# Research with Transcranial, Light-emitting Diode (LED) Treatments to Improve Cognition in Chronic, Traumatic Brain Injury

**Margaret Naeser, PhD, LAc**

**VA Boston Healthcare System, JP Campus**
**Department of Neurology, Boston University School of Medicine**

**Transcranial LED to Improve Cognition in Veterans with Gulf War Illnesses**
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**Transcranial Magnetic Stimulation (TMS) Aphasia Research**
**Neuroimaging (MRI), Aphasia Research Center**

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# Co-Investigators and Collaborators

VA Boston Healthcare System
and/or Boston University
School of Medicine:

Maxine Krengel, PhD
Jeffrey Knight, PhD
Paula Martin, PhD
Michael Ho, PhD
Yelena Bogdanova, PhD, PhD
Carole Palumbo, PhD
Errol Baker, PhD
Ronald Killiany, PhD (BU MRI)
Bang-Bon Koo, PhD (BU MRI)

Megan Yee, MS
Vivian Ho

Outside Collaborators:

Michael R. Hamblin, PhD
Wellman Center for Photomedicine
Massachusetts General Hospital
Harvard Medical School

Ross Zafonte, DO
Physical Medicine and Rehabilitation
Harvard Medical School
Spaulding Rehabilitation Hospital
Charlestown, MA

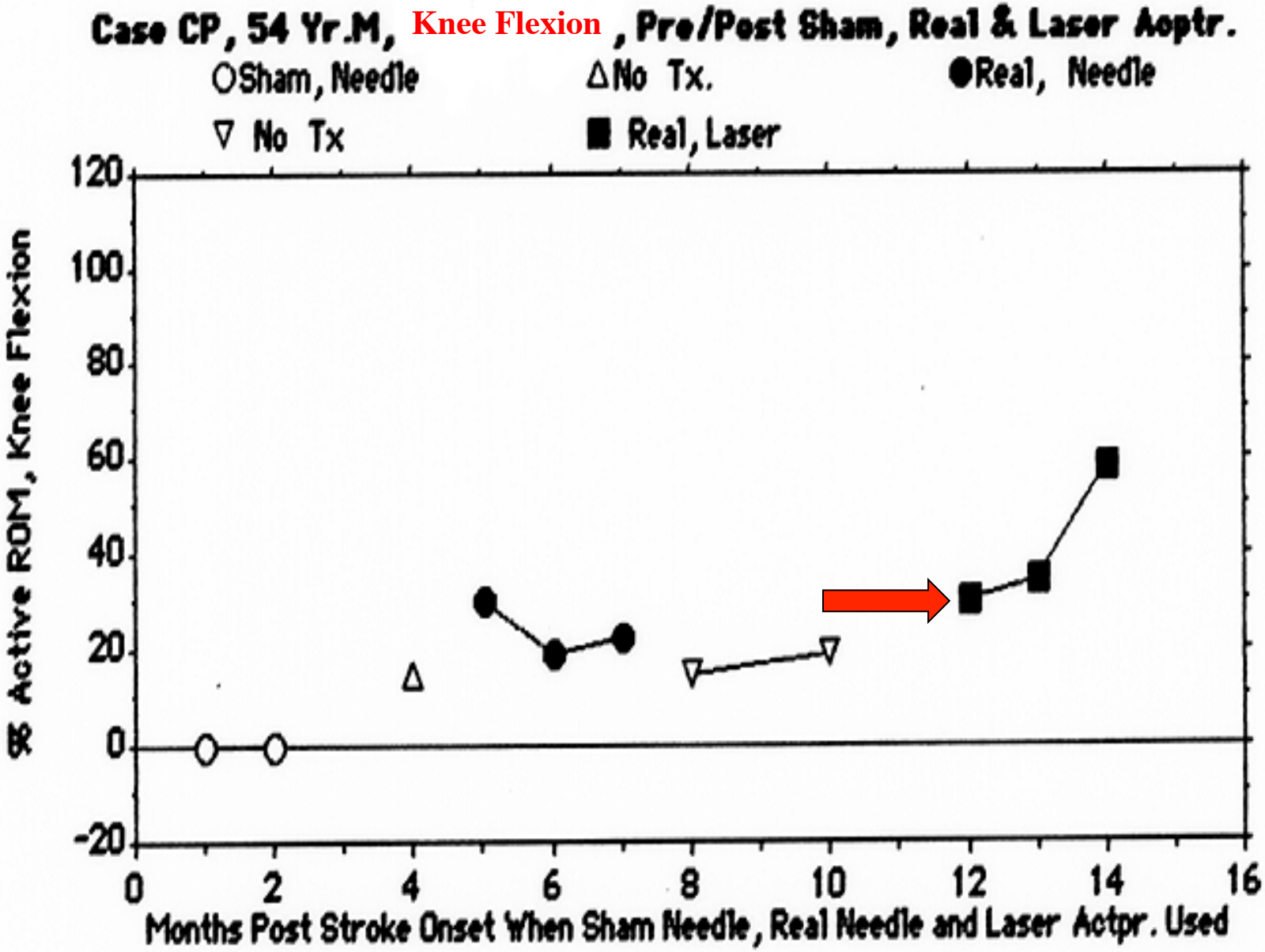
Judith Frazier, RN, EdD
TBI Research Coordinator
Spaulding Rehabilitation Hospital

Hua Shan Hospital
Shanghai, China, 1985.

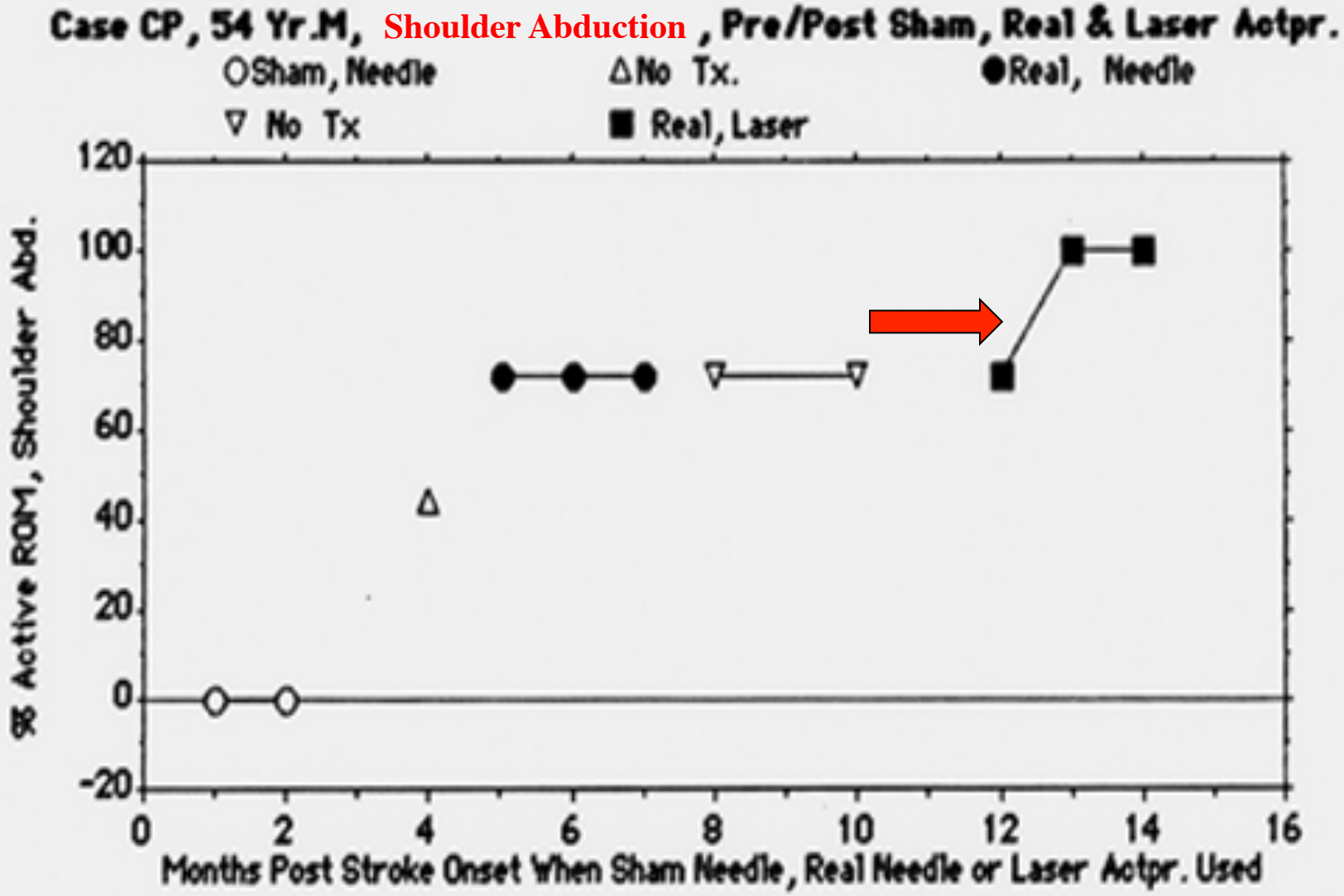
Neurological and
Dermatological
Research Institute

Laser Acupuncture to Treat
Paralysis in Stroke

Personal Observation
Naeser MA. 1985




Naeser, Alexander, Stiassny-Eder Galler, Hobbs, Bachman, Lannin. 1995. Laser Acupuncture in the Treatment of **Paralysis in Stroke Patients**: A CT Scan Lesion Site Study. *Am J Acupuncture*, 23(1):13-28

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Case FJ, 48 Yr. F., 4 Yr. Post Stroke. Left Hemiplegia

**Laser Acptr. Tx.'s**

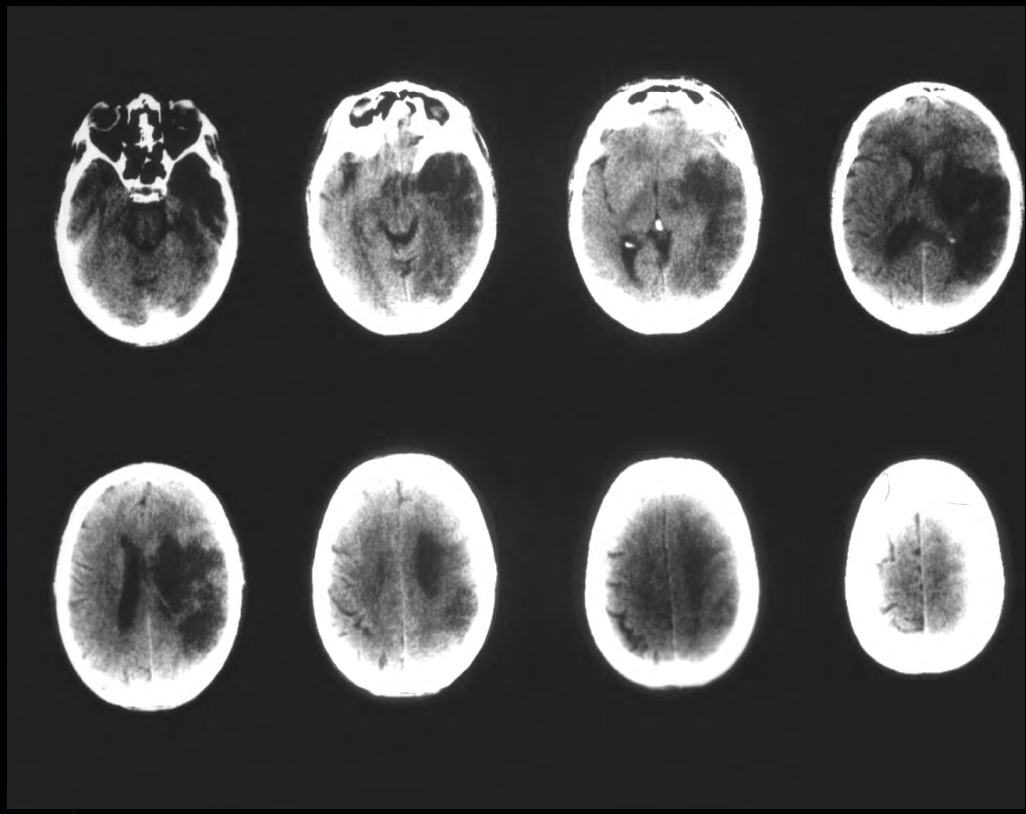
**Arm/Leg, Poor Response**

However, Post Laser Tx.'s, loosened Achilles Tendon, improved walking ability

**Face, Good Response**

Left side of face "lifted" to become more symmetric with the right.

