Transcranial, Near-infrared Photobiomodulation to Improve Cognition in Two, Retired Professional Football Players Possibly Developing CTE

International Brain Injury Association (IBIA), Toronto, March 2019

Naeser MA[1,2*], Martin PI[1,2] , Ho MD[1], Krengel MH[1,2], Bogdanova Y[1,3], Knight JA[1,3,4], Fedoruk AE[1], Hamblin MR[5,6,7], Koo BB[8]

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Figures from the Poster, are included here.

Case 1: Retired CFL Player

- 65 Yr. PhD in exercise physiology, after football career (1980)
- Professor, Graduate Chair and Graduate Coordinator, and National Board-Certified Teacher
- Sports History: Pop Warner (age 10),

  Middle Linebacker in high school and college 1970-1974, and CFL, 1.5 years.

  700+ tackles in high school, college and professional career. Thousands of subconcussive hits.

  "Greatest Defensive Player in History" for BYU,

  2011.

  And #36 of 120, by the Bleacher Report.
- Estimated 4-10 Yr. history of cognitive decline, diagnosed by Neuropsychologist
- At entry: Scored at least 2 SD below average, on one standardized neuropsychological test.

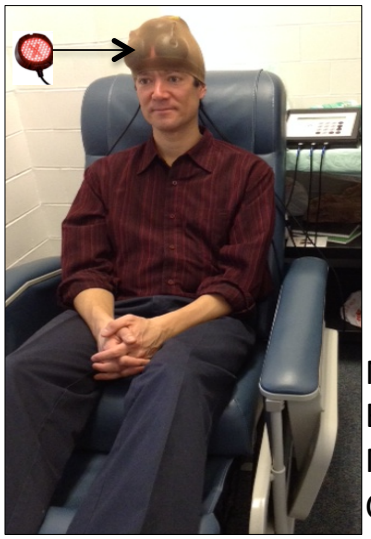
First, Retired Professional Football Player, 65 Yr M

First, Transcranial LED Series:

In-Office, Transcranial LED Therapy

In-Office t-LED Treatment Series: 18 sessions (3x/Wk. for 6 Wks.)

- Non-thermal, 500mW LED device, 22.2 mW/cm^2 FDA, non-significant risk, MedX Health.



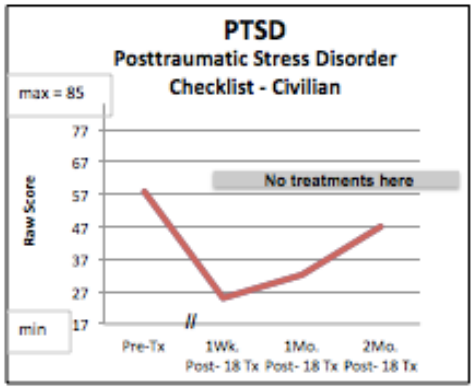
Naeser Lab Boston VA Medical Center

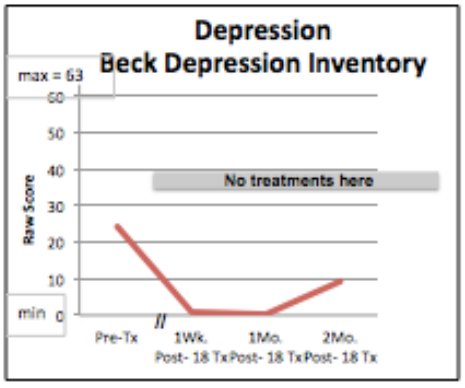
- 9 red 633nm diodes, and 52 near-infrared (NIR) 870nm diodes, in each cluster head

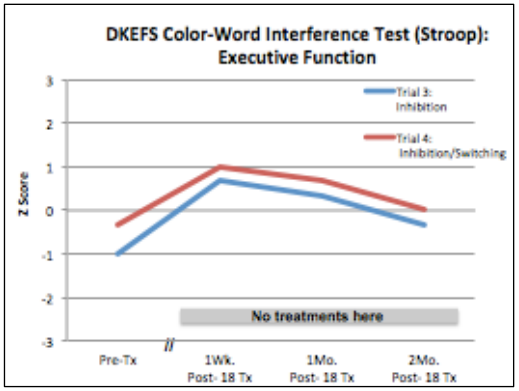
- Six (2-inch diameter) cluster heads used simultaneously; 2 placement sets; 20 min per set

- 26 J/cm^2 per placement Painless, noninvasive, no negative side effects, or adverse events.

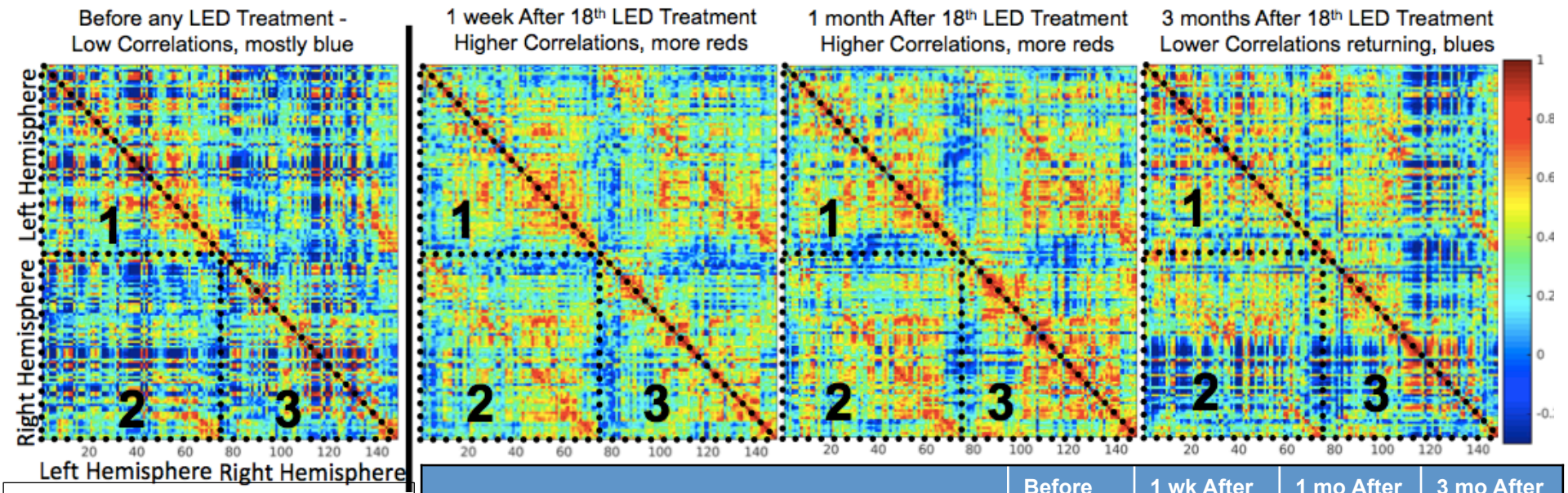
First Football Player Results: *Improved Behavior*, and *Functional Connectivity* on MRI Scans at 1 Wk and at 1 Mo *after 18 LED Treatments, In-Office.* But *scores declined, 2 months later.*







Resting-State Functional-Connectivity MRI Scans - Correlation Matrices, Pre- and Post- Transcranial-LED



1. Within Left Hemisphere Correlations
2. Left to Right Hemisphere Correlations
3. Within Right Hemisphere Correlations

	Before	1 wk After	1 mo After	3 mo After
Number of Correlations in 1, 2 and 3 > +0.60 (%)	1127 (10)	1243 (11)	1693 (16)	1268 (12)
Number of Correlations in 1, 2 and 3 > +0.40-0.59 (%)	2082 (19)	2860 (26)	2978 (27)	2679 (25)

Boston University, Chronic Traumatic Encephalopathy Conference, Boston, MA - Nov. 2017

"Significant Improvements in Cognition, Mood and fMRI scans in a Retired, Professional Football Player after Intervention with Photobiomodulation LED Therapy to the Brain: Case Report" Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Hamblin MR, Koo BB, Naeser MA mnaeser@bu.edu Boston VA Medical Center

