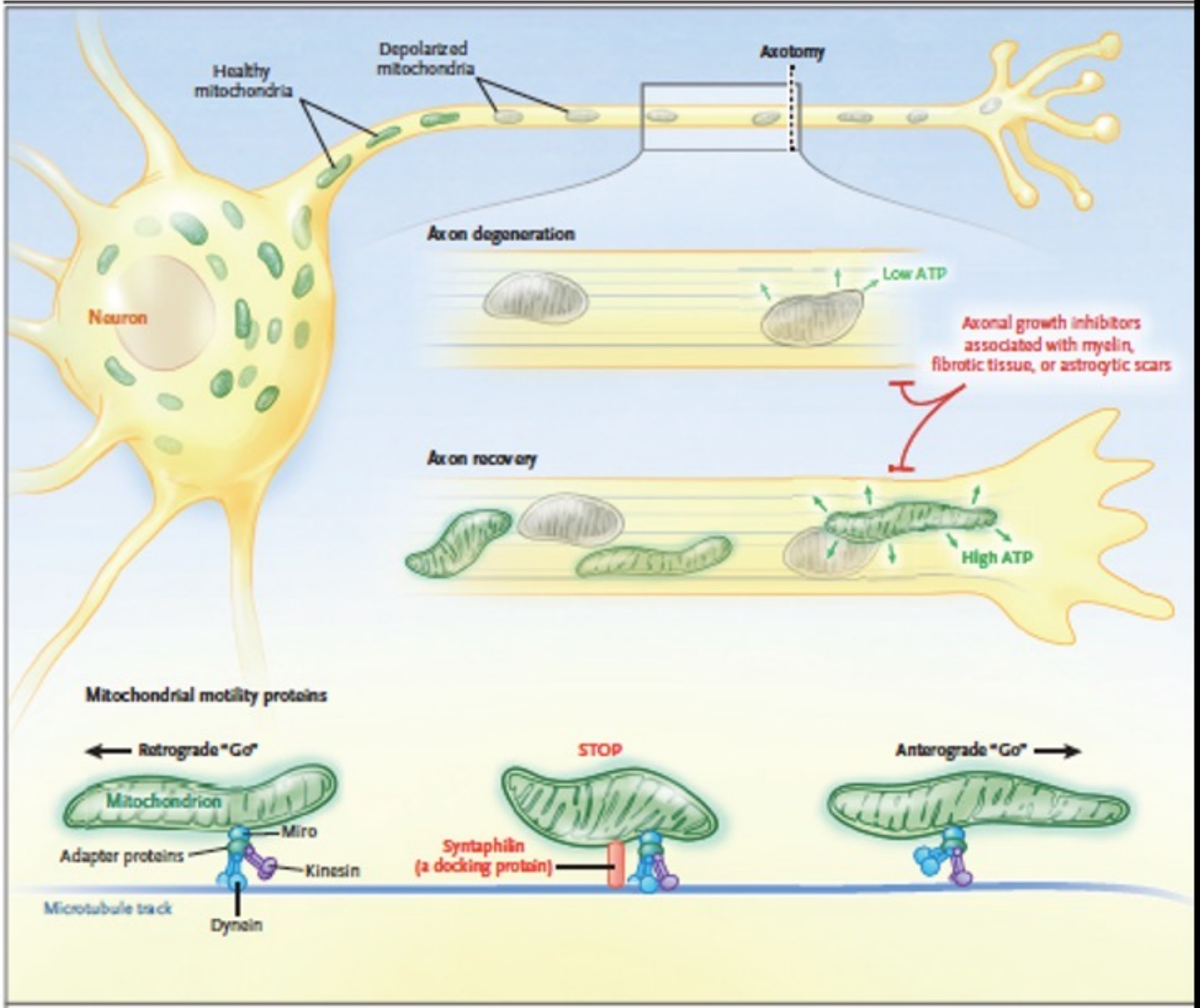


Figure 1. Mitochondrial Motility and Axon Recovery.

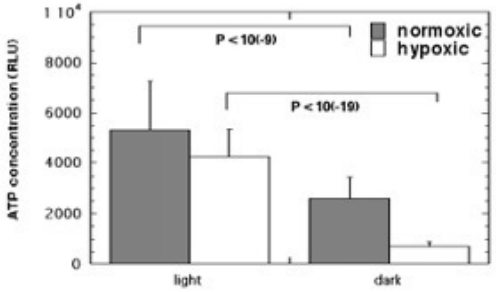
Mitochondria that are close to the site of axonal injury (axotomy) lose their membrane potential and do not produce ATP. In a recent study, Zhou et al.[1] found that the loss of the docking protein syntaphilin increases mitochondrial motility and is associated with the recruitment of healthy mitochondria with high membrane potential (shown in green) into the injured area, thereby enhancing the local energy supply and supporting axon recovery. Mitochondrial transport is driven by molecular motor proteins: dynein proteins, which are responsible for retrograde movement, and kinesin proteins, which are responsible for anterograde movement. Adapter proteins link these motor proteins to Miro proteins in the mitochondrial membrane. Docking proteins, such as syntaphilin, can immobilize mitochondria on microtubules.

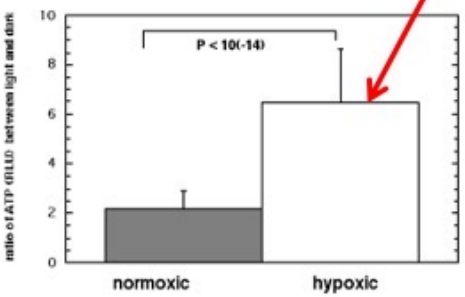
(Kaasik, 2016)

There will be *greater increase in ATP for Hypoxic Cells*, than Normoxic Cells

after exposure to red or near-infrared photons

Low-Level Laser Therapy (LLLT), 1.4 J/cm^2 of 810 nm IR light delivered at 10 mW/cm^2 has bigger effect in increasing ATP **in hypoxic cells** (1 hour under N_2)

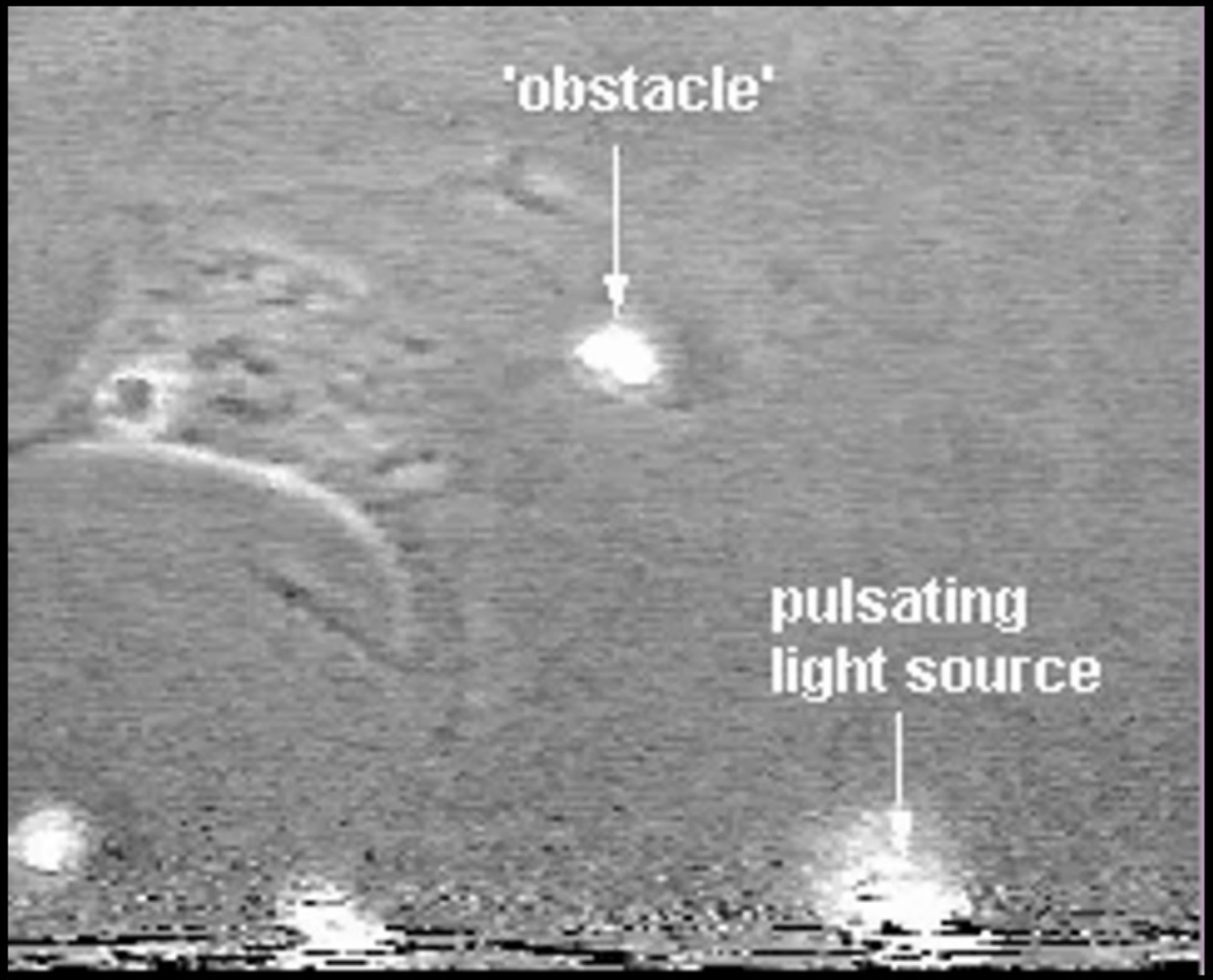




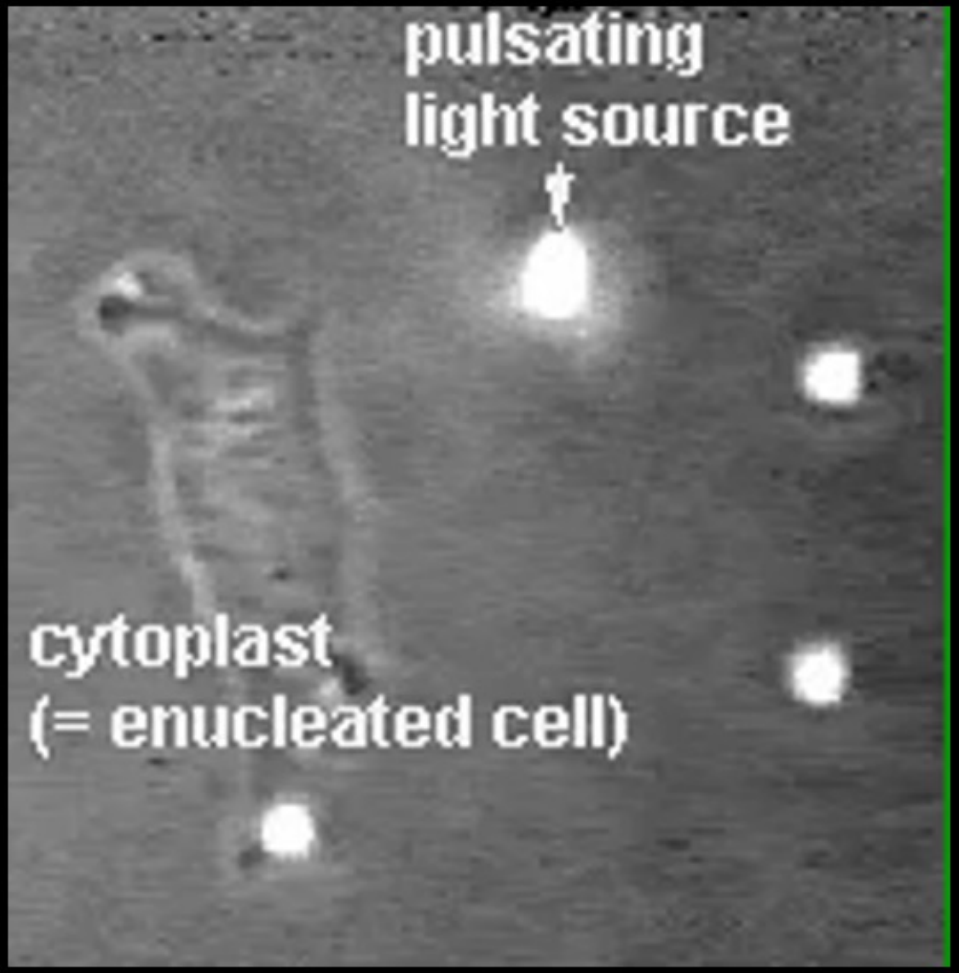
Near-infrared (NIR) photons promote ***a greater increase of ATP in hypoxic cells*** *(6x increase)*, than in normoxic cells (2x increase). Mean luminescence values (+/- SD) from 12 wells of HeLa cells (a human cervical cancer cell line used to demonstrate LLLT effects) treated or not, with 1.4 J/cm^2 of NIR 810 nm light in either normoxic conditions (regular atmosphere) or hypoxic conditions (1 hour exposure to pure nitrogen after 3 cycles of vacuum).

M. Hamblin, PhD, Consultant on VA LED projects; from the Wellman Center for Photomedicine, MGH

Video of mouse fibroblast cell, seeking out a pulsating, near-infrared, laser light.
Note, *the cell maneuvers around an obstacle*, to get to the laser light.
Source: Guenter Albrecht-Buehler, Ph.D., Physicist
Northwestern University Medical School, Chicago



Video of mouse fibroblast cell, seeking out a pulsating, near-infrared, laser light.
The nucleus has been removed from this cell (an enucleated cell), yet the remainder of the cell still seeks out the light - the mitochondria are outside the nucleus.
Source: Guenter Albrecht-Buehler, Ph.D., Physicist
Northwestern University Medical School, Chicago



Anti-inflammatory **effects of Low-level Laser Therapy (LLLT)**

(Hamblin, 2017)

Reports (Castano et al., 2007) demonstrate that ***LLLT reduces cyclooxygenase-2 (COX-2)*** expression levels and ***reduces prostaglandins*** in multiple animal models as well as in vitro (Aimbire et al., 2005; Albertini et al., 2007; Sakurai et al., 2000).

A key inflammatory mediator that has been implicated in pathogenesis of TBI is the cytokine tumor necrosis factor alpha (TNFα).

There are multiple reports showing that ***LLLT reduces TNF α levels in arthritis*** (Aimbire et al., 2006) and other animal models of inflammation.

Low-level laser light therapy ***inhibited microglial activation,*** *in* ***acute, severe TBI,*** after controlled cortical impact in mice (60 Joules/cm^2 with open craniotomy).

(Khuman et al., 2012)

Additional effects of Low-level Laser Therapy (LLLT)

Anti-oxidant Effects

After exposure to red or near-infrared, laser or LED, there will be a ***brief burst of reactive oxygen species (ROS)***.

This will induce redox-sensitive transcription factors,

such as ***nuclear factor-kappa B***,

that ***promote gene transcription***.

The ***mitochondrial superoxide dismutase*** (anti-oxidant effect)

is one of the most upregulated genes

after NF-kB activation (Sompol et al., 2006).

Another highly upregulated gene after NF-kB activation and after LED/LLLT,

is ***heat-shock protein 70***,

a molecular chaperone for protein molecules that

prevents mis-folding and unwanted protein aggregation in telomeres

(Zhang et al., 1994).

Wiley Online Library Early View publication on www.wileyonlinelibrary.com (issue and page numbers not yet assigned; citable using Digital Object Identifier – DOI)

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

Journal of BIOPHOTONICS

(Xuan et al., 2015)

FULL ARTICLE

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

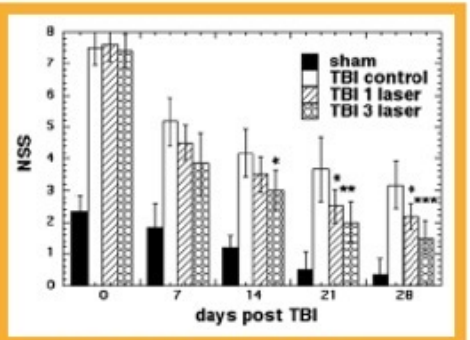
Weijun Xuan[†,1,2,3], *Tanupriya Agrawal*[†,2,3], *Liyi Huang*[2,3,4], *Gaurav K. Gupta*[2,3,5], *and Michael R. Hamblin*[*,2,3,6]

[1] Department of Otolaryngology, First Affiliated College & Hospital, Guangxi University of Chinese Medicine, Nanning, China
[2] Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA 02114, USA
[3] Department of Dermatology, Harvard Medical School, Boston, MA 02115, USA
[4] Department of Infectious Diseases, First Affiliated College & Hospital, Guangxi Medical University, Nanning, 530021, China
[5] Department of Pathology and Laboratory Medicine, Tufts Medical Center, Boston, MA 02111, USA
[6] Harvard-MIT Division of Health Sciences and Technology, Cambridge, MA 02139, USA

Received 25 June 2014, revised 22 July 2014, accepted 24 July 2014
Published online 5 September 2014

Key words: traumatic brain injury, transcranial low level light therapy, synaptogenesis, neurogenesis, BDNF, Synapsin-1

Transcranial low-level laser (light) therapy (LLLT) is a new non-invasive approach to treating a range of brain disorders including traumatic brain injury (TBI). We (and others) have shown that applying near-infrared light to the head of animals that have suffered TBI produces improvement in neurological functioning, lessens the size of the brain lesion, reduces neuroinflammation, and stimulates the formation of new neurons. In the present study we used a controlled cortical impact TBI in mice and treated the mice either once (4 h post-TBI, 1-laser), or three daily applications (3-laser) with 810 nm CW laser 36 J/cm^2 at 50 mW/cm^2. Similar to previous studies, the neurological severity score improved in laser-treated mice compared to untreated TBI mice at day 14 and continued to further improve at days 21 and 28 with 3-laser being better than 1-laser. Mice were sacrificed at days 7 and 28 and brains removed for immunofluorescence analysis. Brain-derived neurotrophic factor (BDNF) was significantly upregulated by laser treatment in the dentate gyrus of the hippocampus (DG) and the subventricular zone (SVZ) but not in the perilesional cortex (lesion) at day 7 but not at day 28. Synapsin-1 (a marker for synaptogenesis, the formation of new connections between existing neurons) was significantly upregulated in lesion and SVZ but not DG, at 28 days but not 7 days. The data suggest that the benefit of LLLT to the brain is partly mediated by stimulation of BDNF production, which may in turn encourage synaptogenesis. Moreover the pleiotropic benefits of BDNF in the brain suggest LLLT may have wider applications to neurodegenerative and psychiatric disorders.



Neurological Severity Score (NSS) for TBI mice

* Correspondence author: e-mail: hamblin@helix.mgh.harvard.edu, Phone: 617-726-6182, Fax: 617-726-8566

Apply **810 nm laser** to head of
Mice after ***Acute TBI***
(Controlled Cortical Impact TBI)

36 J/cm^2 Delivered Energy Density
50 mW/cm^2 The Power Density

Apply laser at **4 hours post- TBI**

Apply laser, **1x per day, for 3 days**.

At **Day 7**, increase in **BDNF**
in Dentate Gyrus, of Hippocampus
And
Subventricular Zone
BDNF promotes Neurogenesis

At **Day 28**, increase in Synapsin-1
in Periesional area
And
Subventricular zone.
Synaptogenesis *was also* ***promoted.***

At Day 28, Improved Behavior.

(Xuan et al., 2014)

Part 2. Traumatic Brain Injury (TBI)

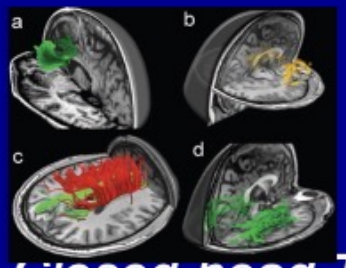
- Each year, 1.7 million patients evaluated for traumatic brain injury (TBI), including *3 TBIs every minute in U.S.*
- Annual cost between $60-$76.5 billion
- *Closed-head, mild TBI, most common (75%)* Loss of Consciousness, <30 Min
- ***20-30% of these, have persistent cognitive dysfunction*** (CDC, 2013)

- With closed-head TBI, *diffuse axonal injury (DAI)*

results, when shearing, stretching, and/or angular forces pull on axons and small vessels.

Normal structural CT scan or Magnetic Resonance Imaging (MRI).

(Taber et al, 2006; Medana et al, 2003)



- *Closed-head TBI from blast injury* is *the major injury* of Veterans returning from Iraq and Afghanistan. (Hoge, McGurk, Thomas *et al.*, 2008)

Traumatic Brain Injury (TBI) often results in Cognitive Dysfunction

- *Chronic, mild TBI* is associated with *persistent* post-concussive symptoms, and problems with:
- attention
- cognitive manipulation of temporal information
- processing speed
- *working memory,* i.e., the ability to hold information in mind, and to manipulate it in light of incoming material.

- These "*executive functions*" are sensitive to *damage in frontal lobes* - orbital, medial (*ant. cingulate gyrus*), and dorsolateral, *prefrontal cortex*.

JOURNAL OF NEUROTRAUMA 31:1008–1017 (June 1, 2014)

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

Also, observed ***Reduced PTSD***, and ***Improved Sleep***

Margaret A. Naeser,[1,2] Ross Zafonte,[3,4] Maxine H. Krengel,[1,2] Paula I. Martin,[1,2] Judith Frazier,[3] Michael R. Hamblin,[5] Jeffrey A. Knight,[6] William P. Meehan III,[7] and Errol H. Baker[1]

Participants: 11 chronic, mild TBI cases (26-62 Yr, 6M) ***persistent cognitive dysfunction, >6 Months***

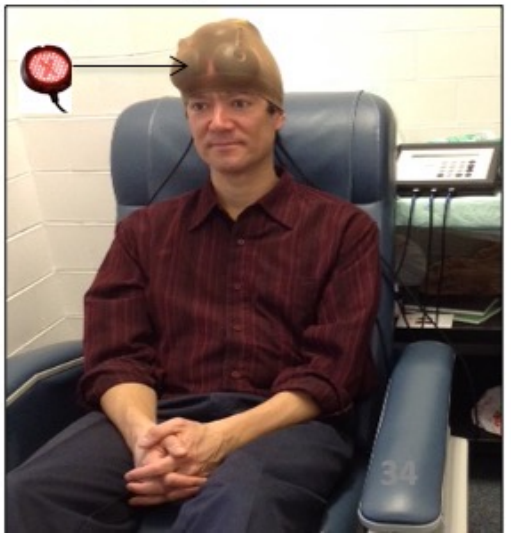
LED Treatment ***started at 10 months to 8 years post-mTBI*** **6 / 11 were >2 years post- TBI**
(MVA, Sports-related-Skiing, Skateboarding, IED blast TBI)

Participants had one or **more *closed-head TBI*** with LOC ranging 0-30 min. **4 / 11, multiple TBIs**

Single cluster head contained ***61 diodes***:
9** red **633 nm diodes (1 mW, each diode)
52** near-infrared **870 nm diodes (12-15 mW, each diode)

Total optical output *Power*: 500 mW (±20%) CW
1 J/cm² = 45 sec
***Power Density*: 22.2 mW/cm²** (±20%)

10 min per area; 13.3 J/cm² per area (0.4 J/cm² to brain cortex)



Bilateral LED Placement Loci: 11 LED head placement loci. Left Side, Right Side, and Midline placements.

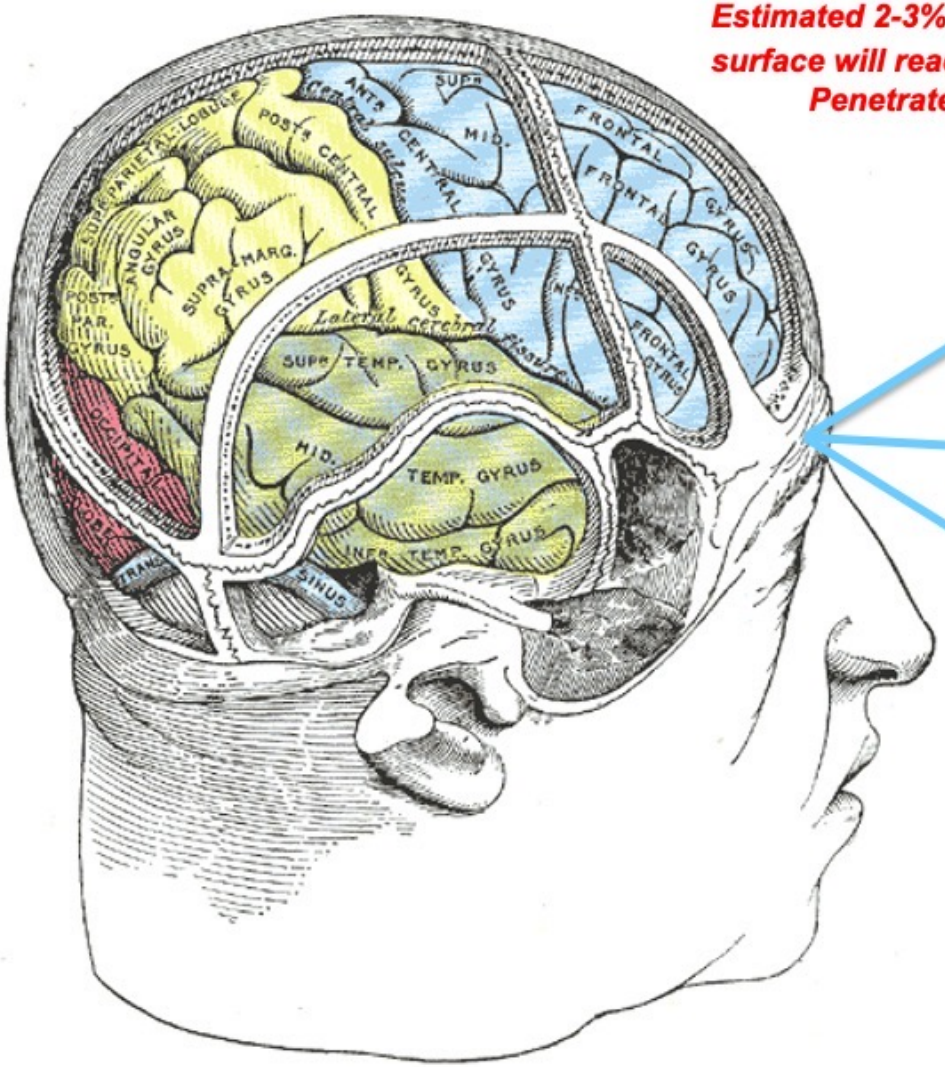
Each treated for 10 min, each. 13.3 J/cm^2 at skin surface,

Estimated 0.4 J/cm^2 at 1cm deep, surface brain cortex.

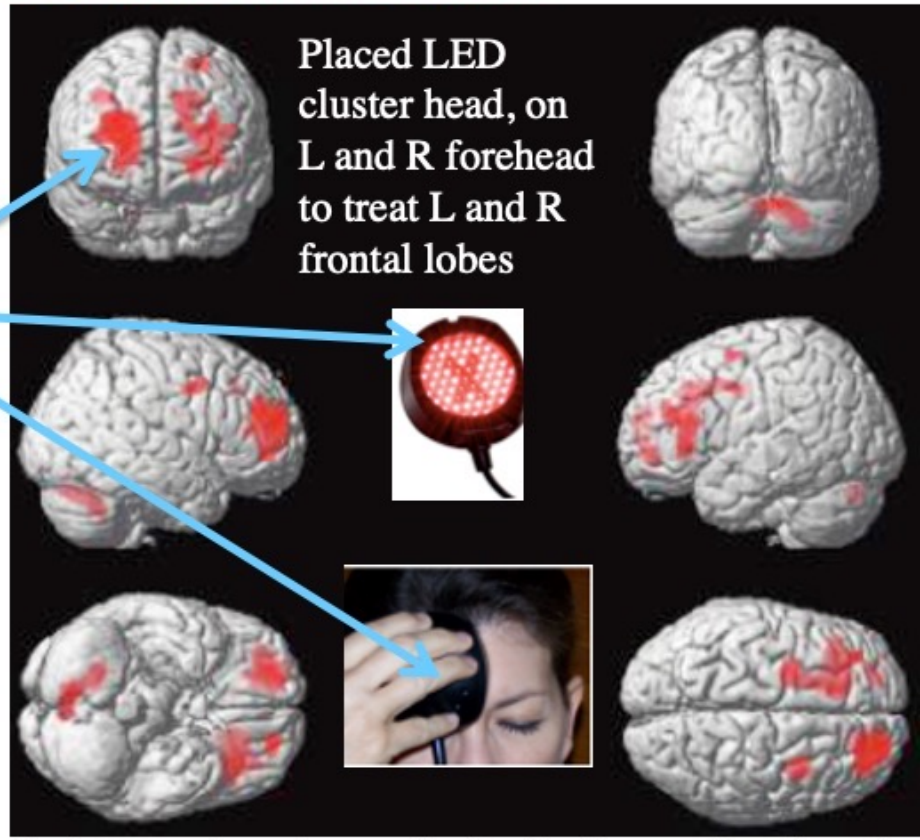
Each 2-inch diameter, LED cluster head, 500 mW (± 20%).

Estimated 2-3% of near-infrared, energy penetration from skin/scalp surface will reach 1 cm deep, to surface brain cortex. Wan, et al., 1981;

Penetrate 4-5 cm, human cadaver scalp/brain. Tedford, et al., 2015.



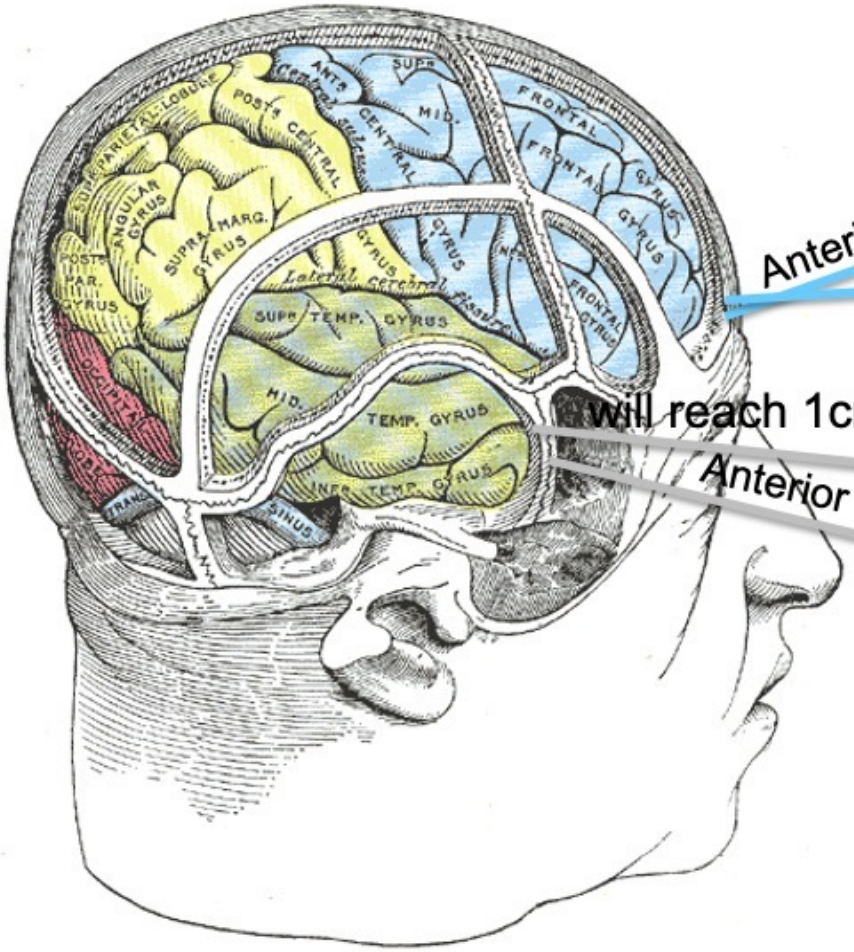
Location of Gyral Areas of Brain Cortex, in Relationship to Bone Suture Lines of Skull.
(Gray1197.png)



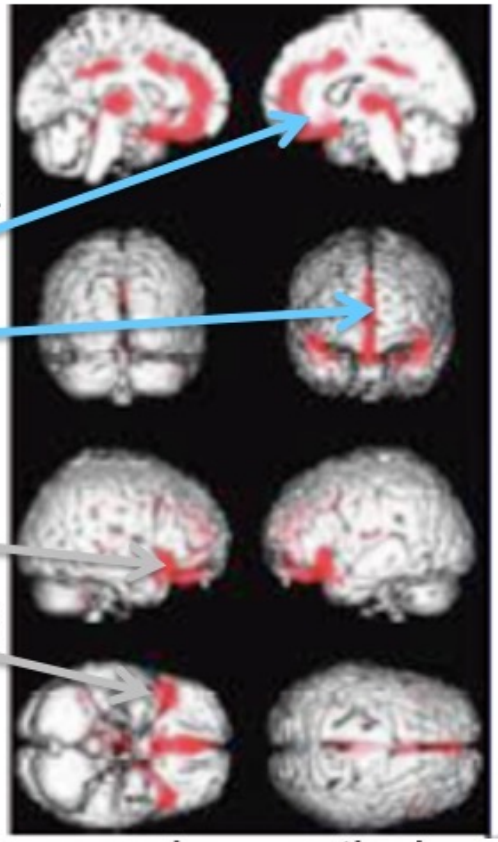
Red areas show *low cortical activation* on **functional MRI *in chronic, traumatic brain injury cases*** [post- motor vehicle accidents (MVA)] with "cognitive dysfunction."

(Sanchez-Carrion et al., 2008; Naeser et al., 2011)

In **TBI**, the **ventral, mesial surface of the frontal lobes** ***(Anterior Cingulate G.,*** and mesial, inferior, prefrontal cortex) are areas with low glucose metabolism in chronic, TBI. This is a target area, with the LED cluster head that is placed at the midline, center front hairline.