Post 5 laser tx.'s, ability to control food and liquids in left side of mouth. Preceding 4 Yrs., unable to do so.



Naeser, Alexander, Stiassny-Eder Galler, Hobbs, Bachman, Lannin. 1995. Laser Acupuncture in the Treatment of **Paralysis in** Stroke Patients: A CT Scan Lesion Site Study. *Am J Acupuncture*, 23(1):13-28

**BEFORE TREATMENT: Right Hand *spasticity still present*, 1.5 Yr. Poststroke**

**Microamps TENS device (MicroStim 100) will be used for 20 Minutes,**

**on two Acupuncture Points: HRT 8 and TW 5**

**High Frequency, 292 Hz., 2 min. *(subthreshold)***

**Low Frequency, 0.3 Hz., 18 min. *(subthreshold)***

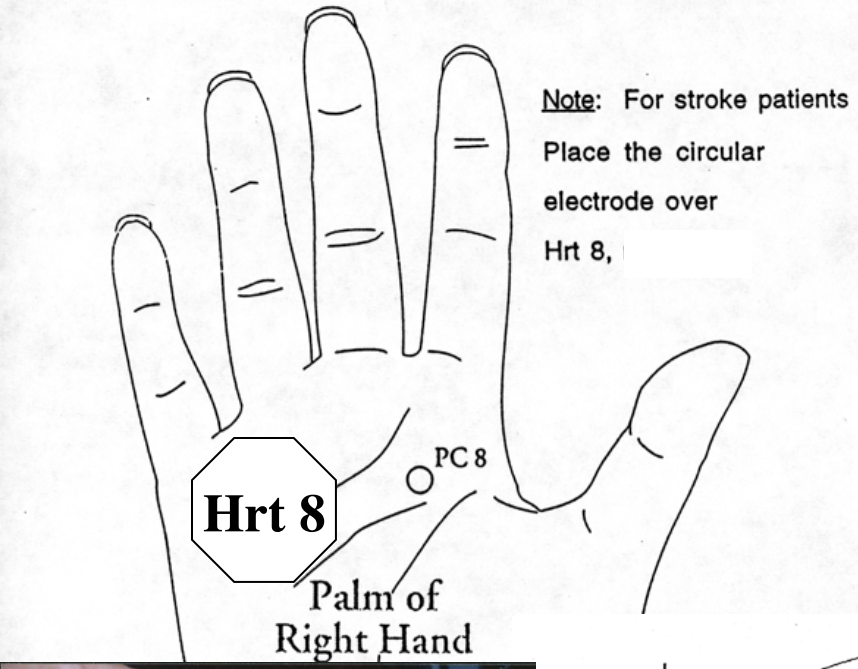
**PLUS, Red-Beam Laser Acupuncture on the finger tips, 4 J/cm$^2$ per point**

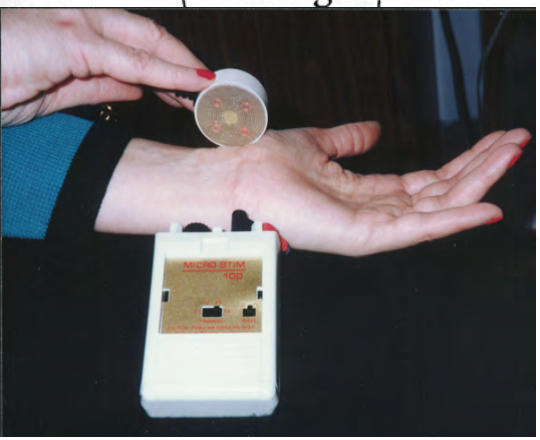
Naeser, Personal Observation in: Hashmi, Huang, Osmani, Sharma, Naeser, Hamblin. 2010 Role of low-level laser therapy in neurorehabilitation. *Arch Physical Medicine & Rehabilitation*, Suppl. 2, S292–S305.

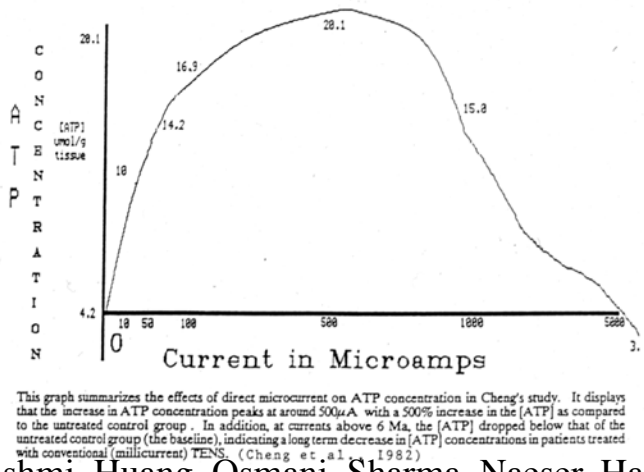
Hand Diagram #1.

## Right Hand (Palm)

**Step 4)** Place the tip of the laser directly on each acupuncture point. With red-beam laser treat each point at 4 Joules/cm$^2$ - Hrt 8, PC8, Lu 9, Hrt 7. See special instructions below for *PC7.



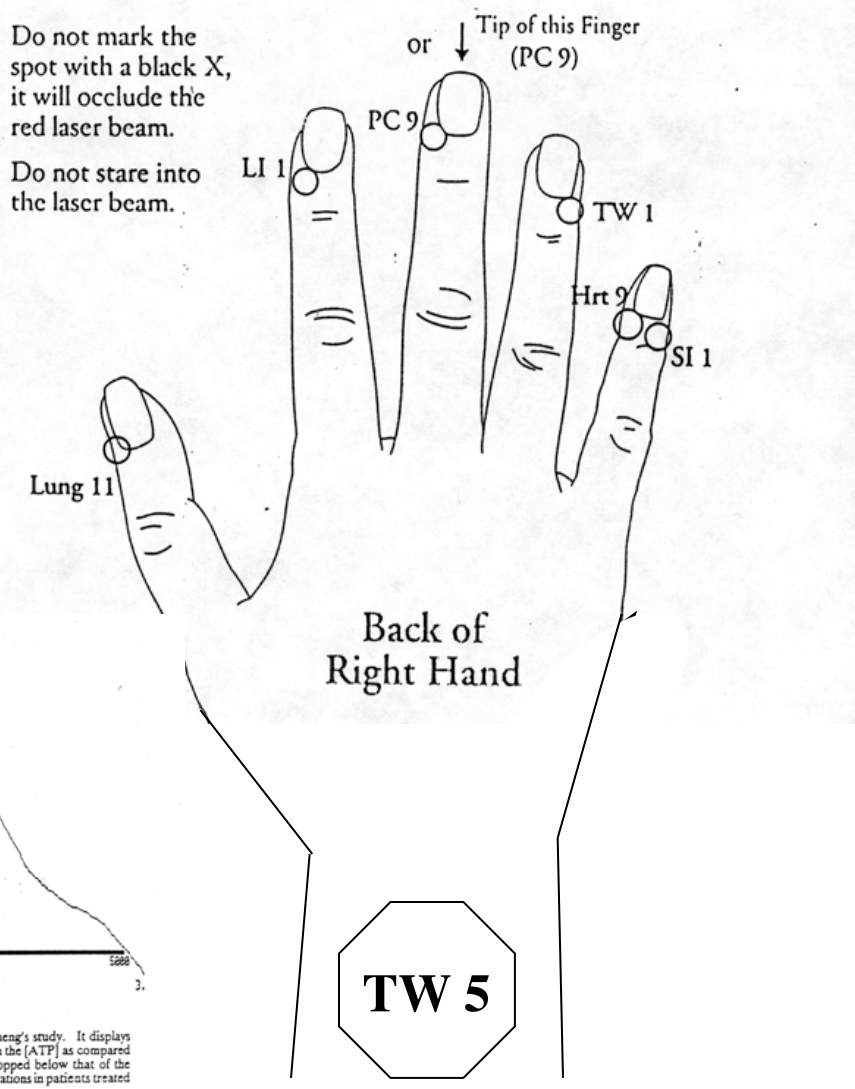



This graph summarizes the effects of direct microcurrent on ATP concentration in Cheng's study. It displays that the increase in ATP concentration peaks at around 500μA with a 500% increase in the [ATP] as compared to the untreated control group. In addition, at currents above 6 Ma, the [ATP] dropped below that of the untreated control group (the baseline), indicating a long term decrease in [ATP] concentrations in patients treated with conventional (millicurrent) TENS. (Cheng et al., 1982)

Hand Diagram #1.

## Right Hand (Back)

**Step 3)** Place the tip of the laser directly on each acupuncture point. With red-beam laser treat each point at 4 Joules/cm$^2$ - Lu 11, LI 1, PC 9, TW 1, Hrt 9, SI 1.




Naeser, Personal Observation in: Hashmi, Huang, Osmani, Sharma, Naeser, Hamblin. 2010 Role of low-level laser therapy in neurorehabilitation. *Arch Physical Medicine & Rehabilitation,* Suppl. 2, S292–S305.