Previous, Transcranial LED Study to Treat Chronic, mTBI

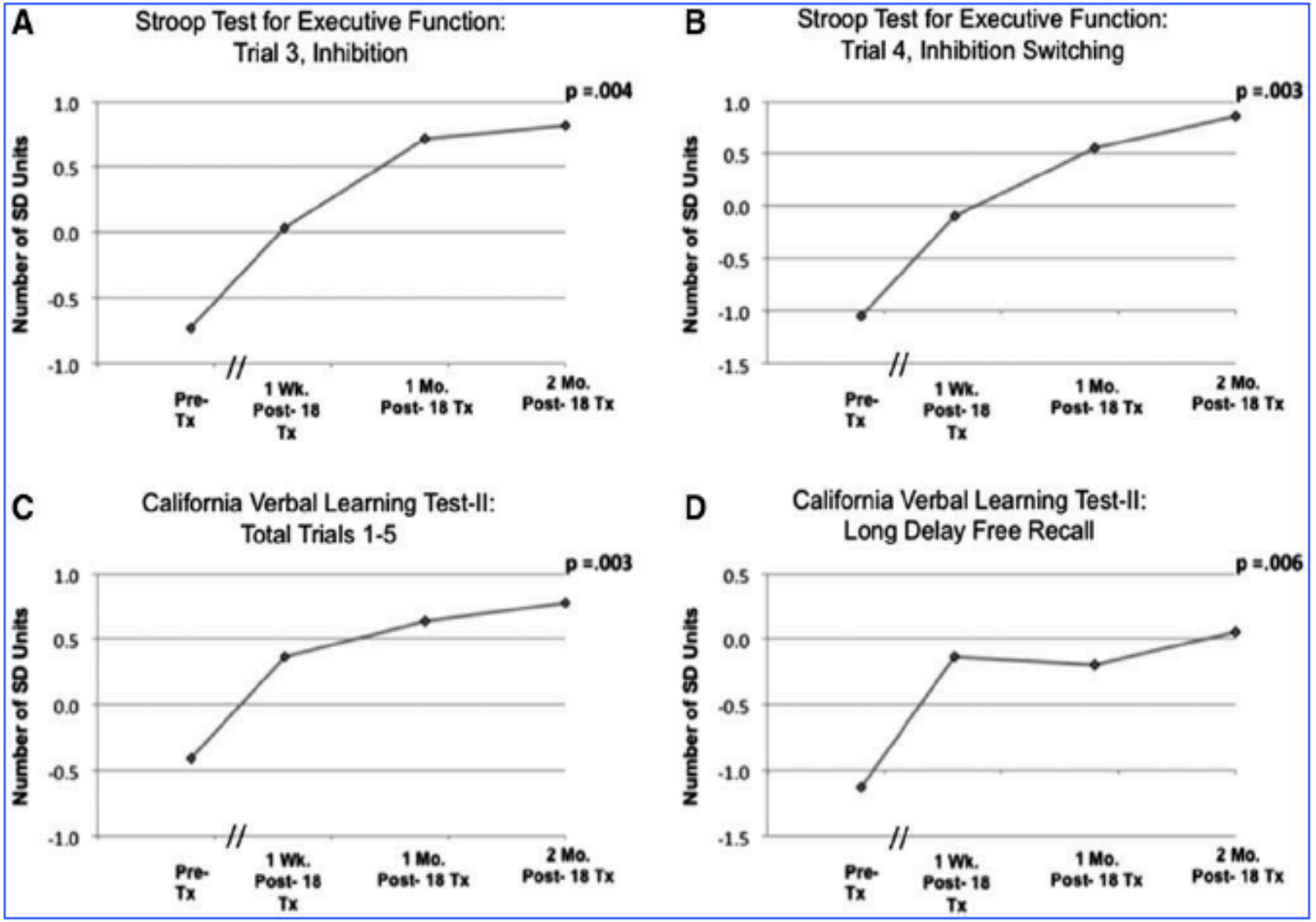
Naeser, Zafonte et al., 2014

Results

11 mTBI Cases

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

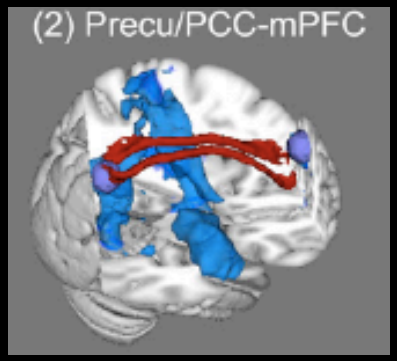
MedX Health, Red/NIR.



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

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

First Football Player - 2nd Series, *At-Home*
Transcranial LED Treatments.
At *3 Mo. after In-Office*
Treatment Series -
the Football Player purchased his own:
Transcranial
plus
Intranasal LED Equipment – Neuro Gamma LED Device



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 CNS disorders.

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

EMBER 2016 | VOL 540 | NATURE | 207

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

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.

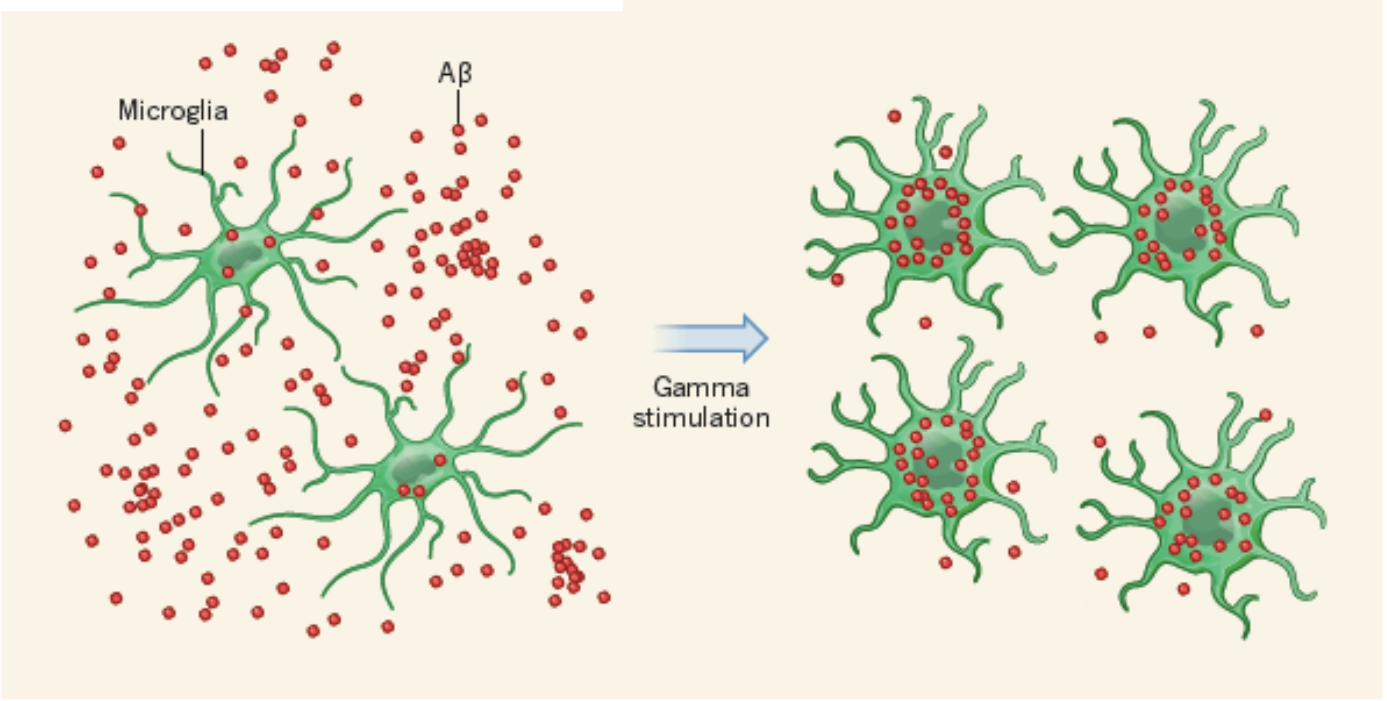
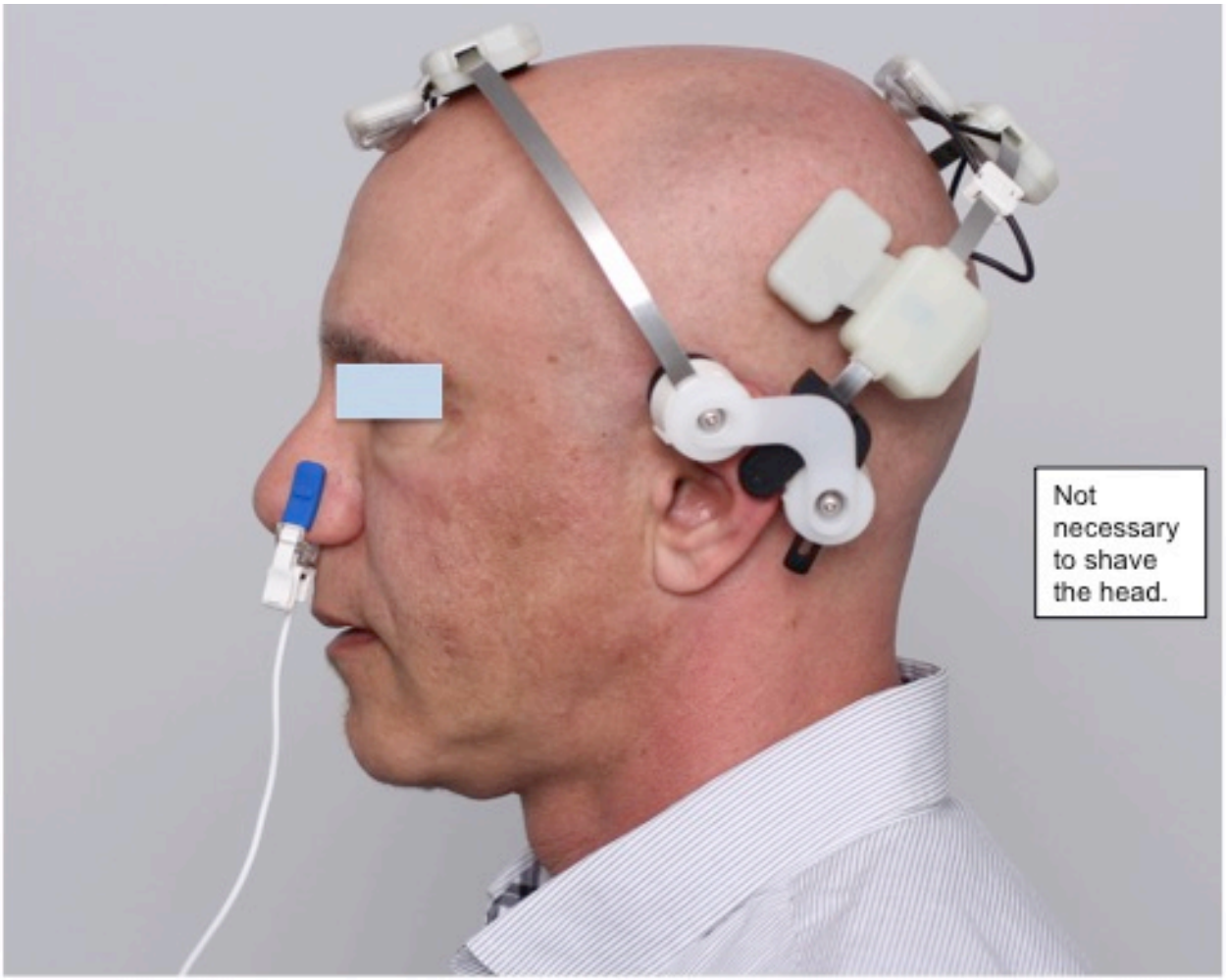