Location of Gyral Areas of Brain Cortex, in Relationship to Bone Suture Lines of Skull.
(Gray1197.png)



Red areas show cortical areas of *low glucose metabolism on* **PET scans** in chronic, TBI cases (post- MVA) with cognitive dysfunction. (Kato et al., 2007; Naeser, 2011)

Spaulding Rehab. Hosp., *Boston.* *Transcranial LED to Treat mTBI:*

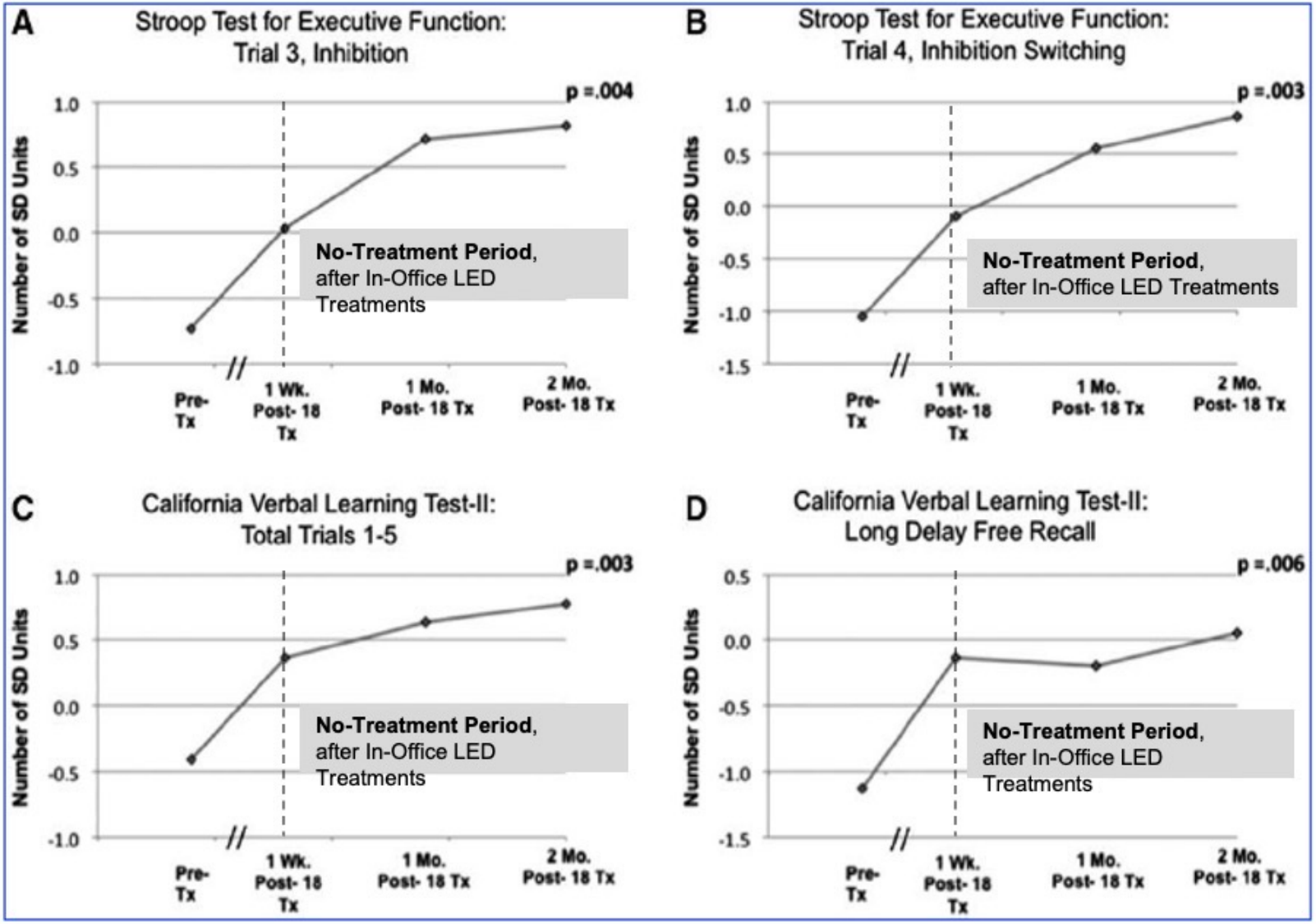
Neuropsychological, Cognitive Test Results

Results

11 mTBI Cases
Most, MVAs, 1 Blast-TBI

Treated *In-Office* With Transcranial LED Cluster Heads.

MedX Health, Red/NIR.

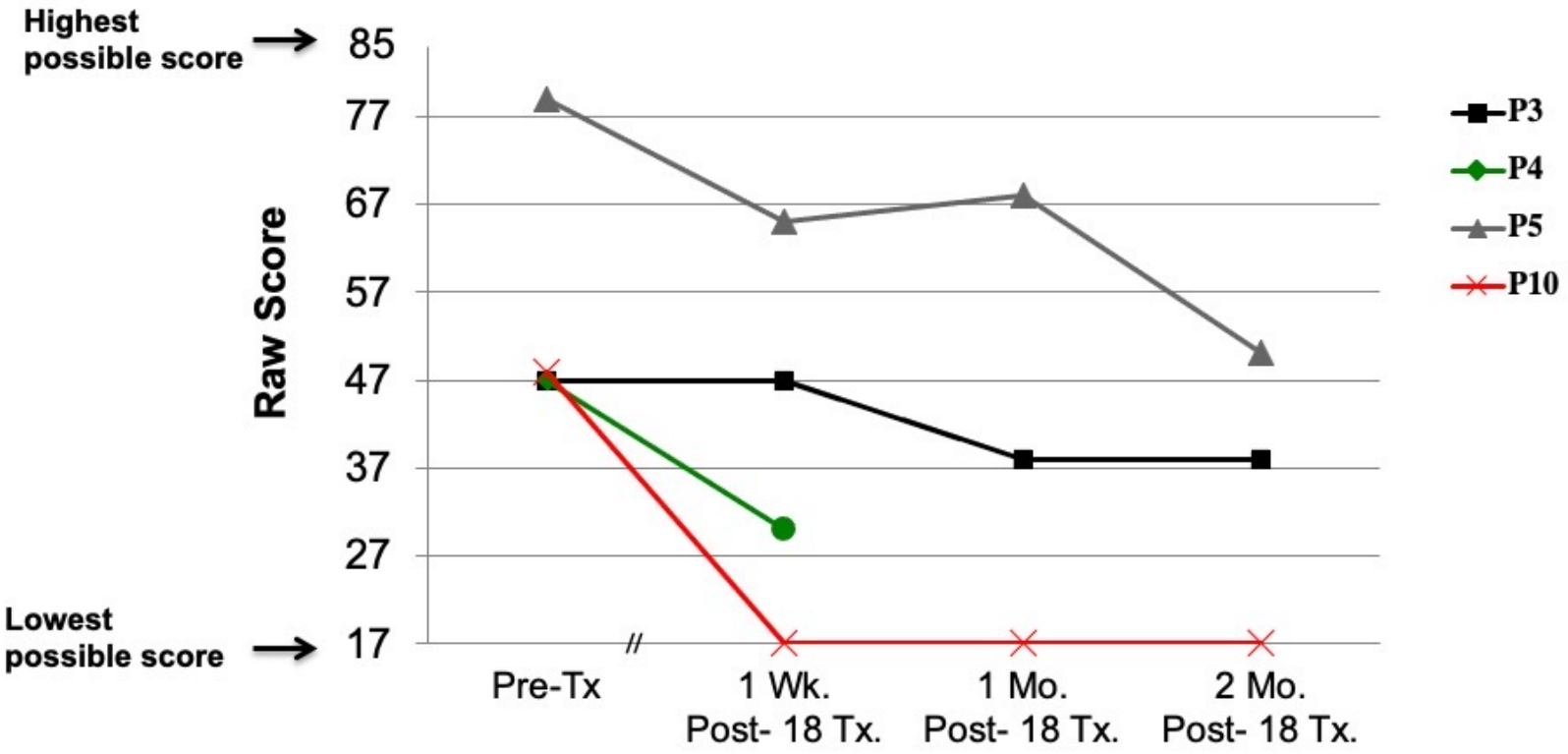


Note: ***These mTBI cases continued to improve in Executive Function and Verbal Memory, at 2 months*** **after the final, 18th In-Office, transcranial LED treatment.**

(Naeser et al, 2014)

Spaulding Rehabilitation Hospital, Boston. Transcranial LED Treatment (Tx) mTBI Study: Pre- and Post- LED Tx. Data

PTSD Checklist, PCL-Civilian **4 / 11 mTBI cases also had PTSD**



Score >36 suggestive of PTSD **based on case referral from specialized clinic (TBI or Pain) or VA Primary Care**

Reliable decrease = 5-10 points

Clinically meaningful decrease = 10-20 points

(Monson et al., 2008; Naeser et al., 2014)

- **Patients and family reported** clear **improvement in** capacities to perform ***social, interpersonal and occupational functions***.

Some comments Post- LED:

- P001 - ***Able to sort bills, write checks, read essays***, **tasks previously unable to do for 5 years, since the TBI**.

- P004 - ***Headache pain was reduced*** **from VAS of 5, down to 2**; and he no longer requires Extra Strength Tylenol or Tylenol, for HA pain. He continues to work as PhD Clinical Psychologist, resumed full-time work, instead of only part-time.

- P005 - Was depressed, and ***non-talkative at entry***, but ***became*** **quite** ***verbal*** and ***talkative*** after a few weeks of LED treatments.

- P006 - ***PTSD*** **Checklist-Civilian** ***was Severe*** **(score of 47) at entry,** and ***improved to Mild*** **(score of 30)** at **1 Week post- the 18th LED treatment**.

- P019 - Had been having recurrent nightmares for 20 mo. (TBI caused when he was sucked into a blast furnace). Post- 3 weeks of transcranial LED treatments, the ***nightmares stopped***.

(Naeser et al., 2014)

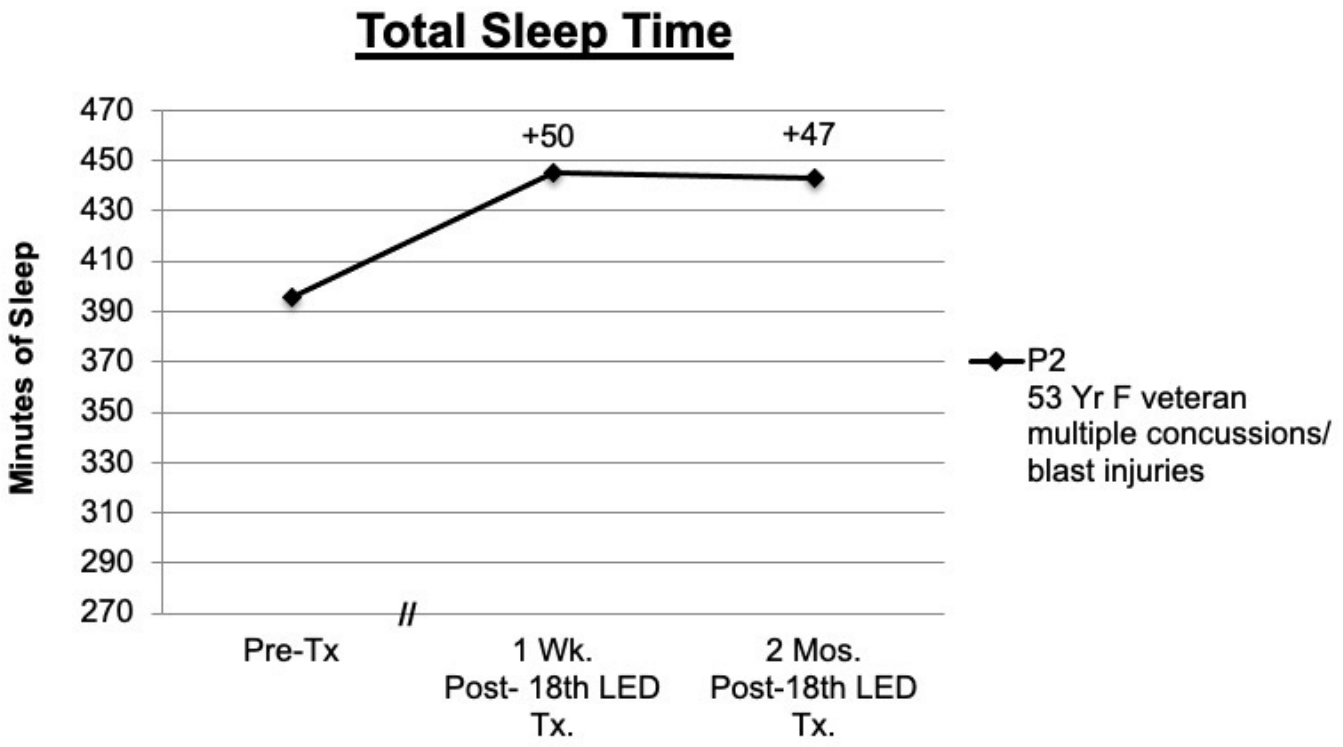
Boston VA Medical Center, LED Tx. TBI, blast TBI (and TBI+PTSD)

Actigraphy Sleep Data

P2, 53 Yr F (Veteran) mTBI+PTSD

Enter Study at 2.5 Yrs. Post- Multiple Concussions and ***IED Blast Injuries (30 - 50)***
Pre- and Post- 18 ***Transcranial*** LED Treatments

Total time scored as sleep

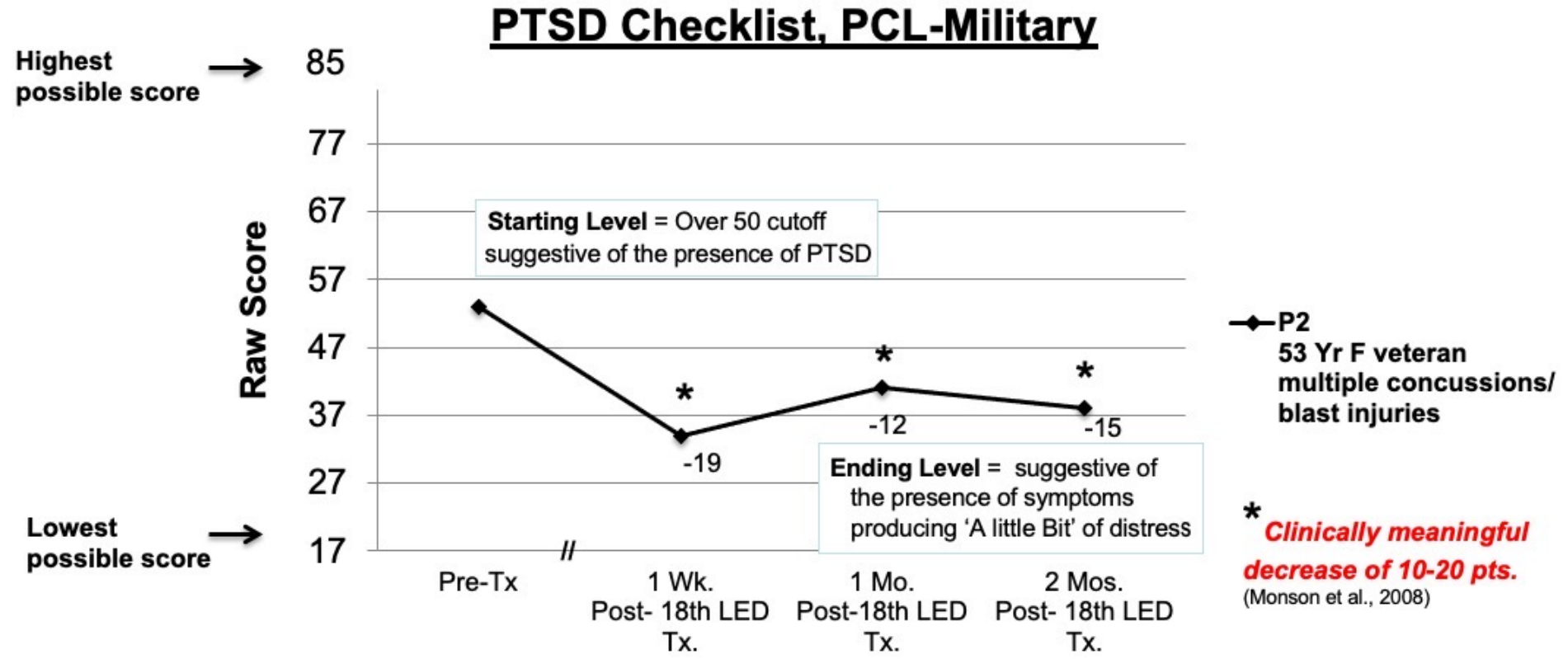


(Naeser et al., 2016)

Boston VA Medical Center, LED Tx. TBI, blast TBI (and TBI+PTSD)

P2, 53 Yr F (Veteran) mTBI+PTSD

Enter Study at 2.5 Yrs. Post- Multiple Concussions, ***IED Blast Injuries (30 - 50)***
Pre- and Post- 18 ***Transcranial*** LED Treatments

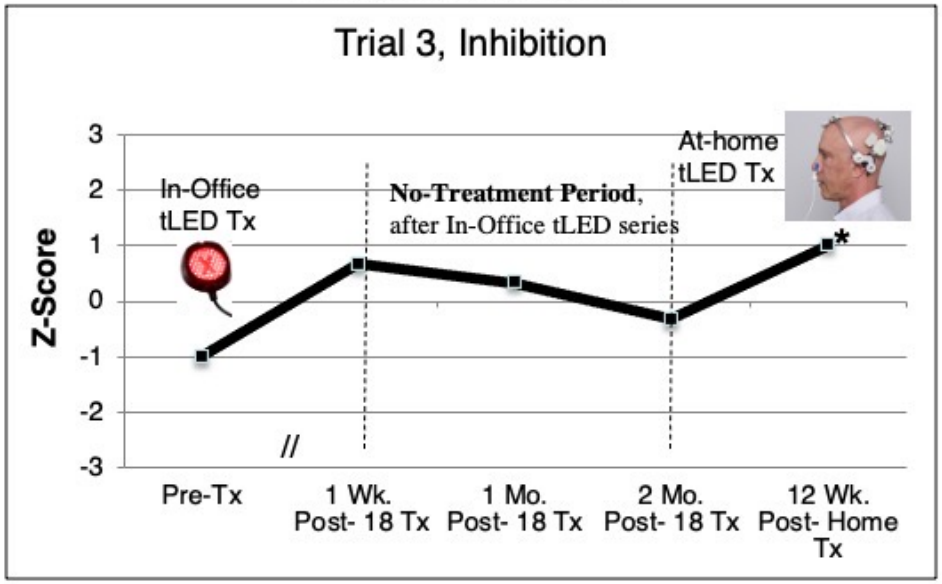


(Naeser et al., 2016)

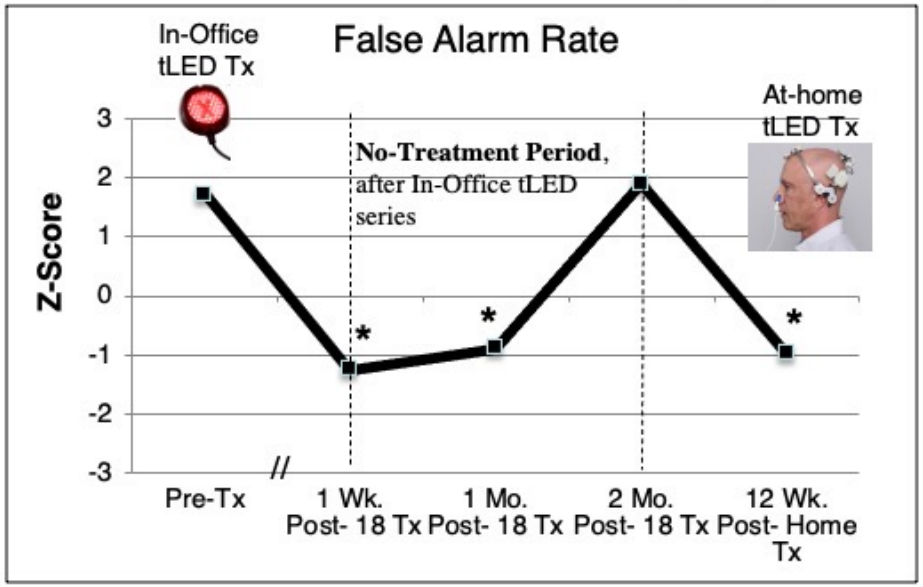
Athlete, tackle football 14 years, *possibly developing CTE*, age 65. *Blast-TBI Veterans also develop CTE.*

Goldstein, Fisher, Tagge et al., 2012

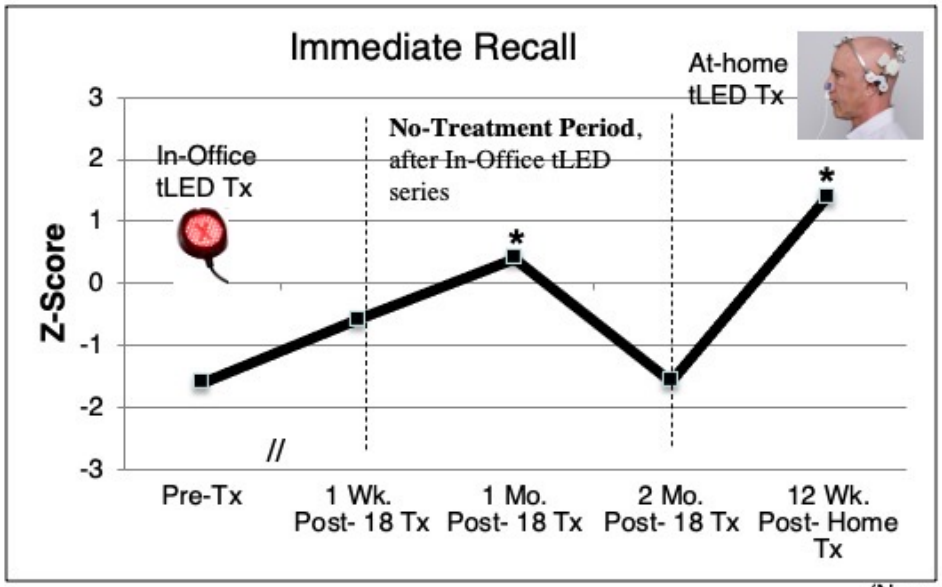
a. **Color Word Interference Test (Stroop)**
Executive Function



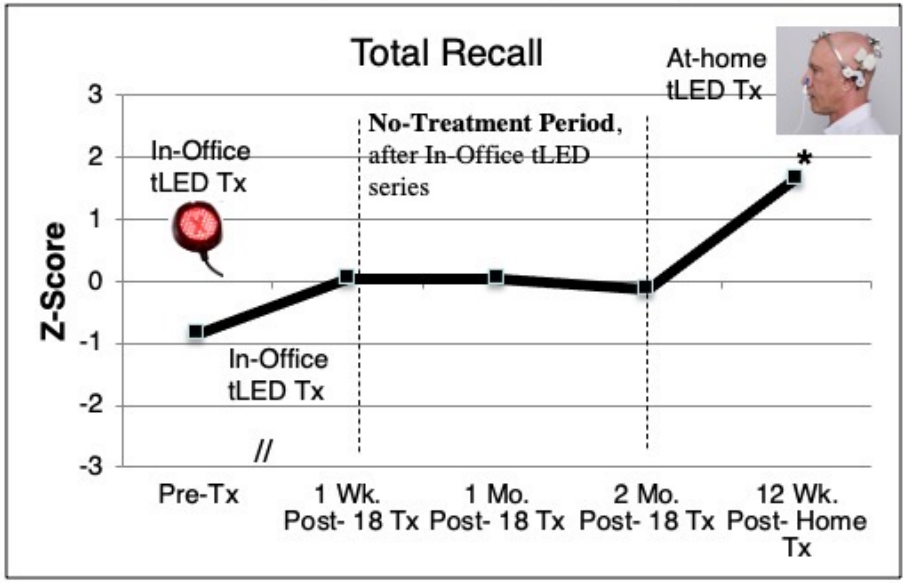
b. **Continuous Performance Test (CPT)**



c. **Brief Visuospatial Memory Test (BVMT)**



d. **Brief Visuospatial Memory Test (BVMT)**

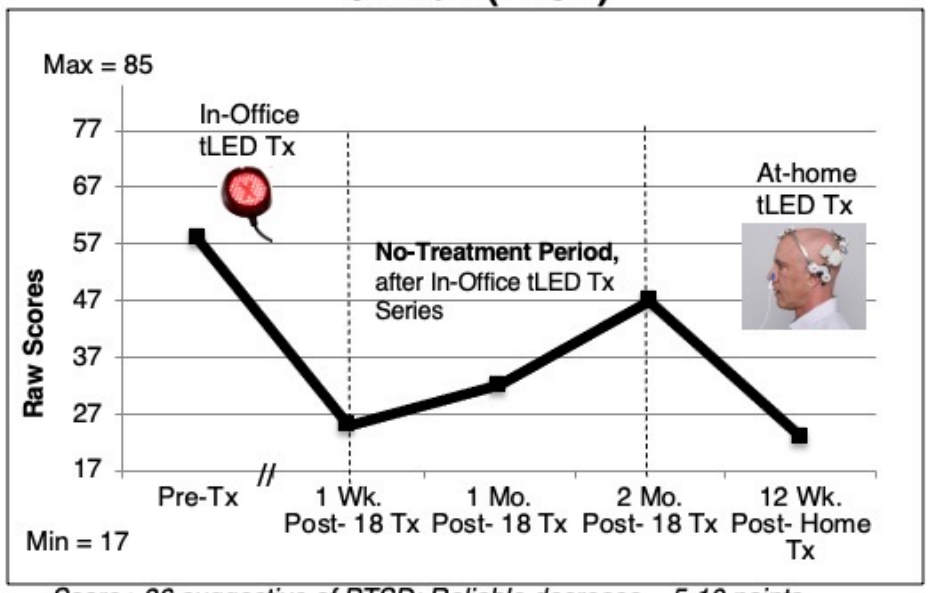


(Naeser et al., 2019)

Athlete, tackle football 14 years, *possibly developing CTE*, age 65. *Blast-TBI Veterans also develop CTE.*

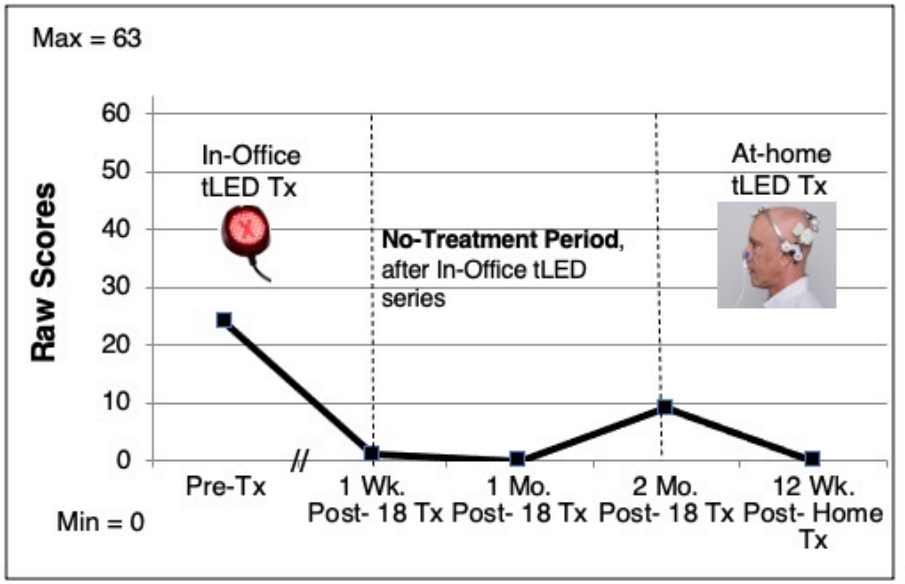
Goldstein, Fisher, Tagge et al., 2012

a. **Post Traumatic Stress Disorder Checklist Civilian (PTSD)**

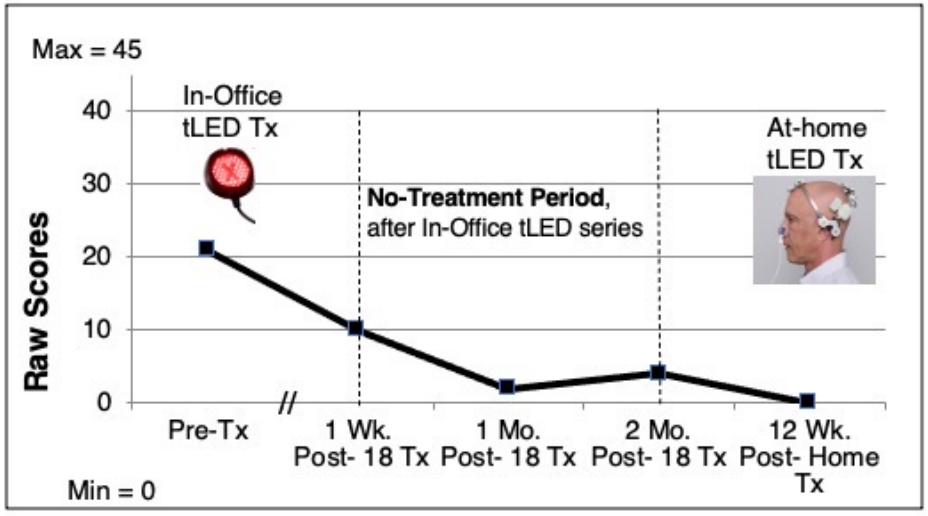


Score >36 suggestive of PTSD; Reliable decrease = 5-10 points
Clinically meaningful decrease = 10-20 points (Monson et al., 2008)

b. **Beck Depression Inventory – II (BDI)**

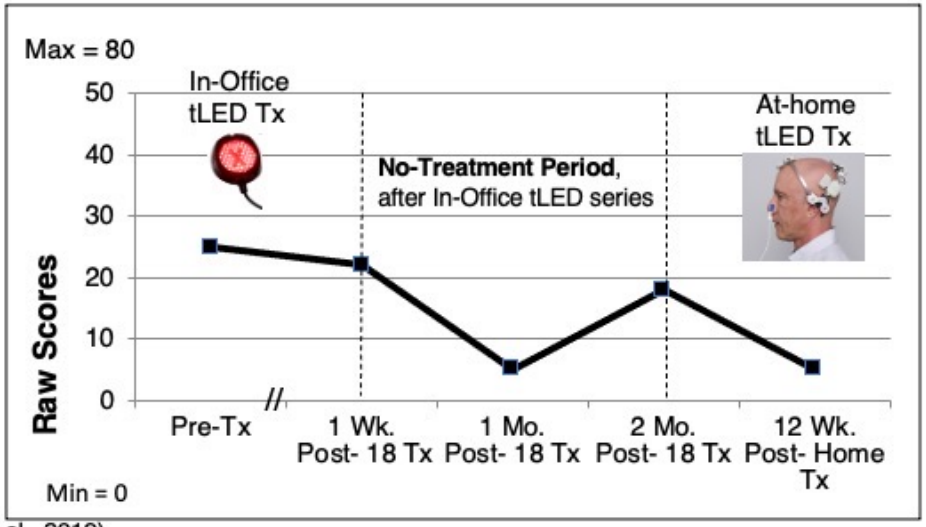


c. **Short Form, McGill Pain Questionnaire**



d. **Dysexecutive Questionnaire**

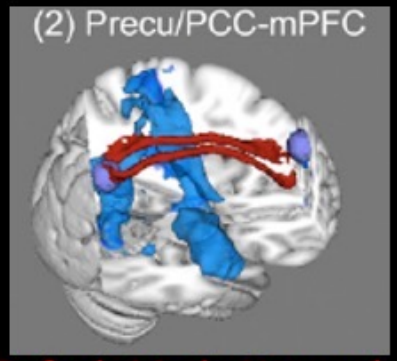
Interference with Family and Community Activities



(Naeser et al., 2019)

Case: Athlete, tackle football 14 Yrs, *possibly developing CTE*, age 65.
At *3 Mo. after In-Office* Treatment Series – started *At-Home* Transcranial LED Treatments.

Neuro Gamma LED Device plus **Intranasal LED**
Blast-TBI Veterans also develop CTE



Default Mode Network

LED device designed to deliver 810 nm, near-infrared photons ***only*** over the 5 cortical node areas of the ***Default Mode Network (DMN)***. LEDs are ***pulsed at 40 Hz.***

DMN is dysregulated in TBI, PTSD, Depression, Chronic Pain, Opioid Addiction, Alzheimer's Disease, Aging, Autism, Down Syndrome, and other central nervous system (CNS) disorders.

(Bonnelle et al., 2011, 2012; Menon, 2011; Garland et al., 2013; Fox et al., 2014; Jung et al., 2014)

Neural synchronization in Alzheimer's disease

Liviu Aron & Bruce A. Yankner

Electrical oscillations generated by neural circuits are disrupted in Alzheimer's disease. Restoring these oscillations in mouse models activates immune cells to clear disease-associated amyloid-β protein from the brain. SEE ARTICLE P.230

At-home tLED Tx

The Neuro Gamma LED Device is Pulsed at 40 Hz.

Iaccarino et al., 2016, *Nature*. Study done at MIT

Mice were genetically manipulated to develop **Alzheimer's Disease**.

40Hz, blinking light was shown only to eyes of mice,
1 Hr. per Day
7 Days

Post-mortem, showed **60% reduction in Amyloid-beta,** and ***40% reduction in tau***, **in Visual Cortex only**.
40Hz signal was delivered **via the eyes/optic nerve**.

No reduction of Amyloid-beta or tau, in **other areas** – **Hippocampus**, etc.

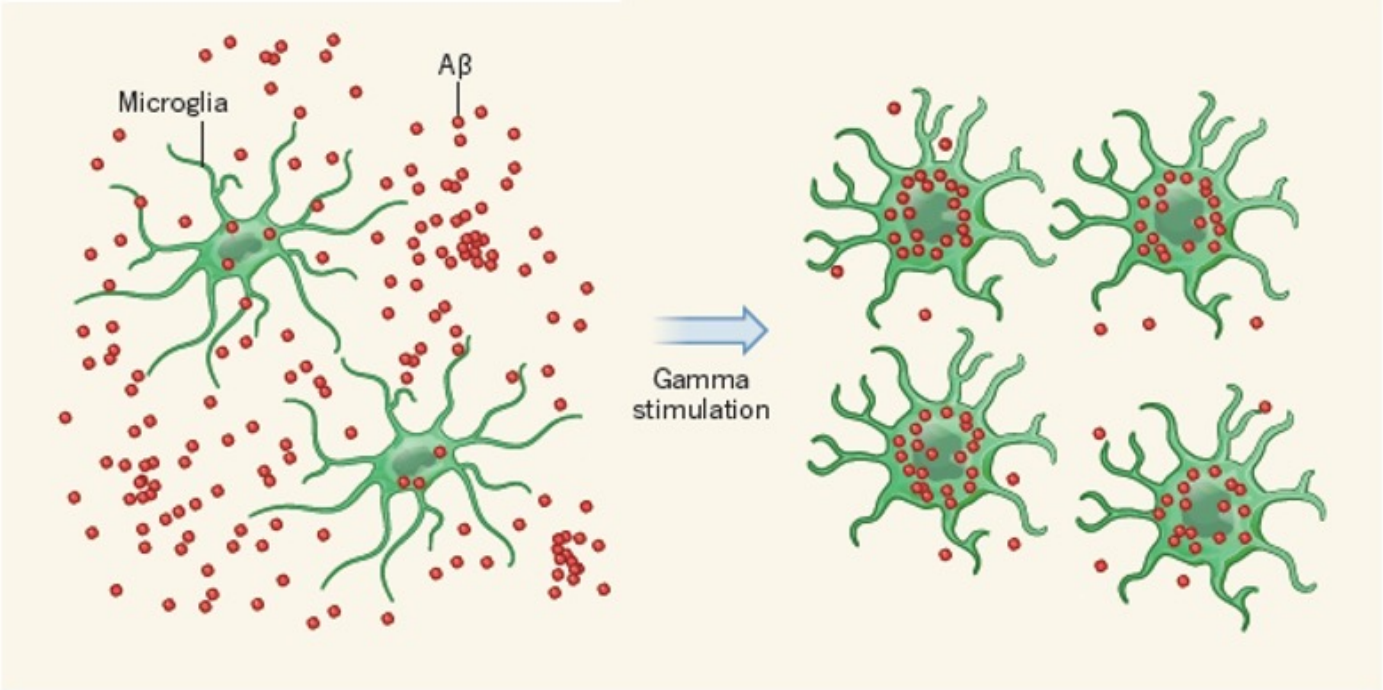


Figure 1 | Gamma oscillations stimulate the clearance of amyloid-β protein deposits. Abnormal aggregation of amyloid-β (Aβ) protein in the brain is associated with Alzheimer's disease. Aβ aggregates might accumulate and promote neurodegeneration in part because immune cells called microglia cannot effectively clear the protein. In addition, synchronized patterns of electrical activity in the brain known as gamma oscillations are disrupted in Alzheimer's. Iaccarino *et al.*[3] restored gamma oscillations in a mouse model of the disease. Such gamma stimulation led to recruitment of microglia to sites of Aβ deposition. The microglia adopted an activated shape, and consequently engulfed and degraded Aβ.

Intranasal, *red*, light-emitting diode (LED) Device.

Wavelength: 633 nm

Power output: 8 mW Used in one nostril, 25 min. Self-timed. One AA battery.