**BEFORE TREATMENT:**

**Hand spasticity still present**
**1.5 Yr. Poststroke**

**1st Treatment**
**Naeser Laser Hand Treatment**

**Microamps TENS (Hrt 8, TW 5)**
**and**
**Red-beam Laser (Jing-Well Pts.)**

**AFTER TREATMENT:**

**Post- 1st, 20-Minute Treatment**

**Hand opens**
**Fingers have more extension**
**and less spasticity**

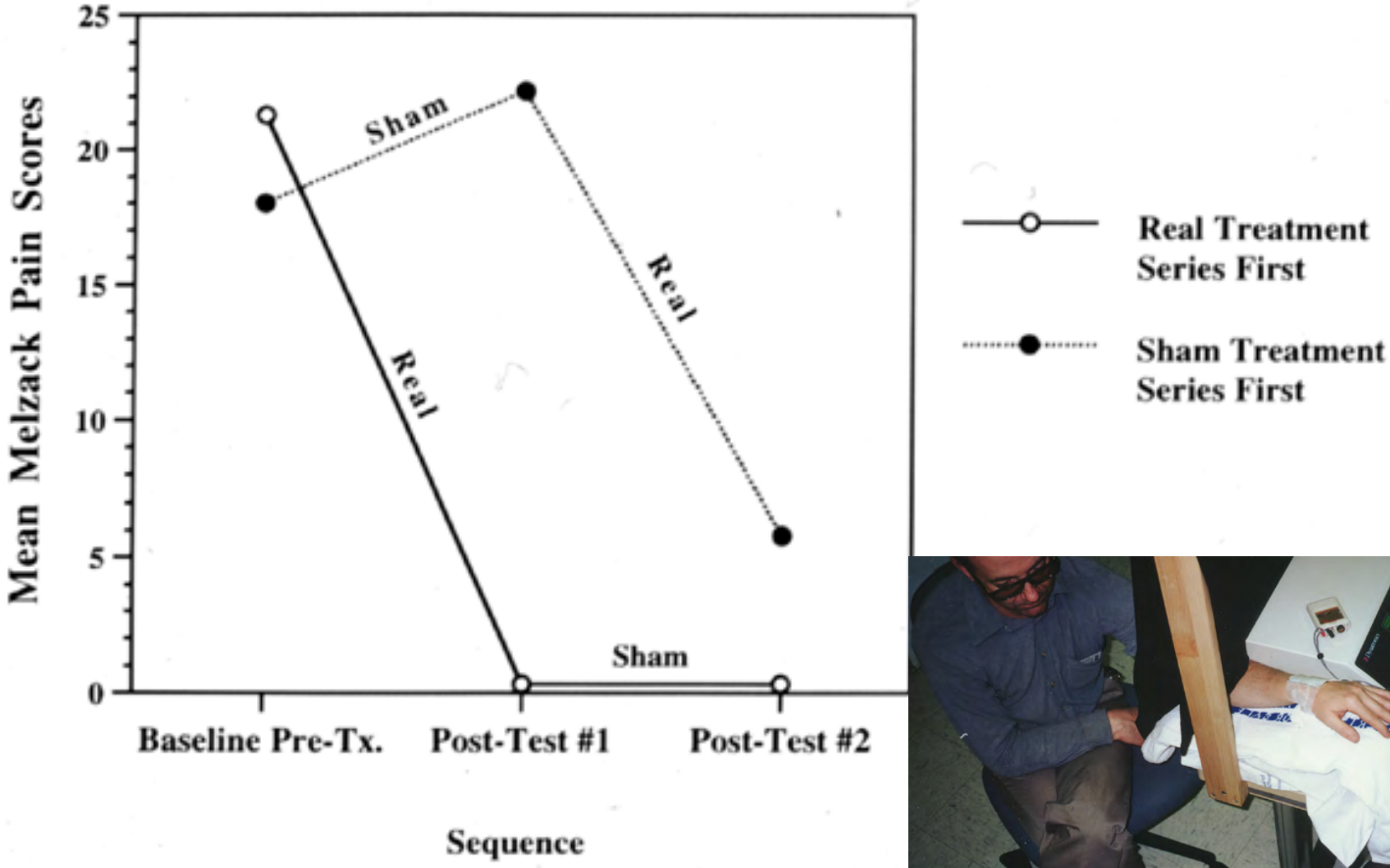
**Requires more treatments,**
**to retain more lasting effect.**

**Patient can treat him/herself.**

Naeser, Personal Observation in: Hashmi, Huang, Osmani, Sharma, Naeser, Hamblin. 2010
Role of low-level laser therapy in neurorehabilitation.
*Arch Physical Medicine & Rehabilitation,* Suppl. 2, S292–S305.

Naeser, Hahn, Lieberman, Branco. 2002

**Carpal Tunnel Syndrome Pain** Treated with Low-Level Laser and Microamps TENS, A Controlled Study. *Arch Physical Medicine & Rehabilitation*, Vol. 83:978-988.






Duration of pain: 3 Mo. to 2 Yr.

# 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%)
- 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 or MRI scan.
  Taber, Warden, Hurley, 2006; Medana, Esiri, 2003
- *Closed-head TBI from blast injury* is *the major injury* of Veterans returning from Iraq and Afghanistan. Hoge, McGurk, Thomas *et al.*, 2008

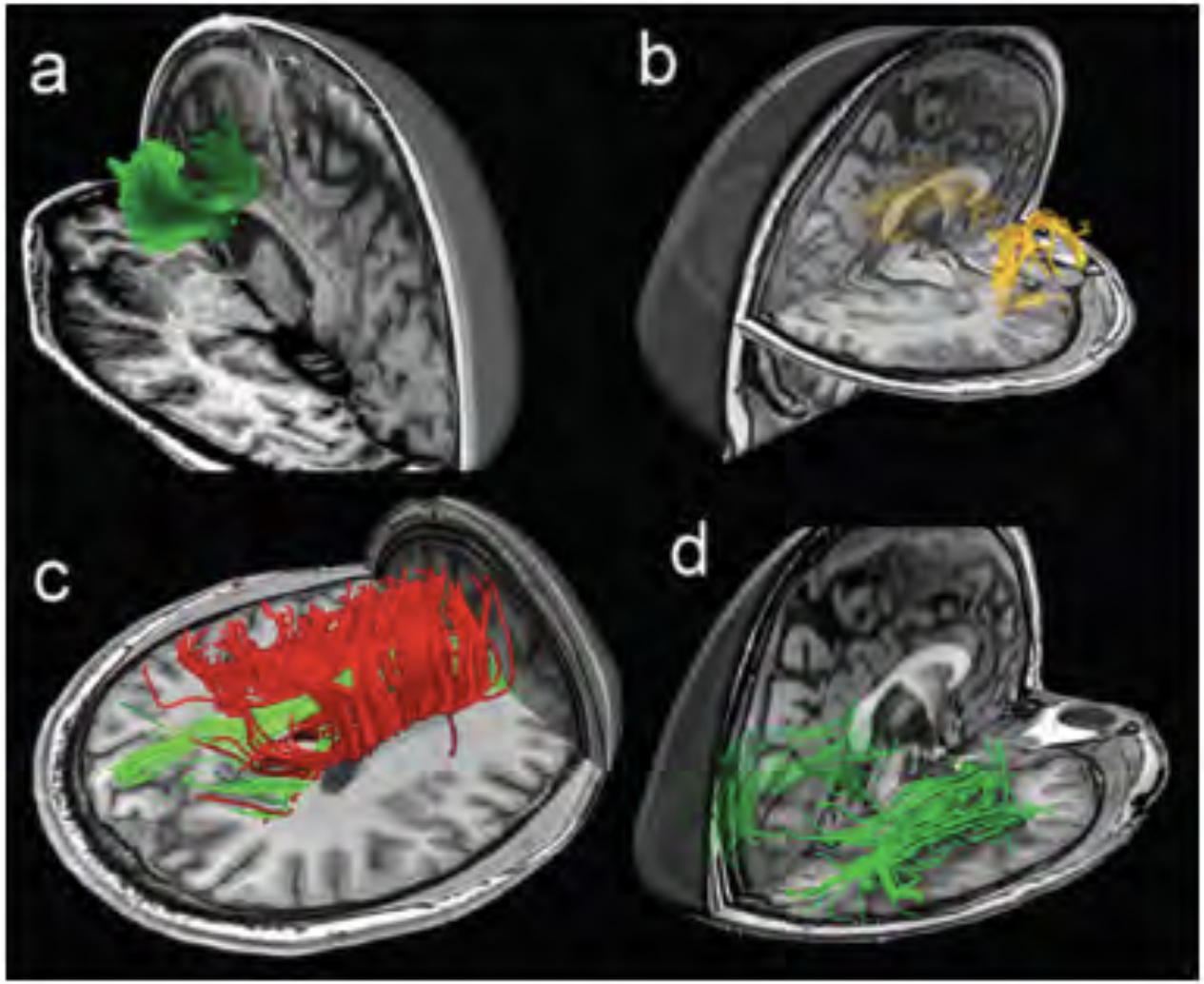



**Figure 1.** Fiber tractography of commonly damaged tracts in mild traumatic brain injury: (a) anterior corona radiata and genu of corpus callosum, (b) uncinate fasciculus, (c) cingulum bundle in green and body of corpus callosum in red, and (d) inferior longitudinal fasciculus.

Niogi & Mukherjee, 2010, *J Head Trauma Rehabil.*

# 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*.

Photomedicine and Laser Surgery
Volume 29, Number 5, 2011

Pp. 351–358
DOI: 10.1089/pho.2010.2814

**Case Report**

# Improved Cognitive Function After Transcranial, Light-Emitting Diode Treatments in Chronic, Traumatic Brain Injury: Two Case Reports

Margaret A. Naeser, Ph.D., L.Ac.,[1,2] Anita Saltmarche, R.N., MHSc,[3]
Maxine H. Krengel, Ph.D.,[1,2] Michael R. Hamblin, Ph.D.,[4,5,6] and Jeffrey A. Knight, Ph.D.[1,2,7]

## Abstract

*Objective:* Two chronic, traumatic brain injury (TBI) cases, where cognition improved following treatment with red and near-infrared light-emitting diodes (LEDs), applied transcranially to forehead and scalp areas, are presented. *Background:* Significant benefits have been reported following application of transcranial, low-level laser therapy (LLLT) to humans with acute stroke and mice with acute TBI. These are the first case reports documenting improved cognitive function in chronic, TBI patients treated with transcranial LED. *Methods:* Treatments were applied bilaterally and to midline sagittal areas using LED cluster heads [2.1″ diameter, 61 diodes (9×633 nm, 52×870 nm); 12–15 mW per diode; total power: 500 mW; 22.2 mW/cm$^2$; 13.3 J/cm$^2$ at scalp (estimated 0.4 J/cm$^2$ to cortex)]. *Results:* Seven years after closed-head TBI from a motor vehicle accident, Patient 1 began transcranial LED treatments. Pre-LED, her ability for sustained attention (computer work) lasted 20 min. After eight weekly LED treatments, her sustained attention time increased to 3 h. The patient performs nightly home treatments (5 years); if she stops treating for more than 2 weeks, she regresses. Patient 2 had a history of closed-head trauma (sports/military, and recent fall), and magnetic resonance imaging showed frontoparietal

# LED Device

FDA-Cleared, Non-significant risk, since 2003

*Circular-shaped*. Cluster-head diameter: 53.45 mm (2.1 inches)
Treatment Area: 22.48 $cm^2$

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

***9** red **633 nm** diodes*

***52** near-infrared **870 nm** diodes*

Each diode was 12–15 mW

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

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

**1 J/$cm^2$ = 45 sec**

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 1cm deep, to reach surface brain cortex. Wan, Parrish, Anderson, Madden, 1981

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011

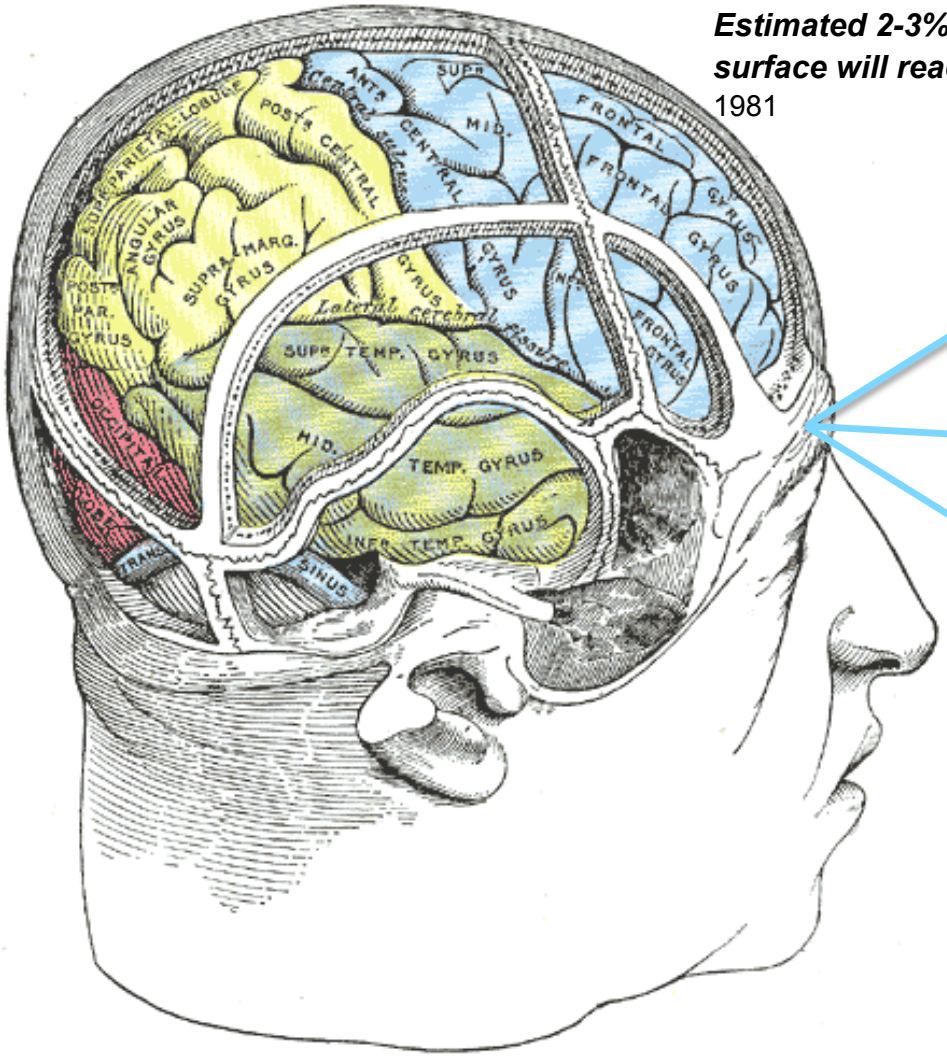
**<u>Bilateral LED Placement Loci</u>: 11 LED head placement loci. Left Side, Right Side, and Midline placements.**