Figure 1 | Gamma oscillations stimulate the clearance of amyloid-β protein deposits. Abnormal aggregation of amyloid-β (Aβ) protein in the brain is associated with Alzheimer's disease. Aβ aggregates might accumulate and promote neurodegeneration in part because immune cells called microglia cannot effectively 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.

General Wellness:

No Medical Claims Made



Vielight Neuro Gamma LED Device.

Designed to treat dementia, especially where build-up of **Amyloid-Beta** and **Tau** are likely.

Is within FDA new Category, low-risk devices: "General Wellness"

Vielight **Neuro Gamma LED device,** NIR 810nm diodes, pulsed at **40 Hz,** (based on Iaccarino et al., 2016). The smaller, flat rectangles each 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, 75 mW); **Precuneus** (midline, high parietal placement half-way between occipital protuberance and vertex, 100 mW; Left **Angular Gyrus** (and Right, not shown) placements, 100 mW (posterior/superior to each ear); (**Hippocampus**)/via olfactory bulb - nose-clip placement, 25 mW.

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

Vielight Toronto, Canada

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)
Red wavelengths have anti-inflammatory effects and
beneficial effect on the RBCs (Mi et al., 2004a; and 2004b).

Can be used at home. Never heats up, very safe, and sold over-the-counter.

LewLim@vielight.com

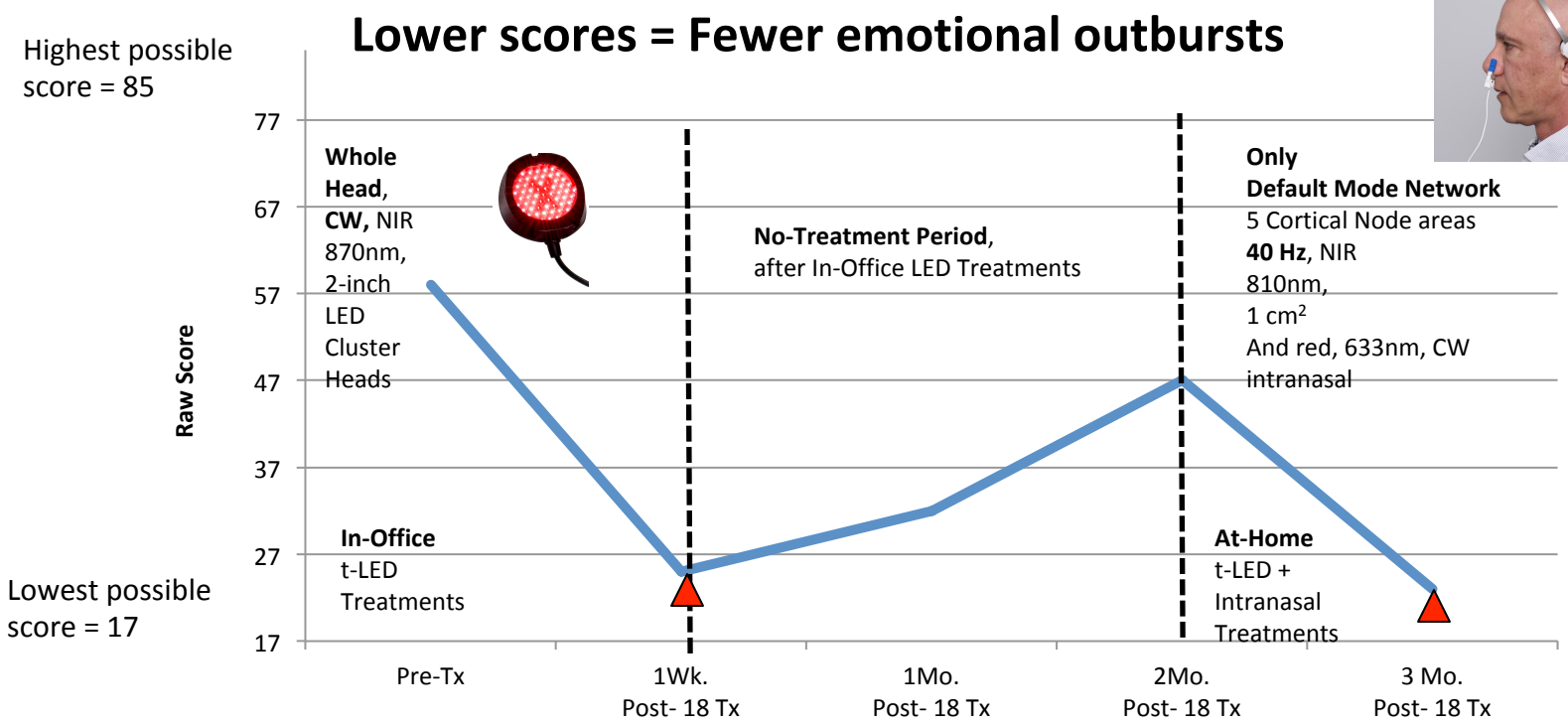
No medical claims are made.

Naeser MA, Martin PI, Krengel MH, Ho MD, Yee MK, Knight JA, Hamblin MR, Bogdanova Y. Boston VA Medical Center

First Football Player - Results for *In-Office* and *At-Home LEDs*:

Emotional Outbursts, PTSD

Post-traumatic Stress Disorder Checklist - Civilian



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)