Beam spot size, delivered to nasal mucosa: 1 cm^2

Energy delivery to nasal mucosa in 25 minutes: 12 J/cm^2

Power density: 8 mW/cm^2

Can be used at home. Red wavelengths *increase melatonin* (Zhao et al., 2012; Salehpour et al., 2020, review)

Never heats up.

Within Low-Risk devices, FDA Category of "General Wellness."

No medical claims made.

The athlete also obtained a red, 633 nm, red

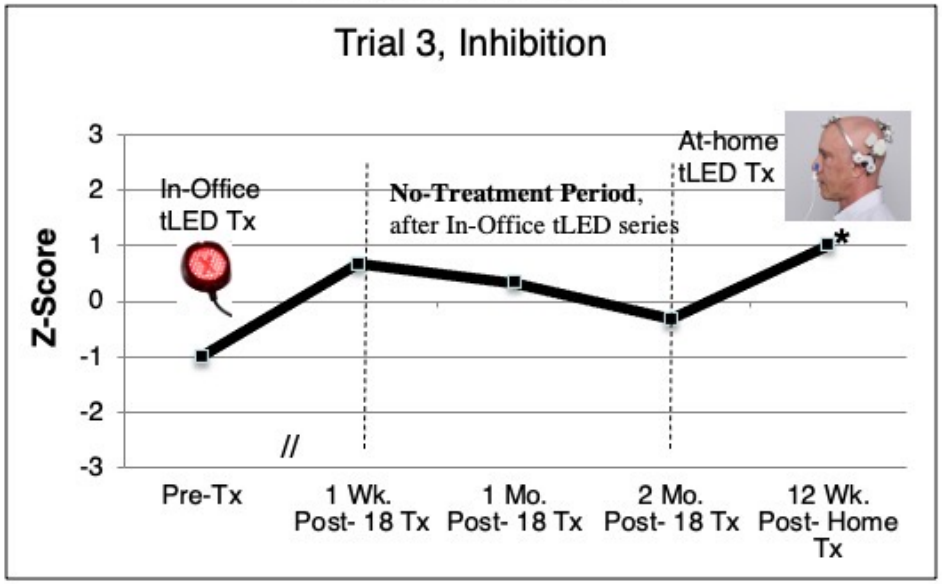
LED Nose-clip device, used at home – 20 min, 6 days per Wk

(Naeser et al., 2019)

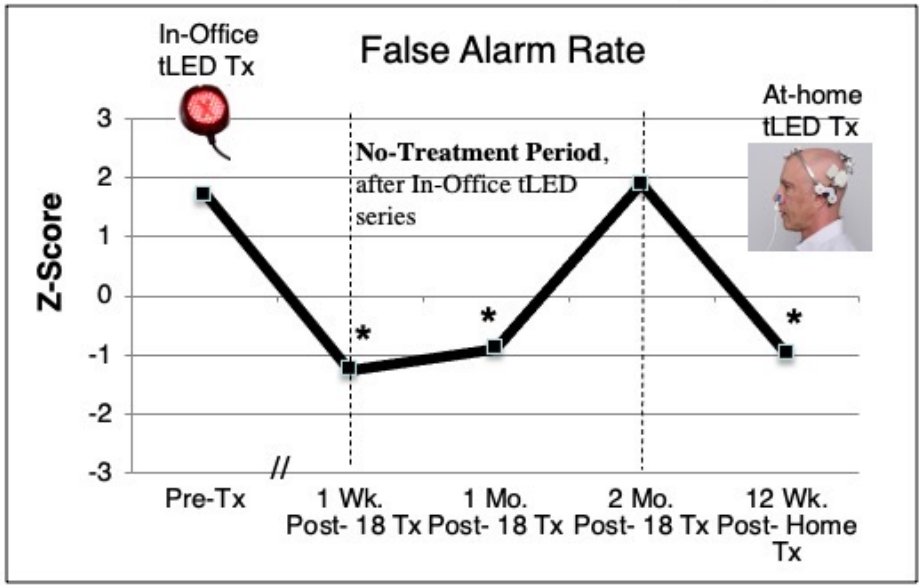
Athlete, tackle football 14 years, *possibly developing CTE*, age 65. *Blast-TBI Veterans also develop CTE.*

Goldstein, Fisher, Tagge et al., 2012

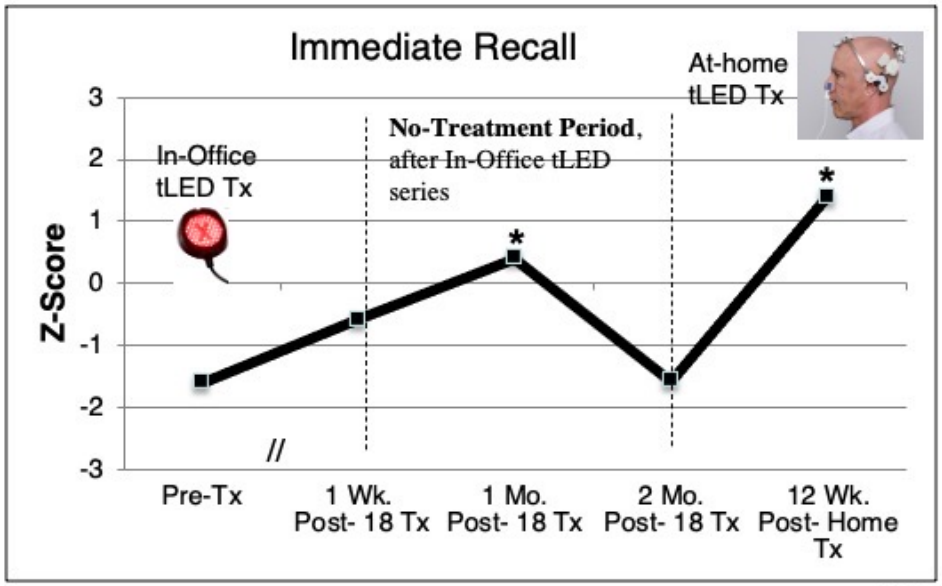
a. **Color Word Interference Test (Stroop)**
Executive Function



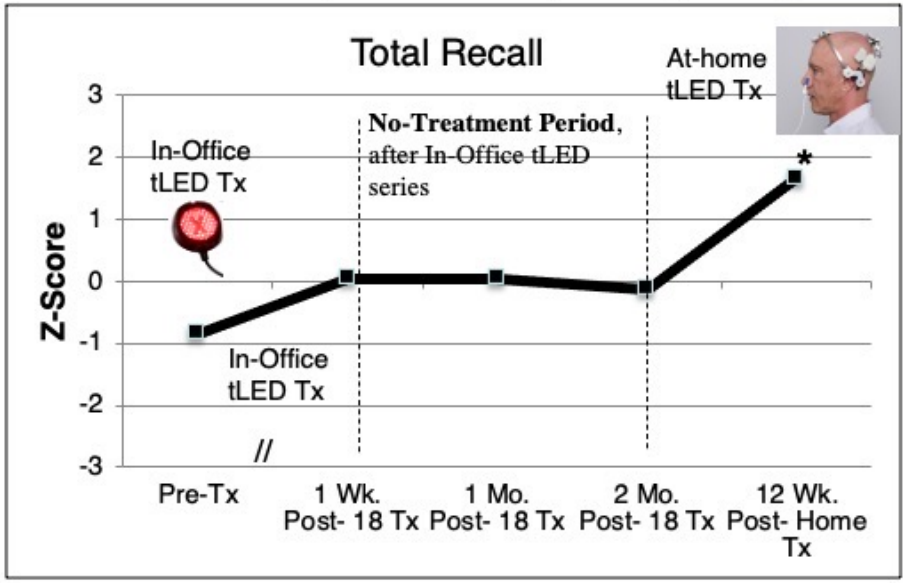
b. **Continuous Performance Test (CPT)**



c. **Brief Visuospatial Memory Test (BVMT)**



d. **Brief Visuospatial Memory Test (BVMT)**

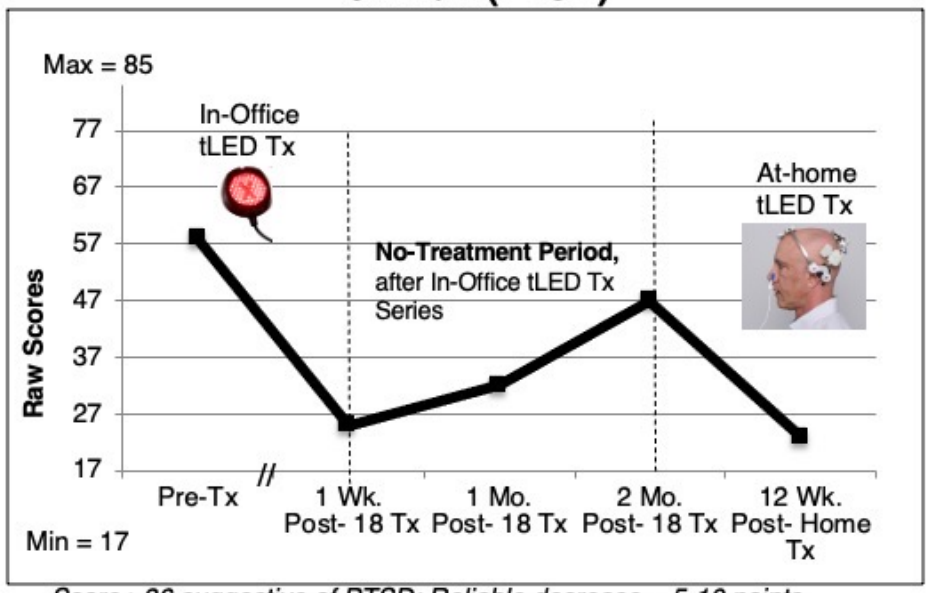


(Naeser et al., 2019)

Athlete, tackle football 14 years, *possibly developing CTE*, age 65. *Blast-TBI Veterans also develop CTE.*

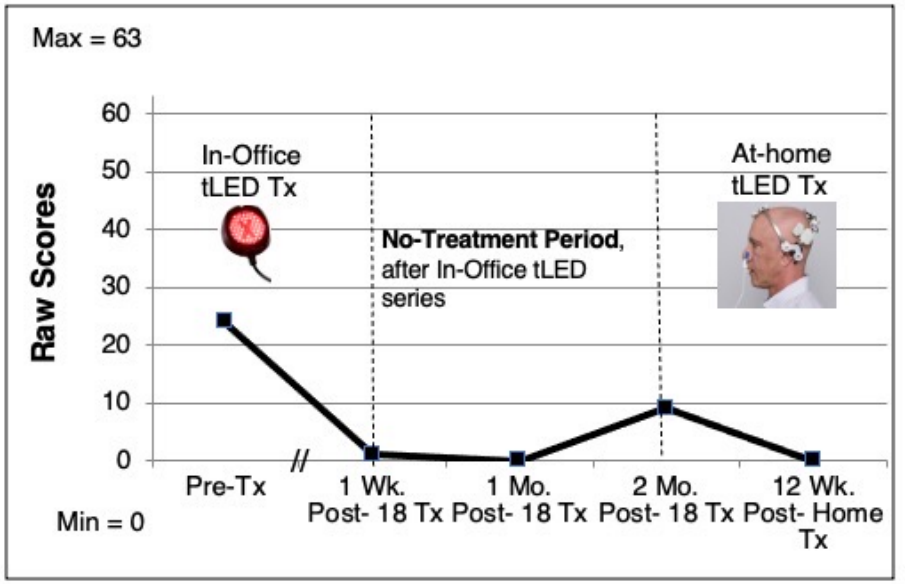
Goldstein, Fisher, Tagge et al., 2012

a. **Post Traumatic Stress Disorder Checklist Civilian (PTSD)**

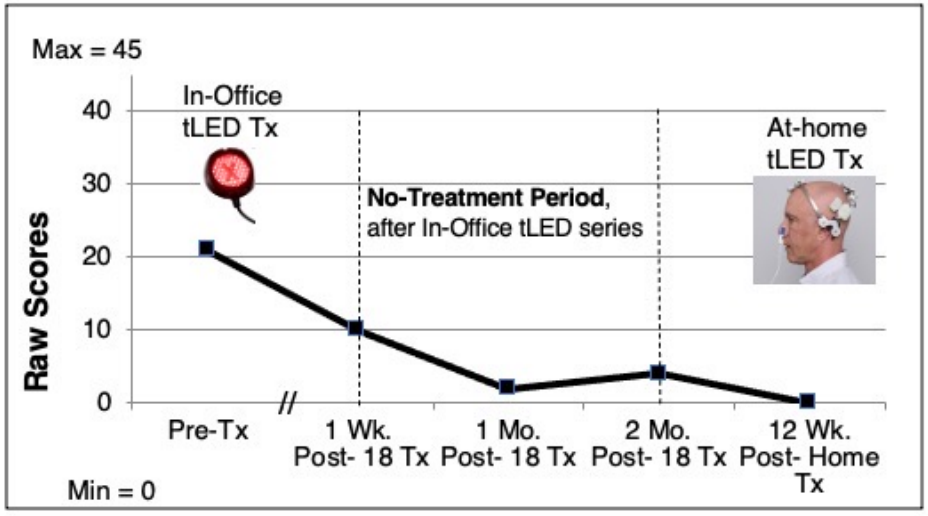


Score >36 suggestive of PTSD; Reliable decrease = 5-10 points
Clinically meaningful decrease = 10-20 points (Monson et al., 2008)

b. **Beck Depression Inventory – II (BDI)**

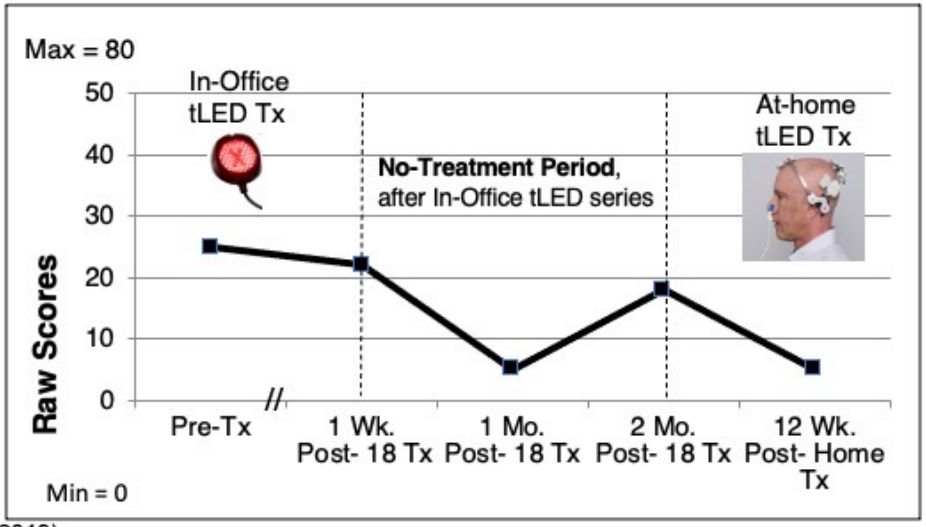


c. **Short Form, McGill Pain Questionnaire**



d. **Dysexecutive Questionnaire**

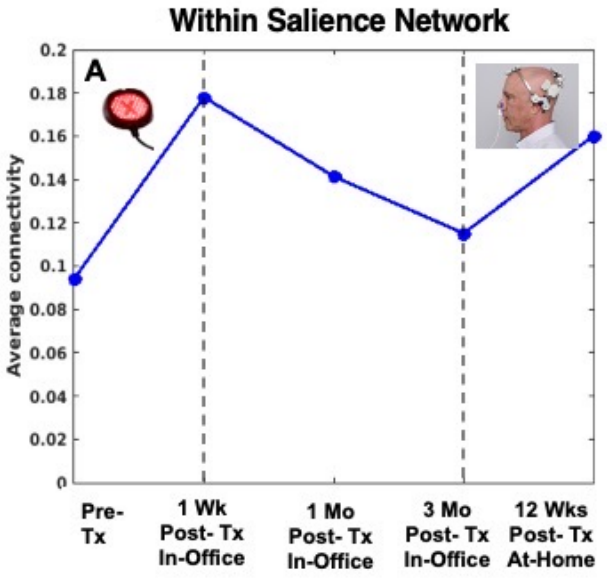
Interference with Family and Community Activities

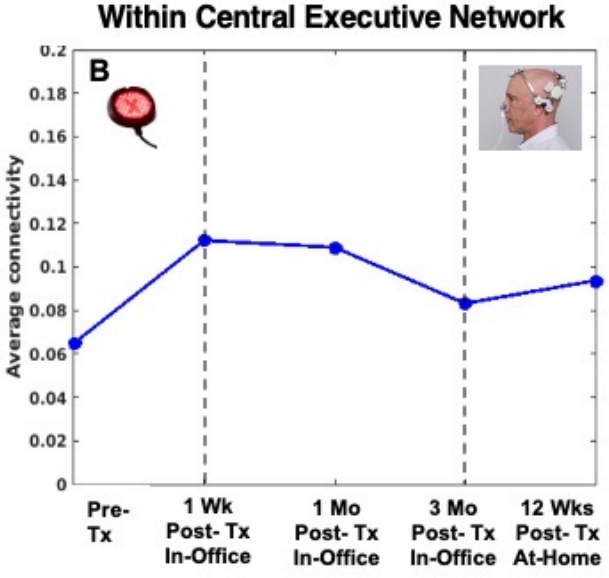


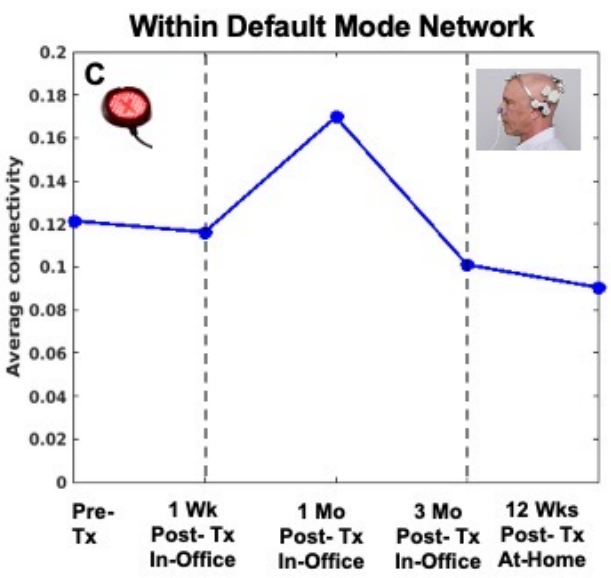
(Naeser et al., 2019)

Resting-state Functional-connectivity MRI, over time. Athlete, age 65, *possible CTE.*

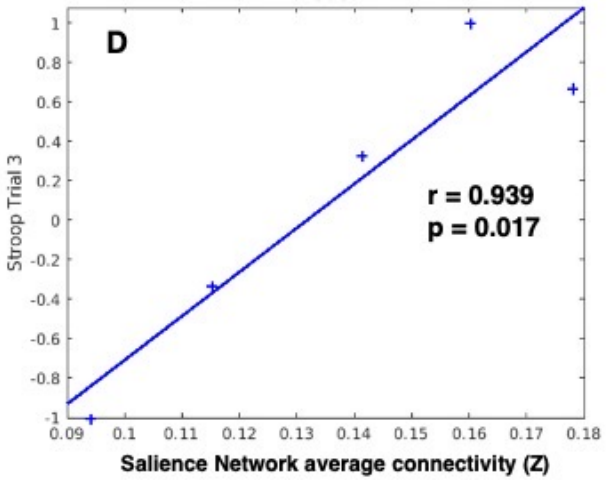
Average Connectivity over time, in each Resting-State Network, *Pre- and Post- tLED Treatments*

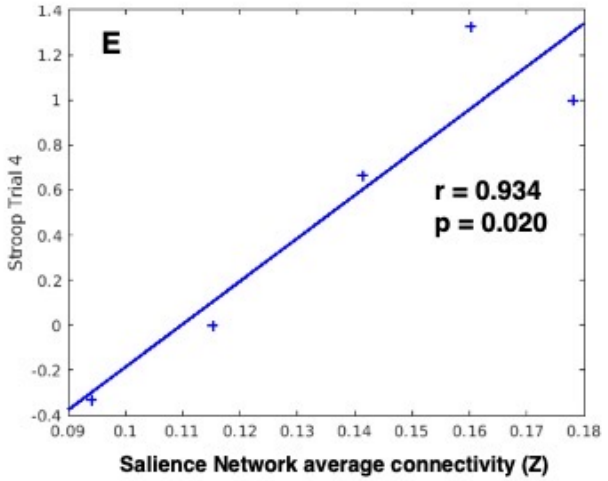






Significant Correlations between Salience Network over time, and Stroop, Trials 3 and 4 (Executive Function)

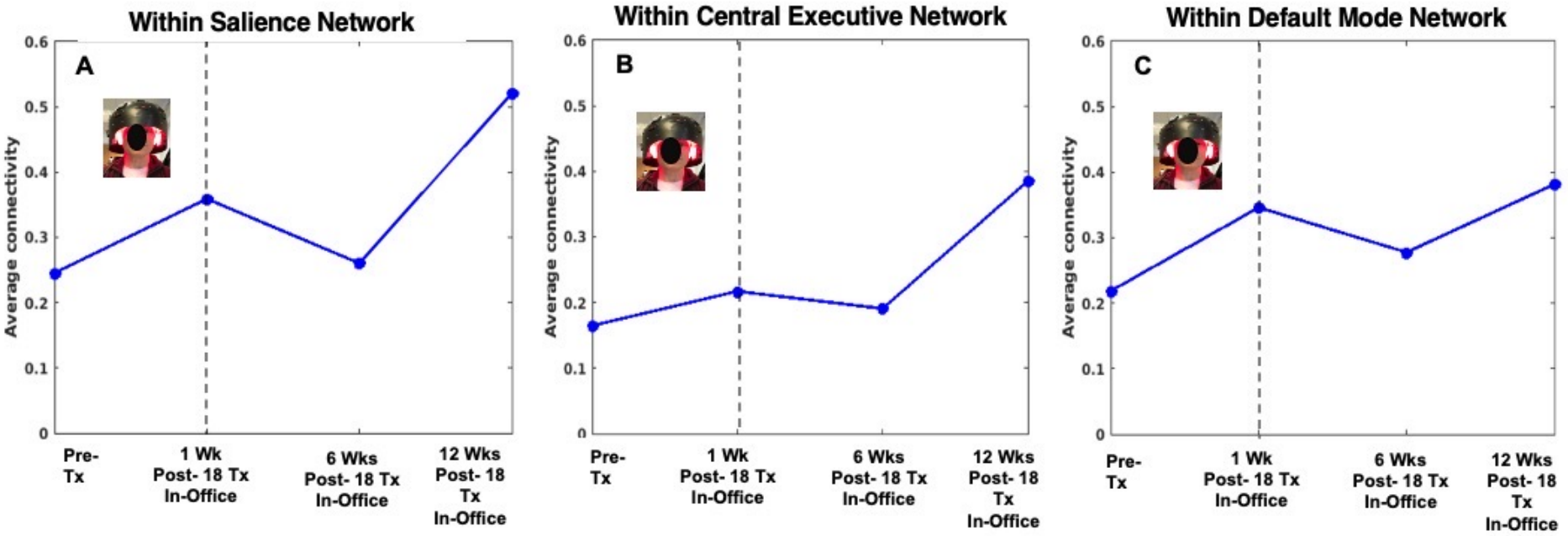




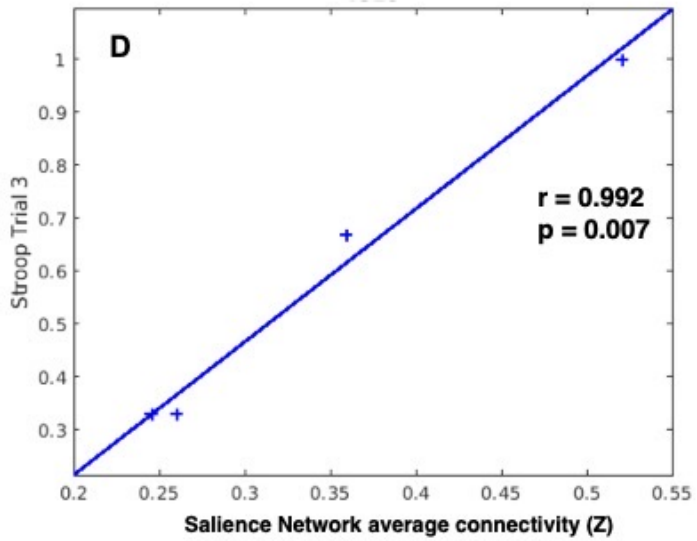
Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Hamblin, Fedoruk, Poole, Cheng, Koo)

Resting-state Functional-connectivity MRI, over time. Athlete, age 55, *possible CTE.*

Average Connectivity over time, in each Resting-State Network, *Pre- and Post- tLED Treatments*



Significant Correlation between Salience Network over time, and Stroop, Trial 3 (Executive Function)



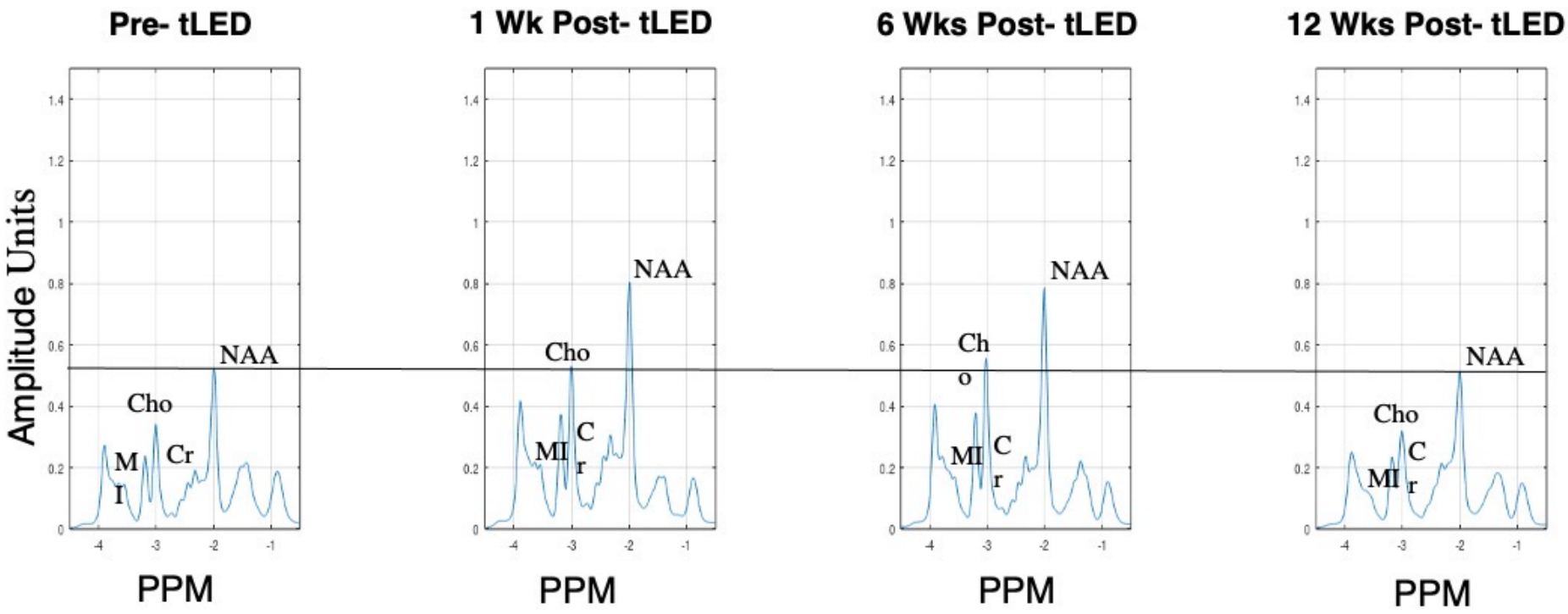
Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Hamblin, Fedoruk, Poole, Cheng, Koo

Athlete, tackle football, 15 Years, ***possibly developing CTE,*** **age 55.** ***Blast-TBI Veterans also develop CTE***

Magnetic Resonance Spectroscopy (MRS)

Anterior Cingulate Cortex, **Metabolite Levels:** ***Increased n-acetyl-aspartate (NAA) at 1 Wk***

and at 6 Wks, Post- the in-Office tLED Treatment Series; less pain and PTSD at those times.



NAA is a neural marker present **only within the body of neural cells**, and **within axons and dendrites** (Simmons, Frondoza, Coyle, 1991)

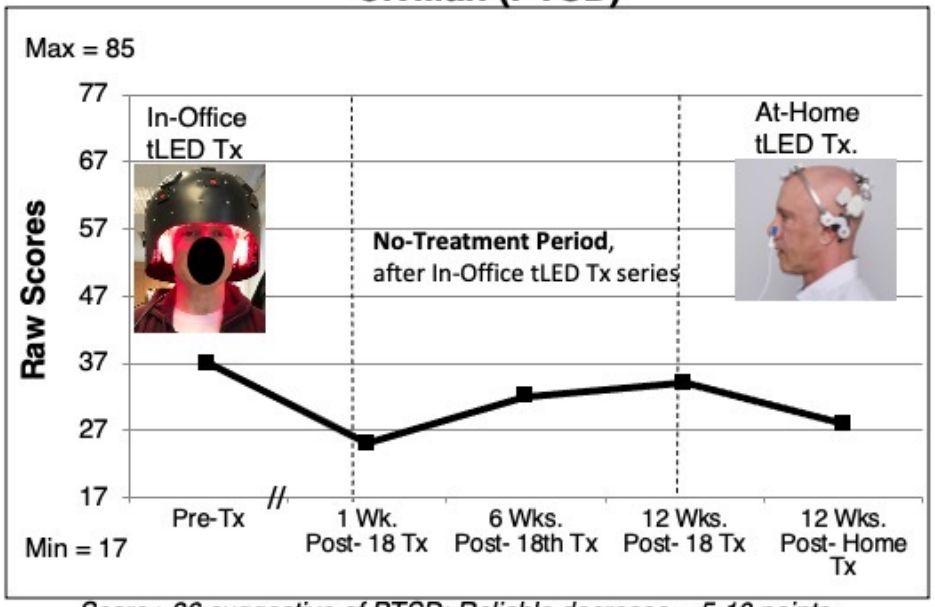
NAA is ***synthesized in the mitochondria of neural cells***, and the ***concentration correlates with oxygen consumption.***

Reduced NAA reported in cognitive impairment; "this may reflect a **combination of loss of neural cells, decreased neural metabolism, loss of dendritic structures, and reduced myelination"** (Minati et al., 2007).

Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Hamblin, Fedoruk, Poole, Cheng, Koo

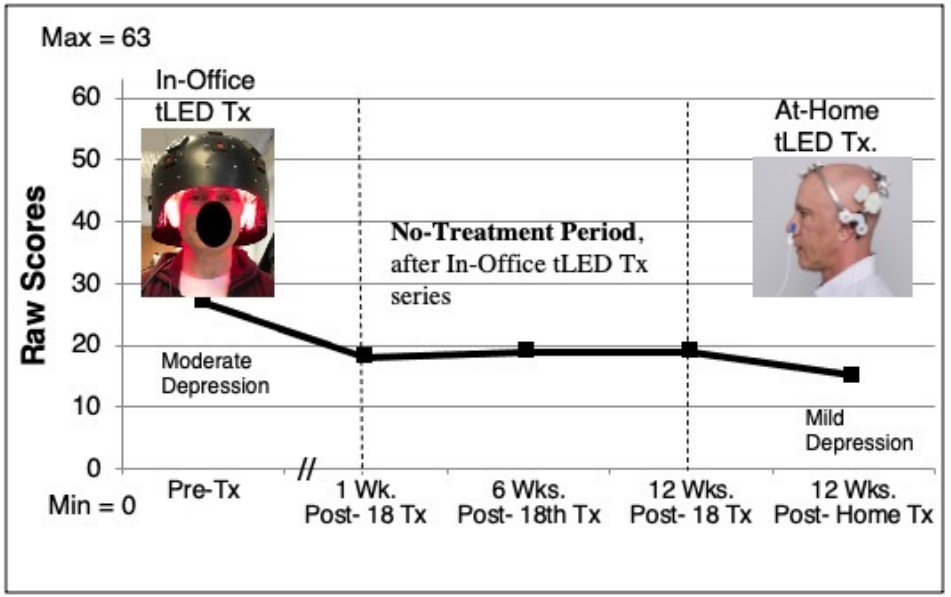
Athlete, tackle football 15 Years, *possibly developing CTE,* age 55. *Blast-TBI Veterans also develop CTE*

a. **Post Traumatic Stress Disorder Checklist Civilian (PTSD)**

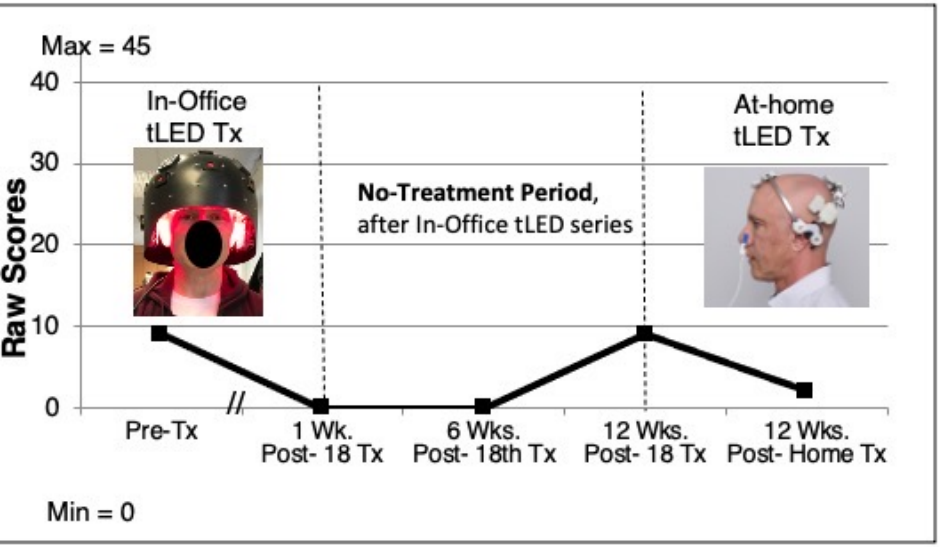


Score >36 suggestive of PTSD; Reliable decrease = 5-10 points
Clinically meaningful decrease = 10-20 points (Monson et al., 2008)

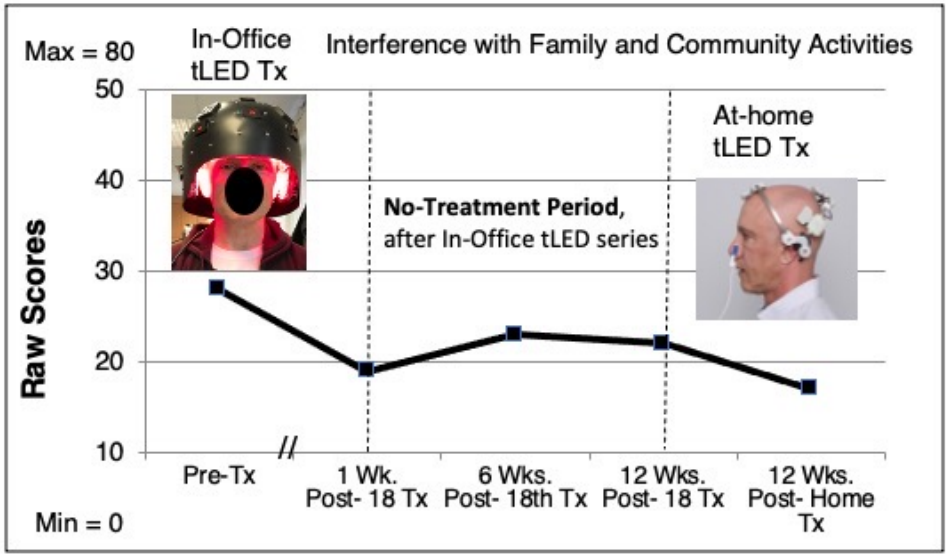
b. **Beck Depression Inventory – II (BDI)**



c. **Short Form, McGill Pain Questionnaire**



d. **Dysexecutive Questionnaire**



Similar Results for *Salience Network*, in Concussion Case, *treated only Default Mode Network*

frontiers in Neurology

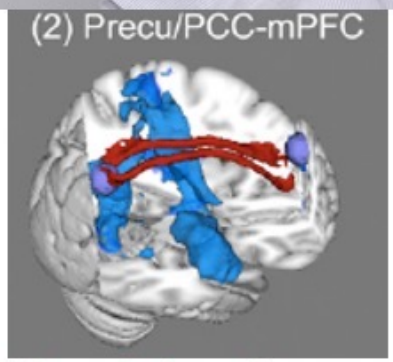
CASE REPORT
published: 08 September 2020
doi: 10.3389/fneur.2020.00962

Chao et al., 2020

Changes in Brain Function and Structure After Self-Administered Home Photobiomodulation Treatment in a Concussion Case

Linda L. Chao[1,2], Cody Barlow[3], Mahta Karimpoor[3] and Lew Lim[3]*

[1] Departments of Radiology & Biomedical Imaging and Psychiatry & Behavioral Sciences, University of California, San Francisco, San Francisco, CA, United States, [2] VA Advanced Imaging Research Center, San Francisco VA Health Care System, San Francisco, CA, United States, [3] Vielight Inc., Toronto, ON, Canada



Treated only the Default Mode Network, 8 Weeks

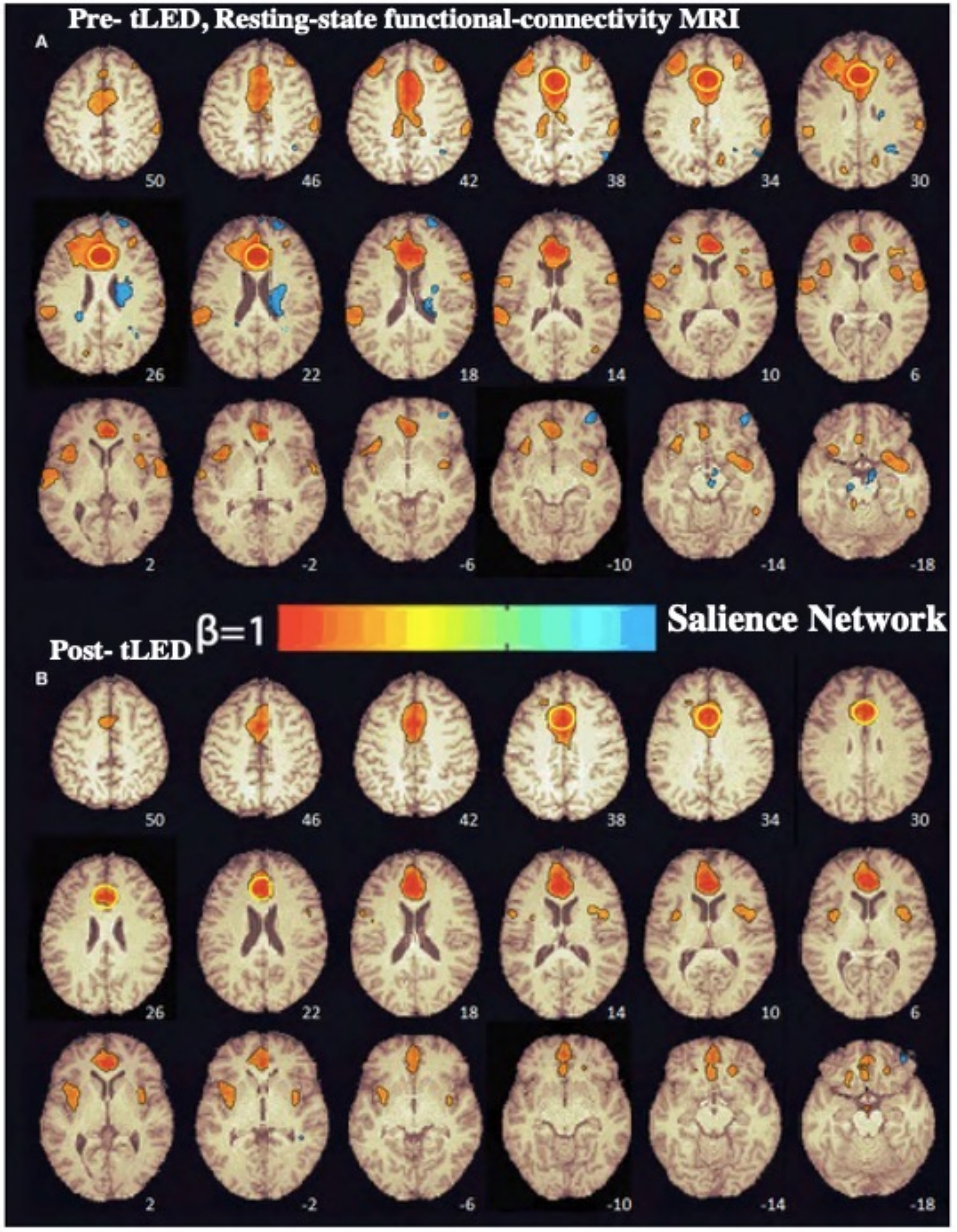
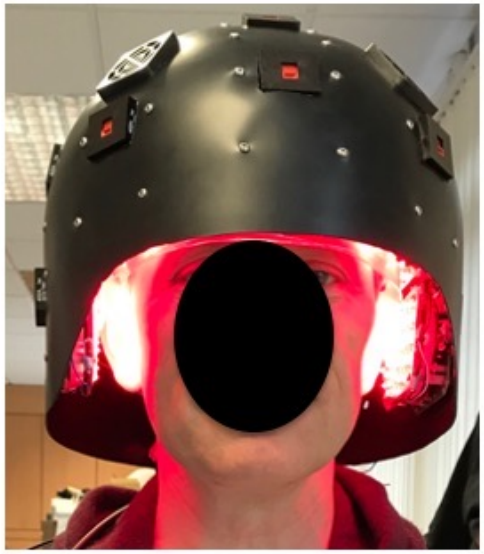


FIGURE 2 | Functional connectivity maps from the pre-treatment **(A)** and post-treatment **(B)** scans showing regions functionally connected to the seed in the anterior cingulate cortex. The numbers at the bottom right indicate the *z* coordinate (mm). The yellow circle denotes the seed in the anterior cingulate cortex. The color bar indicates the beta weight of the functional connections. The maps were thresholded at $\beta \geq 0.4$.

In-Office t-LED series, Thor Helmet, lined with red/near-infrared LEDs.

Athlete, tackle football 16 Years, *possibly developing CTE*, age 57. *Blast-TBI Veterans also develop CTE.*

Goldstein, Fisher, Tagge et al., 2012



Treated 3x per Wk,
6 Weeks

At each visit, Set A and Set B are used.

Set A. Midline Only.

5 LED Placements

Then, turn off the midline placements

Set A	Set B
6.3 cm diameter each	6.3 cm diameter each
1265.6 mW	1075.4 mW
41 mW/cm^2	35 mW/cm^2
34 red 660nm diodes 35 NIR 850 nm diodes	34 red 660nm diodes 35 NIR 850 nm diodes
CW	CW
24.7 sec	29.1 sec
26 Joules/cm^2 per LED cluster head	26 Joules/cm^2 per LED cluster head
10 min 42 sec	12 min 36 sec
Sets A, B: 23 min 18 sec (covers whole head)	

Set B. Only, L and R sides, Simultaneously

10 LED Placements, 5 on each side

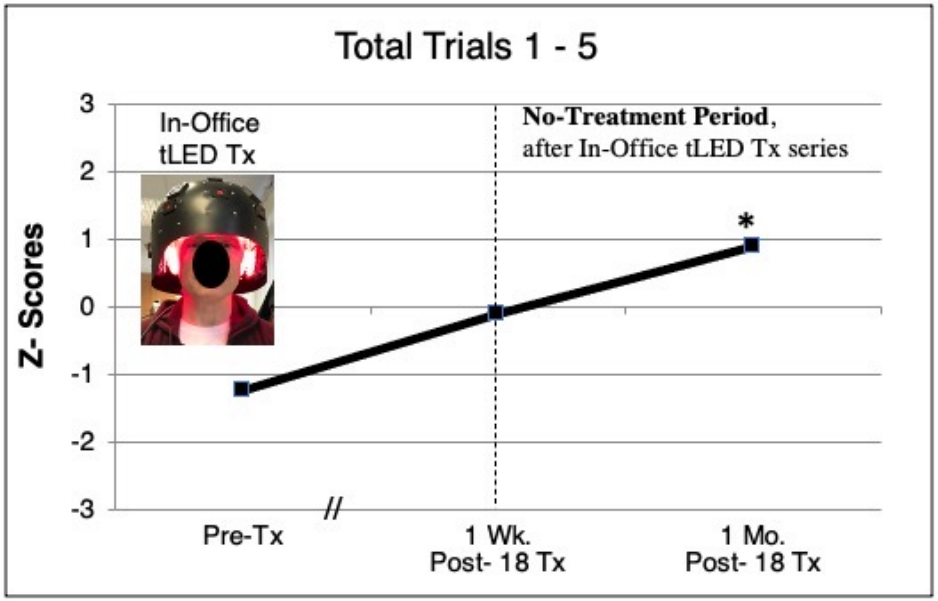
Then, the treatment is finished.

(Naeser et al., 2019)

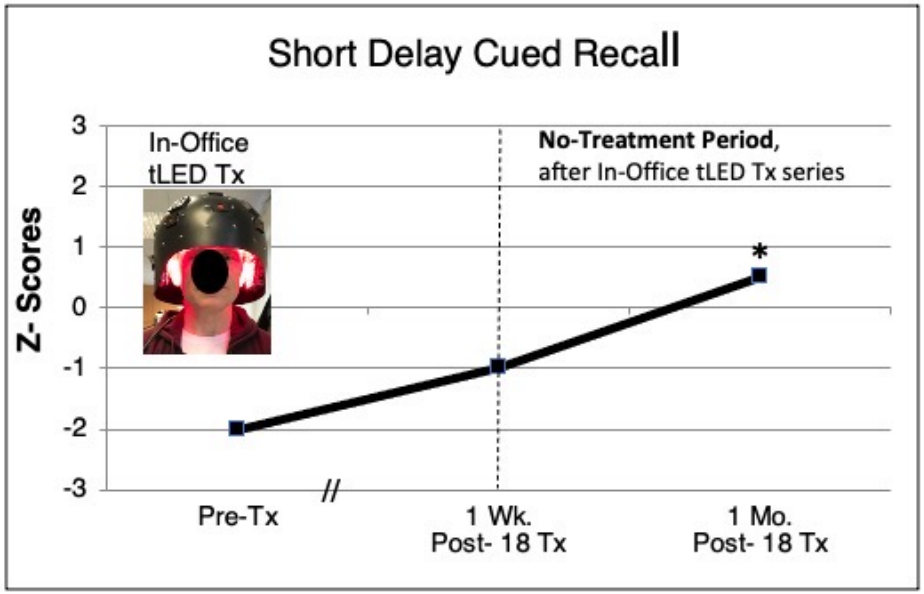
Athlete, tackle football 16 Years, *possibly developing CTE*, age 57. *Blast-TBI Veterans also develop CTE.*

Goldstein, Fisher, Tagge et al., 2012

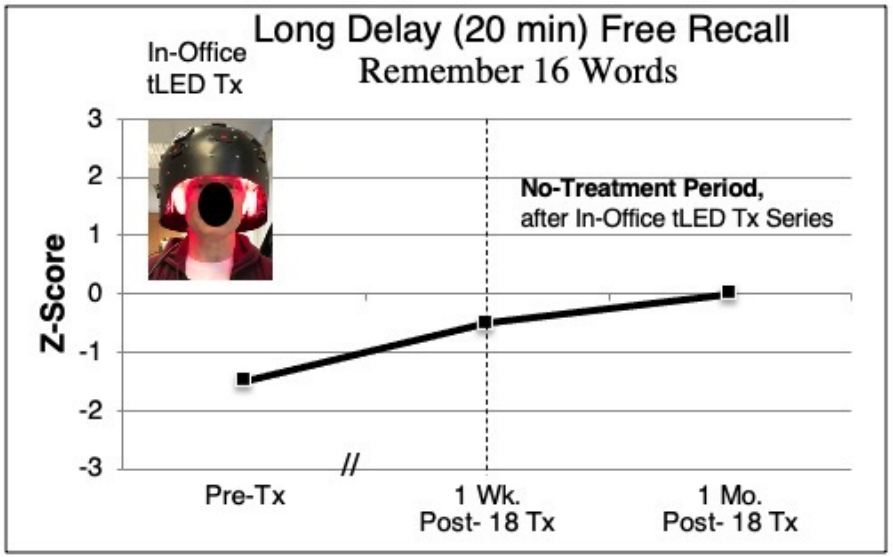
a. **California Verbal Learning Test-II (CVLT)**



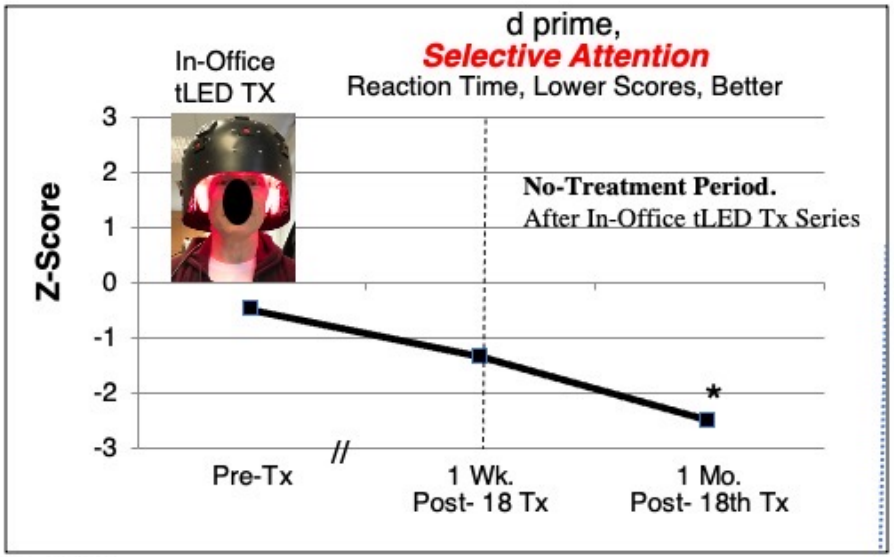
b. **California Verbal Learning Test-II (CVLT)**



c. **California Verbal Learning Test-II (CVLT)**



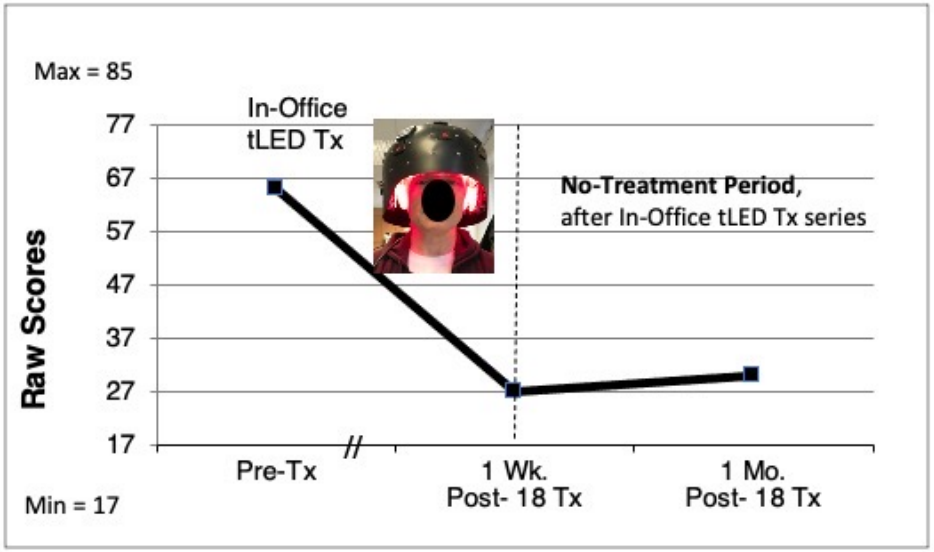
d. **Continuous Performance Test (CPT)**



(Naeser et al., 2019)

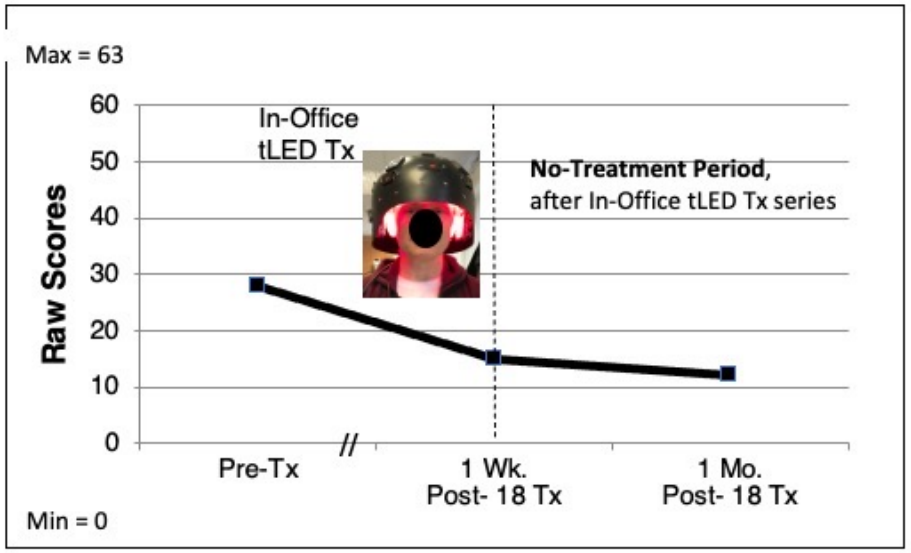
Athlete, tackle football 16 Years, *possibly developing CTE*, age 57. *Blast-TBI Veterans can develop CTE.*

a. **Post Traumatic Stress Disorder Checklist Civilian (PTSD)**

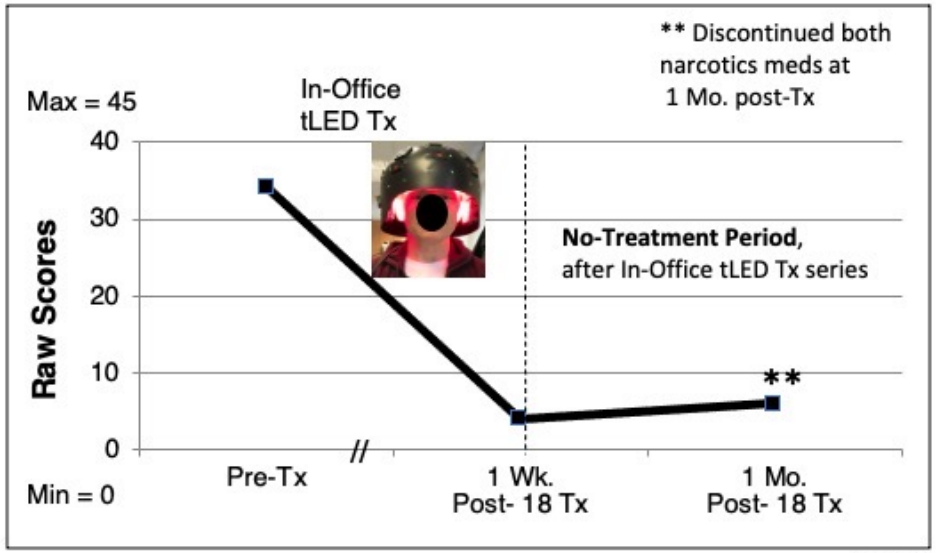


Score >36 suggestive of PTSD; Reliable decrease = 5-10 points
Clinically meaningful decrease = 10-20 points (Monson et al., 2008)

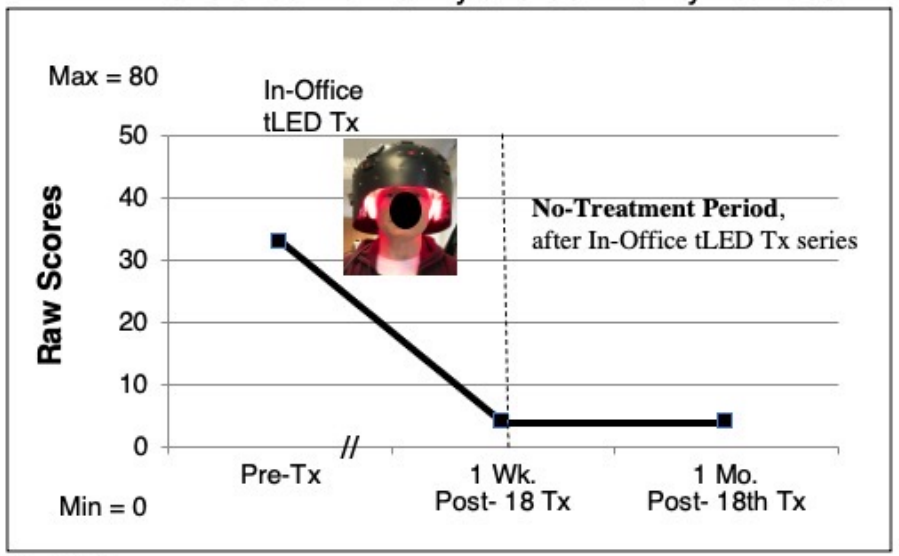
b. **Beck Depression Inventory – II (BDI)**



c. **Short Form, McGill Pain Questionnaire**



d. **Dysexecutive Questionnaire**
Interference with Family and Community Activities

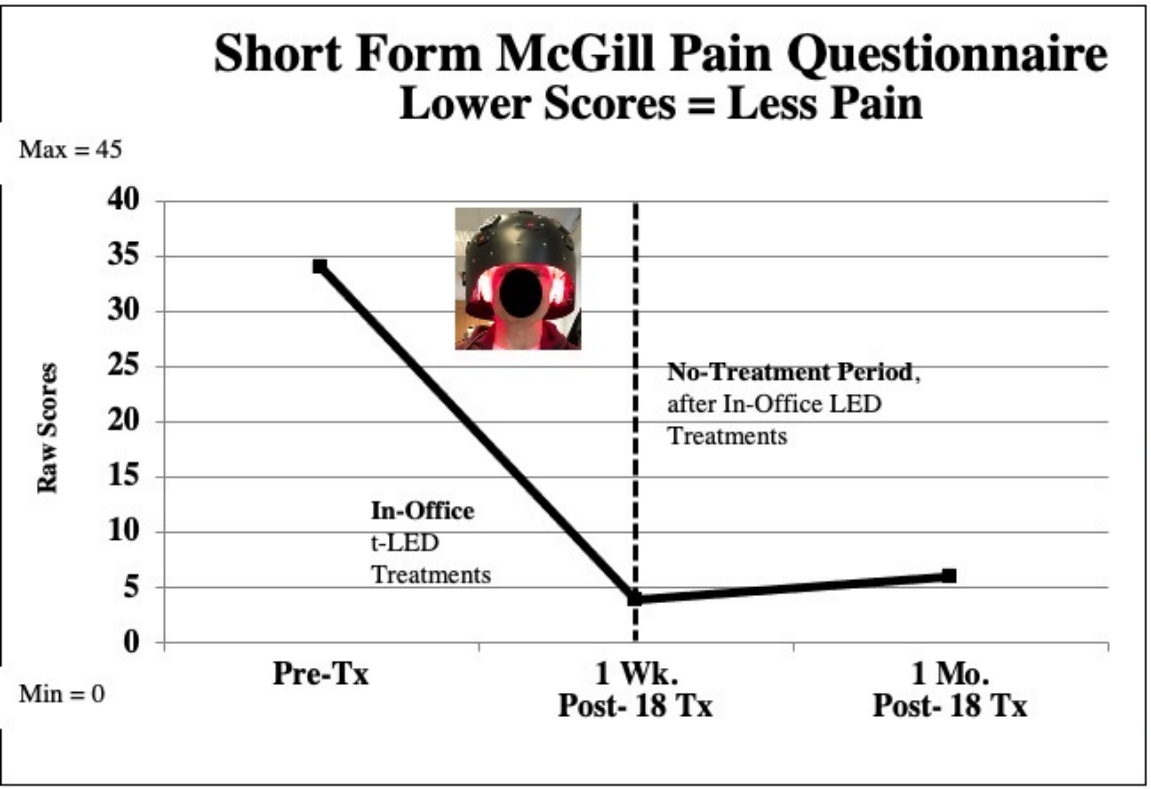


(Naeser et al., 2019)

Athlete, tackle football 16 Years, *possibly developing CTE*, age 57. *Blast-TBI Veterans can develop CTE*

Results after 18 *In-Office* Transcranial LED Treatments

Reduced Pain, *Discontinued 2 Narcotic Medications*, Post- tLED Series



VAS Pain Score Range: 0-10
R Shoulder, 15 Surgeries

***Pre-LED* Pain Meds:**

- **2 Narcotics** – 2 types of oxymorphone
- also **Gabapentin (Neurontin)**

***Pre- LED Pain Score:* - 7/10**

***Post- LED* - at 1 Week – 3/10**

Post- LED* – at 1 Month – 5.5/10

- ****Discontinued both Narcotics, at 1 Month.***
- ***Then obtained his own Neuro Gamma LED device for Home Treatments.*** *No objective follow-up data, but reports "doing well."*

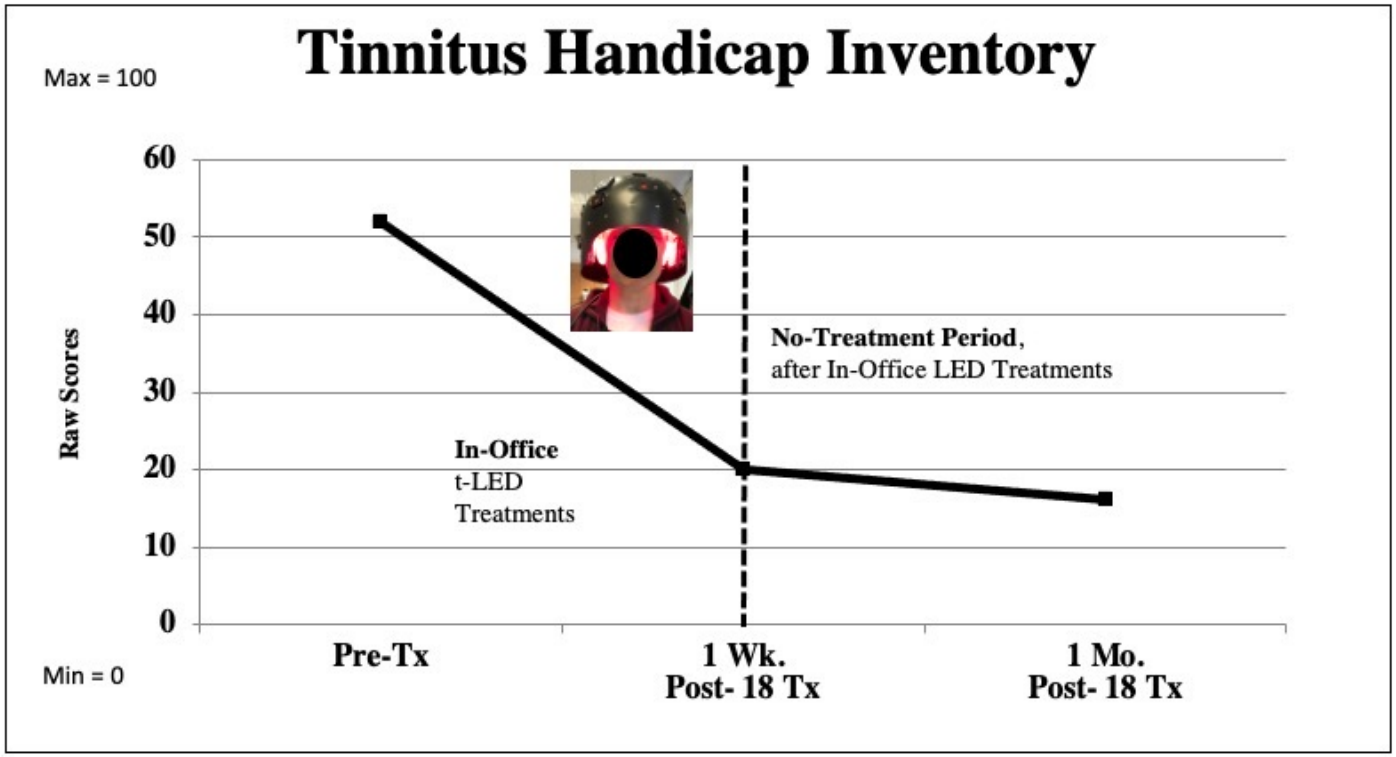
Note: The ***Default Mode Network (DMN) is dysregulated in Chronic Pain, and in Opioid Addiction*** (Garland et al., 2013).

The DMN was treated with the Red/Near-infrared LEDs, that line the Thor Helmet.

Neuro Gamma LED device, for Home Treatment treats *only Default Mode Network.*

(Naeser et al., 2019)

Athlete, tackle football, 16 Years, *possibly developing CTE*, age 57. *Blast-TBI Veterans also develop CTE*

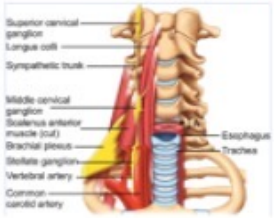


(Naeser et al., 2019)

Photomedicine and Laser Surgery
Volume 36, Number 9, 2018

Pp. 468–471
DOI: 10.1089/pho.2017.4431

Tinnitus Study from Japan
Near-infrared, Application to Neck



Change of Tinnitus with Xenon Phototherapy of the Stellate Ganglion

Masako Shimizu, MD,[1,2] Takashi Matsuzuka, MD, PhD,[1] Fumiaki Matsumi, MD,[2] Hiroshi Ogawa, MD, PhD,[3] and Shigeyuki Murono, MD, PhD[1]

TABLE 1. TINNITUS HANDICAP INVENTORY AND NUMERICAL RATING SCALE BEFORE AND AFTER XPSG IN THE XPSG GROUP

Severity of tinnitus (THI before treatment)	*Number of patients*	*THI score*		*NRS score*	
		Before	*3 months*	*Before*	*3 months*
No handicap	4	7.5±2.2	8.0±3.6	3.5±1.0	3.0±0.6
Mild	9	24.4±1.6	22.4±4.2	4.6±0.7	4.1±0.4
Moderate	9	48.2±1.9	33.3±4.7*	4.3±0.4	3.0±0.3*
Severe	21	78.3±2.7	4.4 5±5.5**	7.5±0.5	5.3±0.6**
Total	43	54.1±4.3	34.6±3.5*	5.8±0.4	4.4±0.3**

NRS, numerical rating scale; THI, tinnitus handicap inventory; XPSG, xenon phototherapy of the stellate ganglion.
*$p<0.05$; **$p<0.01$.

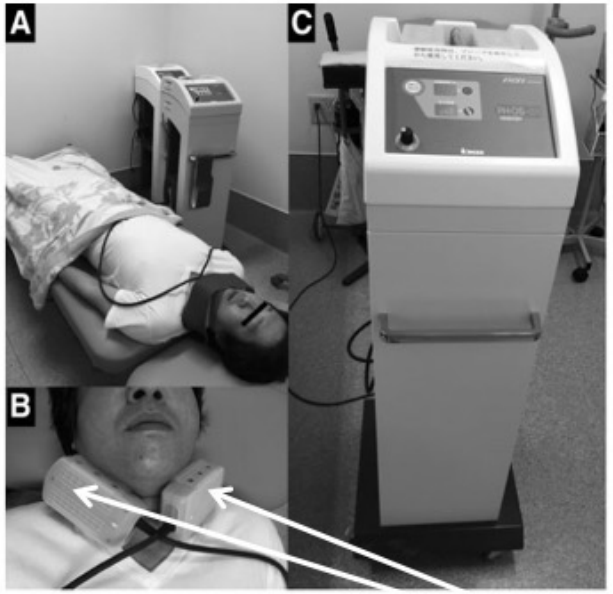


FIG. 1. Treatment was performed in a supine position **(A)**. XPSG probes were placed around stellate ganglion regions **(B)**. Appearance of xenon phototherapy device **(C)**. XPSG, xenon phototherapy of the stellate ganglion.

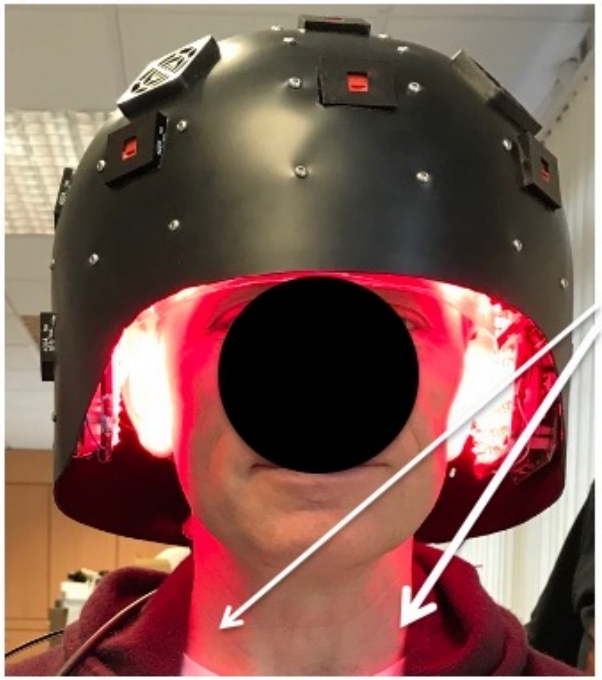


Photo shows that the red, and thus also the near-infrared, (NIR) 850nm photons are ***delivered to both sides of the neck, likely to the stellate ganglion regions,*** which are important areas to treat with NIR photons, to reduce severity of tinnitus, as shown above (Shimizu et al., 2018)

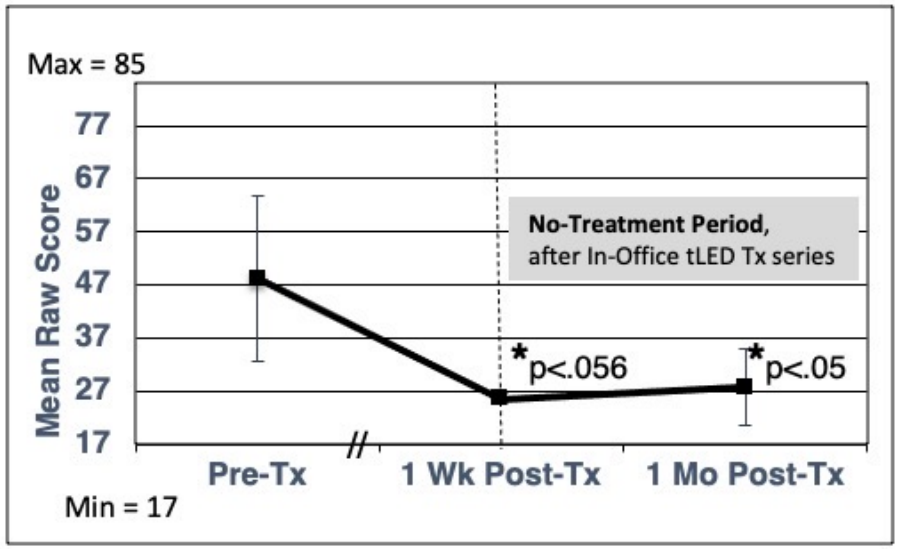
See results for reduced tinnitus in athlete, age 57 Yr., treated with the Helmet, previous slide.

