



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

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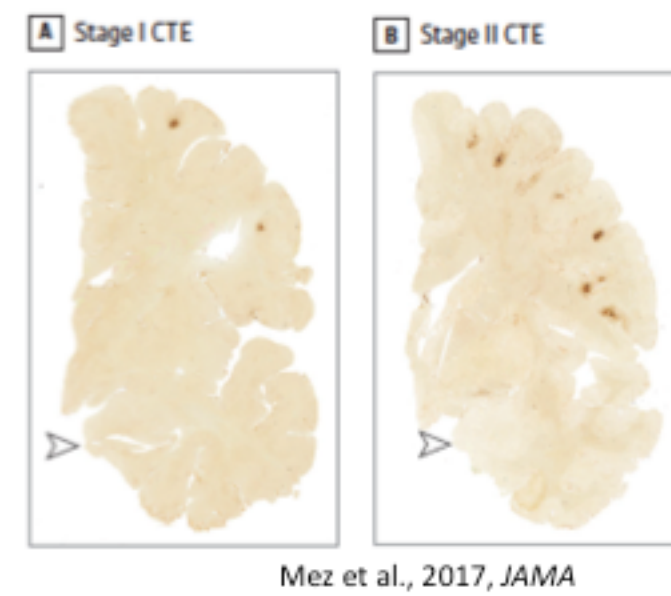
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BACKGROUND

- Photobiomodulation (PBM) therapy is a safe, painless, noninvasive, nonthermal modality that uses red, and/or near-infrared (NIR) wavelengths (600–1100nm) to stimulate, heal, repair damaged cells.
- PBM with red/NIR photons increases ATP production by activating mitochondria in hypoxic/compromised cells. Increased vasodilation, rCBF occurs locally.

- Chronic Traumatic Encephalopathy (CTE)**, associated with **repeated head impacts**, is only diagnosed postmortem, where perivascular tau deposits are concentrated in sulcal depths (McKee et al., 2009).
- Problems include executive dysfunction, poor attention and memory, PTSD, depression and sleep disturbance.
- Two, retired professional football players**, possibly developing CTE received red/NIR transcranial, light-emitting diode (t-LED) treatments.



METHODS

Case 1: Retired CFL Football Player

- 65 Yr., M, 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.
- History of PTSD
- 700+ tackles in college (holds record). Thousands of subconcussive hits.
- 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.

Case 2: Retired NFL Football 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.

In-Office, Transcranial LED Therapy

Case 1: In-Office t-LED Treatment Series: 18 sessions (3x/Wk. for 6 Wks.)

- Non-thermal, 500mW LED device, 22.2 mW/cm² FDA, non-significant risk, MedX Health.
- 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/cm² per placement Painless, noninvasive, no negative side effects, or adverse events.



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

- LEDs target injured/hypoxic brain cells, to improve cellular function
- As mentioned above, red/NIR photons increase adenosine tri-phosphate (ATP) production, and rCBF, locally (Schiffner et al., 2009; Hipskind et al., 2019).
- Animal studies have reported increased neurogenesis and synaptogenesis after photobiomodulation (PBM) treatments in acute TBI (Xuan et al, 2014, 2015).



At-Home, Transcranial LED Therapy

Case 1: 3 months after In-Office series, purchased head-frame device (Vielight Neuro Gamma)

- NIR 810nm, 40 Hz, LEDs of 25, 75 and 100mW; deliver 15, 45, and 60 J/cm²
- Iaccarino et al., (2016) observed decreased beta-amyloid and tau, in visual cortex only, when 40 Hz, light targeted eyes only, in AD mice, 1 Hr/day, 7 days. The 40 Hz increased phagocytosis effect from microglia.
- At-Home, 20 min. treatment **only on the cortical nodes of Default Mode Network**:
 - mesial prefrontal cortex, precuneus, angular gyrus, hippocampal areas
- Case 1 continues t-LED treatments at home, 1 Year; reports doing well.