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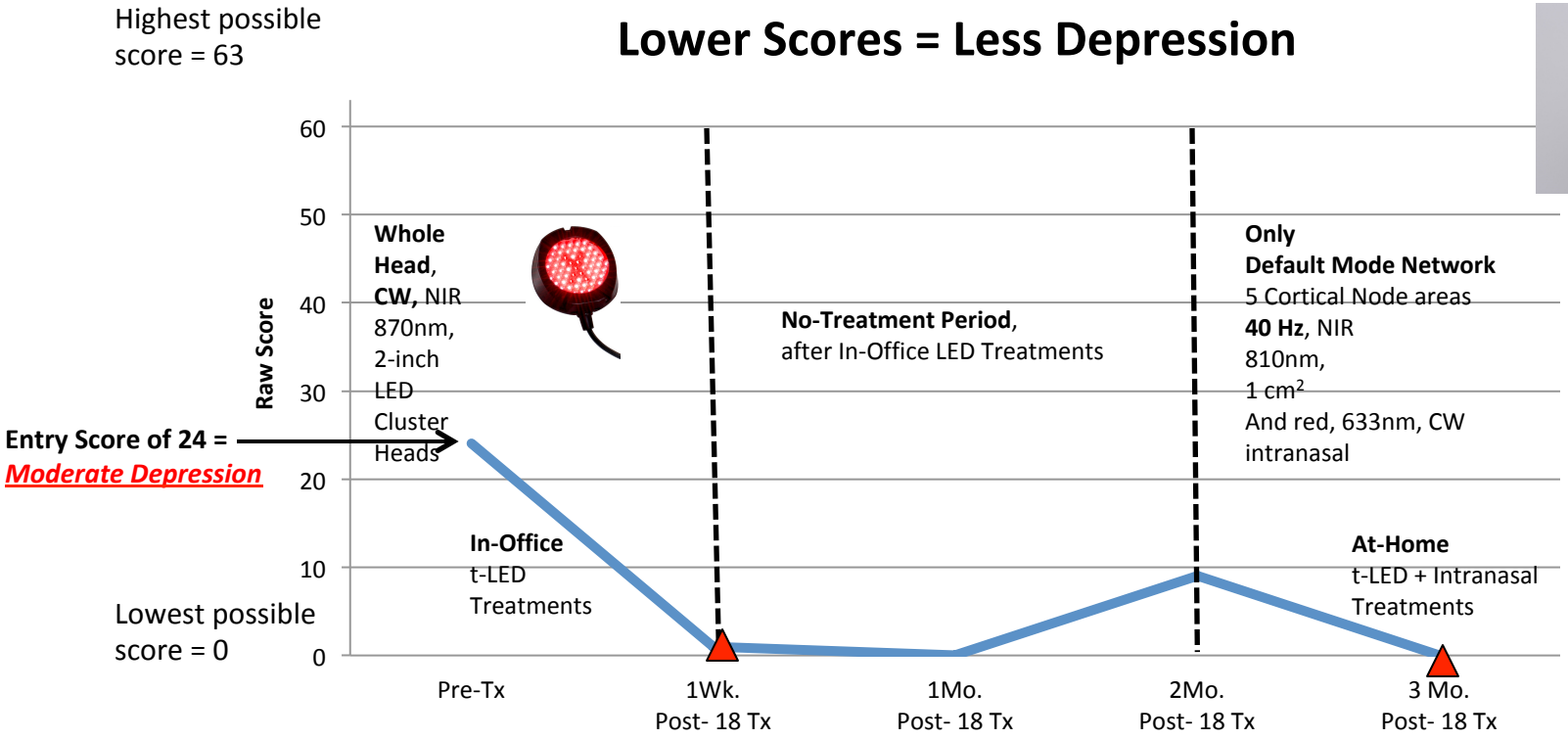
First Football Player -

Beck Depression Inventory - II



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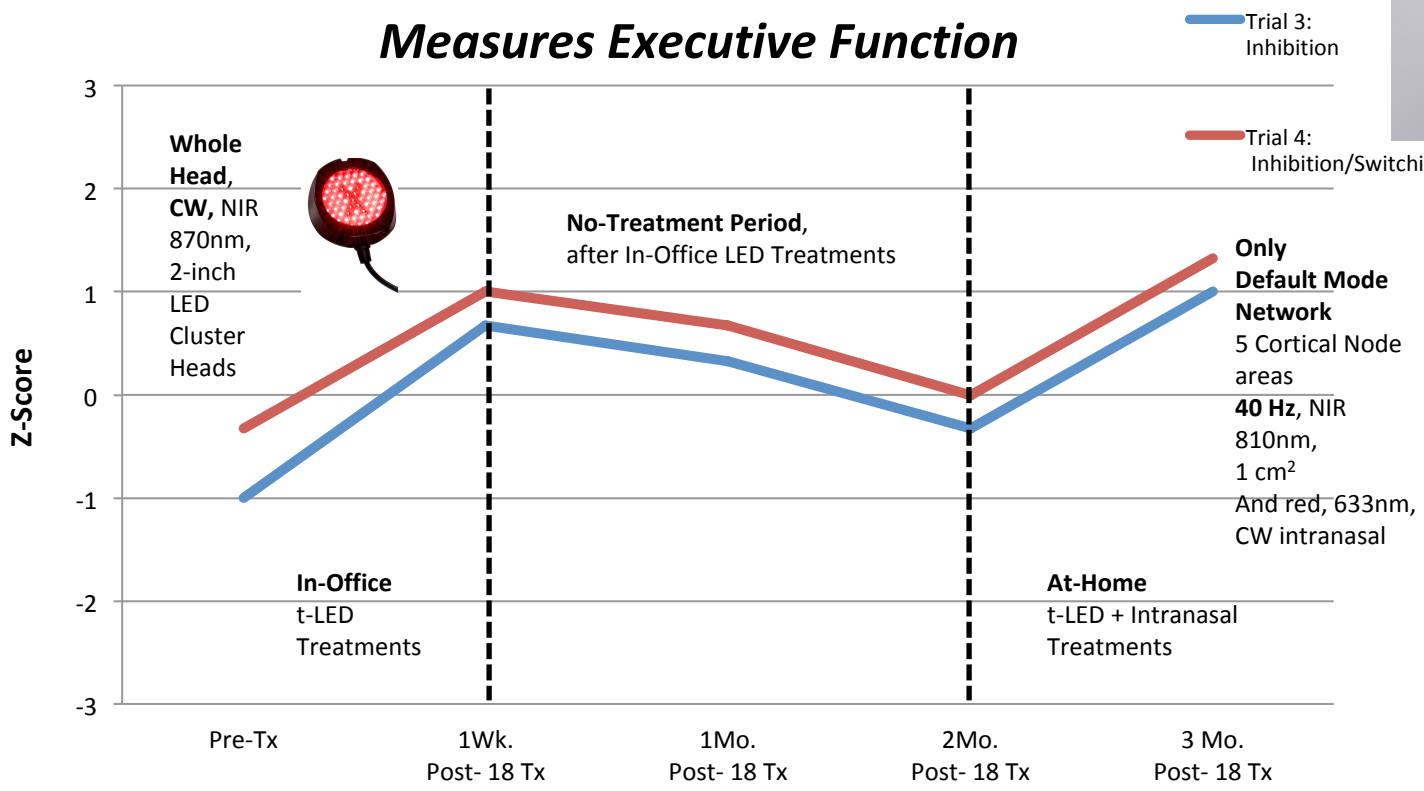
First Football Player -

D-KEFS, Color-Word Interference Test (Stroop)



Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Fedoruk, Hamblin, Koo. IBIA, Toronto, March 2019

First Football Player -

Sleep: Global Score

Pittsburgh Sleep Quality Index

Lower Scores = Better Sleep

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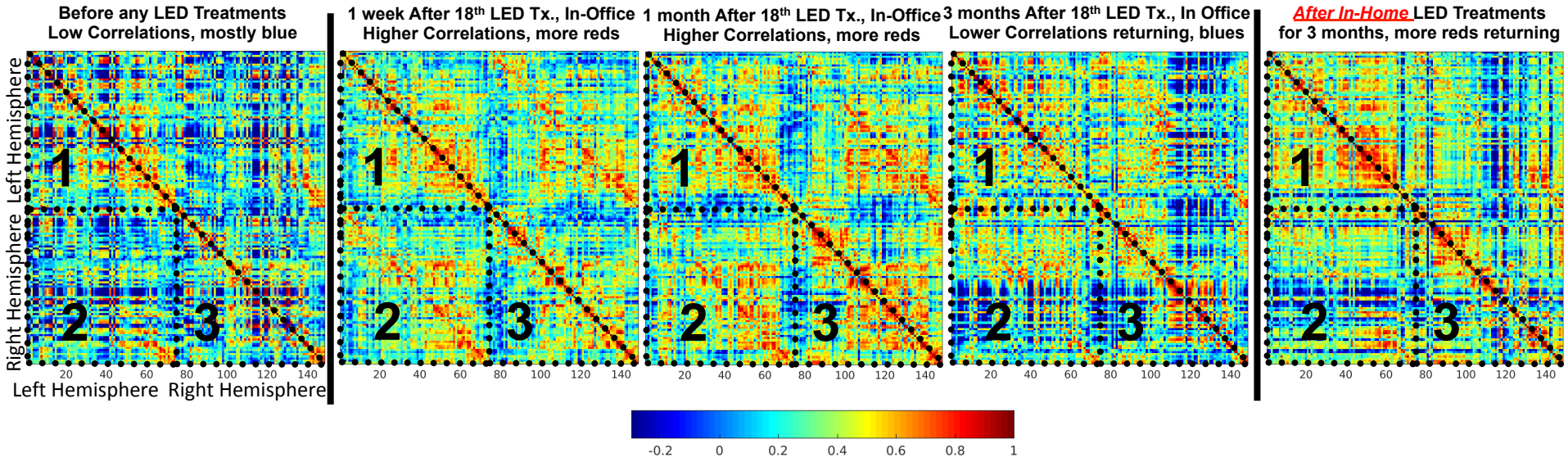
First Football Player - *Improved Functional Connectivity on MRI Scans* after *In-Office* and later, *At-Home* Transcranial LED treatments

Correlation Matrices show that Continued, LED Home Treatments are likely Necessary.