Suggested transcranial photobiomodulation (tPBM) research protocol, to treat Havana Syndrome.

(Naeser et al., 2019)

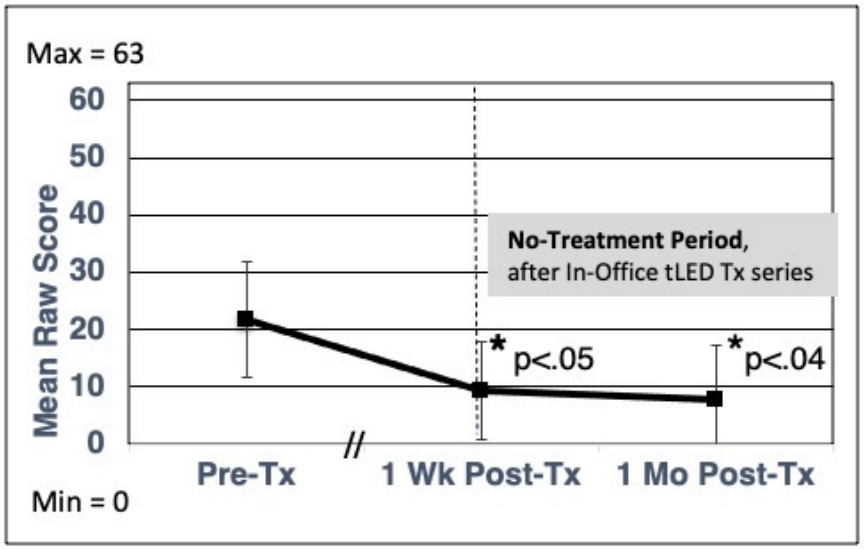
Group Results, n=4 Athletes, with *possible CTE. Results relevant for Veterans, as they can develop CTE.*

Post Traumatic Stress Disorder Checklist Civilian (PTSD)

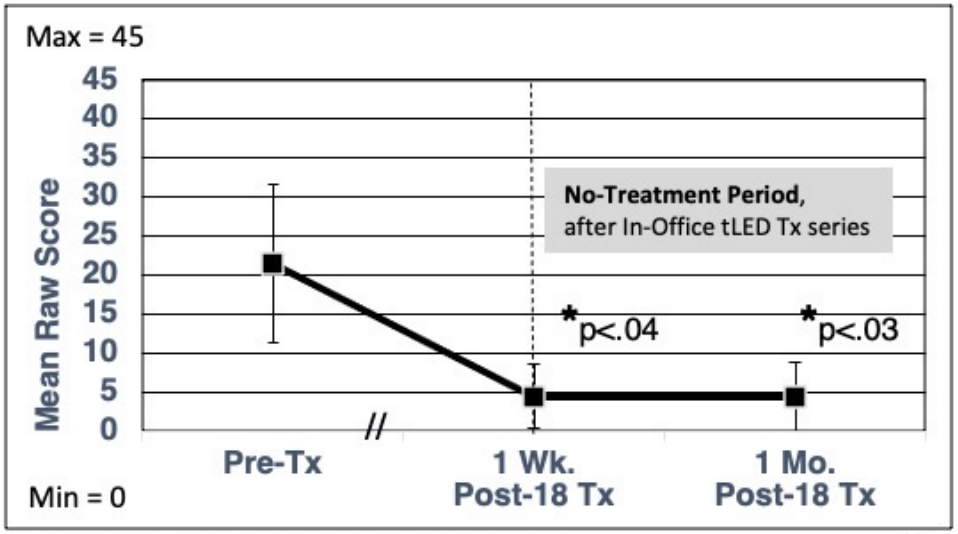


Score >36 suggestive of PTSD; Reliable decrease = 5-10 points
Clinically meaningful decrease = 10-20 points (Monson et al., 2008)

Beck Depression Inventory – II (BDI)

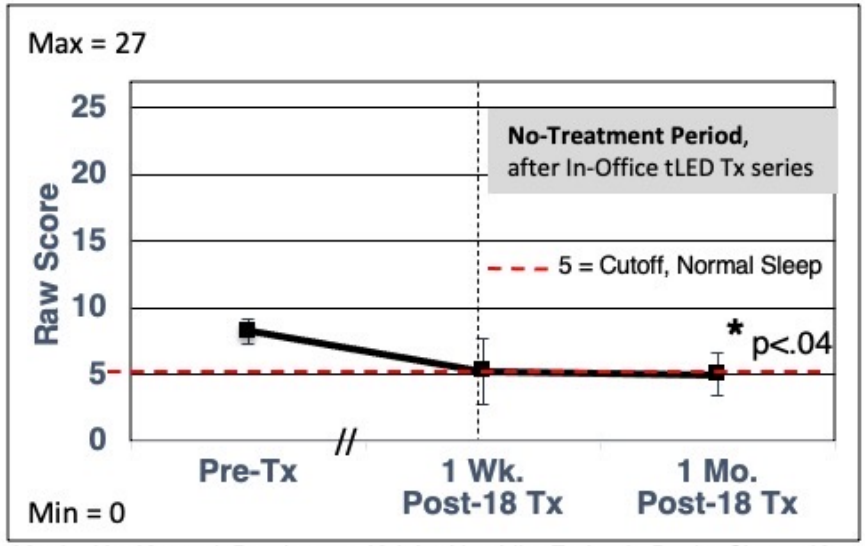


Short Form, McGill Pain Questionnaire



ANOVAs (1-tail), means; and error bars = 1 SD

Pittsburgh Sleep Quality Index (PSQI)



Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Hamblin, Fedoruk, Poole, Cheng, Koo

Possible Mechanisms for Transcranial LED Effects for Improved Sleep

Increase in Melatonin, and Improved Sleep, after Red Light.

Journal of Athletic Training 2012;47(6):673–678
doi: 10.4085/1062-6050-47.6.08

www.nata.org/journal-of-athletic-training

original research

Red Light and the Sleep Quality and Endurance Performance of Chinese Female Basketball Players

Jiexiu Zhao, PhD*; Ye Tian, PhD*; Jinlei Nie, PhD†; Jincheng Xu, MSS‡; Dongsen Liu, MS‡

*Sport Biological Center, China Institute of Sport Science, Beijing, China; †Department of Kinesiology, Macao Polytechnic Institute, China; ‡Department of Kinesiology, Beijing Sport University, China

Context: Good sleep is an important recovery method for prevention and treatment of overtraining in sport practice. Whether sleep is regulated by melatonin after red-light irradiation in athletes is unknown.

Objective: To determine the effect of red light on sleep quality and endurance performance of Chinese female basketball players.

Design: Cohort study.

Setting: Athletic training facility of the Chinese People's Liberation Army and research laboratory of the China Institute of Sport Science.

Patients or Other Participants: Twenty athletes of the Chinese People's Liberation Army team (age = 18.60 ± 3.60 years) took part in the study. Participants were divided into red-light treatment (n = 10) and placebo (n = 10) groups.

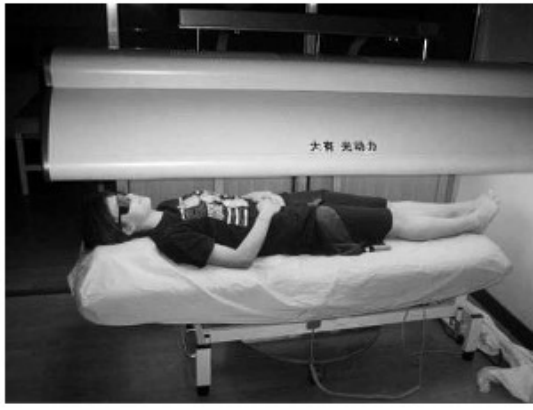
Intervention(s): The red-light treatment participants received 30 minutes of irradiation from a red-light therapy instrument every night for 14 days. The placebo group did not receive light illumination.

Main Outcome Measure(s): The Pittsburgh Sleep Quality Index (PSQI) questionnaire was completed, serum melatonin was assessed, and 12-minute run was performed at preintervention (baseline) and postintervention (14 days).

Results: The 14-day whole-body irradiation with red-light treatment improved the sleep, serum melatonin level, and endurance performance of the elite female basketball players ($P < .05$). We found a correlation between changes in global Pittsburgh Sleep Quality Index and serum melatonin levels ($r = -0.695$, $P = .006$).

Conclusions: Our study confirmed the effectiveness of body irradiation with red light in improving the quality of sleep of elite female basketball players and offered a nonpharmacologic and noninvasive therapy to prevent sleep disorders after training.

Key Words: Pittsburgh Sleep Quality Index, melatonin, 12-minute run



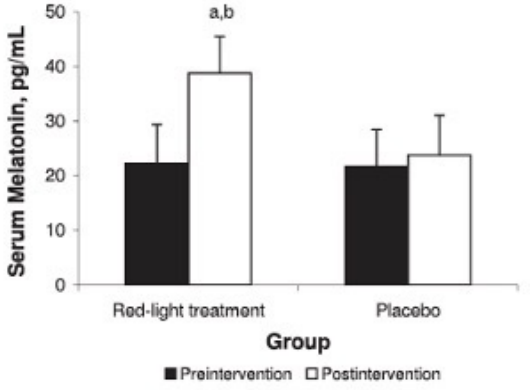


Figure 3. Serum levels of melatonin for the red-light treatment and placebo groups. * Indicates different from preintervention ($P < .01$). [b] Indicates difference between groups at postintervention ($P < .01$).

Possible Mechanisms for Transcranial LED Effects for Improved Sleep

Importance of …Improved Sleep.

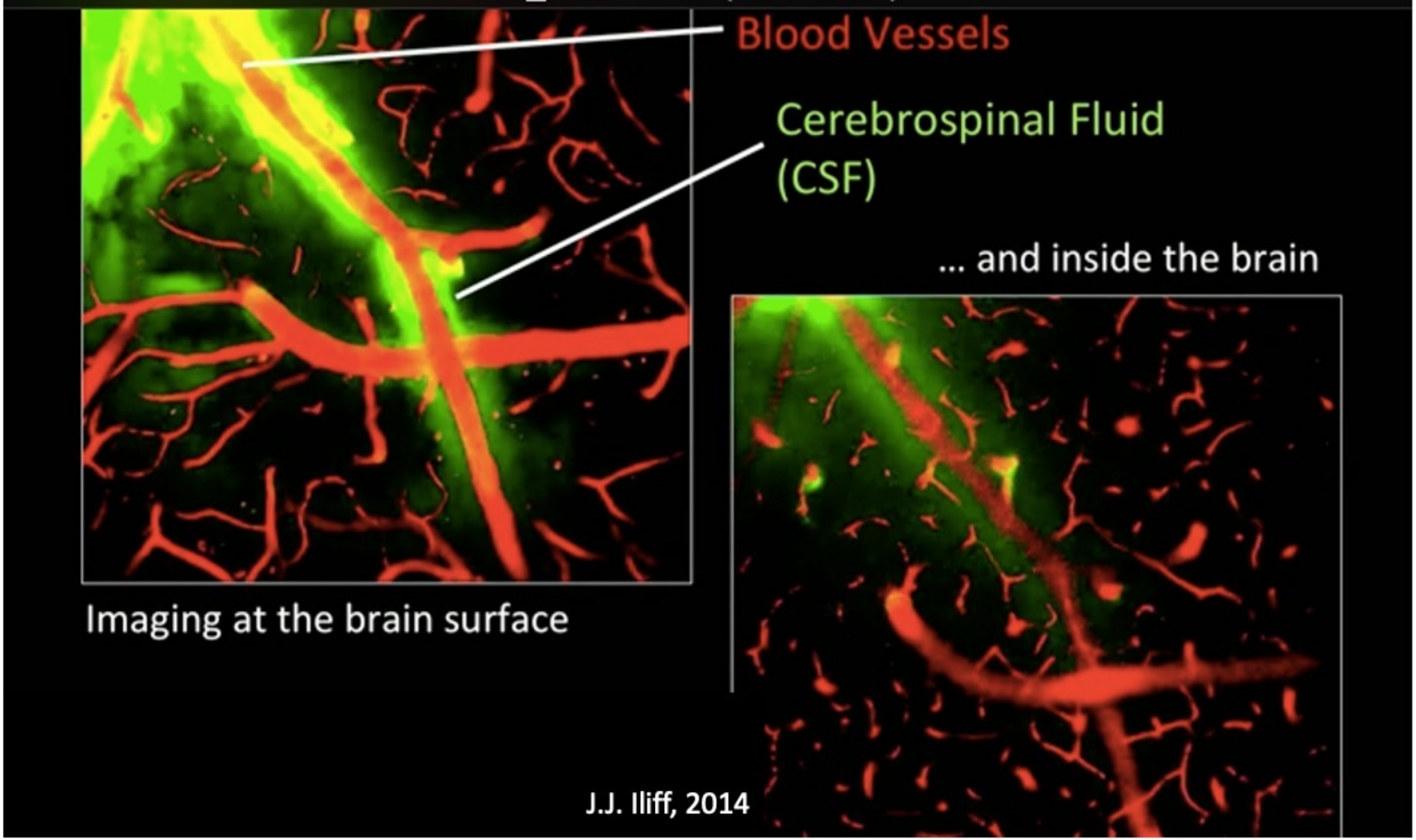
(Xie et al., 2013)

[1]Division of Glial Disease and Therapeutics, Center for Translational Neuromedicine, Department of Neurosurgery, University of Rochester Medical Center, Rochester, NY 14642, USA. [2]Department of Neuroscience and Physiology, Langone Medical Center, New York University, New York, NY 10016, USA.

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie,[1*] Hongyi Kang,[1*] Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

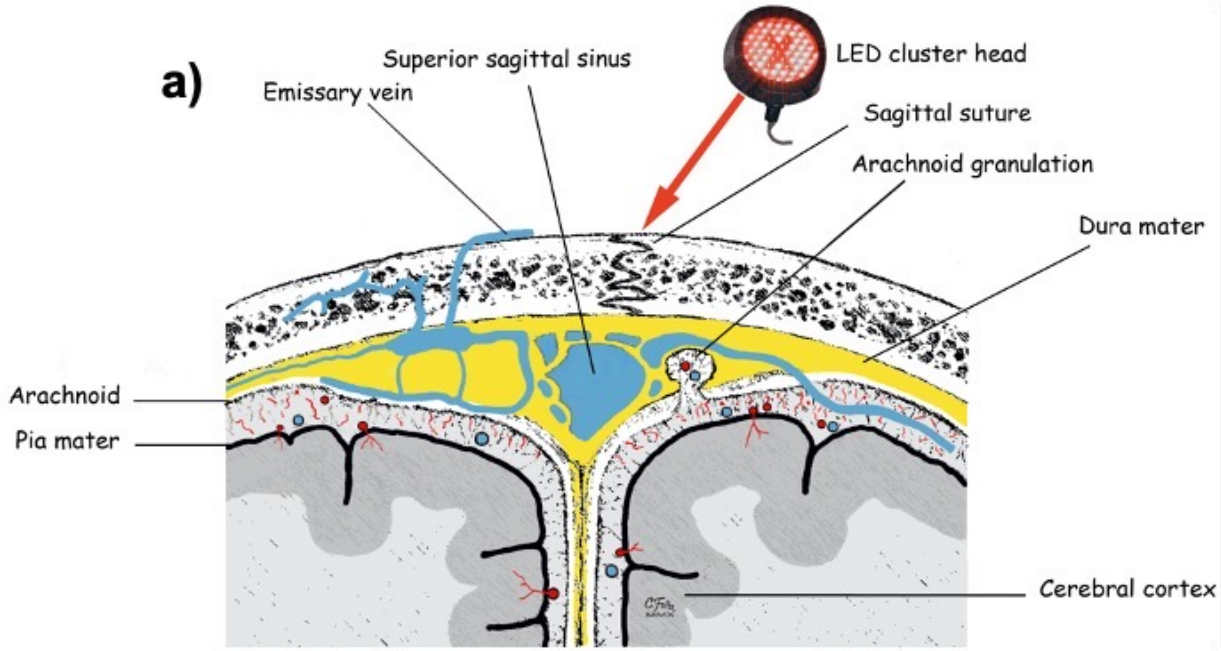
The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

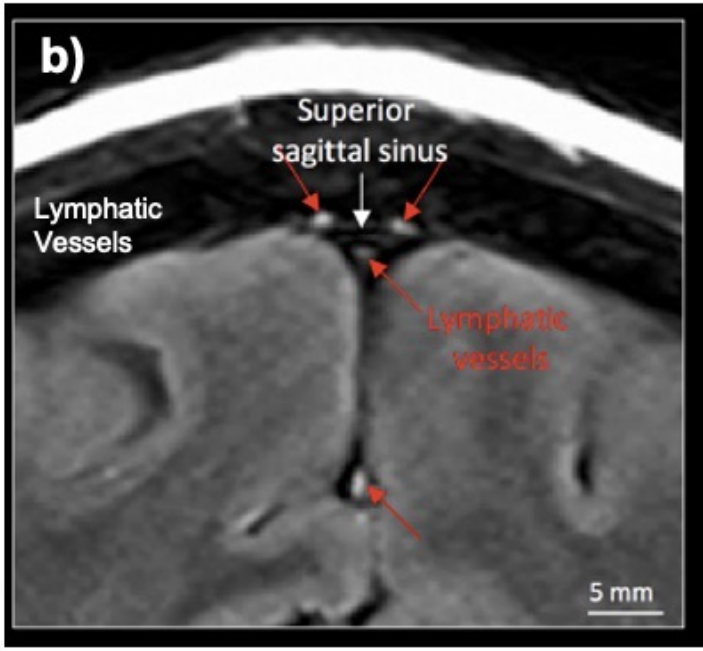


During sleep, cerebral spinal fluid rushes in, and surrounds cells and blood vessels at surface brain cortex, as well as deeper areas – to ***remove amyloid beta waste products*** from between the cells (built up during the day), ***pushing the waste products into blood vessels, for removal.***

In Alzheimer's Disease there is poor sleep and increased buildup of amyloid beta and tau waste products. One goal of treatment for Alzheimer's Disease should be to improve sleep.

Hypothesis: Near-infrared LEDs promote *vasodilation of blood and lymphatic vessels*





a) Frontal view, Coronal Diagram, ***Valveless* Emissary veins**. Red/near-infrared photons, delivered there, to promote vasodilation of blood vessels.

Valveless, emissary veins connect the extracranial venous system with the intracranial venous sinus, including **direct passage from the external scalp to meninges**. Plates Grey's Anatomy, Oxford Univ. Press. (Naeser et al., 2011)

b) Frontal view, Coronal Diagram, **Lymphatic vessels.**
Assist in clearance of abnormal proteins – in CTE, remove p-tau?
NIR 1267nm laser removed beta amyloid in Alzheimer's Disease mice.

(Zinchenko et al., 2019)

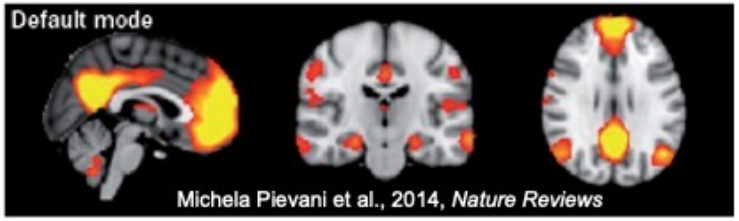
Lymphatic vessels are within dura mater. Visualized post- gadobutrol, T2-FLAIR MRI scans in Humans.

Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Hamblin, Fedoruk, Poole, Cheng, Koo, in prep..

(Absinta, et al., 2017)

Photomedicine and Laser Surgery
Volume 35, Number 8, 2017
Mary Ann Liebert, Inc.
Pp. 432–441
DOI: 10.1089/pho.2016.4227

Part 3. Dementia



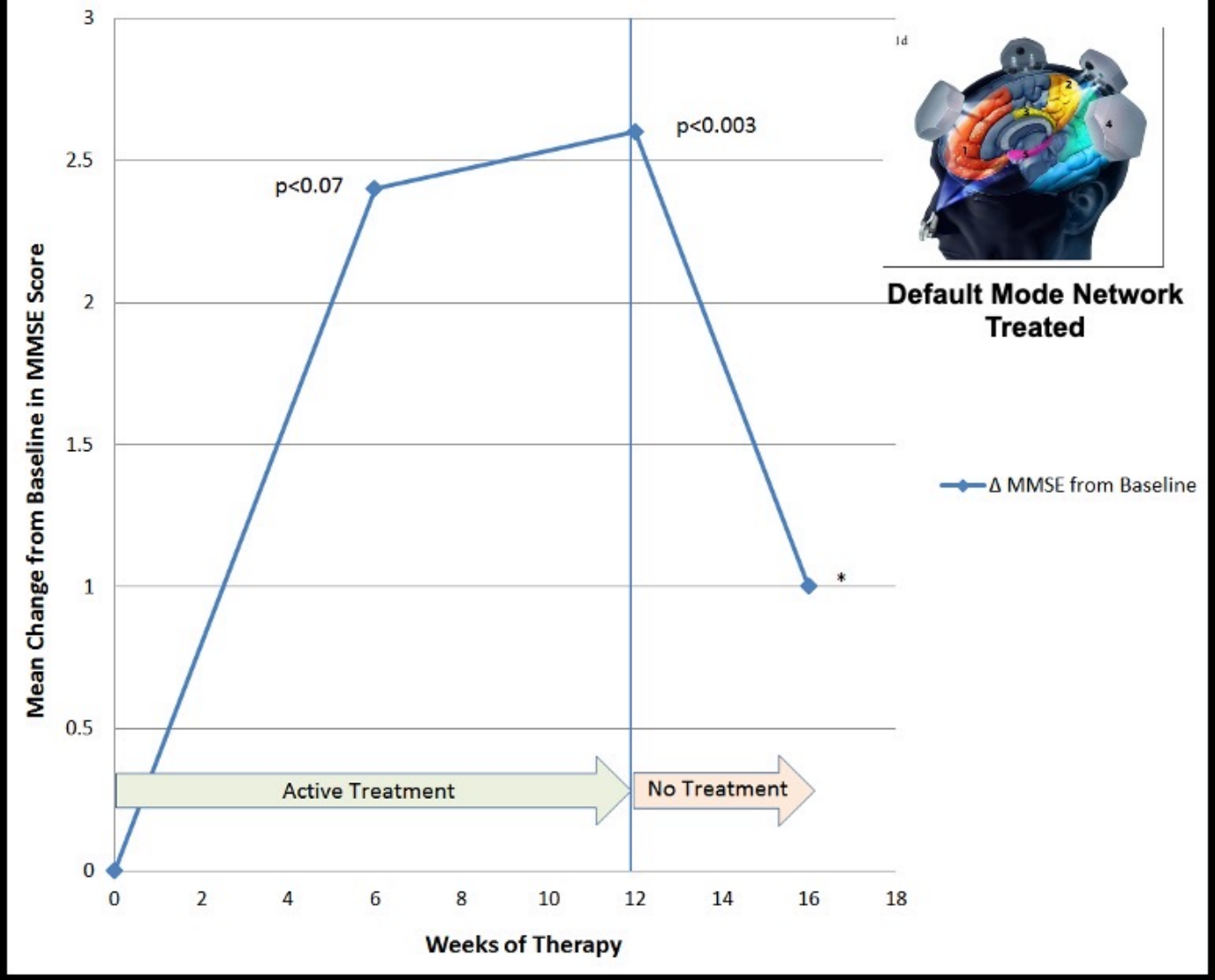
Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report

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]

Abstract

Objective: This study investigated whether patients with mild to moderately severe dementia or possible Alzheimer's disease (AD) with Mini-Mental State Exam (MMSE) Baseline scores of 10–24 would improve when treated with near-infrared photobiomodulation (PBM) therapy. ***Background:*** Animal studies have presented the potential of PBM for AD. Dysregulation of the brain's default mode network (DMN) has been associated with AD, presenting the DMN as an identifiable target for PBM. ***Materials and methods:*** The study used 810 nm, 10 Hz pulsed, light-emitting diode devices combining transcranial plus intranasal PBM to treat the cortical nodes of the DMN (bilateral mesial prefrontal cortex, precuneus/posterior cingulate cortex, angular gyrus, and hippocampus). Five patients with mild to moderately severe cognitive impairment were entered into 12 weeks of active treatment as well as a follow-up no-treatment, 4-week period. Patients were assessed with the MMSE and Alzheimer's Disease Assessment Scale (ADAS-cog) tests. The protocol involved weekly, in-clinic use of a transcranial-intranasal PBM device; and daily at-home use of an intranasal-only device. ***Results:*** There was significant improvement after 12 weeks of PBM (MMSE, $p<0.003$; ADAS-cog, $p<0.023$). Increased function, better sleep, fewer angry outbursts, less anxiety, and wandering were reported post-PBM. There were no negative side effects. Precipitous declines were observed during the follow-up no-treatment, 4-week period. This is the first completed PBM case series to report significant, cognitive improvement in mild to moderately severe dementia and possible AD cases. ***Conclusions:*** Results suggest that larger, controlled studies are warranted. PBM shows potential for home treatment of patients with dementia and AD.

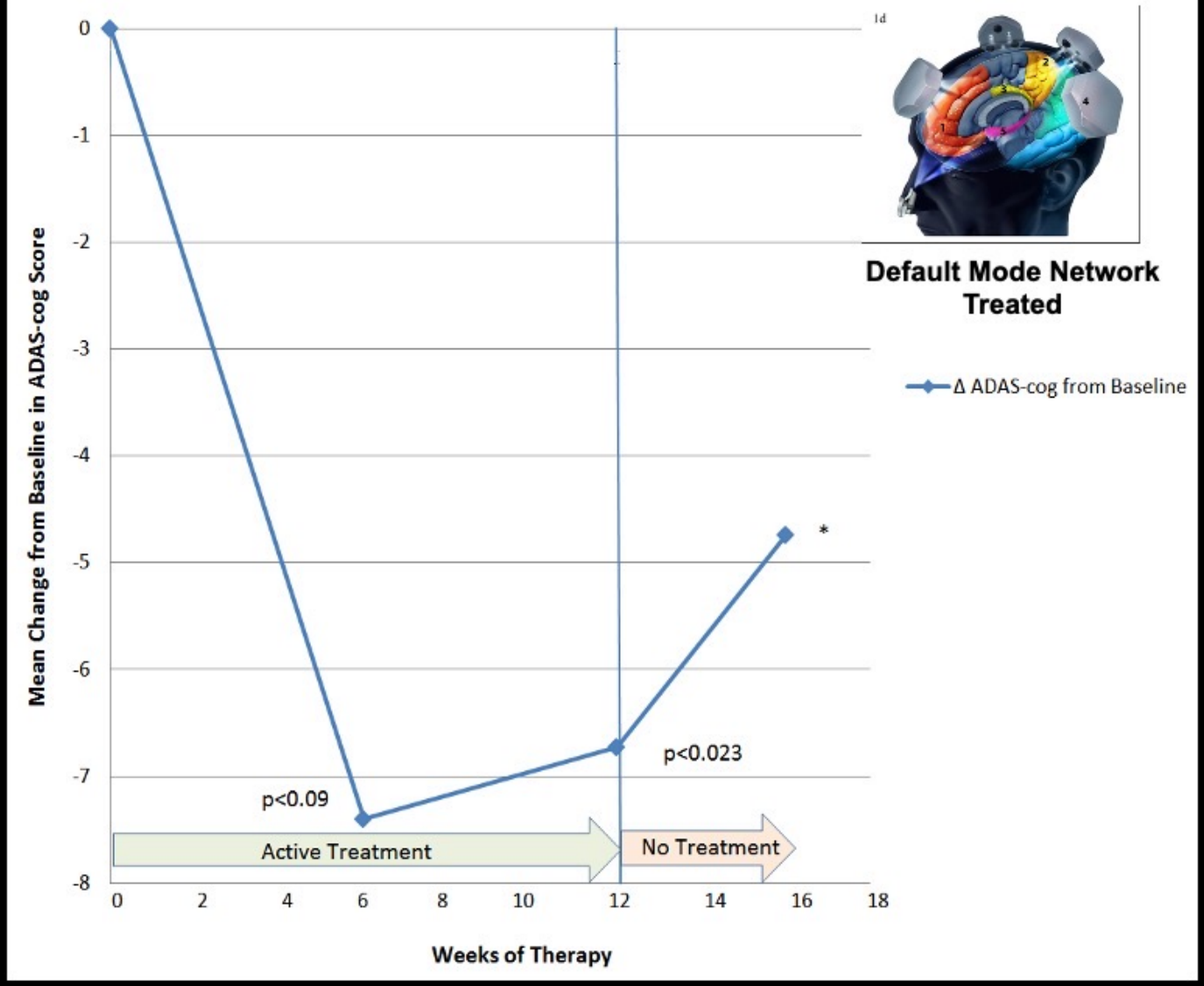
5 Dementia Cases



RESULTS: Mean change from baseline on Mini Mental State Exam (MMSE) scores.
Higher numbers indicate better cognition on this test.

(Saltmarche et al., 2017)

5 Dementia Cases



RESULTS: Mean change from baseline in ADAS-cog scores.

Lower numbers indicate better cognition on this test.

(Saltmarche et al., 2017)

QUALITY OF LIFE (QoL) AND FUNCTIONAL CHANGES, Dementia Patients

Patient #	Baseline	12 Week Treatment Period	No-Treatment Follow-up Period
1	Apprehensive, spoke predominantly Portuguese with family, complained 'her head felt too heavy to hold up, headache'. Only responded to questions. Family stated she was more anxious, decreased ability to cook or clean, less interactive with family.	Openly smiling, laughing, hugged assessor. Stated frequently, head feels 'lighter' 'clearer', no headache. Family stated 'more talkative and active' (i.e., cooking, cleaning, going for walks, answering phone). Able to give a recipe to assessor by memory.	Slowly became more withdrawn, less engaged. More tired, feeling 'cloudy' 'heavy head', headaches returned. Cooked & cleaned less, personal hygiene declined. Did not want to participate in family gatherings.
2	Infrequent eye contact with assessor. Predominantly answered in Italian with long pauses between questions. Stooped posture shuffling gait, Live-in caregiver, assisted with mobility, dressing, personal hygiene, incontinent 6/7 nights. Not initiating conversation, minimal engagement during family visits.	Looked directly at assessor, spoke predominantly English, sense of humour and smiling. Remembered assessor's name, reason for visit and stated 'doing better'. By Week 6, walked into office more upright, steady pace, independent transfers from chairs. Incontinent 1-2/7 nights. Occasionally dressed self without assistance, more communicative, happier with caregiver and family.	First week without PBM treatment, started a rapid decline in behaviour (uncooperative and belligerent); functional decline (required assistance with mobility transfers, hygiene and dressing); and cognitive decline (less able to follow conversation, respond appropriately or remember events). Family requested to have LED treatment resumed.
3	Humor used to cover inability to answer questions. Denied memory loss. Thought he was still working. Read and listened to news. Wife not sure what he remembered. Minimal discussion of news or events.	Patient stated, 'easier to answer test questions', recognized when unable. Wife stated he was more interactive and reading his professional publications. Week 10, foot ulcer returned, below the knee edema, erythema, pain, grimace with transfers from chair, less bright and interactive.	Patient treated at foot clinic, little change. Foot pain all of the time, leg edema below the knee. Less focused during testing, decreased interaction, less humorous, personal hygiene declined (e.g., not clean shaven).
4	Outgoing, humorous, states he feels less happy. Agrees when wife states he is more forgetful, (i.e., only drives familiar routes to destinations, misplaces items). Asked wife for test answers. Working part-time, cooks his own ethnic meals.	Returned to building 'found object sculptures'. Able to re-route driving to accommodate traffic, states less forgetful, needs fewer reminders. Less dependent on wife for 'entertainment', generally happier. Looks less to wife for test answers, laughs, then answered independently.	No decline during 'No Treatment'. Wife confirmed husband had not lost the gains achieved during treatment.
5	Patient open about loss of memory and diagnosis of AD. Interactive, but slightly reserved. Aware when unable to answer test questions, needed	Week 3, stated he felt brighter, world had more colour, less frequently forgot why he went into a room. Worked in garden with wife, preparing to start oil painting again. More humorous,	Gradual decrease in 'brightness and clarity'. Both patient and wife noticed decline in memory, focus, less able to initiate and complete

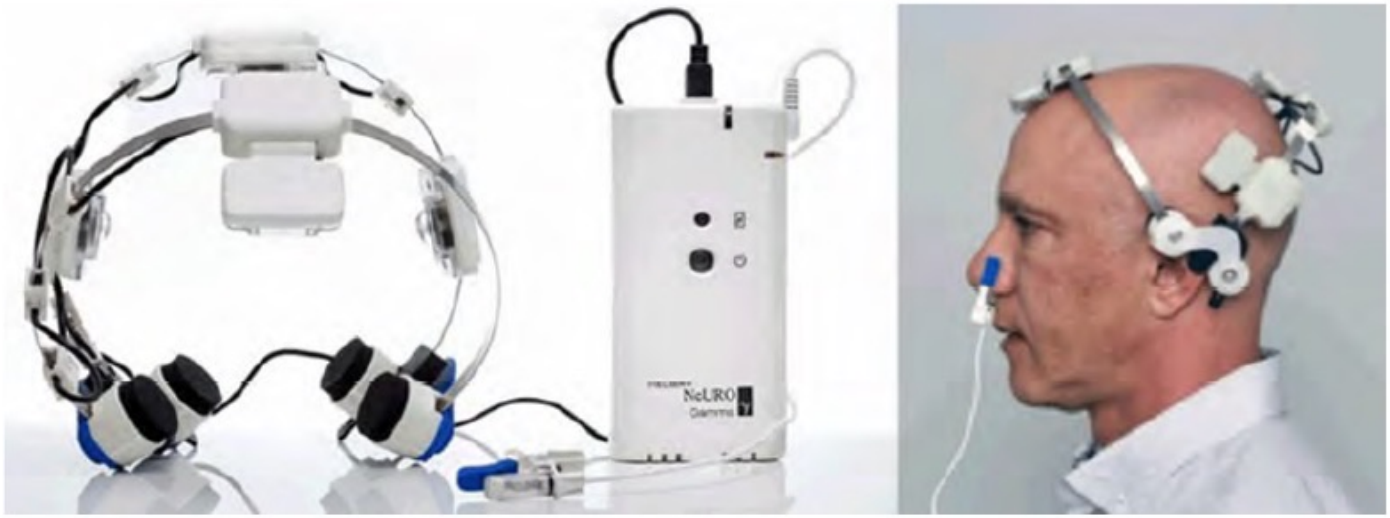
Photobiomodulation, Photomedicine, and Laser Surgery
Volume 37, Number 3, 2019

Pp. 133–141
DOI: 10.1089/photob.2018.4555

Photobiomodulation—Original Research

Effects of Home Photobiomodulation Treatments on Cognitive and Behavioral Function, Cerebral Perfusion, and Resting-State Functional Connectivity in Patients with Dementia: A Pilot Trial

Linda L. Chao, PhD[1–3]



Received PBM, Active Photobiomodulation, 12 Weeks n=4 cases; OR received UC, Usual Care, 12 Weeks n=4

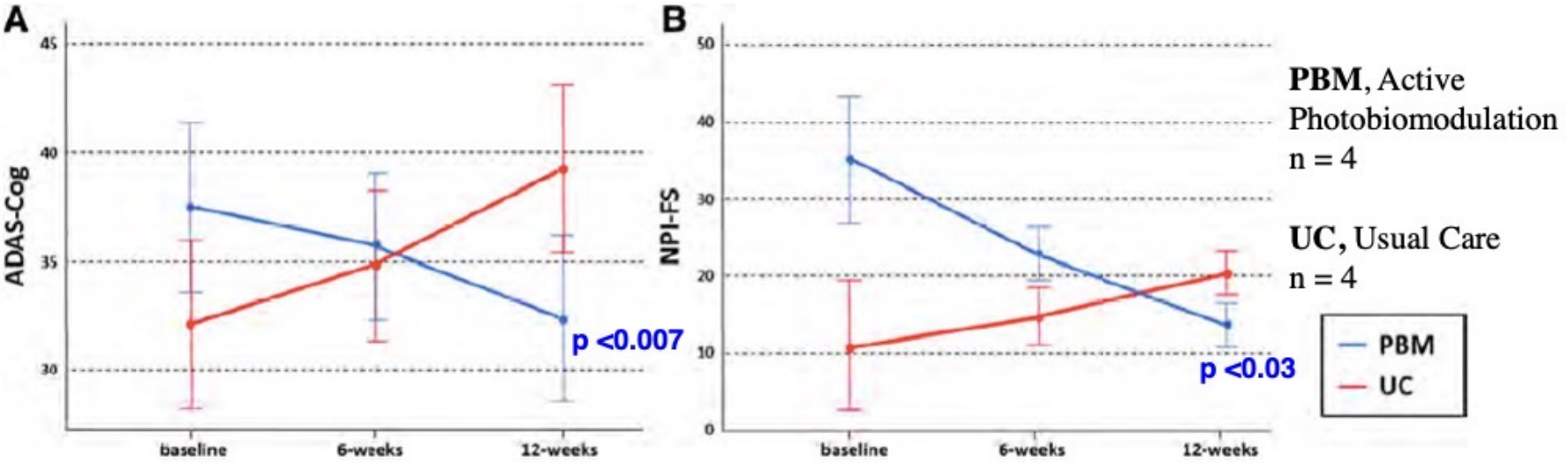


FIG. 3. Mean (±SEM) ADAS-cog **(A)** and NPI-FS **(B)** scores in the PBM (blue line) and Usual Care (red line) groups by time. Lower scores on both measures indicate better function. ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive; NPI-FS, Neuropsychiatric Inventory frequency severity; SEM, standard error of the mean; PBM, photobiomodulation.