OUTCOME MEASURES

Cognitive Measures

- Executive Function and Memory – DKEFS Trail Making Test, Color-Word Interference (Stroop), Controlled Oral Word Association (FAS Test), California Verbal Learning Test-II (CVLT-II), Brief Visuospatial Memory Test – Revised (BVMT-R); Attention – Continuous Performance Test (CPT)

Neuropsychiatric Measures

- PTSD Checklist (PCL-C, civilian version), Beck Depression Inventory (BDI), Pittsburgh Sleep Quality Index (PSQI)

Time Points

- Pre-LED (Baseline) **In-Office** treatment (T1). Post-LED Treatment at 1 Wk. (T2), at 1 Mo. (T3) and at 2 Mo. (T4). **Case 1, only: Also after 3 Mo. of At-Home t-LED Treatments (T5).**

RESULTS

Case 1

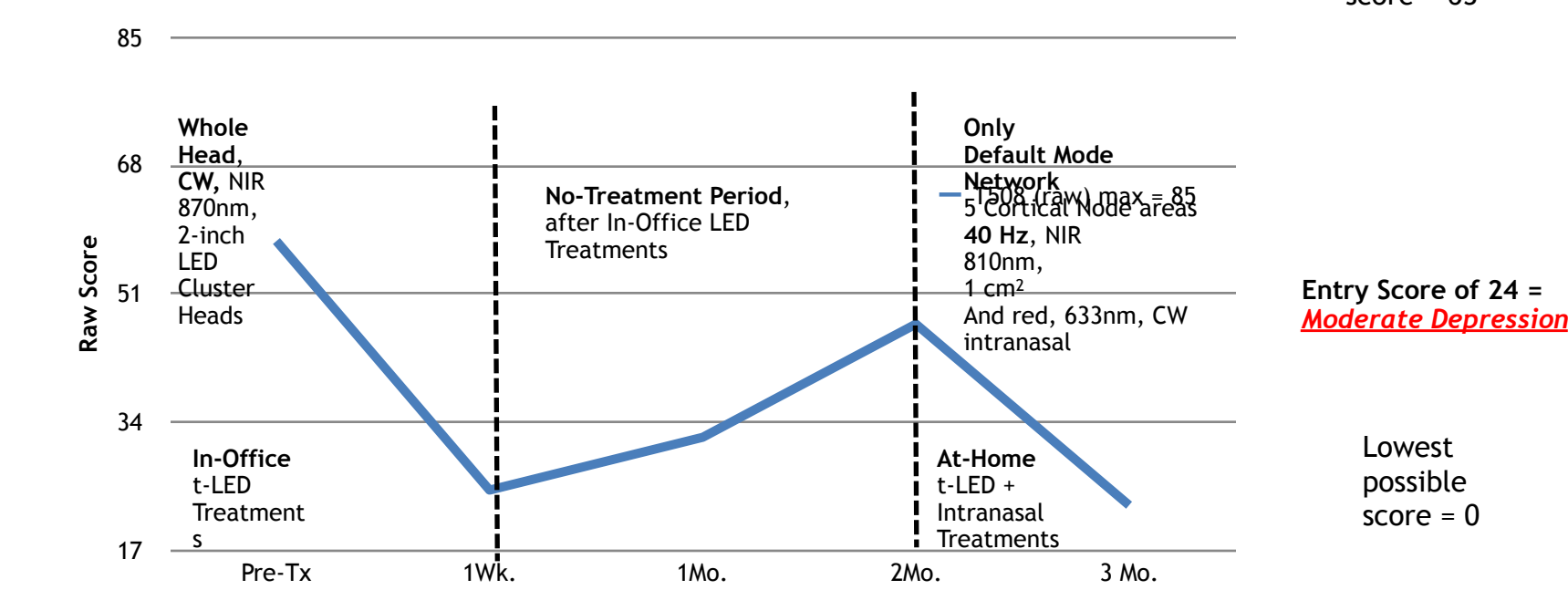
1st Series, In-Office: Post-testing at 1 Wk and 1 Mo after the final, 18th t-LED treatment showed **significant improvements in cognition** (Stroop, CVLT, FAS test, CPT, BVMT-R) and clinically significant **reduction in PTSD and depression** (BDI-II). **After 2 Mo, however, without any LED treatments, some gains began to fall off.**