1. Within Left Hemisphere Correlations
2. Left to Right Hemisphere Correlations
3. Within Right Hemisphere Correlations

	Before LED Tx.	1 wk After In-Office LED	1 mo After In-Office LED	3 mo After In-Office LED	After 3 mo In-Home LED
Number of correlations in 1, 2 and 3 > +0.60 (%)	1127 (10)	1243 (11)	1693 (16)	1268 (12)	1443 (13)
Number of correlations in 1, 2 and 3 > +0.40 to 0.59 (%)	2082 (19)	2860 (26)	2978 (27)	2679 (25)	2918 (27)

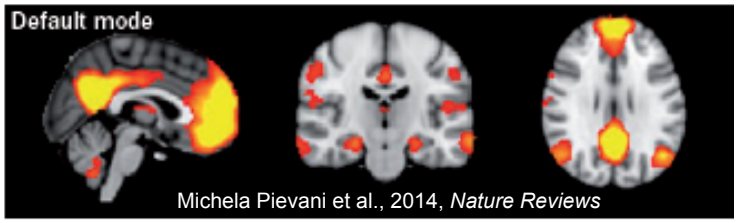
Extension of Poster presented at: Boston University, Chronic Traumatic Encephalopathy (CTE) Conference, Nov. 2017
"Significant Improvements in Cognition, Mood and fMRI scans in a Retired, Professional Football Player after Intervention with Photobiomodulation LED Therapy to the Brain: Case Report" Martin PI, Ho MD, Krengel MH, Bogdanova Y, Knight JA, Hamblin MR, Koo BB, Naeser MA.

Poster for BU CTE Conference. Oct. 2018

LED Research Lab to Treat TBI and possible CTE, Margaret Naeser, PhD, VA Boston Healthcare System, mnaeser@bu.edu.

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

Dementia



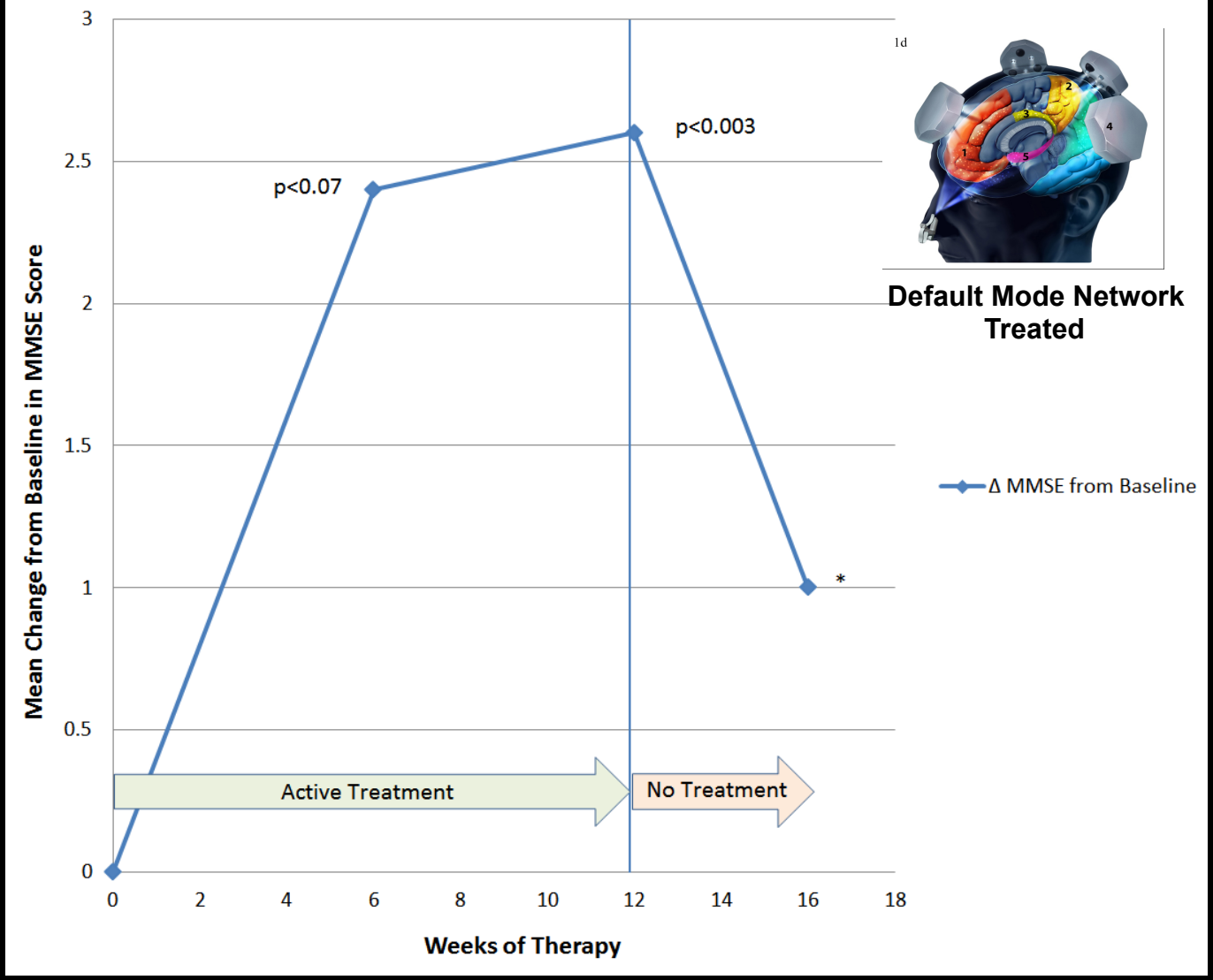
Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report

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

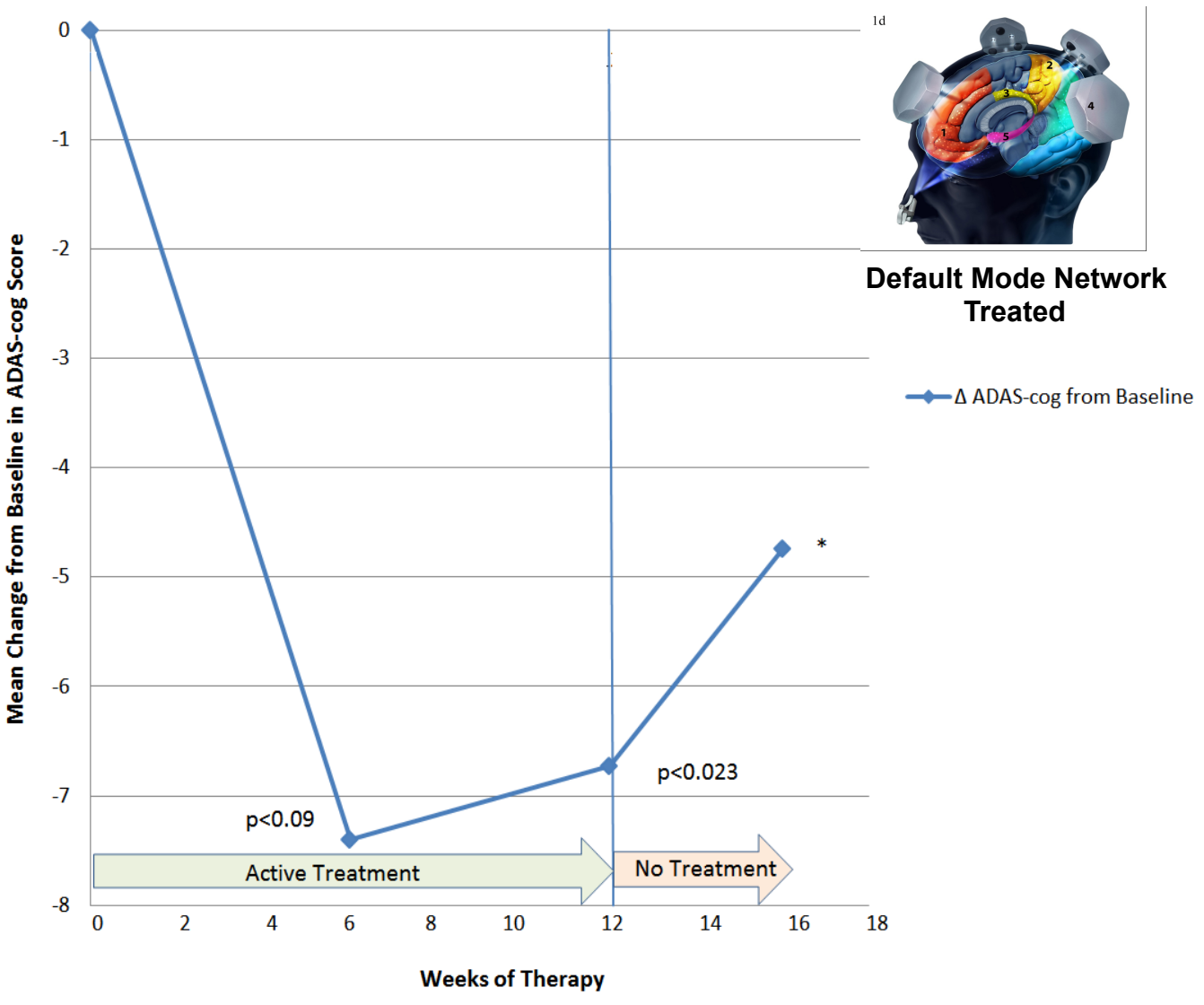


RESULTS: Mean change from baseline on Mini Mental State Exam (MMSE) scores.