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

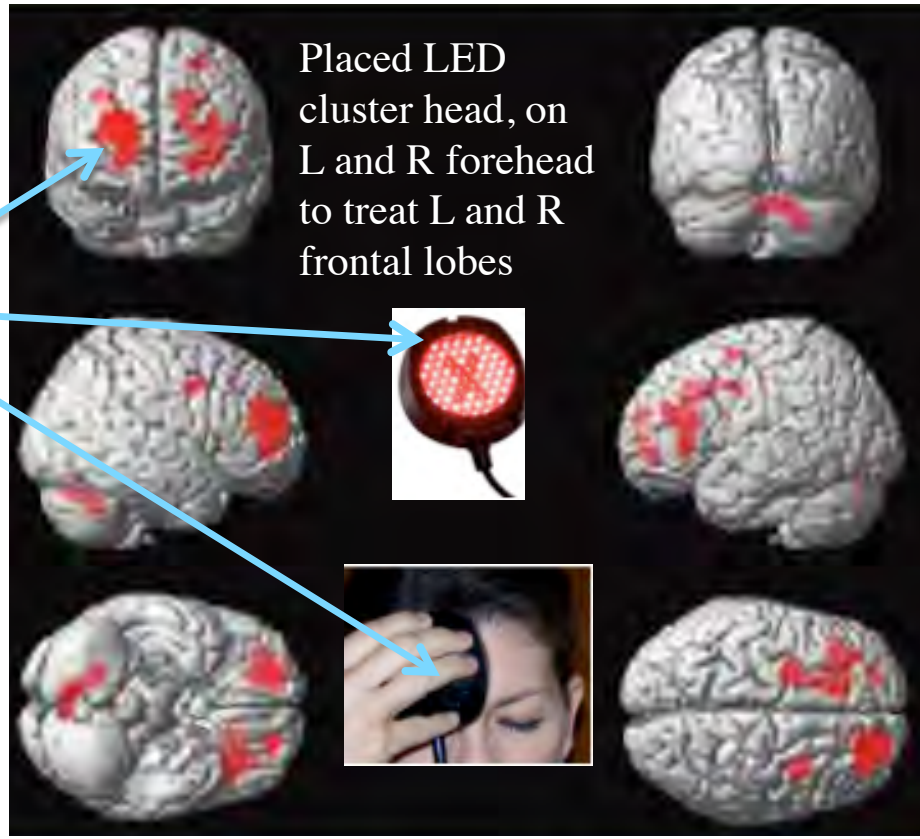
Estimated 0.4 J/cm$^2$ at 1cm deep, surface brain cortex.

Each 2-inch diameter, LED cluster head, 500 mW (<u>+</u> 20%).

***Estimated 2-3% of near-infrared, energy penetration from skin/scalp surface will reach 1 cm deep, to brain cortex.*** Wan, Parrish, Anderson, Madden, 1981




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

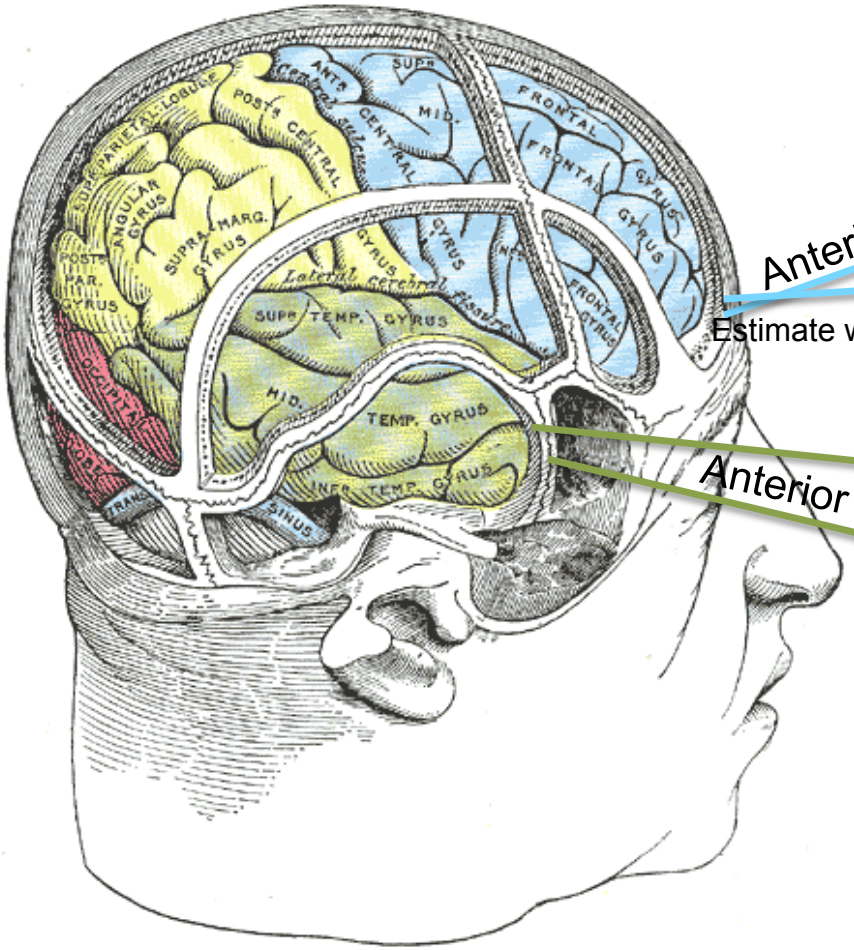



Red areas show *<u>low cortical activation</u>* on **functional MRI *<u>in chronic, traumatic brain injury cases</u>*** (post- motor vehicle accidents) with "cognitive dysfunction."

Sanchez-Carrion et al., *J. Neurotrauma*, 2008

Naeser, Saltmarche, Krengel, Hamblin, Knight. 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.

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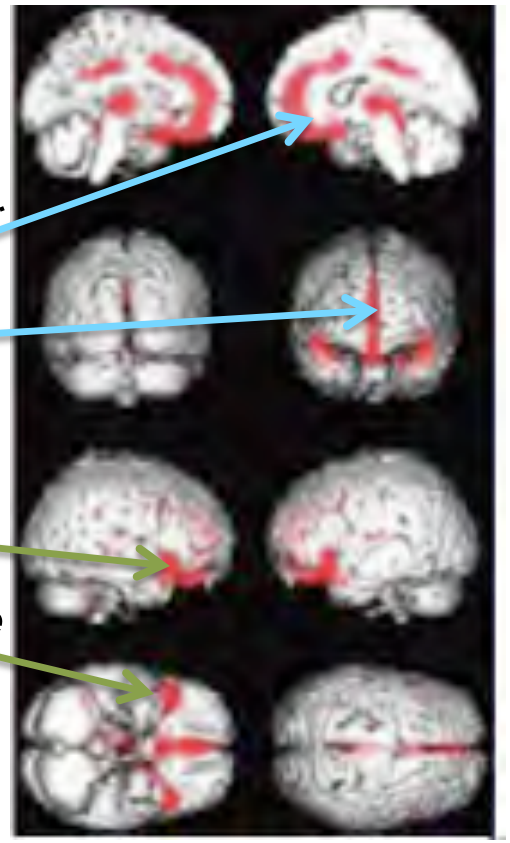



Red areas show cortical areas of *low glucose metabolism on* **PET scans** in chronic, TBI cases (post- MVA) with cognitive dysfunction. Kato et al., 2007

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011

## ***Home Treatments:***

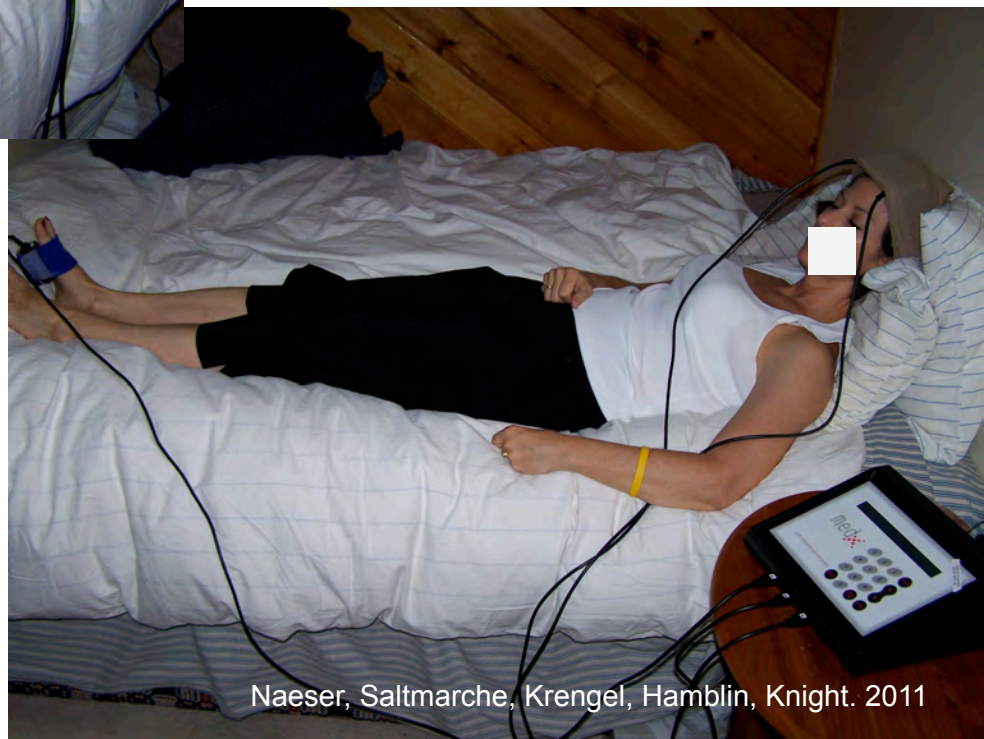
The MedX Console Unit has 3 LED Cluster Heads.