No-Treatment period of 2-3 Mo.: Then, he purchased **his own NIR, LED head-frame device with attached NIR intranasal (Neuro Gamma); and an extra, red intranasal LED device.**

Emotional Outbursts, PTSD

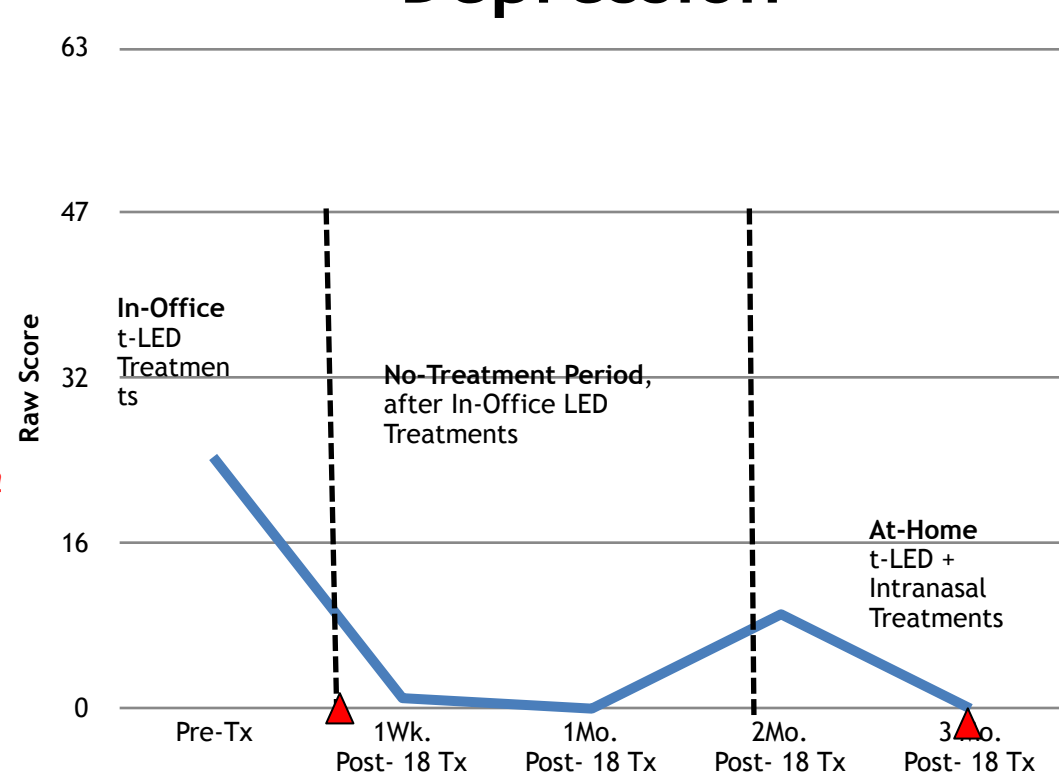
2nd Series, Post-traumatic Stress Disorder: Similar improvements in cognition (Stroop, FAS test, CPT, BVMT-R) along with **reduced PTSD** (fewer emotional outbursts) and **no depression** (Checklist - Civilian).