Higher numbers indicate better cognition on this test.

Saltmarche, Naeser, Ho, Hamblin, Lim, 2017, Photomedicine and Laser Surgery, PMLS

5 Dementia Cases



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

Lower numbers indicate better cognition on this test.

Saltmarche, Naeser, Ho, Hamblin, Lim, 2017, Photomedicine and Laser Surgery, PMLS

The Vielight, NEURO headframe device (Gamma, 40 Hz; or Alpha, 10 Hz) targets near-infrared, 810nm, LEDs over each cortical node of the Default Mode Network, Steps 1. – 5. The clear lens LED must touch the skin. Part the hair under each LED.

Reference Point A, at top, center of head, located straight up, from tip of each ear. Follow the vertical, dotted yellow line.

1. Front Frame:
Clear lens LED placement is at ***top*** center of forehead, ***at*** center front hairline.

2. Back Frame:
Clear lens LED placement, for center back LED is ***located halfway between Reference Points A and B***. Follow dotted red line.

Reference Point B, where the bone, at the back of the head sticks out the most (the occipital protuberance).

5. Noseclip placement:
Gently place the noseclip, clear lens diode, into one nostril. Shift to the other nostril, on the next treatment, etc.

3. and 4. Back Frame:
Left side, **3.** and Right side, **4.** Placements are located above, and at about a 45 degree angle, behind each ear. These will fall into place, after the clear lens LED, center back placement is correctly positioned.

Approximate Cortical Target Areas:

1. **Mesial Prefrontal Cortex**
2. **Precuneus**
3. **L Intraparietal sulcus/ angular gyrus**
4. **R Intraparietal sulcus/ angular gyrus**
5. **Orbito-frontal, olfactory bulbs, connecting to hippocampal areas.**

Naeser, Martin, Ho Lab. June 24, 2019

Case 2: Retired NFL Player

- 57 Yr. M, College degree
- Sports History: High school, college, and *Cornerback* in NFL 1983-1991.
- History of Depression, on medication
- Repetitive head injuries, estimated thousands of subconcussive hits.
- 15 surgeries related to football injuries; *At entry 3 pain medications, including 2 narcotics*
- At entry: Scored at least 2 SD below average, on one standardized neuropsychological test.

Case 2: In-Office t-LED Treatment series: Thor Helmet, lined with red/NIR LEDs.

Treated 3x per Week, 6 Weeks.

James Carroll,
Engineer/Inventor of
Thor Helmet

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

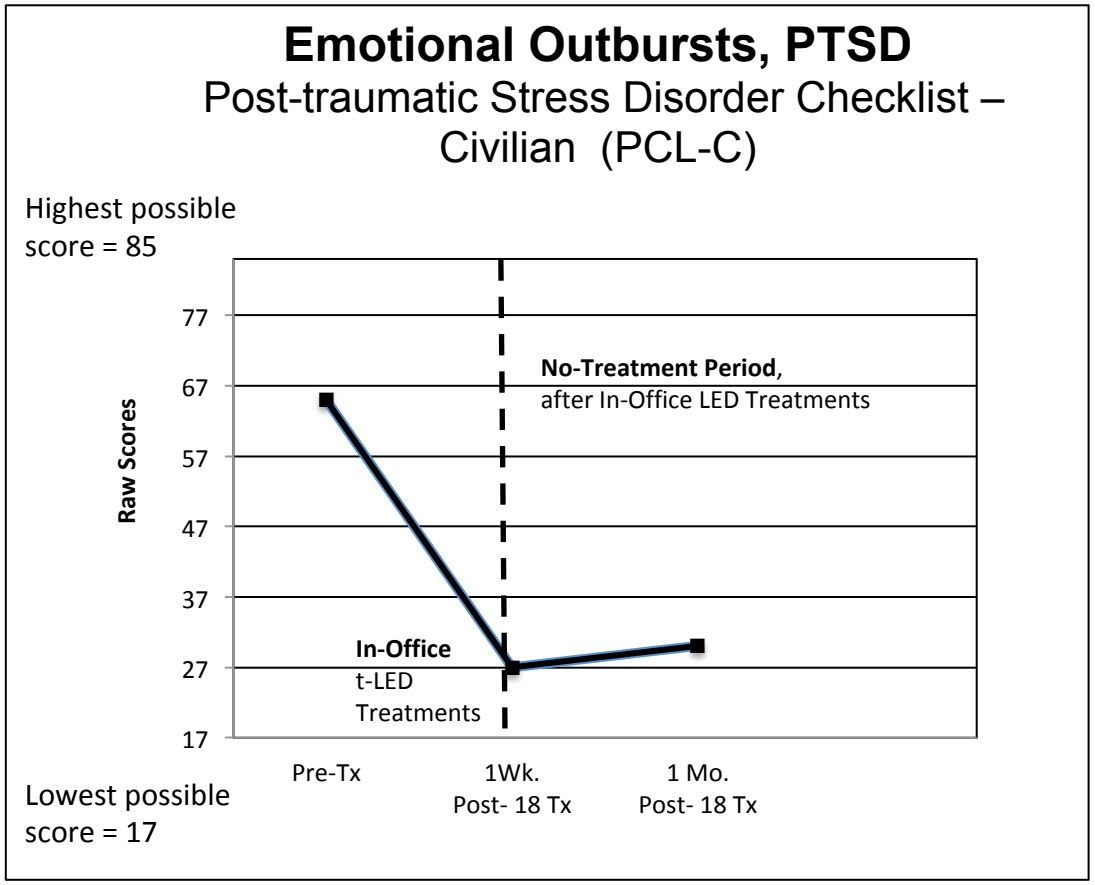
10 LED Placements, 5 on each side

Then, the treatment is finished.

Second Football Player: Retired, NFL Player, age 57

Cornerback, thousands of subconcussive hits to head. 15 Surgeries

Treated with 18 Transcranial LED Treatments, Red/NIR Helmet, *In-Office*



James Carroll
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Thor Helmet

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, Martin, Ho, Krengel, Bogdanova, Knight, Fedoruk, Hamblin, Koo. IBIA, Toronto, March 2019

