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

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Laser Acupuncture to Treat Paralysis in Stroke

Personal Observation
Naeser MA. 1985
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.

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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/cm² per point

Step 4) Place the tip of the laser directly on each acupuncture point. With red-beam laser treat each point at 4 Joules/cm² - Hrt 8, PC 8, Lu 9, Hrt 7. See special instructions below for *PC7.

Step 3) Place the tip of the laser directly on each acupuncture point. With red-beam laser treat each point at 4 Joules/cm² - Lu 11, LI 1, PC 9, TW 1, Hrt 9, SI 1.

Note: For stroke patients
Place the circular electrode over Hrt 8,
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.
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**.
Improved Cognitive Function After Transcranial, Light-Emitting Diode Treatments in Chronic, Traumatic Brain Injury: Two Case Reports

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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/cm²; 13.3 J/cm² at scalp (estimated 0.4 J/cm² 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 cm²

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/cm² (+20%)
1 J/cm² = 45 sec

10 min per area; 13.3 J/cm² per area (0.4 J/cm² 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, Anderson, Madden, 1981

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011
Red areas show low cortical activation on functional MRI in chronic, traumatic brain injury cases (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.

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
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.

*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.

Naeser, Saltmarche, Krengel, Hamblin, Knight. 2011
Right Foot

4 Joules/cm² on each acupuncture point

Sp 1  Liv 1  St 45  GB 44  Liv 3  Bl 67

(Circular Electrode)

(For the left foot, the point locations are anatomically identical.)

The second circular electrode is placed on the sole of the foot opposite to Liv 3 (near Ki 1).

Naeser Laser FOOT Treatment Program

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
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


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

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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/cm²) was applied for 10 min to each of 11 scalp placements (13 J/cm²). 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**  
  (MVA, Sports-related, IED blast TBI)
- 6 / 11 were >2 years post- TBI  
- Participants had one or more **non-penetrating 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.
4) **Stroop Test for Executive Function** (Delis, Kaplan, Kramer, 2001). Trials 1 – 4.
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/cm² applied at each scalp/skin LED placement area

Estimated 0.4 J/cm² 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.
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/cm², 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.
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).
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.

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.

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
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

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

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.

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
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

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

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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
Importance of Improved Sleep.

Xie, et al...Nedergaard, 2013, Science

Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen, Yonghong Liao, Meenakshisundaram Thiagarajan, John O'Donnell, Daniel J. Christensen, Charles Nicholson, Jeffrey J. Iliff, Takahiro Takano, Rashid Deane, Maiken Nedergaard

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.
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)