PBM, Active Photobio-Modulatic

UC, Usual Care

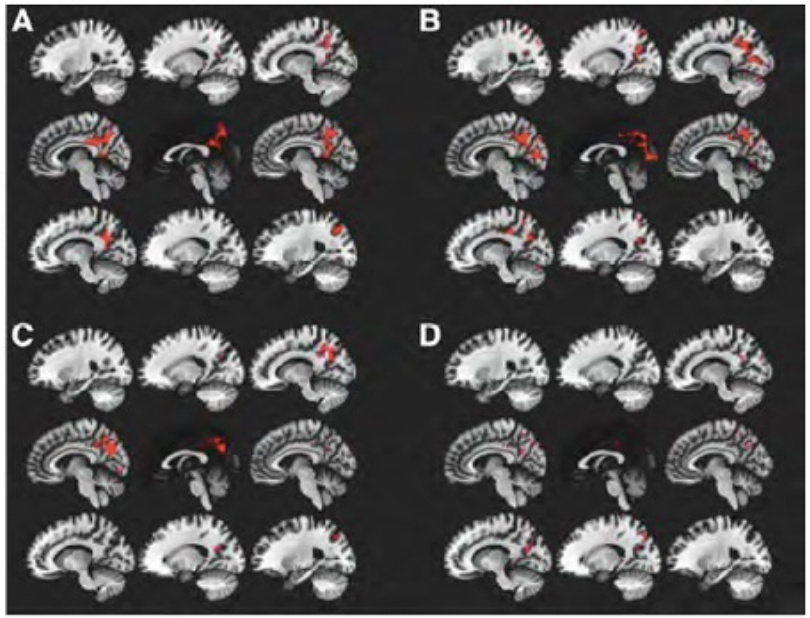
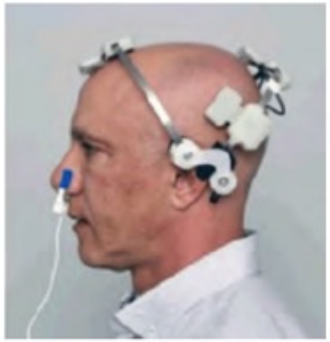


FIG. 5. Default-mode network activity in the PBM group—**(A)** baseline and **(B)** week 12 and in the usual care group—**(C)** baseline and **(D)** week 12. The posterior cingulate cortex (1, −61, and 38) was used as seed in the analysis; Height threshold: $P_{unc} < 0.001$; cluster threshold $P_{FDR} < 0.05$.

mma

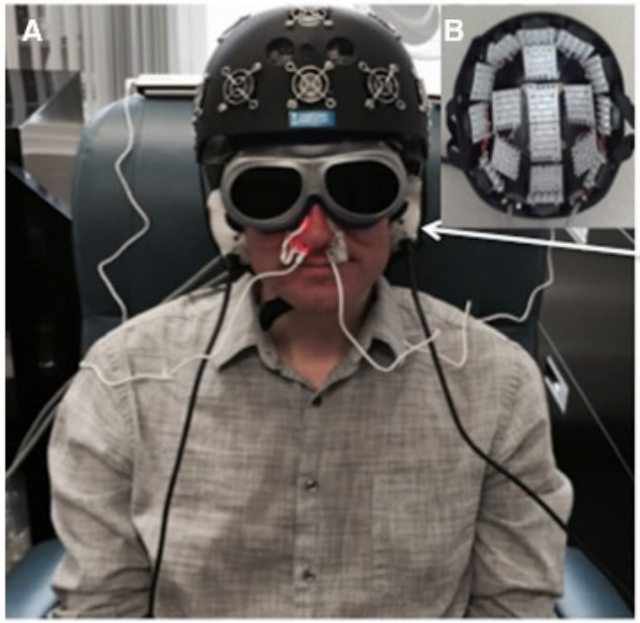


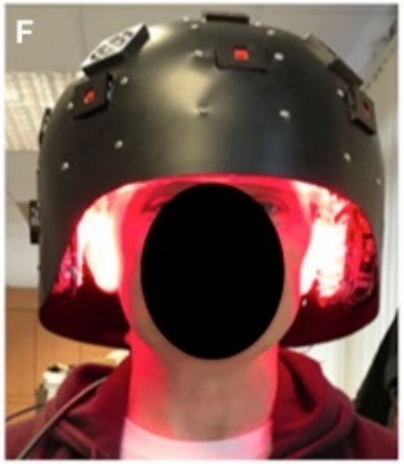
(Chao, 2019)

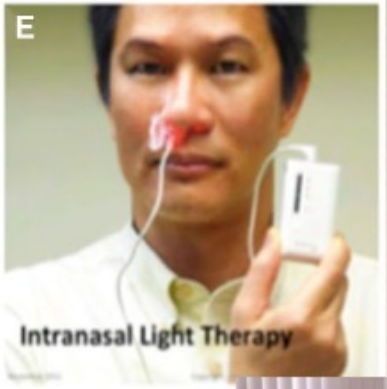
Gulf War Illness. Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in Veterans with GWI. Research funded, Dept. of Veterans Affairs, (CSRD)

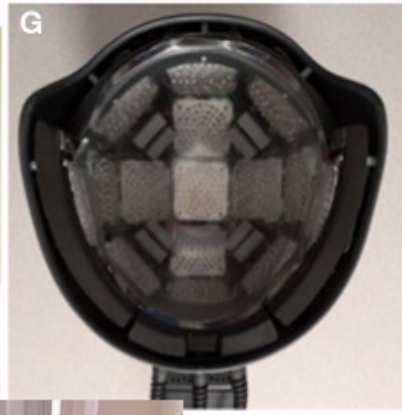
Gulf War Illness veterans, *served in Kuwait*, 1990-91.

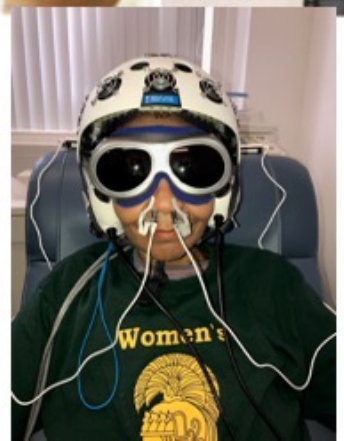
- **30% now have GWI Neurotoxicant Exposures.**
- **Pyridostigmine Bromide Pills – Anti nerve-gas pills.**
- **Organophosphate Pesticides.**
- ***Damage the mitochondria* in muscles and brain.**
- **Exposure to Burning Oil Wells; and some to Sarin gas**
- **200,000 of the 600,000 deployed to Kuwait, now have Chronic, Multi-symptom Illness.**



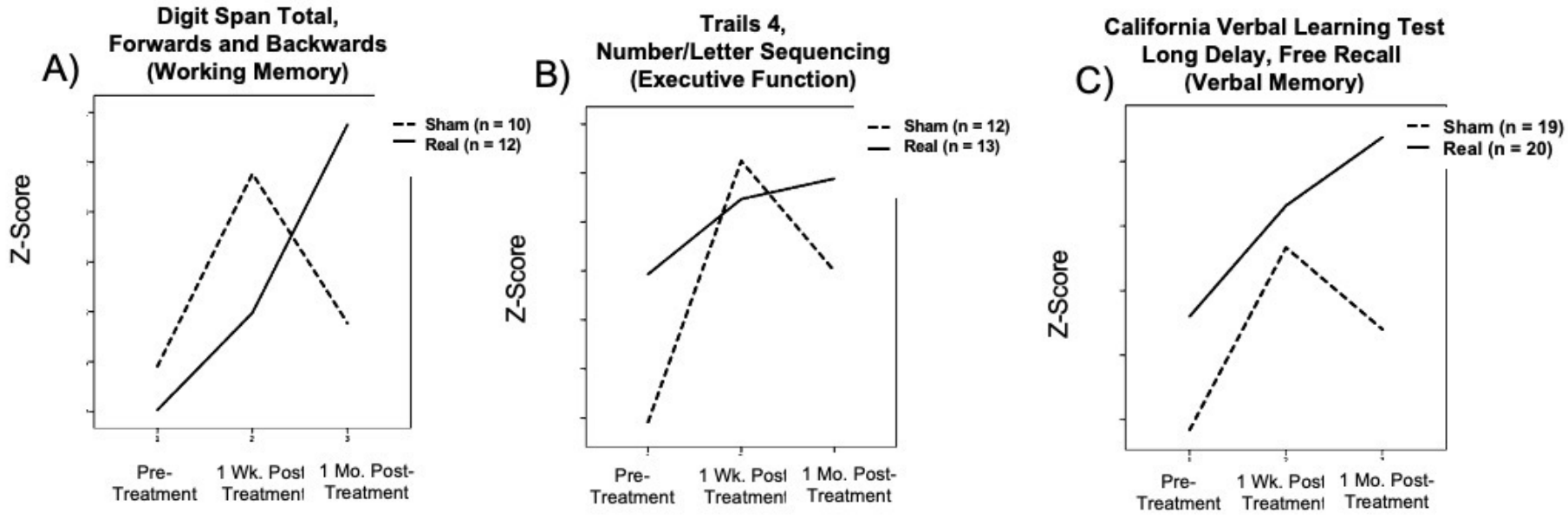








Gulf War Illness. Summary Results: Transcranial PBM to Improve Cognition in GWI



A-C. Both the Real LED and the Sham LED Groups improved at 1 Wk Post- the final, 15th transcranial LED treatment, but ***only those who received Real LED treatments, continued to improve at 1 Mo. Post- the final, 15th tLED treatment.*** Those who received ***Sham LEDs, stayed the same or regressed towards Entry after 1 Mo.*** There may be **a placebo response at the 1-Wk Post-testing**, possibly related to the ***green goggles*** used to sham-out the red, intranasal LED. **Green goggles were worn by all participants and therapist** at all treatment visits. ***Green tinted lenses have a therapeutic effect*** (Huang, Zong, Wilkins et al., 2011).

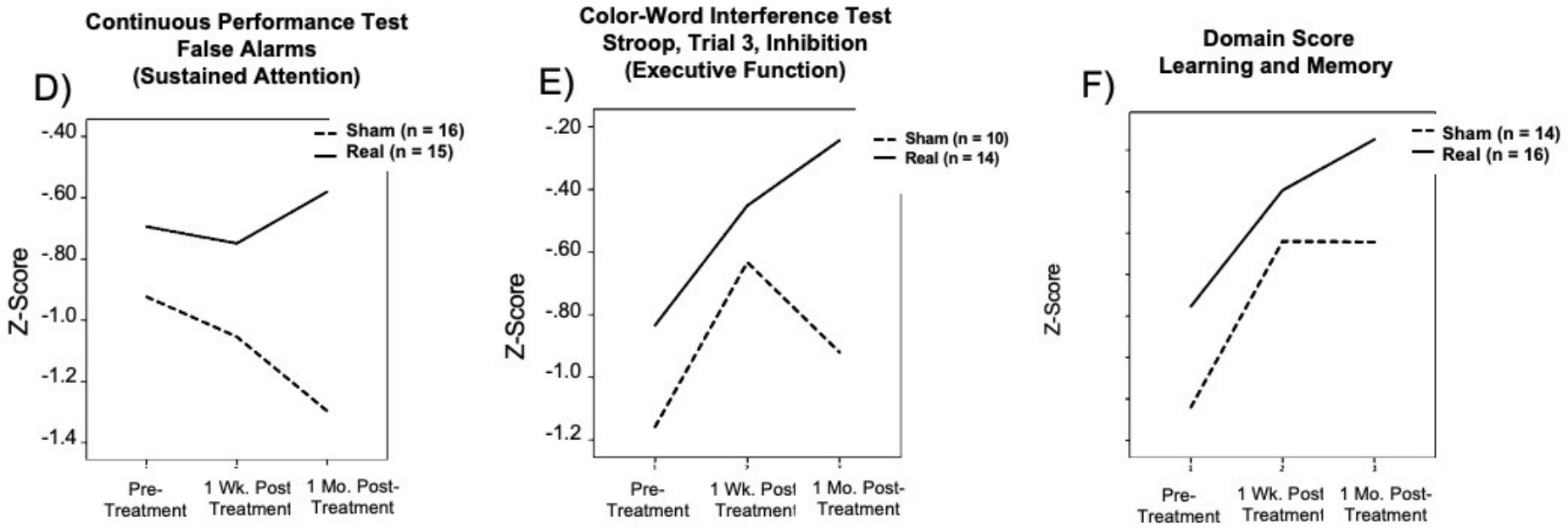
Placebo response wore off at the 1-Mo Post- testing time point, ***for the Sham LEDs. Study, underpowered.*** It was a burden for the GWI participants to come into the office at the Boston VAMC. 2x / Wk, almost 2 Mo, to receive the In-Office tLED treatments.

See published paper for details (Martin, Chao, Krengel et al., 2021, *Frontiers in Neurology*).

Future tLED Home Treatments are recommended for GWI cases

(Chao, 2019; Martin et al., 2021)

Gulf War Illness. Summary Results: Transcranial PBM to Improve Cognition in GWI



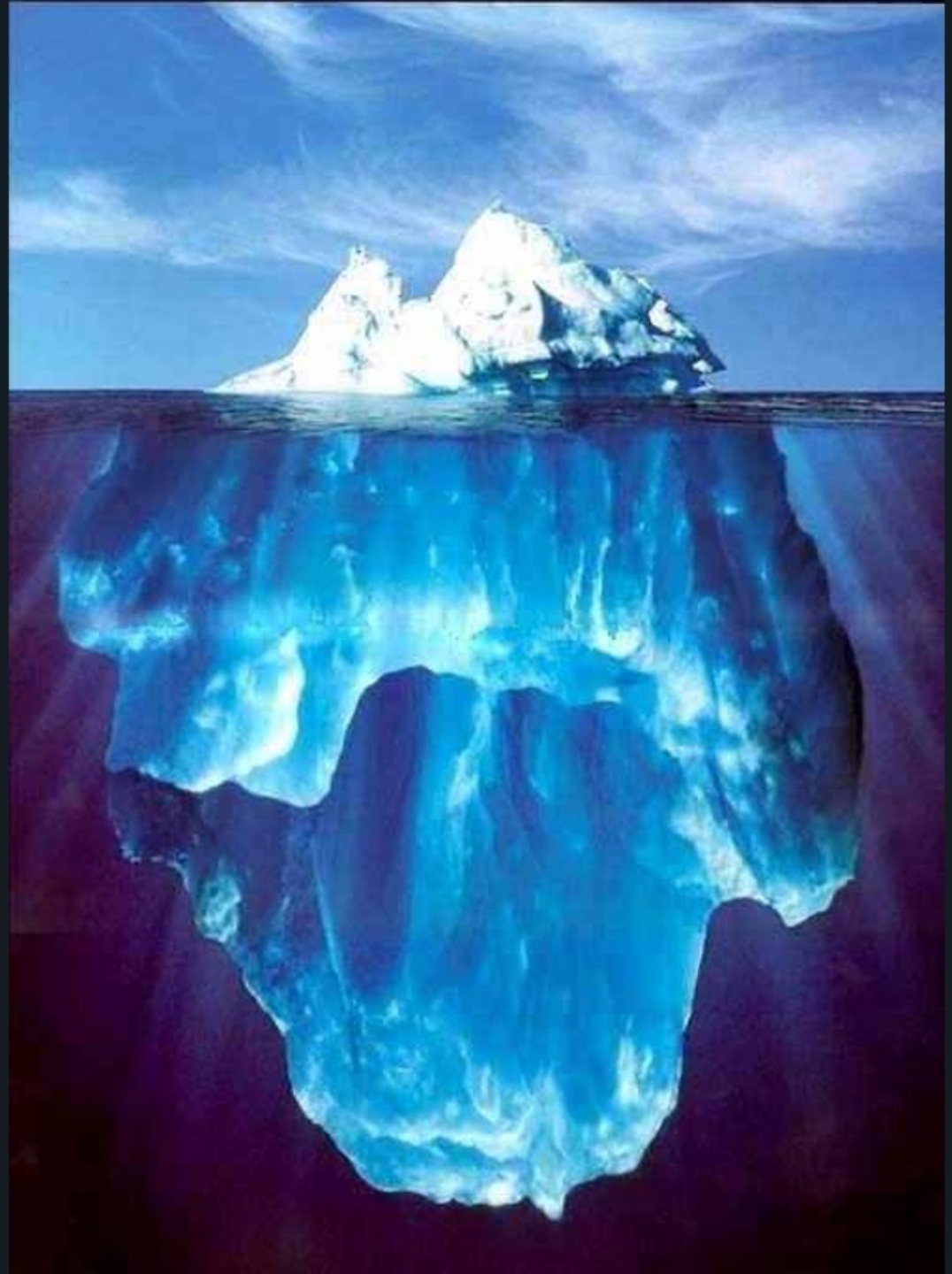
D-F. Both the Real LED and the Sham LED Groups improved at 1 Wk Post- the final, 15th transcranial LED treatment, but ***only those who received Real LED treatments, continued to improve at 1 Mo. Post- the final, 15th tLED treatment.*** Those who received ***Sham LEDs, stayed the same or regressed towards Entry after 1 Mo.*** There may be **a placebo response at the 1-Wk Post-testing**, possibly related to the ***green goggles*** used to sham-out the red, intranasal LED. **Green goggles were worn by all participants and therapist** at all treatment visits. ***Green tinted lenses have a therapeutic effect*** (Huang, Zong, Wilkins et al., 2011).

Placebo response wore off at the 1-Mo Post- testing time point, ***for the Sham LEDs. Study, underpowered.*** It was a burden for the GWI participants to come into the office at the Boston VAMC. 2x / Wk, almost 2 Mo, to receive the In-Office tLED treatments.

See published paper for details (Martin, Chao, Krengel et al., 2021, *Frontiers in Neurology*).

Future tLED Home Treatments are recommended for GWI cases

(Chao, 2019; Martin et al., 2021)



LED Home Treatment Program
for
Chronic, TBI/PTSD

Cases are Screened and Trained, in the in Rehab. Med. Svc., Polytrauma Clinic Boston VAMC.

Used on Trial basis, "LED TBI Clinic," Boston VAMC, JP

Clinical Demonstration Project.
Funded by VA, **Center for Compassionate Care Innovation,** VACO. FY'18, '19. '20

Is within FDA Category, low-risk devices: "General Wellness." No Medical Claims made.

Vielight **Neuro Alpha**, pulsed at **10Hz, 810nm** LED device. The smaller, flat rectangles contain the 810nm diode. Each diode is placed on a cortical node of the ***Default Mode Network*****:** Bilateral **Mesial Prefrontal Cortex** (midline, high forehead placement); **Precuneus** (midline, high parietal placement half-way between occipital protuberance and vertex; Left **Angular Gyrus** (and Right, not shown) area (posterior/ superior to the ear); (**Hippocampus**)/via olfactory bulb - nose-clip, intranasal placement.

LED Parameters for Vielight Neuro Alpha, 10 Hz (or Gamma, 40 Hz) Device – Headframe + Built-in Intranasal Device for use in LED TBI Clinic

Vielight Neuro Alpha Device

A. Headframe. Back frame has green dot on center-back, diode plate.

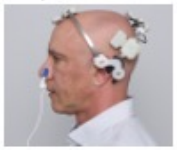
B. Intranasal, nose-clip diode, placed in one nostril.

C. White plastic power source box

D. "R" Side Earpiece Label, here.

LED Parameters for NIR Vielight Neuro Alpha, 10 Hz (or Gamma, 40 Hz)
***Headframe* + Built-in, Intranasal Device used in LED TBI Clinic**

For all light emitting diodes (LEDs):
Wavelength: NIR, 810 nm, Pulse rate: 10 Hz (or 40 Hz), 50% duty-cycle, synchronized
Treatment time: 20 minutes



Headset, 4 LEDs:

Posterior band, 3 LEDs – default positions on precuneus, and L & R angular gyri
For each LED:
Total power per LED = **100 mW**
Beam spot size upon contact ≈ 1 cm^2
Total power output density to scalp per LED = **100 mW/cm^2 @ pulsed 50% duty cycle, 20 min.**
Energy density to scalp per LED on posterior band = 100*20*60*0.50/1000 = **60 J/cm^2**
Total energy dose to scalp from posterior band = 60*3 = **180 J/cm^2**

Anterior band, 1 LED – on the mesial prefrontal cortex
For 1 LED:
Total power of LED = **75 mW**
Beam spot size upon contact ≈ 1 cm^2
Total power output density to scalp, 1 LED = **75 mW/cm^2 @ pulsed 50% duty cycle, 20 min**.
Energy density dose to scalp, 1 LED, anterior band= 75*20*60*0.50/1000 = **45 J/cm^2**
Total energy dose to scalp per headset = 180 J/cm2 + 45 J/cm2 = **225 J/cm^2**

LED Parameters for Vielight Neuro Alpha, 10 Hz (or Gamma, 40 Hz) Device
Built-in Intranasal Device, used in LED TBI Clinic

For all light emitting diodes (LEDs):
Wavelength: 810 nm, Pulse rate: 10 Hz (or 40 Hz), 50% duty-cycle, synchronized
Treatment time: 20 minutes

Built-in Nasal Applicator, 1 LED:

Total power output **= 25 mW**
Beam spot size upon contact **≈ 1 cm^2**
Total power output density to mucosa = **25 mW/cm^2 @ pulsed 50% duty cycle, 20 min.**
Total energy dose to mucosa from intranasal = 25*20*60*0.50/1000 **= 15 J/cm^2**

Total energy dose to scalp from Vielight Neuro Alpha (or Gamma) Device:

From Headframe (225 J/cm^2)
plus
From Nasal Applicator (15 J/cm^2) = 240 J/cm^2
18 LED Treatments, 3x/Wk, 6 Wks (240 J/cm^2 x 18) = 4,320 Total J/cm^2

Gut feeling the wait for relief may be over

Parkinson's disease may have met its match and from an unlikely source.

By SUVI MAHONEN

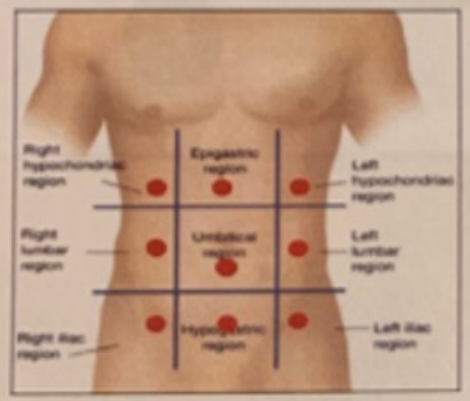
The Australasian Research Institute´s Ann Liebert with Parkinson´s patient Suzanne Fischer. Picture: Ryan Osland

SYMBYX BIOME

PDCare System Treatment Protocol

The LED *Coronet* is used to treat the head. Make sure that it is fitted well, touching the head with the pads around the rim and crown; but not anywhere else. Tilt it back on the head a little. When turned on at the wall, it will give approximately 12 min of red light and 8 min of infrared before turning itself off. There is no on/off switch on the device. Each session therefore is approximately **20 min** long. **Dr Liebert suggests that you use it in the evening every day, to begin with**. Depending on how you go, this increase to 2x per day.

PDCare 904 nm Laser by SYMBYX



The *PDCARE Laser* is used to treat the abdomen and neck. Turn it on with the button on the base (number 6 below) - you will hear 4 short beeps and see a flashing light (number 3 below). Press it onto the spot to be treated (at number 2 below) with enough pressure to turn it on. You will hear 1 beep. The laser will beep every minute. **Dr Liebert suggests that you hold it on each spot on the abdomen for 2 beeps (2 min total).** Treat over your bare abdomen (it won't penetrate clothes very well!) in a grid pattern as shown in the diagram. The top 3 spots just under the ribs and the bottom 3 just above the pelvis.

Dr Liebert also wants you to press the laser against the neck at the base of the skull for 2 beeps - for 2 min total. Your entire *PDCare Laser* treatment will take approximately **22 min**. Make sure you turn off the button on the base (number 6 above) when you have finished to save the batteries (housed behind numbers 4/5 above)! **Use your *PDCare Laser* 3x week, preferably in the morning before exercise.** An instructional video for the laser can be found on our website in the "How to Use" tab. Please see (http://symbyxbiome.com).

For more information on the PD protocol, contact:

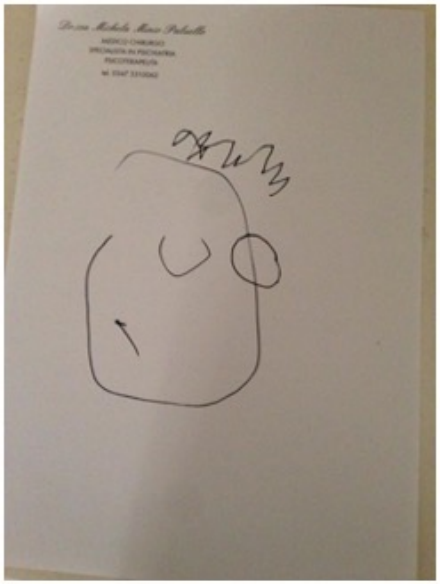
http://symbyxbiome.com

info@symbyxbiome.com

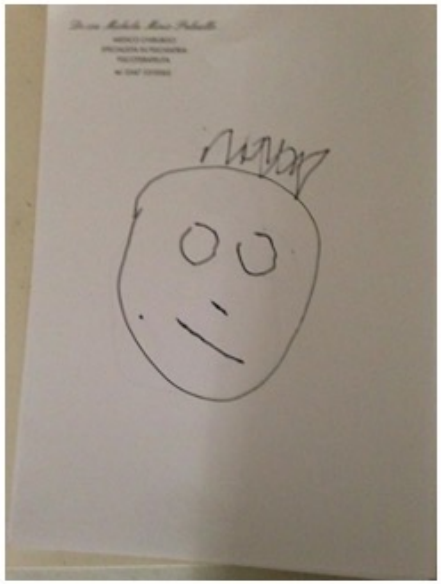
Ann Liebert, PhD

FIG. 1. The picture shows the handheld portion of the Omnilux New U device pressed against the left forehead of the child. Both the right (F4) and the left (F3) sides of the forehead were sequentially treated at each t-PBM session.

Transcranial Photobiomodulation: 8 year-old girl with Down Syndrome Treated both sides, F3 and F4



Baseline



14 days

28 days

after 2nd cycle

Sessions t-PBM ↑↑ ↑↑ ↑↑ ↑↑ // ↑↑↑↑↑↑↑↑

"draw my portrait (your doctor)"

Mannu et al., Cassano P. PMLS 2020, Letter to the Editor

Key Takeaways

- Red and near-infrared. low-level lasers or LEDs increase ATP in hypoxic/compromised cells; promote vasodilation of blood and lymphatic vessels; have anti-inflammatory and anti-oxidant effects.
- In open studies, transcranial red/NIR LEDs showed improved cognition, reduced PTSD, depression, pain and improved sleep in chronic TBI, and athletes possibly developing CTE. Blast-TBI Veterans can develop CTE.
- In open studies, the tLEDs showed improved cognition in dementia. In progressive neurodegenerative disease - if improvements are present after initial series, further home treatments are appropriate.
- In Gulf War Illness cases, tLED home treatments are suggested.

Virtual Neurorehabilitation: LED Home-Based Program for Veterans with TBI and PTSD

Yelena Bogdanova, Ph.D., Ph.D.

26 August 2021

0855 – 0955 (ET)

Disclosures

LED TBI Treatment Program Development Support:

- **VA Rehabilitation Research & Development**
  SPIRE Award, Principal Investigator: Y. Bogdanova
- **VHA Center for Compassionate Care Innovation (CCI)**
  Clinical Demonstration Project, Clinical Lead: Y. Bogdanova
- **VHA Innovators Network**
  SSS FY21 Health Care Accelerator Award
  Project Lead: Y. Bogdanova
- **VA Boston HCS Physical Medicine & Rehabilitation Service**
  Neurorehabilitation Program
  Program Lead: Yelena Bogdanova, PhD, PhD

Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Describe Home-based LED TBI treatment for cognitive and neuropsychiatric symptoms post TBI.
2. Explain the therapeutic effect of LED on cognition, sleep, and PTSD symptoms in TBI.
3. Discuss the application of noninvasive neuromodulation (LED) in rehabilitation of TBI and PTSD.

PRESENTATION OUTLINE

- Overview of a noninvasive neurorehabilitation treatment for TBI and commonly associated neuropsychiatric problems:
- Home-based TBI program, using noninvasive treatment modality, light emitting diodes (LED)
- Therapeutic effects of LED application on cognition, sleep, and PTSD
- Virtual Care LED TBI Home treatment program for TBI and PTSD
- Present the latest evidence and discuss how recent clinical research findings translate into current clinical practice.

Multimodal Neurorehabilitation for TBI & Neuropsychiatric Symptoms

Neurorehabilitation Program: Goals

- Provide comprehensive rehabilitation services & treatment options for ***cognitive (attention, executive function) and commonly associated neuropsychiatric (sleep, PTSD, mood) problems***
- Optimize patients' recovery
- Facilitate their successful return to work and community reintegration.

Multimodal Rehabilitation Approach:

- Most suitable for the patients with ***complex TBI, dual diagnoses, and multiple TBI-related symptoms***
- Targets both cognitive and neuropsychiatric symptoms
- Improves treatment adherence and promotes recovery in complex TBI

TBI Rehabilitation: Challenges

TBI-Associated Deficits Lead to:

- poor insight and lack of mental flexibility necessary to adapt to changes
- impoverished planning ability
- poor motivation and other self-regulation issues

Commonly Associated Neuropsychiatric Issues:

Post-TBI Sleep Disturbances:

- Associated with cognitive performance: sustained attention (Bloomfield et al., 2010) & working memory (Bogdanova et al., 2013)
- Independently predict poorer functional & social outcomes (Chan & Feinstein, 2015; Gilbert et al., 2015)
- Inhibit full participation in rehabilitation treatments (Worthington & Melia, 2006).

TBI/PTSD Comorbidity:

- Detrimental to cognitive functioning (Vasterling et al., 2009; Vasterling & Proctor, 2011; Polusny et al., 2011)
- Predictor of poor long-term outcome (Friedland & Dawson 2001; Moore et al., 2006; Ponsford et al., 2000)
- TBI/PTSD treatment is challenging, as traditional cognitive-behavioral PTSD therapy relies on EF (rev. in Bogdanova & Verfaellie, 2012)

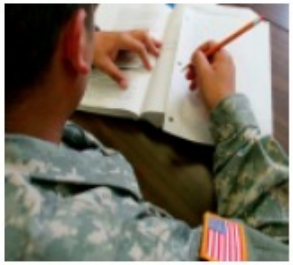
- ***Improving cognitive and PTSD symptoms may help patients to make better recovery across other functional domains.***

MULTIMODAL NEUROREHABILITATION PROGRAM

- Cognitive Training
- Education-focused
- Neuromodulation Treatment
- Combined Interventions

MULTIMODAL NEUROREHABILITATION PROGRAM

Multidisciplinary Assessment
Neurological, neuropsychological and/or neuropsychiatric evaluation



Relevant Program Modules
Treatment plan

Executive Dysfunction, Poor Concentration	→	**Cognitive Training**
Social Integration Issues, Anger Problems	→	**Education-Focused Tx**
Sleep Disturbance, PTSD Symptoms	→	**Neuromodulation Treatment**

NEUROMODULATION TREATMENT

Photobiomodulation (PBM) or Light-Emitting Diode (LED) Therapy

- LED is a non-invasive, portable, and relatively inexpensive treatment modality.
- LED is a painless, non-thermal neuromodulation treatment that directly targets cellular functioning of injured brain cells.
- ***Therapeutic Application*** **of LEDs:**
  - Wound healing (Hopkins, McLoda, Seegmiller, Baxter, 2004; Kovacs, Mester, & Gorog, 1974)
  - Reduction of pain and inflammation in musculoskeletal / orthopedic application (Aimbire et al., 2006; Gam, Thorsen, & Lonnberg, 1993)
  - Mitigation of chemotherapy side effects (Zecha et al., 2016a, 2016b).
  - Psychiatric and neurologic disorders (including TBI), and rehabilitation (rev. in Hamblin et al, 2019; Hashmi et al., 2010).