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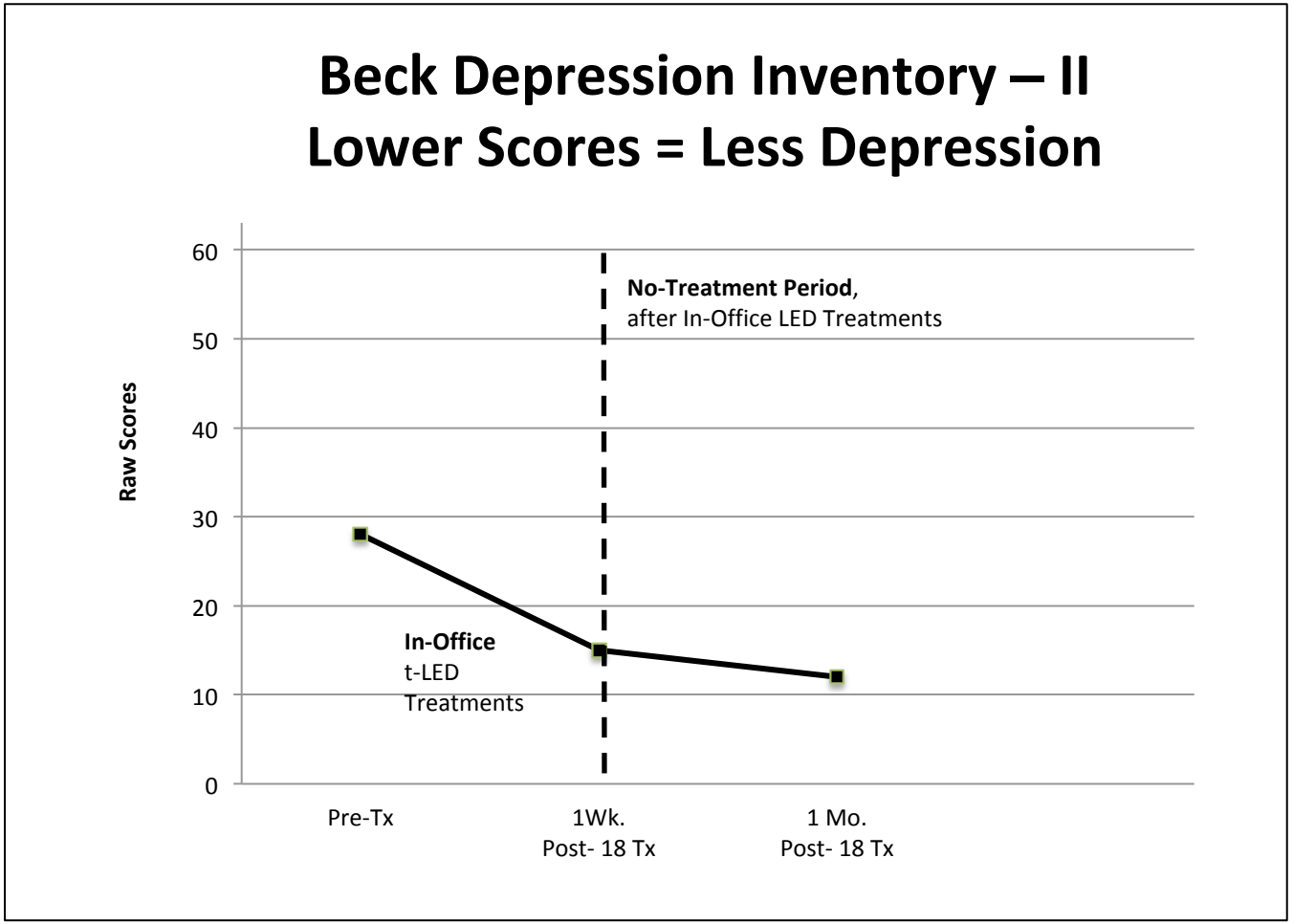

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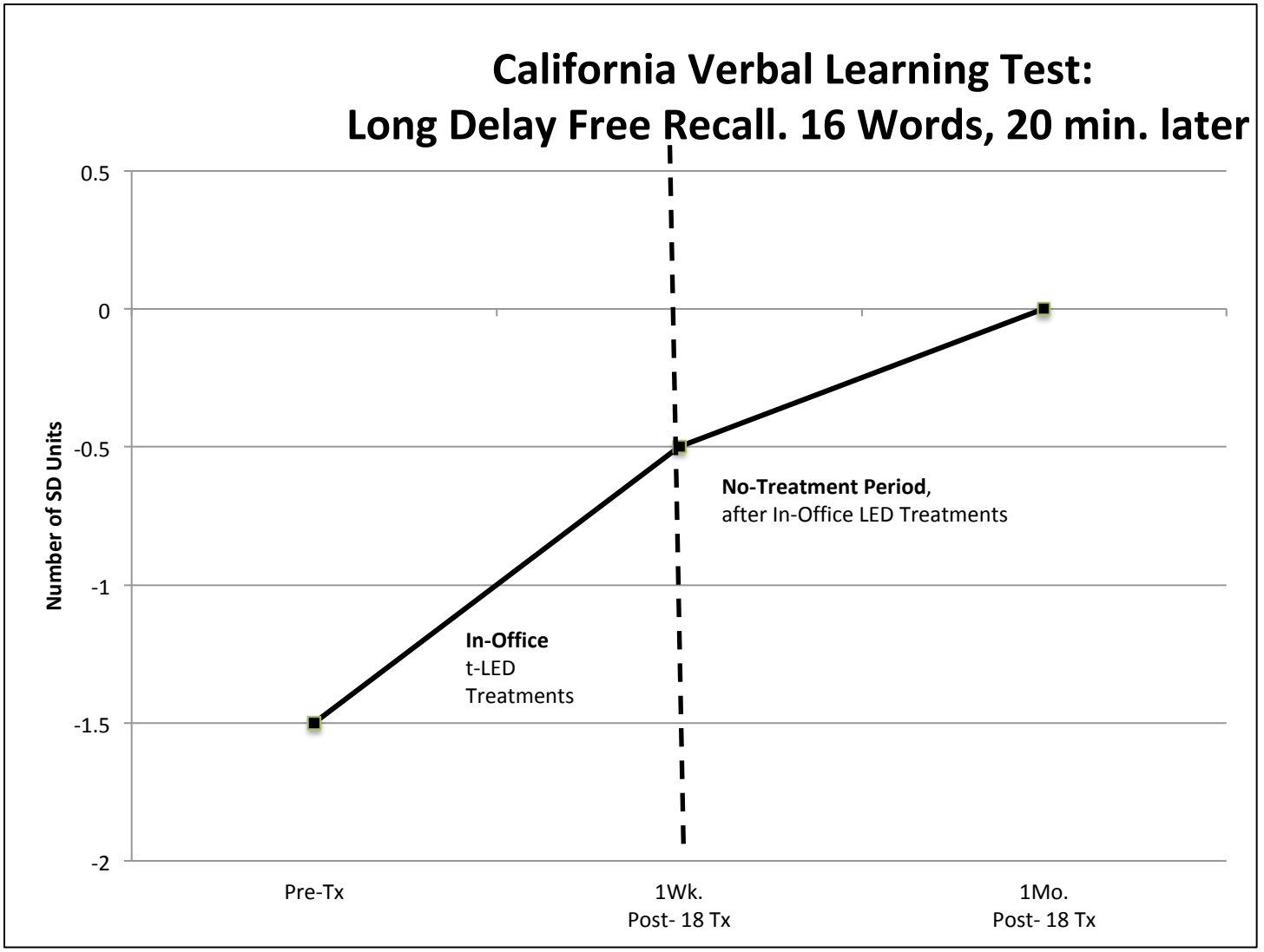

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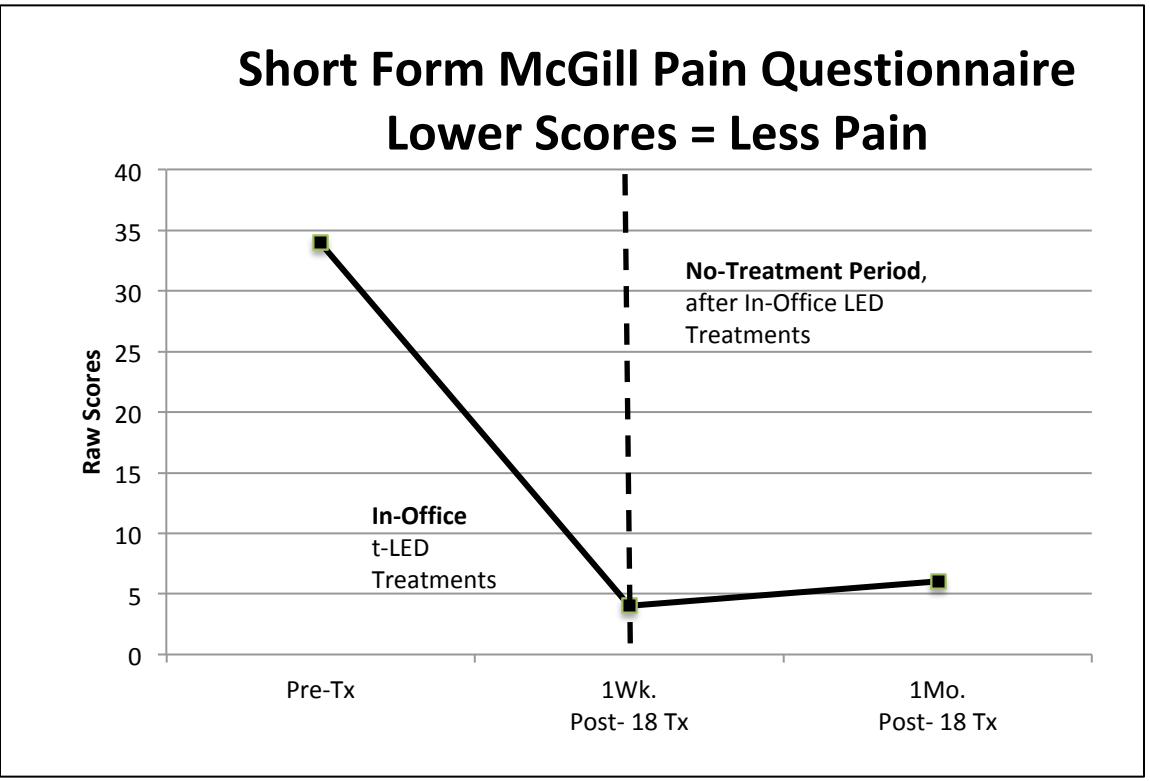
Second Football Player: Retired, NFL Player, age 57