***Three LED cluster heads*** **may be used in three different areas,** ***at the same time*****.**

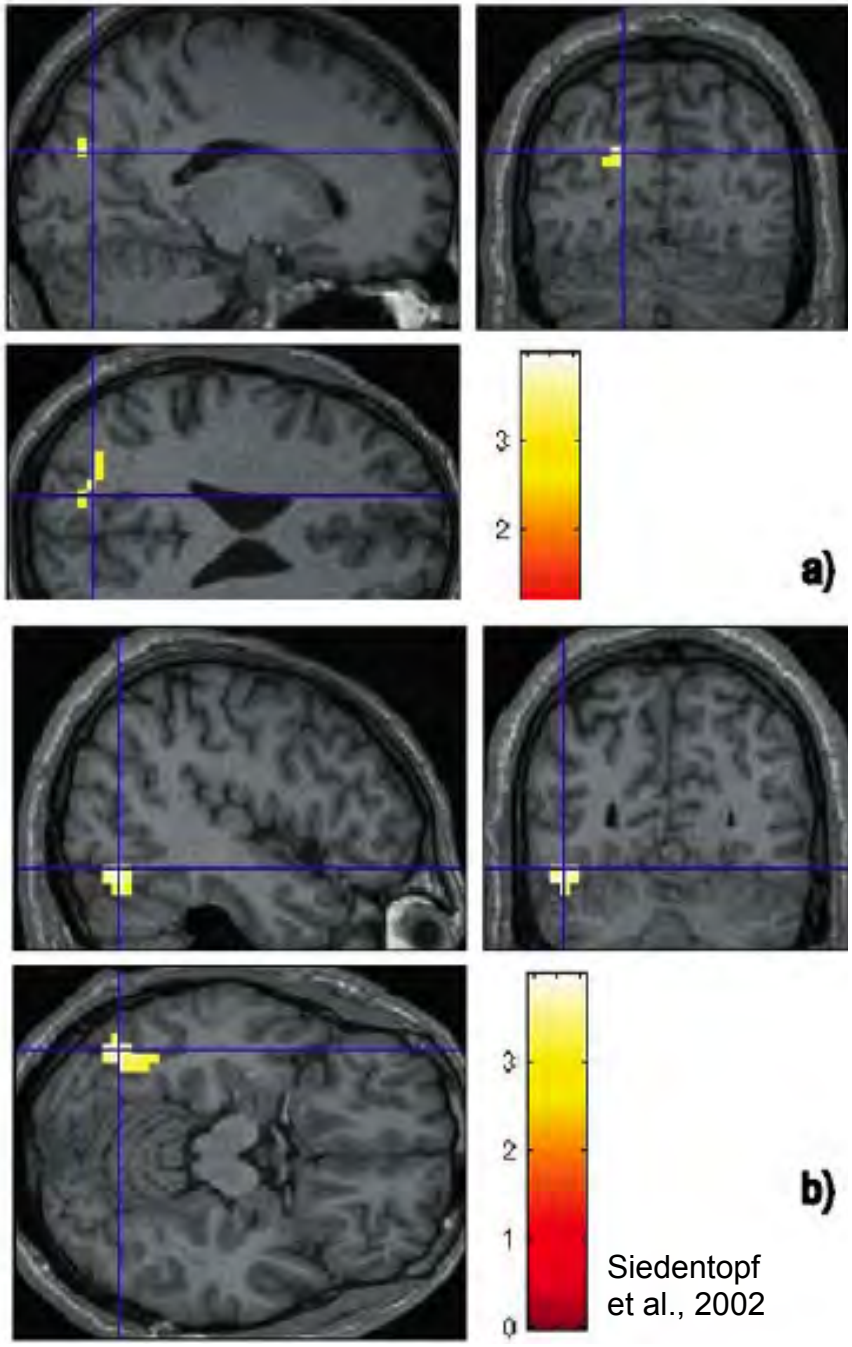
The usual treatment time is 10 minutes, per area.

Here, two LED cluster heads are held in place on the head, with *a loose-fitting elastic cap*.

The LED cluster head placed on the sole of the foot (acupuncture point, Kidney 1), is held in place with a soft, flexible, *elastic band, secured with a velcro strap*.



Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011



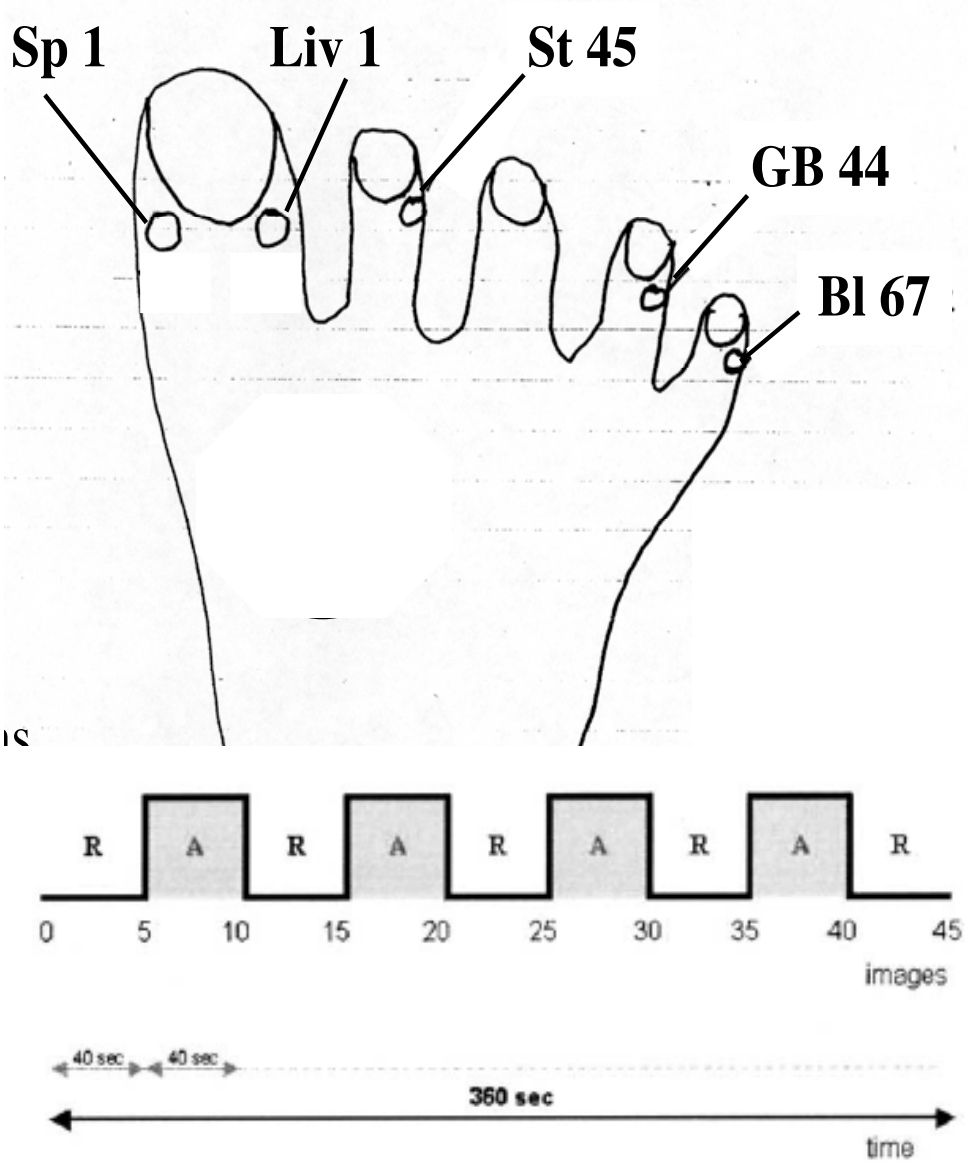




Fig. 1. Sequence design in the fMRI experiment.

Fig.2. Ipsilateral, occipital cerebral activation pattern induced by laser acupuncture to Bl 67. Siedentopf et al., 2002, *Neuroscience Lett*

# P1: Transcranial LED to Improve Cognition in chronic, TBI

Woman, age 59, *closed-head injury*, motor vehicle accident (MVA), 1997

*Highly educated*, *teaching web-design* at a major university

**5 months post- MVA:**

***Resigned from all professional work,*** "post-concussive syndrome"

**2 years post- MVA (age 61):**

***Unable to perform any work***, *depression, and suicidal gesture*

***7 years, post- MVA (age 66):***

***Received first transcranial LED treatments***

***Pre- LED*** **- Able to work on computer for only *20 min.* at a time.**

***Post- 2 Mo. of LED Treatments –***

***Able to work on computer 3 hours***

**Performs nightly, *home treatments* - now, for 6 years (age 73) maintains improved cognition.**

***No depression*; *no more suicidal gestures.***

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011

# P2: Transcranial LED to Improve Cognition in chronic, TBI

Woman, age 52. High-ranking officer, *retired from military*, 20 years of service.

After military retirement, working *as Executive Consultant*, International, Technology Consulting firm.

*4 Yr. after retirement*, closed-head injury, *fell from swing onto concrete.*

*Already had history multiple concussions: civilian and military deployment.*
**6 Mo. post- TBI:** *Onto Medical Disability*, due to *"cognitive dysfunction"*
***11 Mo. post- TBI:*** *Started nightly,* ***home treatments*** *with transcranial LEDs*

**15 Mo. post- TBI:**
***4 Mo. Post- Home, LED treatments*****: *Working full-time*, *Executive Consultant*, *International Technology***
*Cancelled Medical Disability (had been on this 5 months)*
*Reported* ***reduced PTSD symptoms****.*

**3 Yr. post- TBI:** Continues ***home treatments***; continues to be ***employed***.

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011, *Photomedicine and Laser Surgery*

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

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]

**Abstract**

This pilot, open-protocol study examined whether scalp application of red and near-infrared (NIR) light-emitting diodes (LED) could improve cognition in patients with chronic, mild traumatic brain injury (mTBI). Application of red/NIR light improves mitochondrial function (especially in hypoxic/compromised cells) promoting increased adenosine triphosphate (ATP) important for cellular metabolism. Nitric oxide is released locally, increasing regional cerebral blood flow. LED therapy is noninvasive, painless, and non-thermal (cleared by the United States Food and Drug Administration [FDA], an insignificant risk device). Eleven chronic, mTBI participants (26–62 years of age, 6 males) with nonpenetrating brain injury and persistent cognitive dysfunction were treated for 18 outpatient sessions (Monday, Wednesday, Friday, for 6 weeks), starting at 10 months to 8 years post- mTBI (motor vehicle accident [MVA] or sports-related; and one participant, improvised explosive device [IED] blast injury). Four had a history of multiple concussions. Each LED cluster head (5.35 cm diameter, 500 mW, 22.2 mW/cm$^2$) was applied for 10 min to each of 11 scalp placements (13 J/cm$^2$). LEDs were placed on the midline from front-to-back hairline; and bilaterally on frontal, parietal, and temporal areas. Neuropsychological testing was performed pre-LED, and at 1 week, and 1 and 2 months after the 18th treatment. A significant linear trend was observed for the effect of LED treatment over time for the Stroop test for Executive Function, Trial 3 inhibition ($p=0.004$); Stroop, Trial 4 inhibition switching ($p=0.003$); California Verbal Learning Test (CVLT)-II, Total Trials 1–5 ($p=0.003$); and CVLT-II, Long Delay Free Recall ($p=0.006$). Participants reported improved sleep, and fewer post-traumatic stress disorder (PTSD) symptoms, if present. Participants and family reported better ability to perform social, interpersonal, and occupational functions. These open-protocol data suggest that placebo-controlled studies are warranted.

**Key words:** executive function; mTBI; photobiomodulation; treatment for mTBI

# Participants: *Spaulding Rehabilitation Hospital Study,* Harvard Medical School

Dr. Ross Zafonte, Principal Investigator

- **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, IED blast TBI)
- Participants had one or **more** ***non-penetraing TBI*** with LOC ranging 0-30 min.