LED TX: MECHANISM OF ACTION

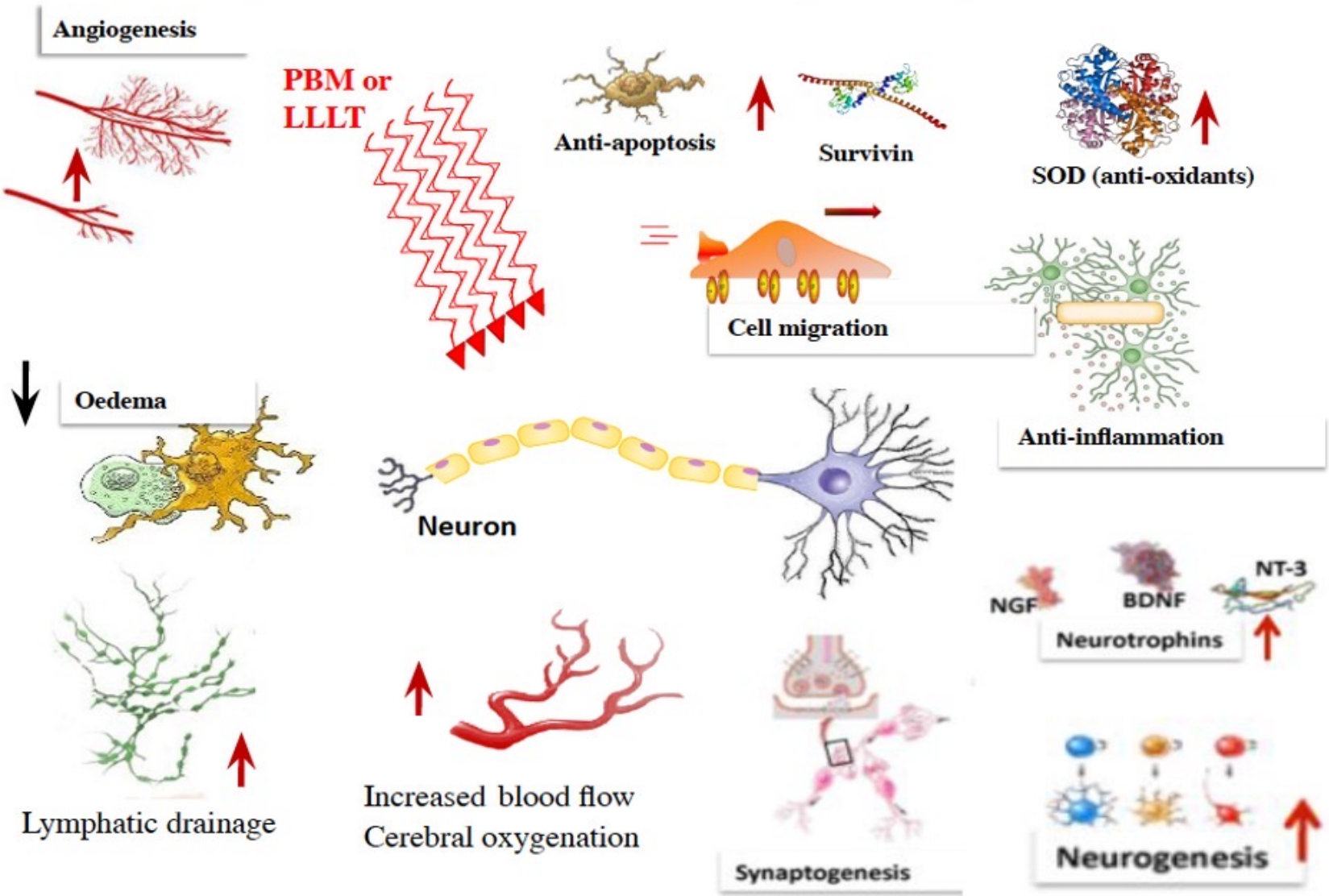
Red/Near-infrared (NIR) LED Therapy

- ***improves function of injured cells*** by promoting:
- increased adenosine tri-phosphate *(*ATP) production and
- increased focal cerebral blood flow (CBF)

Transcranial Red/NIR LED Treatment:

- improves compromised cellular activity of the brain tissue that has been damaged by TBI,
- which can promote recovery of the brain function and
- reduce symptoms in TBI and associated neuropsychiatric issues (sleep, depression, PTSD).

Multiple Mechanisms for PBM (LED Tx) in the Brain



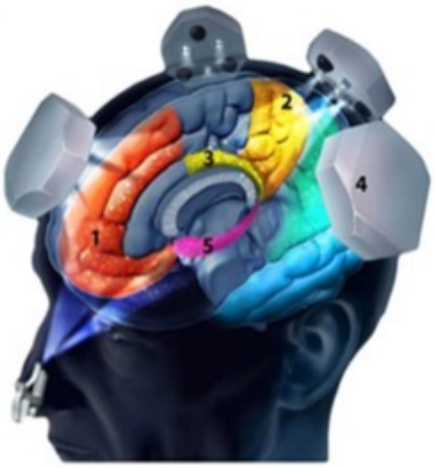
Hamblin, 2018

LED TREATMENT APPLICATIONS

NEUROMODULATION: LED TX

Therapeutic Application of LED:

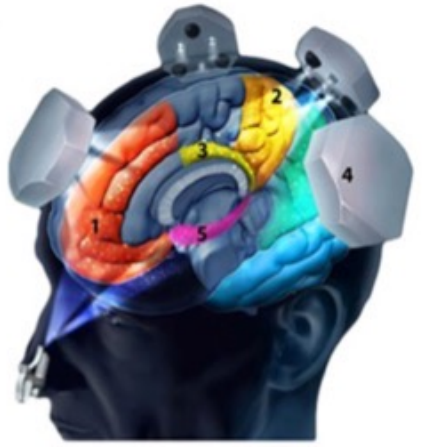
- **Neuropsychiatric Symptoms:**
  depression, PTSD, sleep disturbance
  (Cassano et al., 2015; Bogdanova et al., 2018)
- **Neurologic Disorders:**
  TBI, dementia, Alzheimer's Disease
  (Berman et al., 2017; Saltmarche et al., 2017; Chao, 2019)
- **Stroke and Rehabilitation**
  (Chan et al., 2018; Hamblin, 2018; Hashmi et al., 2010; Naeser et al., 2020)



NEUROMODULATION: LED TX

Therapeutic Application of LED in Chronic TBI:

- **Cognitive Sx** (executive function & verbal memory) in chronic TBI
  (Naeser et al., 2011, 2014; Bogdanova et al., 2017; Hipskind et al., 2019)
- **Mood and PTSD** symptomatology in mild-moderate chronic TBI
  (Naeser et al., 2011, 2014; Bogdanova et al., 2019)
- **Sleep** in patients with mild-moderate chronic TBI
  (Bogdanova et al., 2014, 2018)



Neuroimaging:

- **fMRI** has shown modulation of activation in intrinsic brain networks likely to be affected in TBI (default mode network and salience network). (Naeser et al., 2019; Longo et al., 2020; rev. in Hamblin, 2018).

LED TREATMENT FOR CHRONIC TBI

VA Boston HCS

LED TX FOR CHRONIC TBI: PILOT Randomized Clinical Trial (RCT)

Objective:

- To evaluate effect of LED Tx on cognition and sleep in Veterans with chronic mTBI

Study Design:

- **Randomized, double-blind, sham-controlled pilot trial**
- Participants were randomized into two groups: Active LED (G1) or Sham LED (G2, control) Tx
- All study participants underwent:
  - Baseline assessment
  - **LED treatment (16 sessions, 2 times/week for 8 weeks)**
  - Post-intervention assessment, 1week post-LED treatment
- All participants were administered standardized neuropsychological and neuropsychiatric measures.
- LED Tx were conducted in-office, using NIR LED helmets and Red/NIR intranasal clips.

Funded by the VA Rehabilitation Research & Development, SPIRE Award

LED TBI PILOT RCT: Study Participants

Participants:

- Veterans with mTBI (medical records, clinical evaluation)
- With chronic cognitive dysfunction (at least 2 SD below average on one, or 1 SD below average on at least two neuropsychological tests of executive function and memory)
- Divided into two groups using a blocked randomization procedure:
  Active LED or Sham Tx
- Groups matched on demographic & neuropsychiatric characteristics:
  Age, WTAR, BDI-II, PCL-M (all *p*s: non-sig)

Inclusion Criteria:

- Ages 21-55
- Report TBI during deployment
- Meet ACRM criteria for mild TBI
- Chronic cognitive dysfunction (see above)

Exclusion Criteria:

- Evidence of penetrating head injury
- Intracranial surgical intervention
- Other CNS complications or neurological illness
- Evidence of malingering (TOMM Trial 2 or Retention < 45/50)

Bogdanova et al., *Arch PMR*, 2017

LED TBI PILOT RCT: Methods

Transcranial LED TX:

- Non-invasive, painless, non-thermal neuromodulation Tx
- Directly targets cellular functioning of injured & hypoxic brain cells
- Red/NIR photons increase ATP production and increase rCBF

Study Tx Schedule:

- Administered as a series of 16 sessions (2x/week for 8 weeks)
- LED Tx sessions were conducted in-office, with NIR LED helmets and Red/NIR intranasal clips
- Sham Tx: Identical Sham LED Helmet and Intranasal LEDs were designed for this study.

NIR LED Helmet

NIR Intranasal (shown) and Red Intranasal LED diodes

LED TBI PILOT RCT: TREATMENT OUTCOME

Improvement on Measures of Attention & Executive Fx Post-LED Tx in Active Tx Group

- The Active LED treatment group (G1) showed significant improvements on standardized measures of attention ($p<0.03$) and executive function ($p<0.5$).
- No significant changes in the Sham control group (G2) [all ps>0.21].

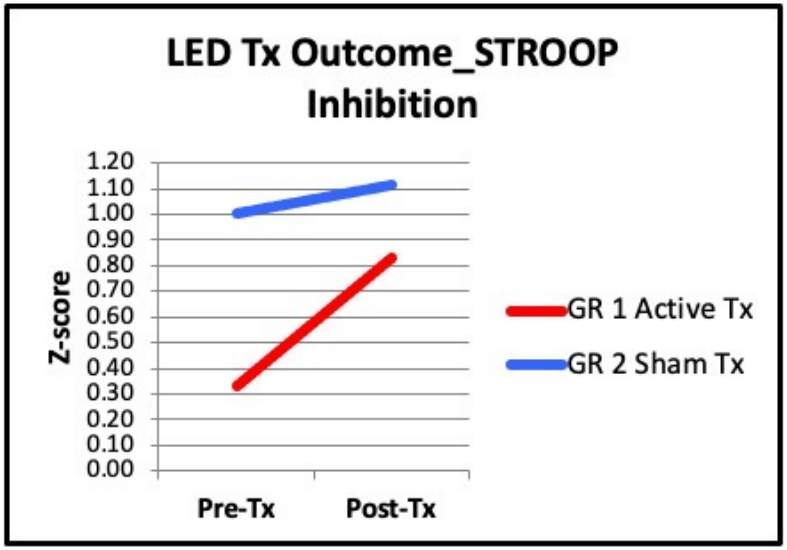


Figure 1.

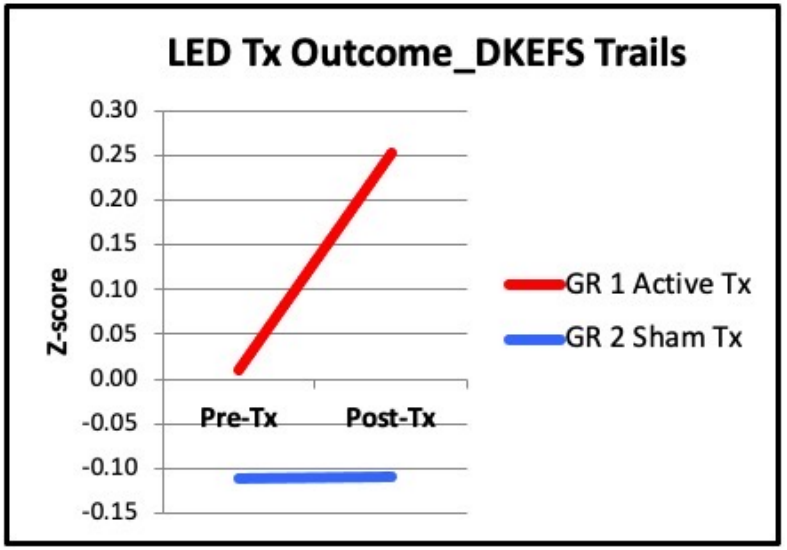


Figure 2.

(Bogdanova et al., 2017)

LED TBI PILOT RCT: TREATMENT OUTCOME

Significant Improvement in Sleep Quality Post-LED Treatment in Active Tx Group

- The active LED treatment group (G1) demonstrated a significant reduction in self-reported sleep problems (PSQI) [$p<0.05$]. (Fig. 3 and 4)
- No significant changes in the Sham LED control group (G2) [$p=0.11$].

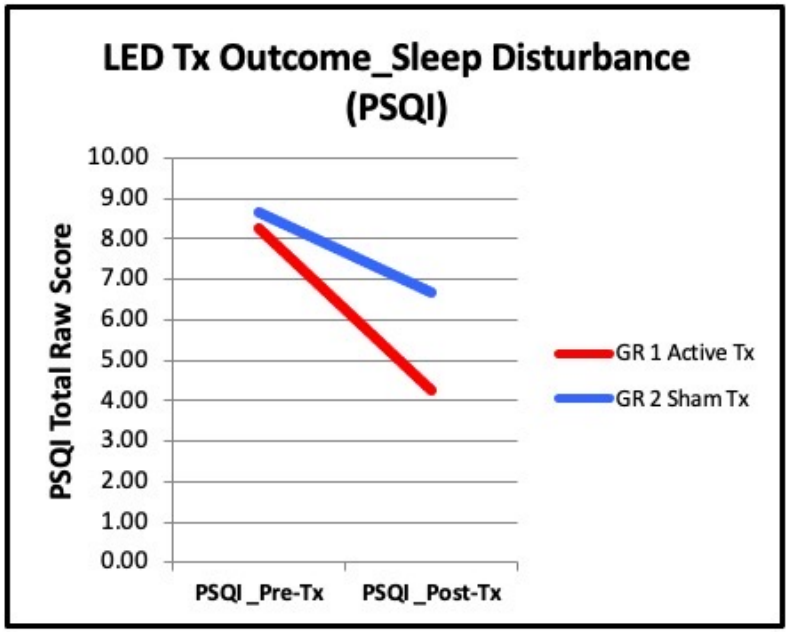


Figure 3. Changes in Sleep Quality Post-LED Treatment in Active (G1) and Sham (G2) Tx Groups.

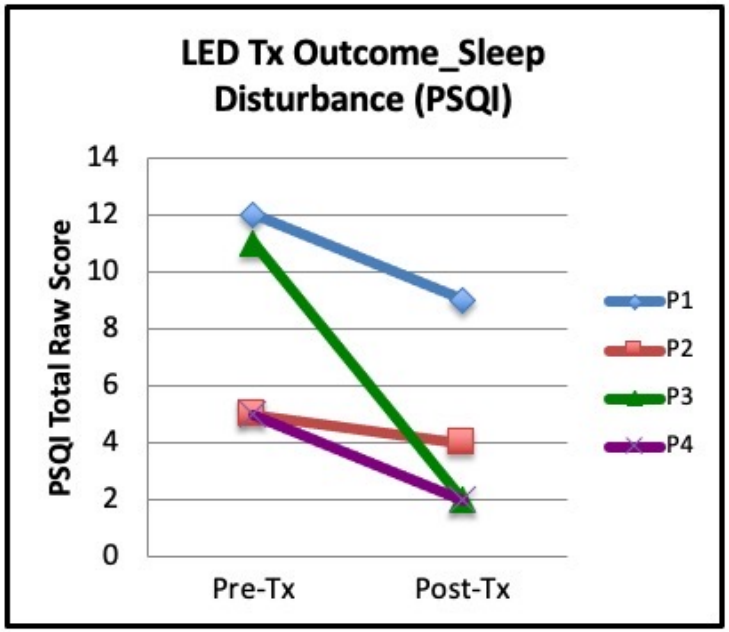


Figure 4. Improvement in Sleep Quality Post-LED Treatment in Active Tx Group.

(Bogdanova et al., 2017)

LED TBI PILOT RCT: SUMMARY

- Preliminary results from this pilot clinical trial showed that transcranial LED treatment improves cognition (attention and executive function) and sleep quality in Veterans with chronic mTBI.
- Our findings suggest that this novel, noninvasive, non-pharmacologic therapeutic approach has potential to reduce persistent cognitive symptoms and associated neuropsychiatric symptoms (sleep disturbance) in chronic TBI.
- These findings provide evidence that eight-week active treatment of chronic mTBI with transcranial LEDs is safe and effective, as compared to sham LED.

(Bogdanova et al., 2017)

LED TBI HOME TREATMENT PROGRAM

The LED TBI Home Treatment Clinical Demonstration Project

supported by the VHA Center for Compassionate Care Innovation (CCI)

LED TBI CLINIC
VA Boston HCS Physical Medicine & Rehabilitation Service, VA Boston HCS.

LED Providers:
Yelena Bogdanova, PhD, PhD (Clinical Neuropsychologist & Program Lead)
Karina Gilbert, PhD (Clinical Psychologist)

Program Support:
Program Coordinator
MSA

LED TBI HOME TX PROGRAM

12-week Home Tx Program, with tele-health support

- For Veterans with chronic TBI and related neuropsychiatric symptoms (PTSD, depression, sleep disturbance)
- LED Home Tx: **3xWeek, 25 minutes,** using NIR LED headset and red/NIR intranasal clips.

LED TBI Clinic Services:

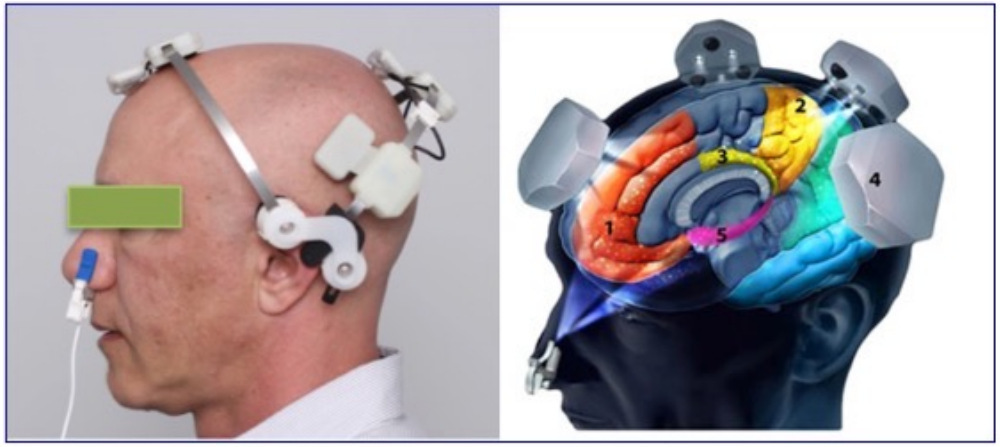
- Clinical evaluation
- Individualized treatment plan
- LED Home treatment education and training
- In-office initial LED treatment
- LED device issue & maintenance
- Telehealth home treatment monitoring and support
- Follow-up evals (6 weeks, 12 weeks, 6 months)

LED TBI HOME TX PROGRAM

LED TBI Home Tx Clinical Protocol:

- Each Veteran's is issued a personal LED device
- Patients are trained to properly use and clean the LED device at home by the LED Provider
- LED Tx is administered at home by a patient once a day, 3 days/Wk (every-other-day)
- Patients are asked to complete a simple Tx Log
- Clinic provider calls the patient (weekly) to assure adherence to the LED Home Tx protocol
- Follow up visits are scheduled by clinic stuff: virtual and/or in person [pre-pandemic]

LED Tx Schedule: 12 weeks, 3 times/Week, (25 min)



(A) **Transcranial NeuroAlpha LED device**. The LED cluster heads are placed on four placement areas on the head, designed to treat the Default Mode Network (DMN).

(B) **Targeted DMN nodes**: (1) Mesial prefrontal cortex, (2) Precuneus, (3) Posterior cingulate cortex, (4) Inferior parietal lobe, and (5) Hippocampus. (Protocol developed by Naeser et al., 2018; Bogdanova et al., 2018)

LED TBI HOME TX: CLINICAL DEMONSTRATION

Program Objectives:

- To evaluate effectiveness of transcranial light-emitting diode (LED) home-based treatment program for the Veterans with chronic mild to moderate TBI and PTSD.

Design: Clinical Program Evaluation, Case Series

- All patients underwent:
  - Baseline assessment
  - LED Treatment at home (**3xWk for 12 Wks**)
  - Post- intervention assessment immediately after 12 Wks of LED treatment
  - All patients were administered standardized neuropsychological and neuropsychiatric measures.
- All patients received Telehealth home treatment monitoring and support:
  - Weekly virtual visits (first 12 weeks)
  - Monthly virtual visits (Long-term Tx, 12 months+)

LED TBI Home Tx Program

Participants:

- Veterans with m-mod TBI (medical records, clinical evaluation)
- Suffering persistent TBI symptoms for six months or greater
- Who have not had success with other evidence-based treatments for TBI
- Participants endorsed persistent cognitive dysfunction (attention, executive function, memory) and neuropsychiatric symptoms (sleep disturbance, PTSD, mood)

Inclusion Criteria:

- Age 21-70
- History of mild-moderate TBI
- Persistent cognitive dysfunction (see above)

Exclusion Criteria:

- Evidence of penetrating head injury
- Intracranial surgical intervention
- Other CNS complications or neurological illness
- Active substance abuse

LED TBI HOME TX: CLINICAL DEMONSTRATION

Outcome Measures:

All patients were administered a series of standardized neuropsychological and neuropsychiatric measures.

Neuropsychological Measures:

- *Attention/Executive Function:* DKEFS Trails 2 and Trails 4; DKEFS Stroop*
- *Memory:* California Verbal Learning Test-II* (alternating versions)

Neuropsychiatric Measures:

- PTSD Checklist (PCL-5)*
- Beck Depression Inventory-II (BDI-II)
- Pittsburgh Sleep Quality Index (PSQI)*
- Neurobehavioral Symptom Inventory (NSI)

Daily Functioning Measures:

- Attention Rating and Monitoring Scale (ARMS)
- Prospective-Retrospective Memory Quest. (PRMQ)

* Primary Outcome measures

LED TBI HOME TREATMENT OUTCOME

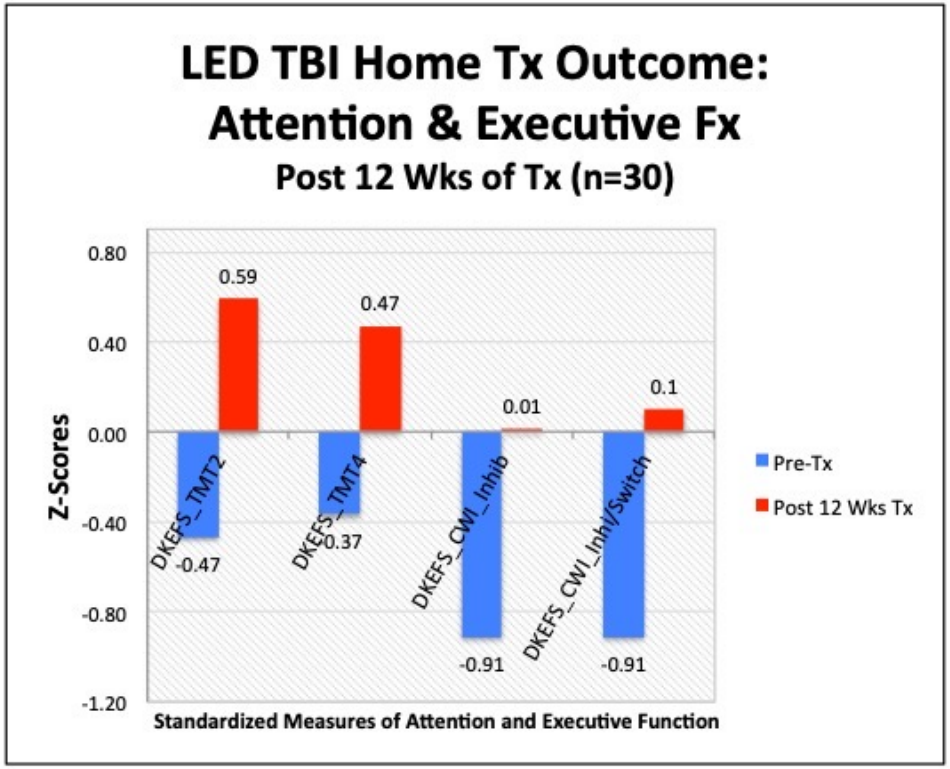
Post 12Wk LED Home Tx Program:

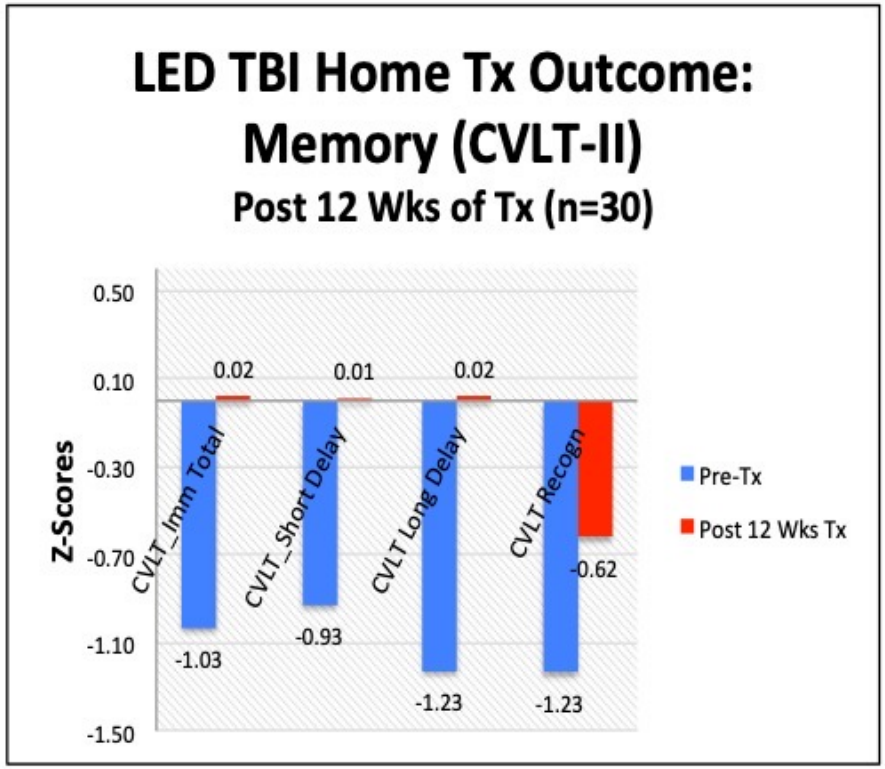
- All patients demonstrated ***significant improvement*** in at least two functional domains:
  - Cognitive (attention, executive function, learning)
  - Mood/PTSD
  - Daily Functioning
  - Neurobehavioral Symptoms
- No adverse effects were reported

LED TBI HOME TREATMENT OUTCOME

Improvement in Cognitive Function Post-LED Tx

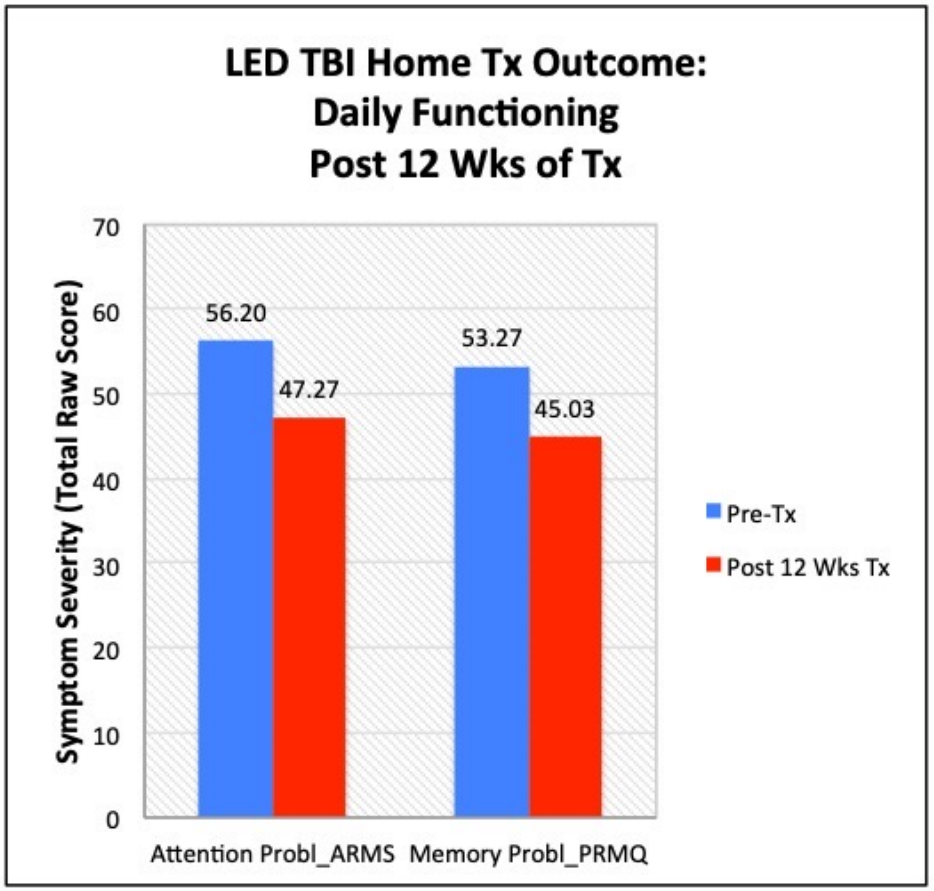
- Patients showed significant improvement on the standardized measures of attention, executive function (all *ps*<0.001) and memory (*ps*<0.01).





LED TBI HOME TREATMENT OUTCOME

Improvement in Daily Function Post-LED Tx



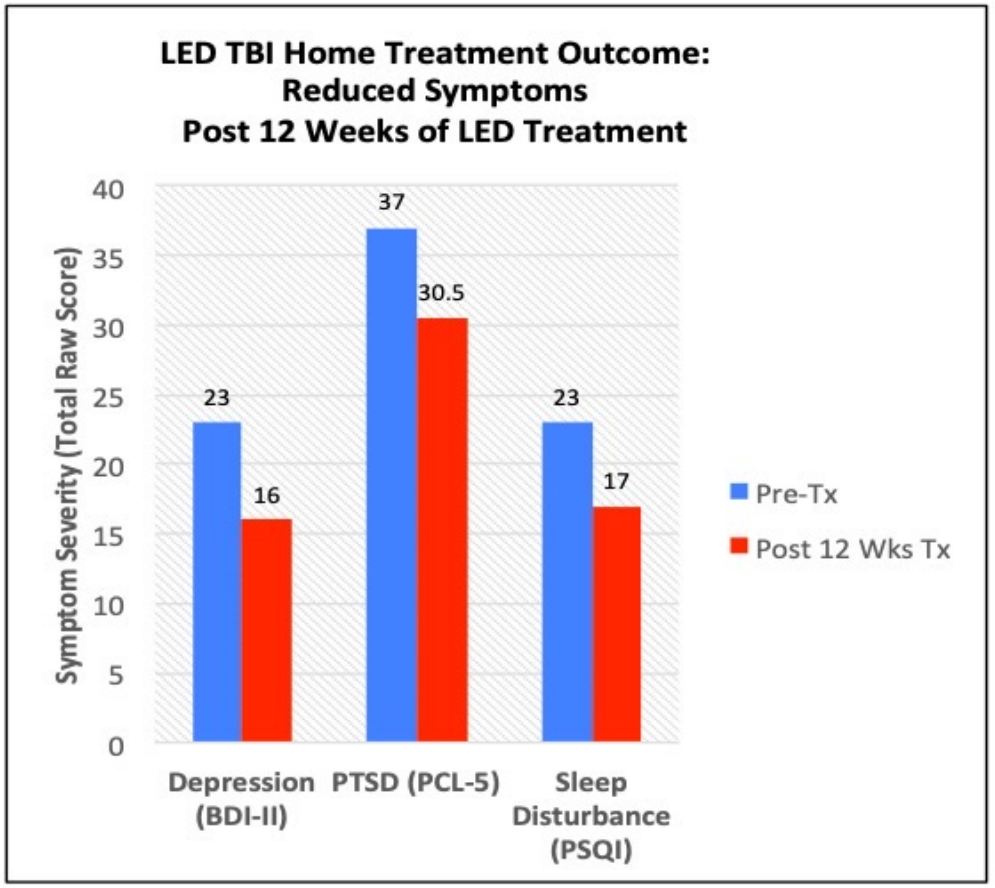
The Veterans showed significant improvement in Daily Cognitive Function post 12 Wks of LED Home:

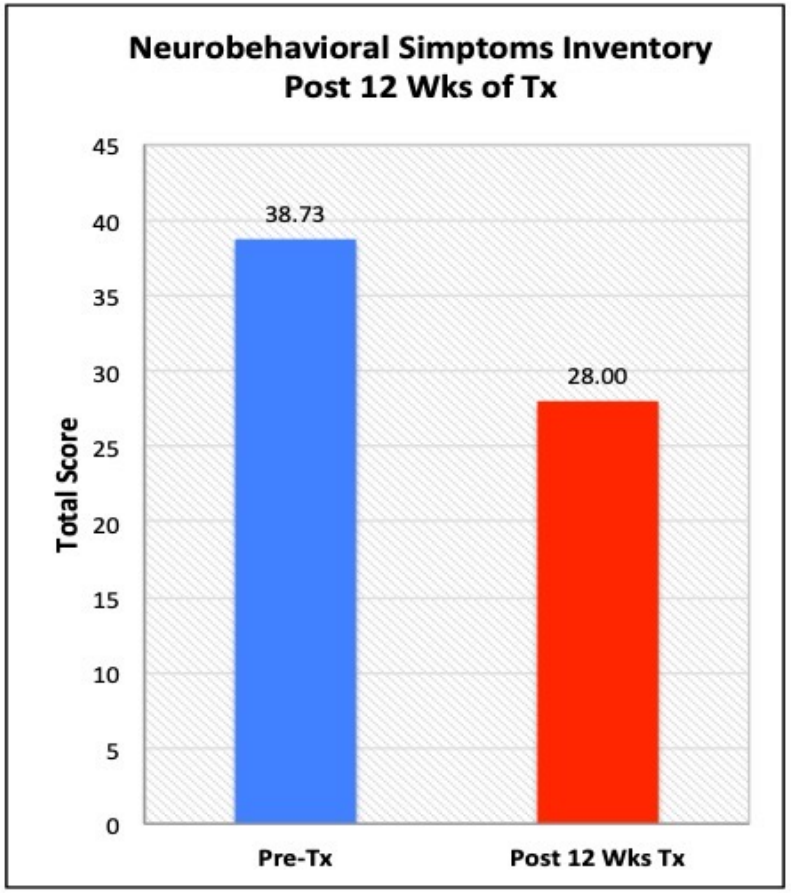
- Attention Rating and Monitoring Scale (ARMS) ($p<0.001$) and
- Prospective-Retrospective Memory Questionnaire (PRMQ) ($p<0.001$).

TREATMENT OUTCOME (Cont.)

Improvement in Neuropsychiatric Symptoms Post-LED Tx

- Post-12 Wks of LED Home Tx, patients showed: significant symptom reduction on measures of depression (BDI-II) [$p<0.001$], PTSD (PCL-5) [$p<0.01$], and sleep (PSQI) [$p<0.001$].
- Significant reduction in neurobehavioral symptoms (NSI) [$p<0.001$].





CONCLUSIONS

- The results of this clinical program evaluation showed that transcranial LED Home Treatment improves cognitive (attention, executive function, learning/memory) and neuropsychiatric symptoms (mood, PTSD, sleep) in Veterans with chronic mild-moderate TBI.
- Our findings suggest that this noninvasive, non-pharmacologic, LED home treatment with tele-health support improves daily function and neurobehavioral symptoms in chronic TBI.
- These findings provide additional evidence that twelve-week home-based treatment of chronic mild-moderate TBI with transcranial LEDs is safe and effective for clinical use.

Transcranial LED Therapy for TBI & PTSD

NIR LED Headset and Intranasal clip

Effective	Painless
Safe	Portable
Non-invasive	Cost-effective

Red/near-infrared (NIR) LED therapy directly targets cellular functioning of injured brain cells

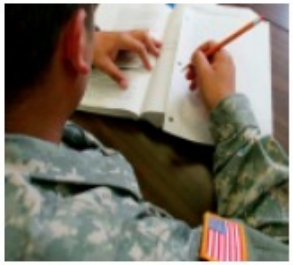
Red/NIR LED Tx improves function of injured cells by promoting increased ATP production and release of nitric oxide.