Treated with 18 Transcranial LED Treatments, Red/NIR Helmet, *In-Office*

Reduced Pain, and Discontinued 2 Narcotics, Post- LED 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 purchased his own Vielight Neuro Gamma LED device for Home Treatments.***

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

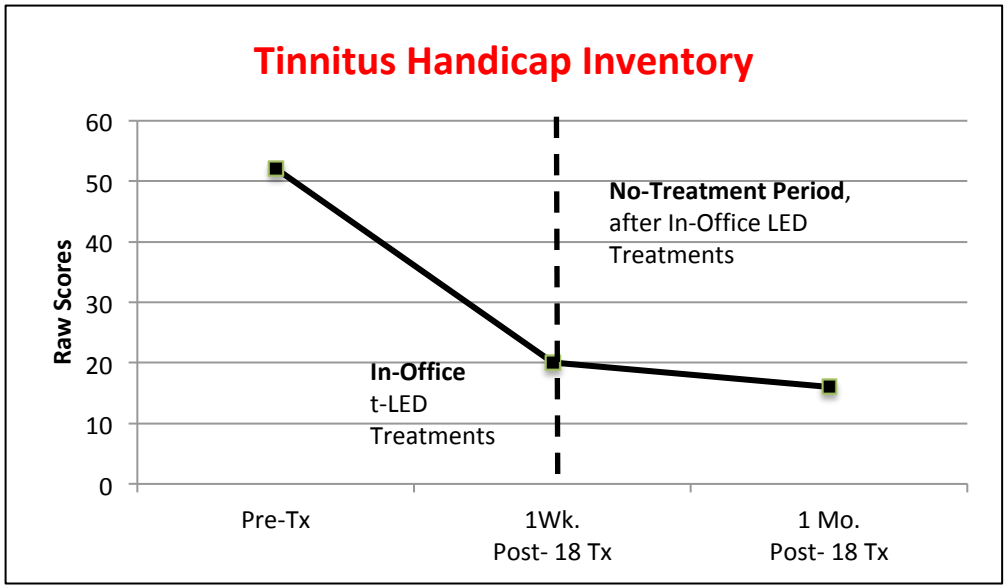
The DMN was treated with the Red/Near-infrared LEDs, that line the Thor Helmet.

Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Fedoruk, Hamblin, Koo. IBIA, Toronto, March 2019

Second Football Player: Retired, NFL Player, age 57

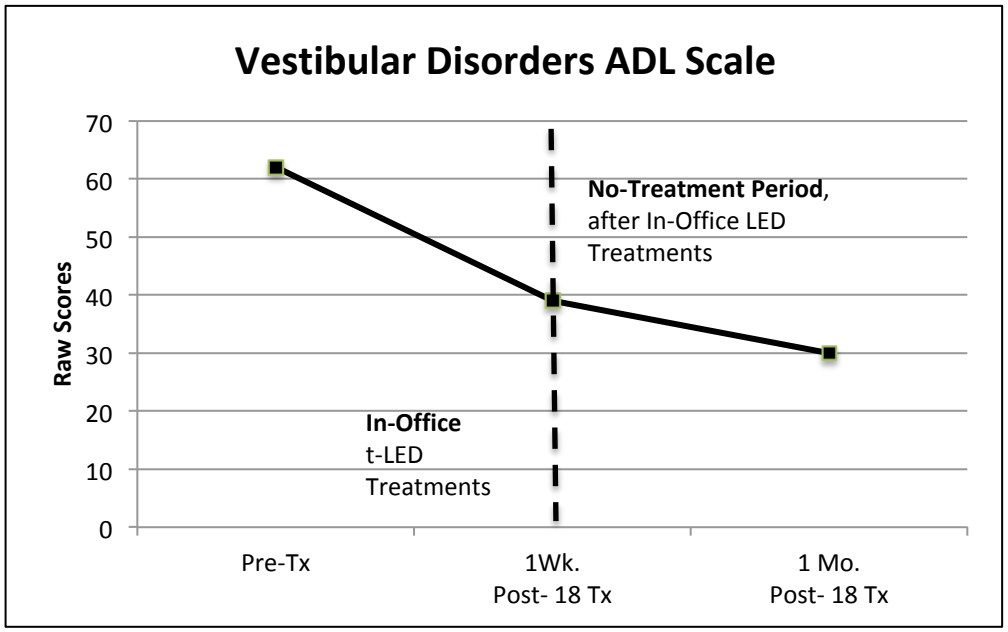
Treated with 18 Transcranial LED Treatments, Red/NIR Helmet, *In-Office*

Maximum score = 100



Minimum score = 0

Maximum score = 280



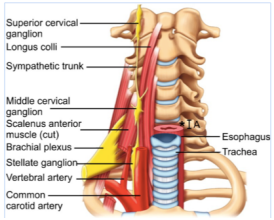
Minimum score = 0

Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Fedoruk, Hamblin, Koo. IBIA, Toronto, March 2019

Tinnitus Study from Japan
Near-infrared, Application to Neck

Photomedicine and Laser Surgery
Volume 36, Number 9, 2018

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



Change of Tinnitus with Xenon Phototherapy of the Stellate Ganglion

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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

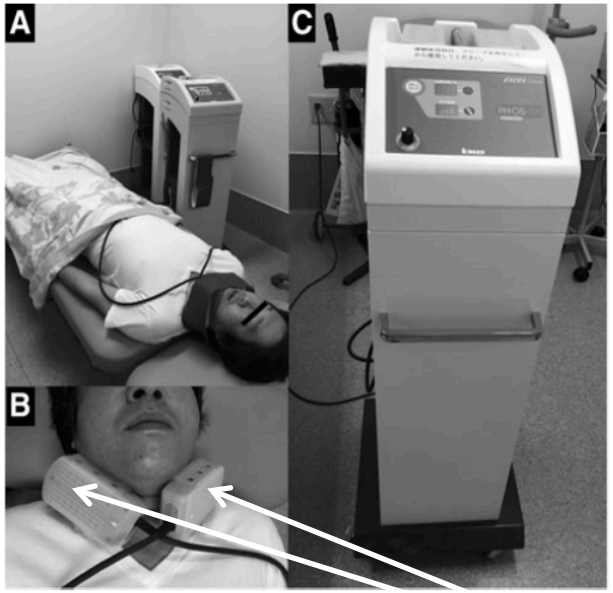

FIG. 1. Treatment was performed in a supine position **(A)**. XPSG probes were placed around stellate ganglion regions **(B)**. Appearance of xenon phototherapy device **(C)**. XPSG, xenon phototherapy of the stellate ganglion.

James Carroll, Engineer/Inventor of the Thor Helmet. 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, Journal Photomedicine and Laser Surgery).

See results for reduced tinnitus, in Second Football Player, age 57 Yr., treated with the Thor Helmet, previous slide.

Naeser, Martin, Ho, Krengel, Bogdanova, Knight, Fedoruk, Hamblin, Koo. IBIA, Toronto, March 2019

CONCLUSIONS

- **Cases 1 and 2**: Results at 1 Wk. and 1 Mo. ***after the final, In-Office LED*** treatment showed ***improvements on PTSD, depression, executive function, memory, and sleep***. This is ***a typical pattern of improvement in mild-moderate TBI, Post- LED*** (Naeser, Zafonte et al., 2014).

- **Case 1: At 2 Mo. after the final, In-Office LED treatment, scores declined without any continued LED treatments.** This is ***an atypical pattern for mild-moderate TBI.***

  Other mild-moderate TBI cases *(car accidents, falls)* treated with the same t-LED protocol, ***showed continued improvements, or stable scores at 2 Mo. Post-*** the final LED treatment (Naeser, Zafonte et al., 2014).

- ***This pattern for Case 1 is more typical of a progressive, neurodegenerative disease*** – *e.g., pattern observed with dementia cases, possible Alzheimer's Disease* (Saltmarche, Naeser et al., 2017). ***Worsening progression in Case 1***, may be ***compatible with possible CTE.***

CONCLUSIONS cont'd

- **Case 1:** **Resting-state functional-connectivity MRI scans (rs-fcMRI)** at ***1 Wk*** *and at* ***1 Mo after final, In-Office*** LED treatment showed ***increased functional connectivity***, *which* ***paralleled improved PTSD, depression, cognition, and sleep, at those times***.

  At 3 Mo. after the final, In-Office LED treatment, however, the ***rs-fcMRI scan*** showed ***less functional connectivity on the rs-fcMRI***, which ***paralleled worsening on some tests, at that time***.

- **Case 1:** ***After 3 Mo. of At-Home LED treatments***, the ***rs-fcMRI showed return of some increased functional connectivity*** *(left hemisphere)*. This ***paralleled*** *the* ***improvements in PTSD, depression, cognition and sleep, at that time***.

- Continued t-LED treatments may be necessary, long-term. Controlled studies, warranted.

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