  **4 / 11, multiple TBIs**
- At Entry: Must have scored at least 2 SD below average on one,
  or 1 SD below average on at least two,
  neuropsychological tests (NP) administered at Screening:

- **Screening NP Tests**:

1) **Trail Making Test** (Reynolds, 2002). Trails A and Trails B.
2) **Controlled Oral Word Association Test**/FAS Test (Spreen & Benton, 1977; Benton & Hamsher, 1989). Total Words generated, for the letters, F, A and S.
3) **California Verbal Learning Test, Second Edition.** (Delis, Kramer, Kaplan, Ober, 2000).
4) **Stroop Test for Executive Function** (Delis, Kaplan, Kramer, 2001). Trials 1 – 4.

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J..of Neurotrauma*

- **Method:** LED cluster heads were ***applied to 11 scalp areas:***

  Along the ***midline/mid-sagittal line***, from the front hairline to the back hairline;

  and ***bilateral dorso-lateral prefrontal***, temporal, parietal, and occipital areas.

- A total of ***5-6 LED cluster heads*** were ***applied to the scalp simultaneously***.

  2 sets of LED cluster head placement loci, 10 min. per set.
  13 Joules/$cm^2$ applied at each scalp/skin LED placement area

  Estimated 0.4 J/$cm^2$ at 1 cm, close to surface brain cortex, but unknown

- Total LED treatment time per visit was 20 minutes.

**LED Treatment Schedule:**

- 18 LED Tx.'s *(M,W,F; 6 Wks)* as outpatients, Spaulding Rehabilitation Hospital, Boston.

**Neuropsych. Testing, Pre- and Post LED:**

- Pre- LED at Entry
- 1 Wk. post- the 18th LED Tx.
- 1 Mo. post- the 18th LED Tx.
- 2 Mo. post- the 18th LED Tx.

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J..of Neurotrauma*

a) **Sample LED cluster head**, showing the side that was applied to the skin.

The "X" shows location of the 9 red diodes embedded within the LED cluster head.

The 52 near-infrared (NIR) diodes surrounding the "X" are not visible to the eye.

Each red/NIR LED cluster head had a 2.1-inch diameter, and the total power output was 500mW.


b) **View of subject being treated**, and example of three LED placement areas on the head from Set A (1st, 2nd and 3rd LED placements described in Table 2).

During each treatment, 6 LED cluster heads were used simultaneously ***(13 Joules/cm$^2$, 10 minutes per LED placement***).

Immediately after treatment using the Set A LED placements, the LED cluster heads were moved to other placements on the scalp (Set B) for 10 minutes.

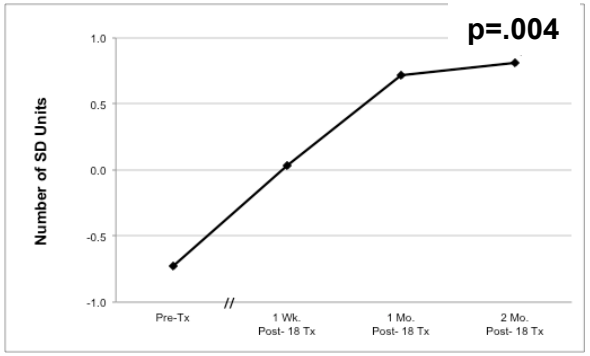
The LED cluster heads were held in place with a soft, nylon cap. ***Total treatment time per visit was 20 minutes***; it was painless, noninvasive and nonthermal.

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J..of Neurotrauma*

# Results

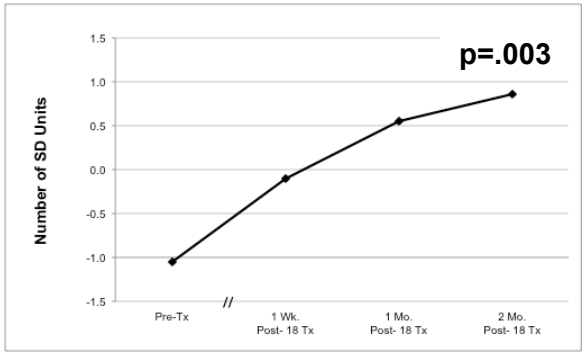
A

Stroop Test for Executive Function:
Trial 3, Inhibition



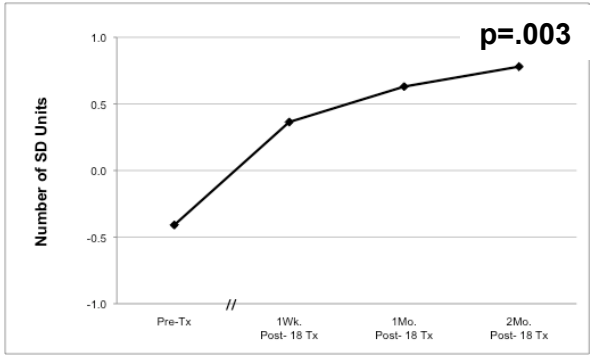

B

Stroop Test for Executive Function:
Trial 4, Inhibition Switching



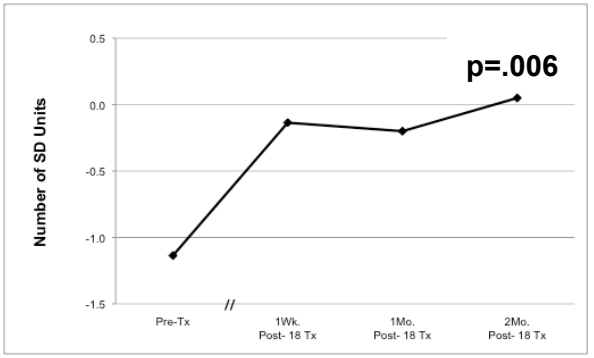

C

California Verbal Learning Test-II:
Total Trials 1-5



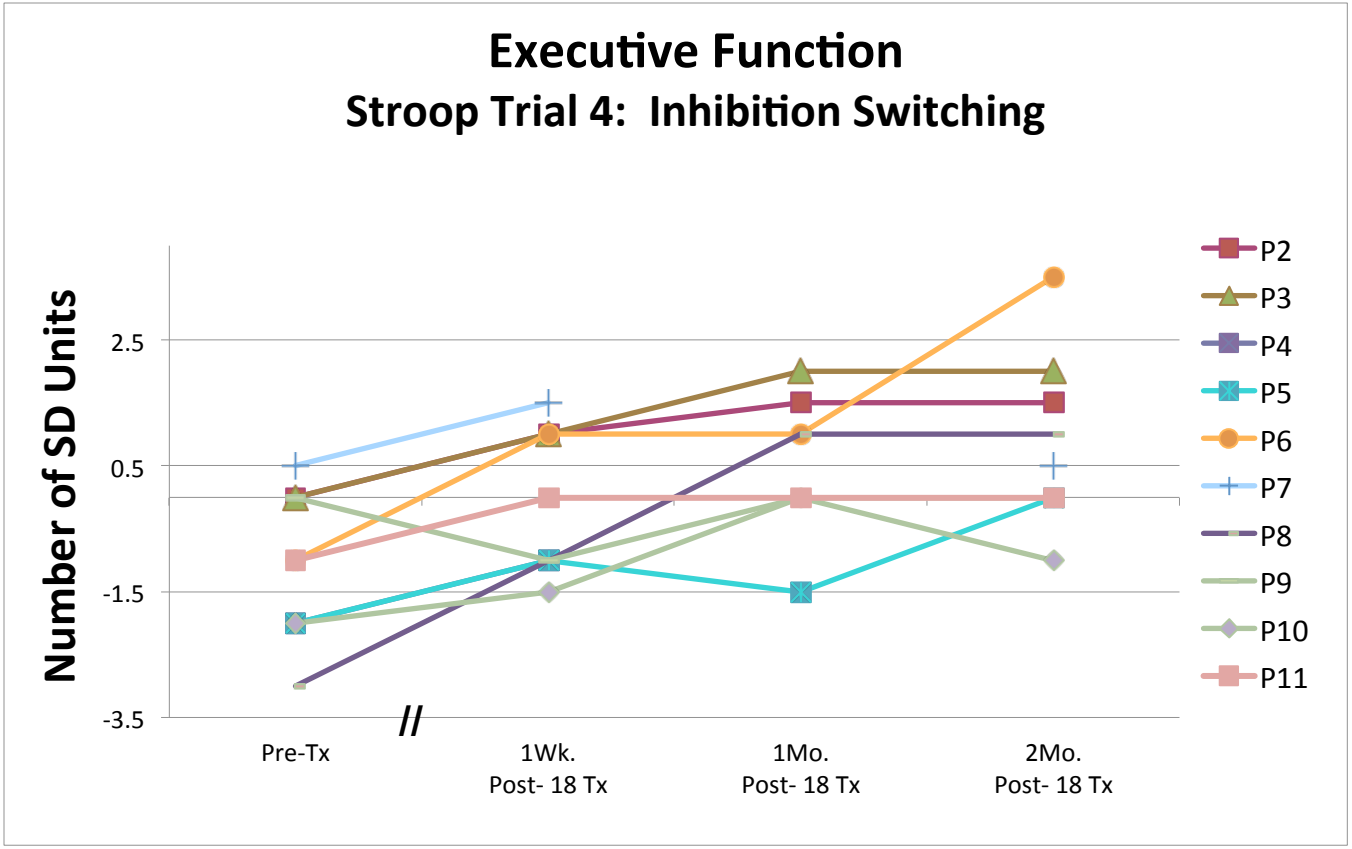

D

California Verbal Learning Test-II:
Long Delay Free Recall




Graphs showing a **significant linear trend over time** for the effect of LED treatments on specific neuropsychological tests: A) Stroop Test for Executive Function, Trial 3 inhibition **(p=.004)**; B) Stroop, Trial 4 inhibition switching **(p=.003)**; C) California Verbal Learning Test (CVLT)-II, Total Trials 1-5 **(p=.003)**; and D) CVLT-II, Long Delay Free Recall **(p=.006**).

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J..of Neurotrauma*

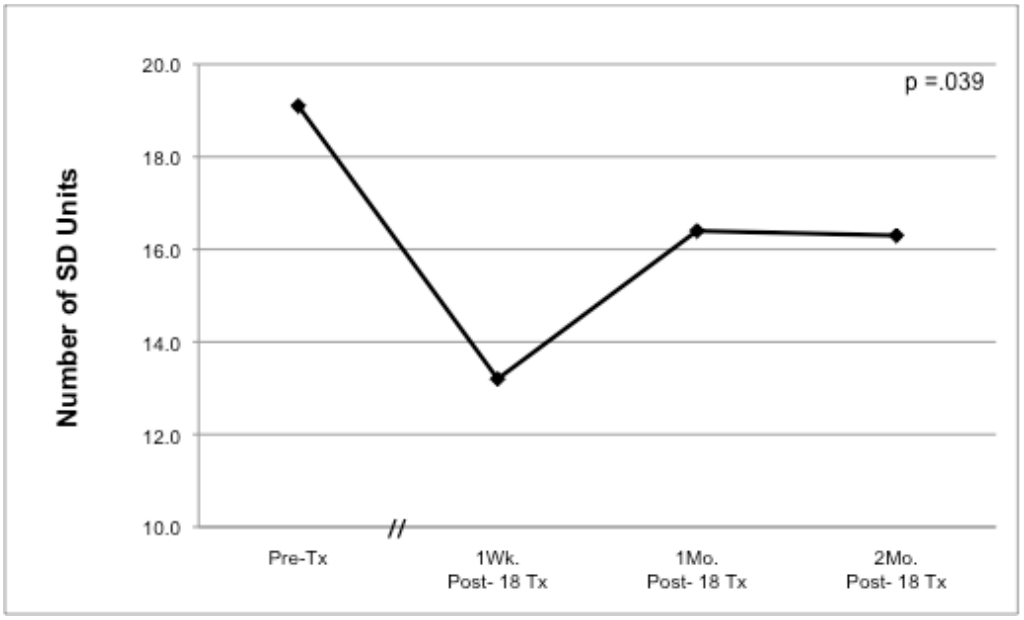



**Executive Function, Stroop Trial 4 inhibition switching:** Graph showing pre- and post- LED test scores for each participant (SD adjusted for age and education).