Nitric oxide release promotes focal vasodilation and increases focal cerebral blood flow.

MULTIMODAL NEUROREHABILITATION PROGRAM

Multidisciplinary Assessment

Neurological, neuropsychological and/or neuropsychiatric evaluation



Relevant Program Modules

Treatment plan

Executive Dysfunction, Poor Concentration → **Cognitive Training:**
- Improves ability to focus, to complete tasks
- Improves organizational skills

LED TBI Home Treatment Program
- Improves focus and concentration

Social Integration Issues, Anger Problems → **Education-focused Training & Support**
- Education & management of symptoms
- Effective communication training, social skills
- Targeted behavioral treatment, social support

Sleep Disturbance, PTSD Symptoms → **Education-focused Treatment & MH Support**
- Symptom education and management
- Sleep hygiene component, PTSD Sx reduction

LED TBI Home Treatment Program
- LED Tx of Sleep and PTSD symptoms

LED TBI PROGRAM: Sustainability

1 Year after the start of the LED TBI Program:

- Polytrauma patient weighted work (PWW) **more than doubled** over FY18 (104%)
- Sustainability **improved to 85%** [sustainable]

During 2nd Year (FY19) PWW increased:

- **170%** compared to FY17
- **32%** year-over-year

*The VABHS LED TBI program is considered **fiscally feasible and replicable** at other VA facilities.*

(LED Treatment for TBI, *Advisory Council Report*, 2020)

VIRTUAL CARE LED TBI PROGRAM

Year 3: Transition to Virtual Care:

- Deliver clinical care via VA Video Connect (VVC) to:
  - Reduce the burden of travel for Veterans with TBI
  - Improve Tx accessibility for Veterans with limited mobility, living in remote areas
- Accept referrals from VA facilities across the US

The VABHS LED Virtual Care Program:

- Provides continuous care during public health emergency (COVID-19)
- Provides safe access to TBI treatment for patients at higher risk for serious illness

Since the Start of the Pandemic:

- Deliver continuous virtual care to more than 80 Veterans already enrolled in Home Tx Program
- Provide LED TBI Home treatment for the out-of-state Veterans

Virtual Care LED TBI Program development is supported by the VHA CCI and VHA Innovation Network.

LED TBI Home Tx Program: Key Takeaways

Defense Health Agency

- The results from the LED pilot RCT[1] and LED clinical program evaluation[2] showed that transcranial **LED Home Tx improves cognitive** (attention, executive function, learning/memory) **and neuropsychiatric symptoms** (mood, PTSD, sleep) in patients with chronic mild-moderate TBI.
- These results suggest that noninvasive, non-pharmacologic LED Home treatment with tele-health support **improves daily function and neurobehavioral symptoms in chronic TBI**[1-3].
- The LED TBI Home Tx Program, converted to Virtual Care following the COVID-19 pandemic restrictions, demonstrated higher treatment adherence and lower dropout rates, as compared to the standard In-office LED treatment[4].
- These results provide evidence that twelve-week home-based treatment of chronic mild-moderate TBI with transcranial LEDs is safe and effective for clinical use.

1. (Bogdanova Y. et al. 2017)
2. (Bogdanova Y. et al., 2019)
3. (Martin P. et al., 2018)
4. (Bogdanova Y. et al, 2020)

Future Directions

- Development of multimodal treatment programs to address multiple comorbidities (such as TBI, PTSD, mood, and sleep problems)
- Using advance neuromodulation techniques to enhance the treatment and promote recovery in TBI and TBI/PTSD
- Promote interdisciplinary collaborations to further the development of combination treatments
- Clinical trials to further evaluate efficacy of novel neurorehabilitation treatments for TBI and PTSD
- Identify biomarkers/predictors of successful recovery and Tx outcome using:
  - Neuroimaging
  - Electrophysiological measures
  - Advanced neuroscience techniques

Thank You!

CONTACT INFO:

Yelena Bogdanova, PhD, PhD

Yelena.Bogdanova@va.gov

References

Ayuk, S.M., Houreld, N.N., Abrahamse, H. (2018). Effect of 660 nm visible red light on cell proliferation and viability in diabetic models in vitro under stressed conditions. *Lasers Med Sci, 33*, 1085–1093. https://doi.org/10.1007/s10103-017-2432-2

Bogdanova, Y., Gilbert, K., Baird, L., Naeser, M.A. (2019). LED home treatment program for chronic TBI and PTSD: Clinical program evaluation. Abstract. *Archives of Physical Medicine and Rehabilitation, 100*(12), e187-188. https://doi.org/10.1016/j.apmr.2019.10.077

Bogdanova, Y., Gilbert, K., Baird, L. (2020). Virtual care and home-based treatment for TBI during COVID-19 pandemic. *Archives of Physical Medicine and Rehabilitation, 102*(4), e19. https://doi.org/10.1016/j.apmr.2021.01.058

Bogdanova, Y., Ho, V.T., Martin, P.I., Ho, M.D., Yee, M.K., Hamblin, M.R., Naeser, M.A (2017). Transcranial LED treatment for cognitive dysfunction and sleep in chronic TBI: Randomized controlled pilot trial. *Archives of Physical Medicine and Rehabilitation, 98*(10), e122 -123. https://doi.org/10.1016/j.apmr.2017.08.398

Bonnelle, V., Ham, T.E., Leech, R., Kinnunen, K.M., Mehta, M.A., Greenwood, R.J., Sharp, D.J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. *Proc Natl Acad Sci USA,* 201113455. https://doi.org/10.1073/pnas.1113455109

Bonnelle, V., Leech, R., Kinnunen, K.M., Ham, T.E., Beckmann, C.F., De Boissezon, X., Greenwood, R.J., Sharp, D.J. (2011). Default mode network connectivity predicts sustained attention deficits after traumatic brain injury. *Journal of Neuroscience, 31*, 13442–13451. https://doi.org/10.1523/JNEUROSCI.1163-11.2011

References

Cassano, P., Petrie, S.R., Hamblin, M.R., Henderson, T.A., Iosifescu, D.V. (2015). Review of transcranial photobiomodulation for major depressive disorder: targeting brain metabolism, inflammation, oxidative stress, and neurogenesis. *Neurophoton., 3*(3), 031404. https://doi.org/10.1117/1.NPh.3.3.031404

Chao L. L. (2019). Effects of Home Photobiomodulation Treatments on Cognitive and Behavioral Function, Cerebral Perfusion, and Resting-State Functional Connectivity in Patients with Dementia: A Pilot Trial. *Photobiomodulation, photomedicine, and laser surgery, 37*(3), 133–141. https://doi.org/10.1089/photob.2018.4555

Chao, L.L. (2019). Improvements in Gulf War Illness Symptoms After Near-Infrared Transcranial and Intranasal Photobiomodulation: Two Case Reports. *Military medicine, 184*(9-10), e568–e574. https://doi.org/10.1093/milmed/usz037

Chao, L. L., Barlow, C., Karimpoor, M., & Lim, L. (2020). Changes in Brain Function and Structure After Self-Administered Home Photobiomodulation Treatment in a Concussion Case. *Frontiers in neurology, 11*, 952. https://doi.org/10.3389/fneur.2020.00952

Cicerone, K.D., Goldin, Y., Ganci, K., Rosenbaum, A., Wethe, J.V., Langenbahn, D., … Bogdanova, Y., Harley, J.P. (2019). Evidence-Based Cognitive Rehabilitation: Systematic Review of the Literature From 2009 Through 2014. *Archives of Physical Medicine and Rehabilitation, 100*(8), 1515-1533. https://doi.org/10.1016/j.apmr.2019.02.011

References

Dmochowski, G. M., Shereen, A. D., Berisha, D., & Dmochowski, J. P. (2020). near-infrared light increases functional connectivity with a non-thermal mechanism. *Cerebral cortex communications, 1*(1), tgaa004. https://doi.org/10.1093/texcom/tgaa004

Eells, J. T., Henry, M. M., Summerfelt, P., Wong-Riley, M. T., Buchmann, E. V., Kane, M., Whelan, N. T., & Whelan, H. T. (2003). Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proceedings of the National Academy of Sciences of the United States of America, 100*(6), 3439–3444. https://doi.org/10.1073/pnas.0534746100

Ferraresi, C., Parizotto, N. A., Pires de Sousa, M. V., Kaippert, B., Huang, Y. Y., Koiso, T., Bagnato, V. S., & Hamblin, M. R. (2015). Light-emitting diode therapy in exercise-trained mice increases muscle performance, cytochrome c oxidase activity, ATP and cell proliferation. *Journal of biophotonics, 8*(9), 740–754. https://doi.org/10.1002/jbio.201400087

Goldstein, L. E., Fisher, A. M., Tagge, C. A., Zhang, X. L., Velisek, L., Sullivan, J. A., Upreti, C., Kracht, J. M., Ericsson, M., Wojnarowicz, M. W., Goletiani, C. J., Maglakelidze, G. M., Casey, N., Moncaster, J. A., Minaeva, O., Moir, R. D., Nowinski, C. J., Stern, R. A., Cantu, R. C., Geiling, J., … McKee, A. C. (2012). Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science translational medicine, 4*(134), 134ra60. https://doi.org/10.1126/scitranslmed.3003716

References

Greicius, M. D., Srivastava, G., Reiss, A. L., & Menon, V. (2004). Default-mode network activity distinguishes Alzheimer's disease from healthy aging: evidence from functional MRI. *Proceedings of the National Academy of Sciences of the United States of America, 101*(13), 4637–4642. https://doi.org/10.1073/pnas.0308627101

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America, 100*(1), 253–258. https://doi.org/10.1073/pnas.0135058100

Ham, B. J., Chey, J., Yoon, S. J., Sung, Y., Jeong, D. U., Ju Kim, S., Sim, M. E., Choi, N., Choi, I. G., Renshaw, P. F., & Lyoo, I. K. (2007). Decreased N-acetyl-aspartate levels in anterior cingulate and hippocampus in subjects with post-traumatic stress disorder: A proton magnetic resonance spectroscopy study. *The European journal of neuroscience, 25*(1), 324–329. https://doi.org/10.1111/j.1460-9568.2006.05253.x

Hamblin M. R. (2017). Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS biophysics, 4*(3), 337–361. https://doi.org/10.3934/biophy.2017.3.337

Hamblin, M.R. (2018). Photobiomodulation for traumatic brain injury and stroke. *J Neuro Res., 96*, 731– 743. https://doi.org/10.1002/jnr.24190

Hashmi, J.T., Huang, Y.Y., Osmani, B.Z., Sharma, S.K., Naeser, M.A., & Hamblin, M.R. (2010). Role of low-level laser therapy in neurorehabilitation. *Arch Phys Med & Rehab, S2*, S292–S305.

References

Hipskind, S.G., Grover, F.L. Jr., Fort, T.R., Helffenstein D., Burke, T.J., Quint, S.A., Bussiere, G., Stone, M., Hurtado, T. (2019). Pulsed transcranial red/near-infrared light therapy using light-emitting diodes improves cerebral blood flow and cognitive function in veterans with chronic traumatic brain injury: A case series. *Photobiomodul Photomed Laser Surg.* https//doi.org/10.1089/photob.2018.4489

Holmes, E., Barrett, D. W., Saucedo, C. L., O'Connor, P., Liu, H., & Gonzalez-Lima, F. (2019). Cognitive enhancement by transcranial photobiomodulation is associated with cerebrovascular oxygenation of the prefrontal cortex. *Frontiers in Neuroscience, 13*, 1129. https://doi.org/10.3389/fnins.2019.01129

Huang, Y.Y., Gupta, A., Vecchio, D., de Arce, V.J., Huang, S.F., Xuan, W., & Hamblin, M.R. (2012). Transcranial low level laser (light) therapy for traumatic brain injury. *J Biophotonics, 5*(11-12), 827-837.

Iaccarino, H. F., Singer, A. C., Martorell, A. J., Rudenko, A., Gao, F., Gillingham, T. Z., Mathys, H., Seo, J., Kritskiy, O., Abdurrob, F., Adaikkan, C., Canter, R. G., Rueda, R., Brown, E. N., Boyden, E. S., & Tsai, L. H. (2016). Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature, 540*(7632), 230–235. https://doi.org/10.1038/nature20587

Jagdeo, J. R., Adams, L. E., Brody, N. I., & Siegel, D. M. (2012). Transcranial red and near infrared light transmission in a cadaveric model. *PloS one, 7*(10), e47460. https://doi.org/10.1371/journal.pone.0047460

References

Kark, S.M., Gilbert, K., Gehrman, P. & Bogdanova, Y. (2015). Sleep disturbances, TBI and PTSD: Implications for treatment and recovery. *Clinical Psychology Review, 40,* 195-212. https://doi.org/10.1016/j.cpr.2015.05.008

Karu, T., Pyatibrat, L., & Kalendo, G. (1995). Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. Journal of photochemistry and photobiology. B, *Biology, 27*(3), 219–223. https://doi.org/10.1016/1011-1344(94)07078-3

Karu, T. I., Pyatibrat, L. V., & Afanasyeva, N. I. (2005). Cellular effects of low power laser therapy can be mediated by nitric oxide. *Lasers in surgery and medicine, 36*(4), 307–314. https://doi.org/10.1002/lsm.20148

Katz, D. I., Bernick, C., Dodick, D. W., Mez, J., Mariani, M. L., et al. (2021). National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for Traumatic Encephalopathy Syndrome. *Neurology, 96*(18), 848–863. https://doi.org/10.1212/WNL.0000000000011850

Khuman, J., Zhang, J., Park, J., Carroll, J. D., Donahue, C., & Whalen, M. J. (2012). Low-level laser light therapy improves cognitive deficits and inhibits microglial activation after controlled cortical impact in mice. *Journal of neurotrauma, 29*(2), 408–417. https://doi.org/10.1089/neu.2010.1745

Kosel, K. C., Van Hoesen, G. W., & West, J. R. (1981). Olfactory bulb projections to the parahippocampal area of the rat. *The Journal of comparative neurology, 198*(3), 467–482. https://doi.org/10.1002/cne.901980307

References

Kress, B. T., Iliff, J. J., Xia, M., Wang, M., Wei, H. S., Zeppenfeld, D., Xie, L., Kang, H., Xu, Q., Liew, J. A., Plog, B. A., Ding, F., Deane, R., & Nedergaard, M. (2014). Impairment of paravascular clearance pathways in the aging brain. *Annals of neurology, 76*(6), 845–861. https://doi.org/10.1002/ana.24271

Lee, E. B., Kinch, K., Johnson, V. E., Trojanowski, J. Q., Smith, D. H., & Stewart, W. (2019). Chronic traumatic encephalopathy is a common co-morbidity, but less frequent primary dementia in former soccer and rugby players. *Acta neuropathologica, 138*(3), 389–399. https://doi.org/10.1007/s00401-019-02030-y

Linares, S. N., Beltrame, T., Ferraresi, C., Galdino, G., & Catai, A. M. (2020). Photobiomodulation effect on local hemoglobin concentration assessed by near-infrared spectroscopy in humans. *Lasers in medical science, 35*(3), 641–649. https://doi.org/10.1007/s10103-019-02861-x

Liu, TC-Y., Cheng, L., Su, W-J., Zhang, Y-W., Shi, Y., Liu, A-H., Zhang, L-L., Qian, Z-Y. (2012). Randomized, double-blind, and placebo-controlled clinic report of intranasal low-intensity laser therapy on vascular diseases. *International Journal of Photoenergy, 2012*, 489713. https://doi.org/10.1155/2012/489713

Longo, M.G.F., Tan, C.O., Chan, S., et al. (2020). Effect of transcranial low-level light therapy vs sham therapy among patients with moderate traumatic brain injury: a randomized clinical trial. *JAMA Netw Open, 3*(9), e2017337. https://doi.org/10.1001/jamanetworkopen.2020.17337

References

Louveau, A., Herz, J., Alme, M. N., Salvador, A. F., Dong, M. Q., Viar, K. E., Herod, S. G., Knopp, J., Setliff, J. C., Lupi, A. L., Da Mesquita, S., Frost, E. L., Gaultier, A., Harris, T. H., Cao, R., Hu, S., Lukens, J. R., Smirnov, I., Overall, C. C., Oliver, G., ... Kipnis, J. (2018). CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nature neuroscience*, *21*(10), 1380–1391. https://doi.org/10.1038/s41593-018-0227-9

Louveau, A., Smirnov, I., Keyes, T. J., Eccles, J. D., Rouhani, S. J., Peske, J. D., Derecki, N. C., Castle, D., Mandell, J. W., Lee, K. S., Harris, T. H., & Kipnis, J. (2015). Structural and functional features of central nervous system lymphatic vessels. *Nature*, *523*(7560), 337–341. https://doi.org/10.1038/nature14

Martin, P. I., Chao, L., Krengel, M. H., Ho, M. D., Yee, M., Lew, R., Knight, J., Hamblin, M. R., & Naeser, M. A. (2021). Transcranial photobiomodulation to improve cognition in Gulf War illness. *Frontiers in neurology*, *11*, 574386. https://doi.org/10.3389/fneur.2020.574386

Martin, PI, Ho, MD, Bogdanova, Y, Krengel, M, Knight, J, Hamblin, M.R., Koo, B., Naeser, M.A. (2018). LED therapy improves functional connectivity and cognition in professional football player with chronic TBI: Case study. *Abstract. Archives of Physical Medicine and Rehabilitation, 99*(10), e104 - e105. https://doi.org/10.1016/j.apmr.2018.07.374

McKee, A. C., Alosco, M. L., & Huber, B. R. (2016). Repetitive head impacts and chronic traumatic encephalopathy. *Neurosurgery clinics of North America, 27*(4), 529–535. https://doi.org/10.1016/j.nec.2016.05.009

References

McKee, A. C., Cairns, N. J., Dickson, D. W., Folkerth, R. D., Keene, C. D., Litvan, I., Perl, D. P., Stein, T. D., Vonsattel, J. P., Stewart, W., Tripodis, Y., Crary, J. F., Bieniek, K. F., Dams-O'Connor, K., Alvarez, V. E., Gordon, W. A., & TBI/CTE group (2016). The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta neuropathologica*, *131*(1), 75–86. https://doi.org/10.1007/s00401-015-1515-z

McKee, A. C., Cantu, R. C., Nowinski, C. J., Hedley-Whyte, E. T., Gavett, B. E., Budson, A. E., Santini, V. E., Lee, H. S., Kubilus, C. A., & Stern, R. A. (2009). Chronic traumatic encephalopathy in athletes: progressive tauopathy after repetitive head injury. *Journal of neuropathology and experimental neurology*, *68*(7), 709–735. https://doi.org/10.1097/NEN.0b013e3181a9d503

McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain : A journal of neurology*, *136*(Pt 1), 43–64. https://doi.org/10.1093/brain/aws307

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: A network model of insula function. *Brain structure & function*, *214*(5-6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Mester, E., Spiry, T., Szende, B., & Tota, J. G. (1971). Effect of laser rays on wound healing. *American journal of surgery*, *122*(4), 532–535. https://doi.org/10.1016/0002-9610(71)90482-x

References

Mez, J., Daneshvar, D. H., Abdolmohammadi, B., Chua, A. S., Alosco, M. L., ... McKee, A. C. (2020). Duration of American football play and chronic traumatic encephalopathy. *Annals of neurology*, *87*(1), 116–131. https://doi.org/10.1002/ana.25611

Mi, X. Q., Chen, J. Y., Liang, Z. J., & Zhou, L. W. (2004). In vitro effects of helium-neon laser irradiation on human blood: Blood viscosity and deformability of erythrocytes. *Photomedicine and laser surgery*, *22*(6), 477–482. https://doi.org/10.1089/pho.2004.22.477

Minati, L., Grisoli, M., & Bruzzone, M. G. (2007). MR spectroscopy, functional MRI, and diffusion-tensor imaging in the aging brain: a conceptual review. *Journal of geriatric psychiatry and neurology*, *20*(1), 3–21. https://doi.org/10.1177/0891988706297089

Monson, C. M., Gradus, J. L., Young-Xu, Y., Schnurr, P. P., Price, J. L., & Schumm, J. A. (2008). Change in posttraumatic stress disorder symptoms: do clinicians and patients agree?. *Psychological assessment*, *20*(2), 131–138. https://doi.org/10.1037/1040-3590.20.2.131

Montenigro, P. H., Baugh, C. M., Daneshvar, D. H., Mez, J., Budson, A. E., Au, R., Katz, D. I., Cantu, R. C., & Stern, R. A. (2014). Clinical subtypes of chronic traumatic encephalopathy: Literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. *Alzheimer's research & therapy*, *6*(5), 68. https://doi.org/10.1186/s13195-014-0068-z

Morries, L. D., Cassano, P., & Henderson, T. A. (2015). Treatments for traumatic brain injury with emphasis on transcranial near-infrared laser phototherapy. *Neuropsychiatric disease and treatment, 11*, 2159–2175. https://doi.org/10.2147/NDT.S65809

References

Naeser, M., Martin, P., Ho, M., Krengel, M., Bogdanova, Y., Knight, J., Fedoruk, A., Hamblin, M., Koo, B.B. (2019). Transcranial, near-infrared photobiomodulation to improve cognition in two retired professional football players possibly developing CTE. *Brain Injury, 33*(S1), 134-135. https://doi.org/0.1080/02699052.2019.1608749

Naeser, M. A., Martin, P. I., Ho, M. D., Krengel, M. H., Bogdanova, Y., Knight, J. A., Yee, M. K., Zafonte, R., Frazier, J., Hamblin, M. R., & Koo, B. B. (2016). Transcranial, red/near-infrared light-emitting diode therapy to improve cognition in chronic traumatic brain injury. *Photomedicine and laser surgery, 34*(12), 610–626. https://doi.org/10.1089/pho.2015.4037

Naeser, M., Martin, P., Ho, M., Krengel, M., Bogdanova, Y., Knight, J., Fedoruk, A., Hamblin, M., Koo, B.B. (2018). Transcranial PBM to improve cognition in chronic TBI, and in a 65 yr. retired, professional football player with possible CTE. *North American Association for Photobiomodulation Therapy (NAALT) Conference*, Detroit, MI.

Naeser, MA, Martin, PI, Ho, MD, Krengel, MH, Bogdanova, Y, Knight, JA, Yee, MK, Zafonte, R, Frazier, JA, Hamblin, MR, Koo, BB (2016). Transcranial, Red/near-infrared light-emitting diode (LED) therapy for chronic, traumatic brain injury. *Photomedicine and Laser Surgery, 34*(12), 610-626. https://doi.org/10.1089/pho.2015.4037

References

Naeser, M.A., Martin, P.I., Ho, M.D., Krengel, M.H., Bogdanova, Y., et al. (2017). Low Level Light Therapy for rehabilitation in traumatic brain injury and stroke, including chronic aphasia. Chapter 39, 761-808. In Handbook of Low-level Laser Therapy. Eds: MR Hamblin, MVP de Sousa, & T Agrawal. Pan Stanford. https://www.taylorfrancis.com/books/e/9781315364827/chapters/10.1201/9781315364827-45

Naeser, M.A., Martin, P.I., Ho, M.D., Krengel, M.H., Bogdanova, Y., Knight, J.A., Yee, M.K., Zafonte, R., Frazier, J.A., Hamblin, M.R., Koo, B.B. (2015). Red/Near-Infrared Light-Emitting Diode Therapy for Traumatic Brain Injury. SPIE 9467, *Micro- and Nanotechnology Sensors, Systems, and Applications VII,* 94670M. https://doi.org/10.1117/12.2176345

Naeser, M. A., Saltmarche, A., Krengel, M. H., Hamblin, M. R., & Knight, J. A. (2011). Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. *Photomedicine and laser surgery, 29*(5), 351–358. https://doi.org/10.1089/pho.2010.2814

Naeser, M. A., Zafonte, R., Krengel, M. H., Martin, P. I., Frazier, J., Hamblin, M. R., Knight, J. A., Meehan, W. P., 3rd, & Baker, E. H. (2014). Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: Open-protocol study. *Journal of neurotrauma*, *31*(11), 1008–1017. https://doi.org/10.1089/neu.2013.3244

References

Nawashiro, H., Wada, K., Nakai, K., & Sato, S. (2012). Focal increase in cerebral blood flow after treatment with near-infrared light to the forehead in a patient in a persistent vegetative state. *Photomedicine and laser surgery, 30*(4), 231–233. https://doi.org/10.1089/pho.2011.3044

Otti, A., Guendel, H., Wohlschläger, A., Zimmer, C., & Noll-Hussong, M. (2013). Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. *BMC psychiatry, 13*, 84. https://doi.org/10.1186/1471-244X-13-84

Raichle M. E. (2015). The brain's default mode network. *Annual review of neuroscience, 38*, 433–447. https://doi.org/10.1146/annurev-neuro-071013-014030

Raper, D., Louveau, A., & Kipnis, J. (2016). How Do Meningeal Lymphatic Vessels Drain the CNS?. *Trends in neurosciences, 39*(9), 581–586. https://doi.org/10.1016/j.tins.2016.07.001

Saltmarche, A. E., Naeser, M. A., Ho, K. F., Hamblin, M. R., & Lim, L. (2017). Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report. *Photomedicine and laser surgery, 35*(8), 432–441. https://doi.org/10.1089/pho.2016.4227

Salehpour, F., Gholipour-Khalili, S., Farajdokht, F., Kamari, F., Walski, T., Hamblin, M. R., DiDuro, J. O., & Cassano, P. (2020). Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: a narrative review. *Reviews in the neurosciences*, *31*(3), 269–286. https://doi.org/10.1515/revneuro-2019-0063

References

Salehpour, F., Hamblin, M. R., & DiDuro, J. O. (2019). Rapid Reversal of Cognitive Decline, Olfactory Dysfunction, and Quality of Life Using Multi-Modality Photobiomodulation Therapy: Case Report. *Photobiomodulation, photomedicine, and laser surgery*, *37*(3), 159–167. https://doi.org/10.1089/photob.2018.4569

Saltmarche, A. E., Naeser, M. A., Ho, K. F., Hamblin, M. R., & Lim, L. (2017). Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report. *Photomedicine and laser surgery*, *35*(8), 432–441. https://doi.org/10.1089/pho.2016.4227

Schiffer, F., Johnston, A. L., Ravichandran, C., Polcari, A., Teicher, M. H., Webb, R. H., & Hamblin, M. R. (2009). 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. *Behavioral and brain functions : BBF*, *5*, 46. https://doi.org/10.1186/1744-9081-5-46

Schiffer, F., Reichmann, W., Flynn, E., Hamblin, M. R., & McCormack, H. (2020). A Novel Treatment of Opioid Cravings With an Effect Size of .73 for Unilateral Transcranial Photobiomodulation Over Sham. *Frontiers in psychiatry, 11*, 827. https://doi.org/10.3389/fpsyt.2020.00827

Semyachkina-Glushkovskaya, O., Abdurashitov, A., Klimova, M., Dubrovsky, A., Shirokov, A., Fomin, A., Terskov, A., Agranovich, I., Mamedova, A., Khorovodov, A.(2020). Photostimulation of cerebral and peripheral lymphatic functions. *Translational Biophotonics, 2*, e201900036.

References

Shimizu, M., Matsuzuka, T., Matsumi, F., Ogawa, H., & Murono, S. (2018). Change of Tinnitus with Xenon Phototherapy of the Stellate Ganglion. *Photomedicine and laser surgery*, *36*(9), 468–471. https://doi.org/10.1089/pho.2017.4431

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences*, *1071*, 67–79. https://doi.org/10.1196/annals.1364.007

Simic, G., Babic, M., Borovecki, F., & Hof, P. R. (2014). Early failure of the default-mode network and the pathogenesis of Alzheimer's disease. *CNS neuroscience & therapeutics*, *20*(7), 692–698. https://doi.org/10.1111/cns.12260

Simmons, M. L., Frondoza, C. G., & Coyle, J. T. (1991). Immunocytochemical localization of N-acetyl-aspartate with monoclonal antibodies. *Neuroscience*, *45*(1), 37–45. https://doi.org/10.1016/0306-4522(91)90101-s

Stein, T. D., Alvarez, V. E., & McKee, A. C. (2014). Chronic traumatic encephalopathy: a spectrum of neuropathological changes following repetitive brain trauma in athletes and military personnel. *Alzheimer's research & therapy*, *6*(1), 4. https://doi.org/10.1186/alzrt234

Stern, R. A., Daneshvar, D. H., Baugh, C. M., Seichepine, D. R., Montenigro, P. H., Riley, D. O., Fritts, N. G., Stamm, J. M., Robbins, C. A., McHale, L., Simkin, I., Stein, T. D., Alvarez, V. E., Goldstein, L. E., Budson, A. E., Kowall, N. W., Nowinski, C. J., Cantu, R. C., & McKee, A. C. (2013). Clinical presentation of chronic traumatic encephalopathy. *Neurology*, *81*(13), 1122–1129. https://doi.org/10.1212/WNL.0b013e3182a55f7f

References

Stern, R. A., Adler, C. H., Chen, K., Navitsky, M., Luo, J., Dodick, D. W., Alosco, M. L., Tripodis, Y., Goradia, D. D., Martin, B., Mastroeni, D., Fritts, N. G., Jarnagin, J., Devous, M. D., Sr, Mintun, M. A., Pontecorvo, M. J., Shenton, M. E., & Reiman, E. M. (2019). Tau Positron-Emission Tomography in Former National Football League Players. *The New England journal of medicine*, *380*(18), 1716–1725. https://doi.org/10.1056/NEJMoa1900757

Stevens, M. C., Lovejoy, D., Kim, J., Oakes, H., Kureshi, I., & Witt, S. T. (2012). Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain imaging and behavior*, *6*(2), 293–318. https://doi.org/10.1007/s11682-012-9157-4

Tagge, C. A., Fisher, A. M., Minaeva, O. V., Gaudreau-Balderrama, A., Moncaster, J. A., Zhang, X. L., Wojnarowicz, M. W., Casey, N., Lu, H., Kokiko-Cochran, O. N., Saman, S., Ericsson, M., Onos, K. D., Veksler, R., Senatorov, V. V., Jr, Kondo, A., Zhou, X. Z., Miry, O., Vose, L. R., Gopaul, K. R., … Goldstein, L. E. (2018). Concussion, microvascular injury, and early tauopathy in young athletes after impact head injury and an impact concussion mouse model. *Brain: a journal of neurology*, *141*(2), 422–458. https://doi.org/10.1093/brain/awx350

Tedford, C. E., DeLapp, S., Jacques, S., & Anders, J. (2015). Quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue. *Lasers in surgery and medicine*, *47*(4), 312–322. https://doi.org/10.1002/lsm.22343

Tian, F., Hase, S. N., Gonzalez-Lima, F., & Liu, H. (2016). Transcranial laser stimulation improves human cerebral oxygenation. *Lasers in surgery and medicine*, *48*(4), 343–349. https://doi.org/10.1002/lsm.22471

References

Uozumi, Y., Nawashiro, H., Sato, S., Kawauchi, S., Shima, K., & Kikuchi, M. (2010). Targeted increase in cerebral blood flow by transcranial near-infrared laser irradiation. *Lasers in surgery and medicine*, *42*(6), 566–576. https://doi.org/10.1002/lsm.20938

Wan, S., Anderson, R. R., & Parrish, J. A. (1981). Analytical modeling for the optical properties of the skin with in vitro and in vivo applications. *Photochemistry and photobiology*, *34*(4), 493–499. https://doi.org/10.1111/j.1751-1097.1981.tb09391.x

Wang, X., Tian, F., Reddy, D. D., Nalawade, S. S., Barrett, D. W., Gonzalez-Lima, F., & Liu, H. (2017). Up-regulation of cerebral cytochrome-c-oxidase and hemodynamics by transcranial infrared laser stimulation: A broadband near-infrared spectroscopy study. *Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism, 37*(12), 3789–3802. https://doi.org/10.1177/0271678X17691783

Wang, X., Tian, F., Soni, S. S., Gonzalez-Lima, F., & Liu, H. (2016). Interplay between up-regulation of cytochrome-c-oxidase and hemoglobin oxygenation induced by near-infrared laser. *Scientific reports, 6,* 30540. https://doi.org/10.1038/srep30540

Wong-Riley, M. T., Liang, H. L., Eells, J. T., Chance, B., Henry, M. M., Buchmann, E., Kane, M., & Whelan, H. T. (2005). Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. *The Journal of biological chemistry*, *280*(6), 4761–4771. https://doi.org/10.1074/jbc.M409650200

References

Xiao X, Guo Y, Chu X, Jia S, Zheng X, Zhou C (2005). Effects of low power laser irradiation in nasal cavity on cerebral blood flow perfusion of patients with brain infarction. *Chinese Journal of Physical Medicine, 27*, 418–420.

Xuan, W., Agrawal, T., Huang, L., Gupta, G. K., & Hamblin, M. R. (2015). Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. *Journal of biophotonics*, *8*(6), 502–511. https://doi.org/10.1002/jbio.201400069

Xuan, W., Vatansever, F., Huang, L., & Hamblin, M. R. (2014). Transcranial low-level laser therapy enhances learning, memory, and neuroprogenitor cells after traumatic brain injury in mice. *Journal of biomedical optics*, *19*(10), 108003. https://doi.org/10.1117/1.JBO.19.10.108003

Zhao, J., Tian, Y., Nie, J., Xu, J., & Liu, D. (2012). Red light and the sleep quality and endurance performance of Chinese female basketball players. Journal of athletic training, 47(6), 673–678. https://doi.org/10.4085/1062-6050-47.6.08

Zinchenko, E., Navolokin, N., Shirokov, A., Khlebtsov, B., Dubrovsky, A., Saranceva, E., Abdurashitov, A., Khorovodov, A., Terskov, A., Mamedova, A., Klimova, M., Agranovich, I., Martinov, D., Tuchin, V., Semyachkina-Glushkovskaya, O., & Kurts, J. (2019). Pilot study of transcranial photobiomodulation of lymphatic clearance of beta-amyloid from the mouse brain: breakthrough strategies for non-pharmacologic therapy of Alzheimer's disease. *Biomedical optics express, 10*(8), 4003–4017. https://doi.org/10.1364/BOE.10.004003

Zomorrodi, R., Loheswaran, G., Pushparaj, A., & Lim, L. (2019). Pulsed Near Infrared Transcranial and Intranasal Photobiomodulation Significantly Modulates Neural Oscillations: A pilot exploratory study. *Scientific reports, 9*(1), 6309. https://doi.org/10.1038/s41598-019-42693-x

Questions?

How to Obtain CE/CME Credits

To receive CE/CME credit, you must register by 0745 ET on 27 August 2021 to qualify for the receipt of CE/CME credit or certificate of attendance. You must complete the program posttest and evaluation before collecting your certificate. The posttest and evaluation will be available through 9 September 2021 at 2359 ET. Please complete the following steps to obtain CE/CME credit:

1. Go to URL: https://www.dhaj7-cepo.com/content/aug-2021-ccss-exploration-innovations-health-care
2. Search for your course using the **Catalog**, **Calendar**, or **Find a course** search tool.
3. Click on the REGISTER/TAKE COURSE tab.
   a. If you have previously used the CEPO CMS, click login.
   b. If you have not previously used the CEPO CMS click register to create a new account.
4. Follow the onscreen prompts to complete the post-activity assessments:
   a. Read the Accreditation Statement
   b. Complete the Evaluation
   c. Take the Posttest
5. After completing the posttest at 80% or above, your certificate will be available for print or download.
6. You can return to the site at any time in the future to print your certificate and transcripts at: https://www.dhaj7-cepo.com/
7. If you require further support, please contact us at: dha.ncr.j7.mbx.cepo-cms-support@mail.mil