**P8 was active duty Military with IED blast, TBI (and other mTBIs)** 3 years before entry. He was treated with transcranial LED and then returned for further evaluation by his Unit.

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J. Neurotrauma*

# Beck Depression Inventory-II




**Depression significantly decreased from Baseline to Post- 1Wk.** ($p<0.045$).

Then, it rose slightly and reached asymptote (but less than at Baseline), similar to Schiffer et al. (2009).

Subjects may need additional LED Tx.

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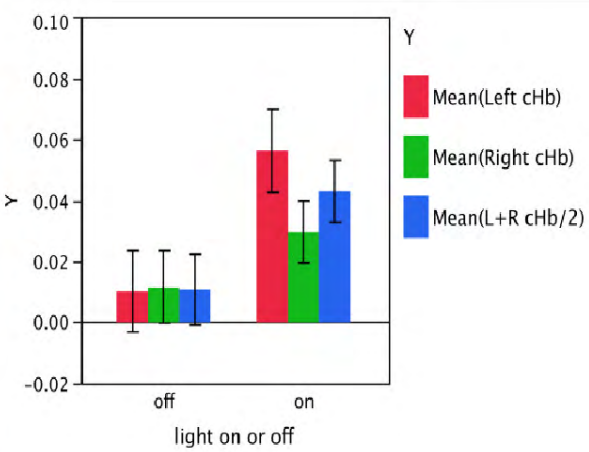
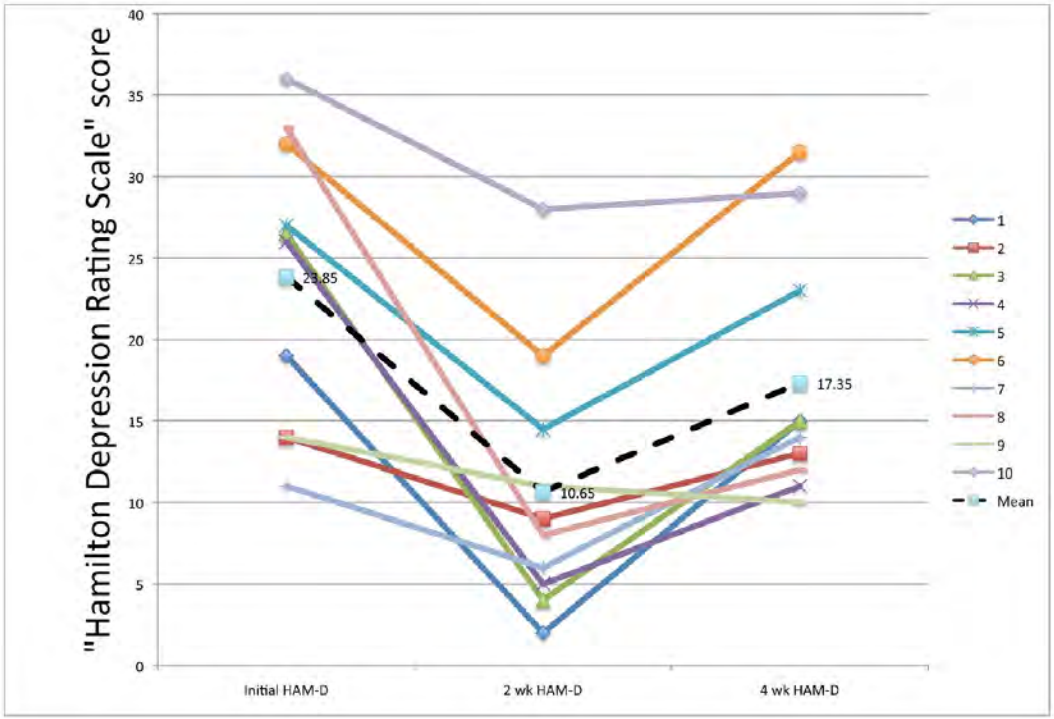



**Increase in regional cerebral blood flow (rCBF)** at left and right frontal poles, Post-Transcranial NIR LED to **treat major depression** (n=10).

LED cluster head is shown at F3 (corner of left forehead).The rCBF was measured with NIR spectroscopy (INVOS system, shown with electrodes placed on the L and R forehead areas).

Schiffer, et al., 2009

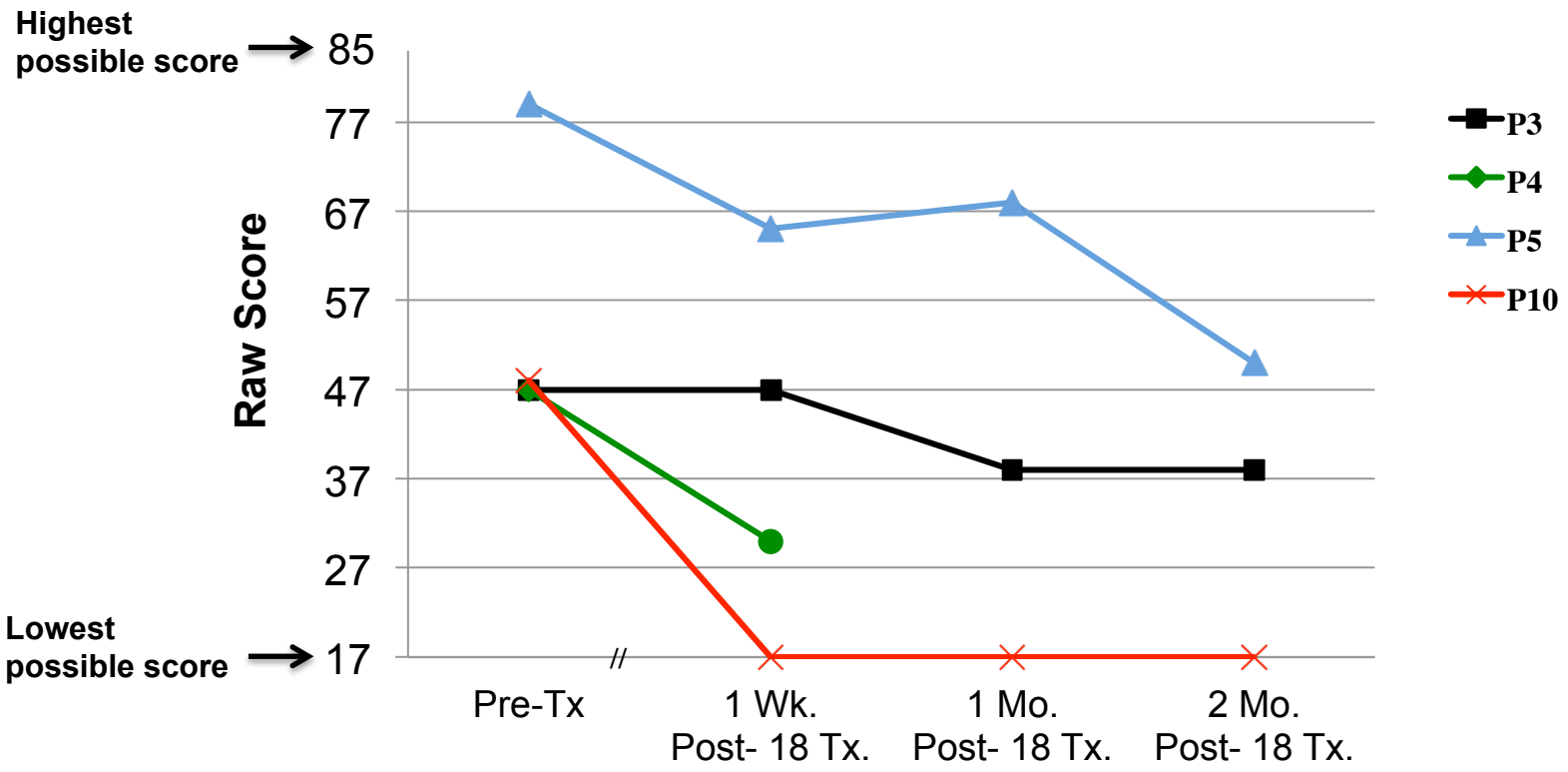



**Significantly (p=.001) reduced Depression scores** (Hamilton D Rating Scale) at +2 weeks after one transcranial, NIR LED treatment to F3, F4 frontal areas (10-20 EEG system) for 4 minutes to each area, in 10 severe, chronic depression cases. A high score suggests more depression. Fifteen or above is suggestive of a clinical depression, and below 8 is suggestive of a remission. The legend numbers correspond to patient numbers.

Schiffer, Johnston, ...Hamblin, 2009

# *Spaulding Rehabilitation Hospital*, Transcranial LED Tx mTBI Study: Pre- and Post- LED Tx. Data

**PTSD Checklist, PCL-Civilian** **Only 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, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J. Neurotrauma*

- **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, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J. Neurotrauma*

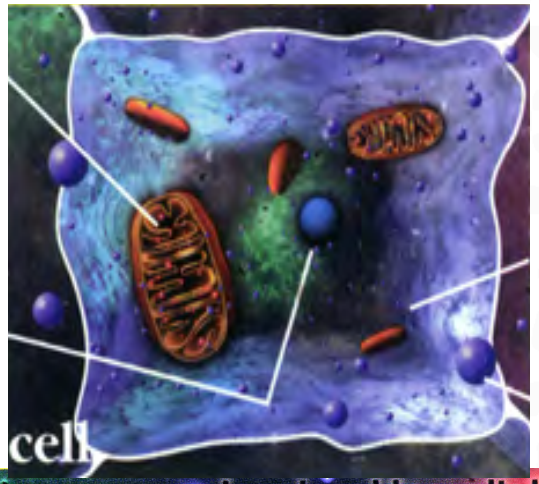
# Possible Mechanisms of Action for LED Treatments

Specific mechanisms, unknown - some possible mechanisms include:

## 1. Stimulation of mitochondria with increase in ATP production.

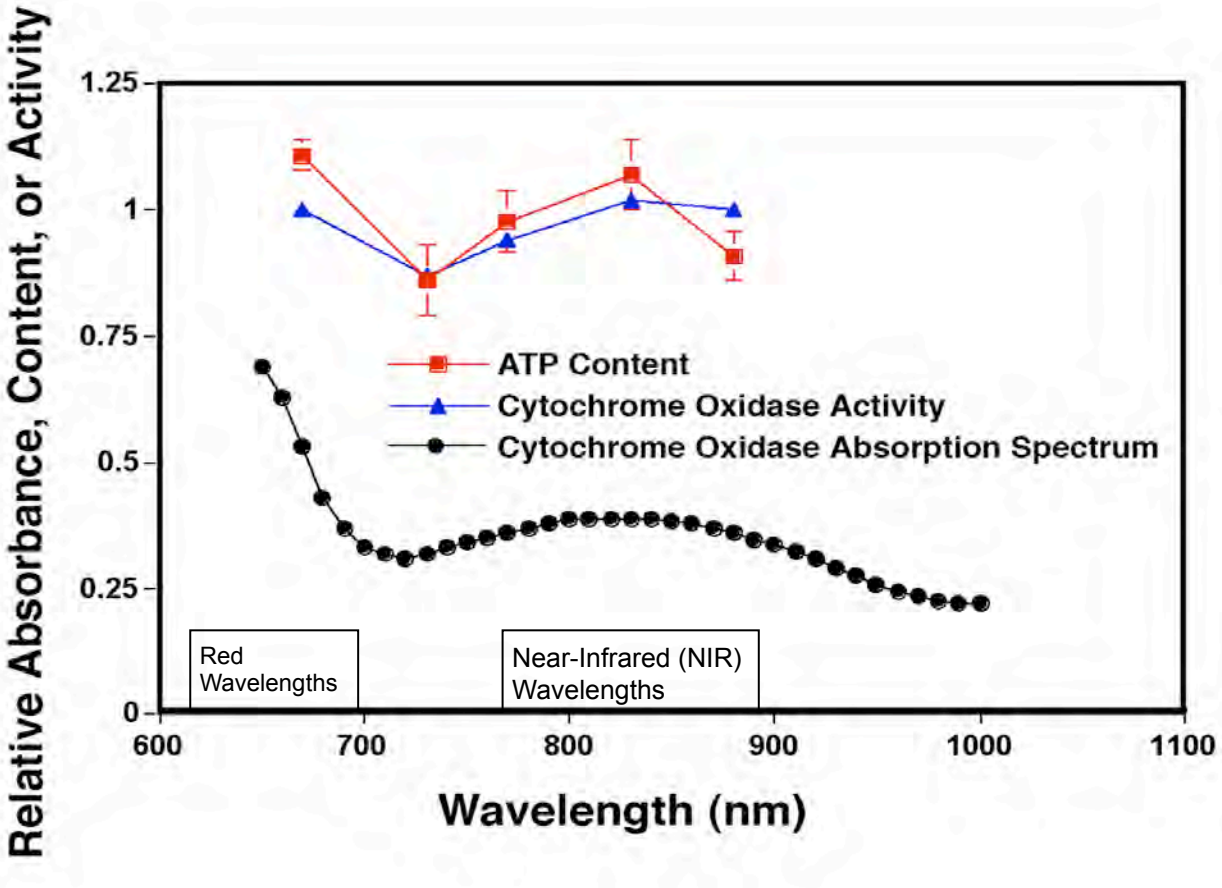
Cytochrome c oxidase, in last complex of the electron transport chain in **mitochondria,** maximally absorbs light in wavelengths of ***red and near infra-red (NIR)***.

***Increases ATP production*** **(improving cellular respiration and oxygenation).** Karu, 1995, 1999





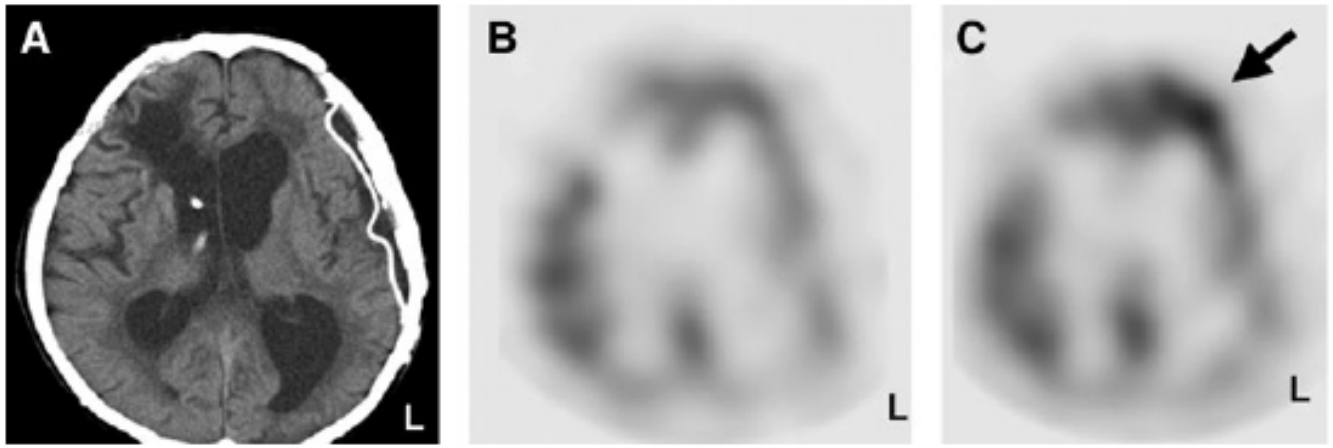
Felix Kramer, Zurich Switzerland




Wong-Riley et al., J. Biological Chemistry, 2005

# Possible Mechanisms for Transcranial LED Effects, cont'd

2. **Nitric Oxide released** (from hypoxic cells) to outside the cell wall, **promoting vasodilation**.




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

**B)** SPECT scan also at 7 Mo.; pre- transcranial LED therapy.

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

Nawashiro et al., 2011

# Possible Mechanisms for Transcranial LED Effects, cont'd

## 3. Increase in Melatonin, and Improved Sleep.

Zhao et al., 2012

*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

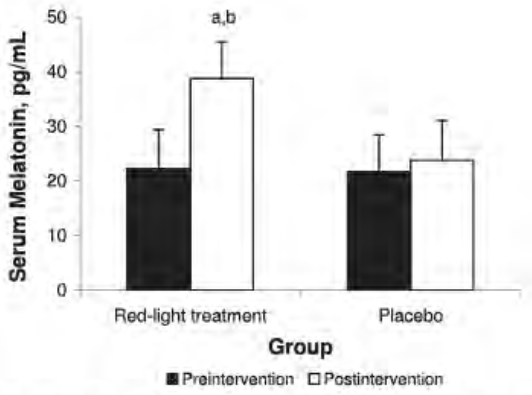



**Figure 3. Serum levels of melatonin for the red-light treatment and placebo groups. [a] Indicates different from preintervention ($P < .01$). [b] Indicates difference between groups at postintervention ($P < .01$).**

# Possible Mechanisms for Transcranial LED Effects, cont'd

## Importance of …Improved Sleep.

Xie, et al…Nedergaard, 2013, *Science*

[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.

*These authors contributed equally to this work.
†Corresponding author. E-mail: nedergaard@urmc.rochester.edu

# Sleep Drives Metabolite Clearance from the Adult Brain

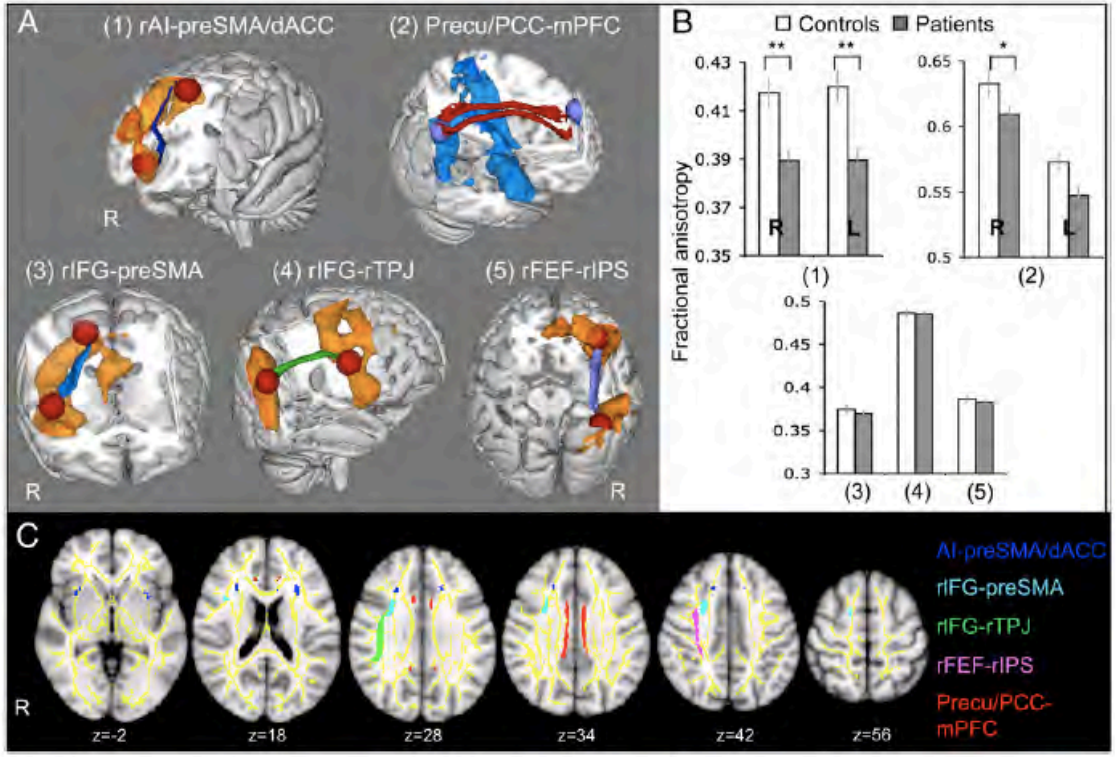
Lulu Xie,[1*] Hongyi Kang,[1*] Qiwu Xu,[1] Michael J. Chen,[1] Yonghong Liao,[1] Meenakshisundaram Thiyagarajan,[1] John O'Donnell,[1] Daniel J. Christensen,[1] Charles Nicholson,[2] Jeffrey J. Iliff,[1] Takahiro Takano,[1] Rashid Deane,[1] Maiken Nedergaard[1]†

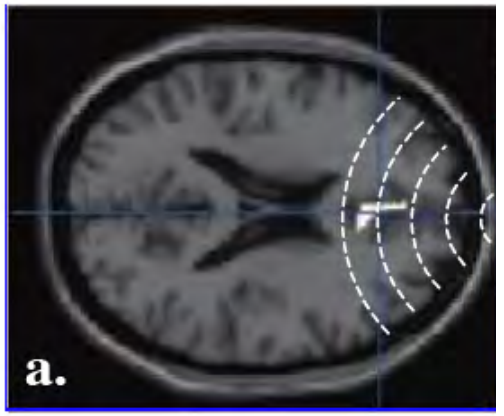
The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural 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.

# Possible Mechanisms for Transcranial LED Effects, cont'd

## 4. Improved 'functional connectivity' in the brain, in Default Mode Network (DMN).

Transcranial LED placement at center front hairline (right column, a., b.), could promote improved function in the ***ventral mesial pre-frontal cortex (mPFC) node of the DMN. This anterior, midline LED placement, plus the posterior, midline LED placement, Precuneus/PCC node, could improve functional connectivity of the Default Mode Network (DMN).*** DMN shown as see horizontal red lines, below. Bonnelle et al, 2012 Fig. 2, A(2)



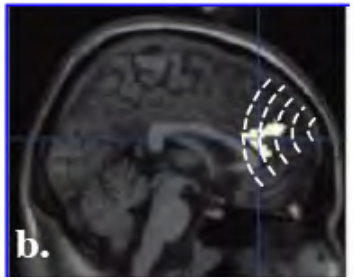




**Fig. 2.** Comparison of white matter structure between patients and controls. (*A* and *C*) White matter tracts of interest are represented in 3D on the MNI-152 T1 1-mm brain 3D template (*A*) and in 2D on axial MNI-152 T1 1-mm brain views, overlaid on tract-based spatial statistics (TBSS) white matter skeleton (yellow) (*C*). (*A*) The resulting probabilistic tractography tracts are shown for the connections between the rAI and the preSMA/dACC (dark blue) (1), the precu/PCC and vmPFC bilaterally (red) (2), the rIFG and the preSMA (light blue) (3), the rIFG and the right TPJ (rTPJ) (green; 4) and the rFEF and rIPS (lilac/pink; 5). Orange and blue areas represent the mean BOLD signal change in patients and controls for the contrasts StC > Go and Go > StC, respectively. (*B*) The bar charts show FA ± SEM within each tract compared between TBI patients (gray) and 30 age-matched controls (white). R, right; L, left. $*P < 0.05$; $**P < 0.005$.

Bonnelle et al. 2012, *PNAS.* "Salience network integrity predicts **default mode network function after TBI."**

Naeser, Zafonte, Krengel, Martin, Frazier, Hamblin, Knight, Meehan, Baker. 2014, *J. Neurotrauma*