Lower scores = Fewer emotional outbursts



Beck Depression Inventory Checklist - Civilian

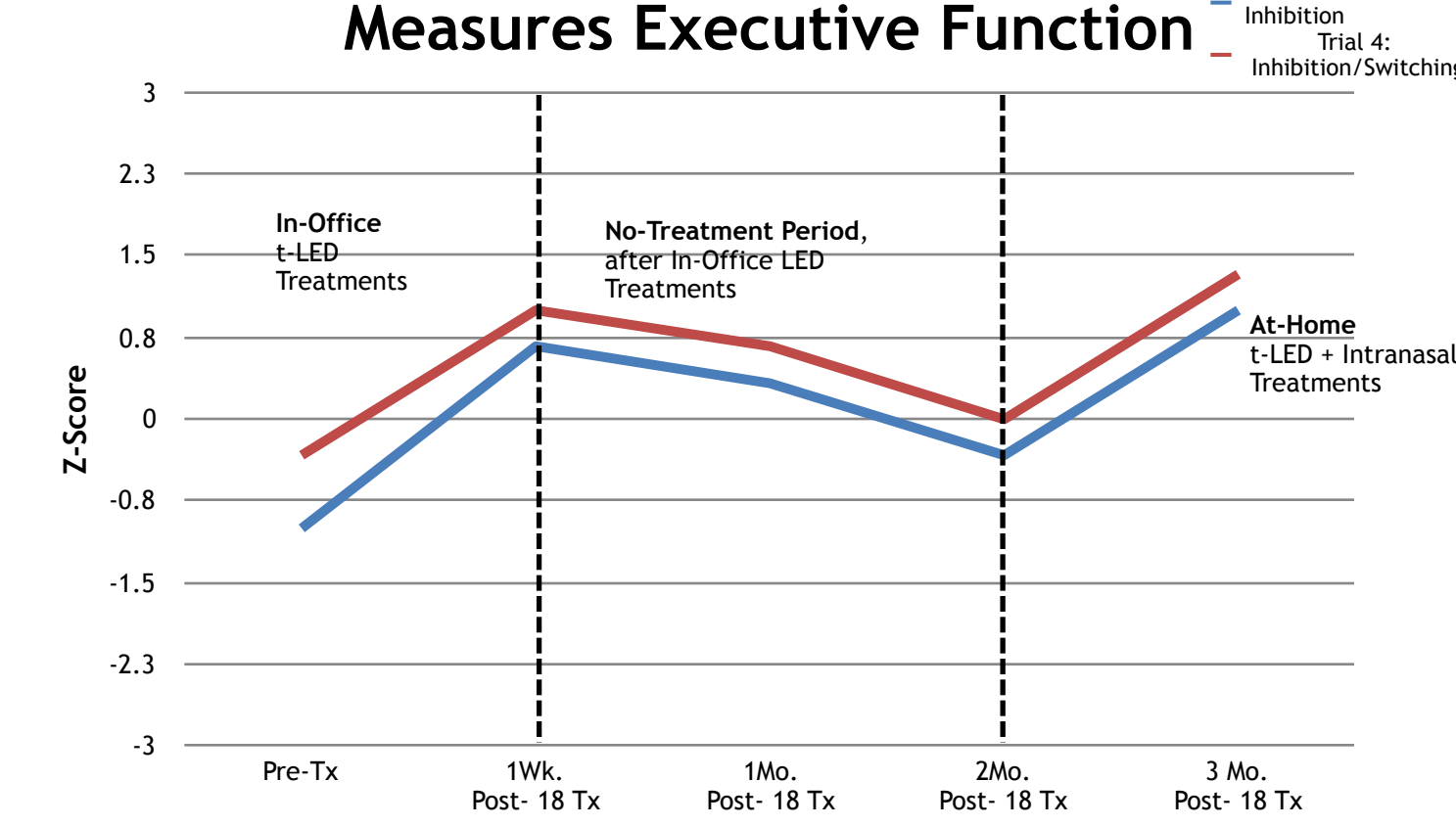
Lower Scores = Less Depression



RESULTS

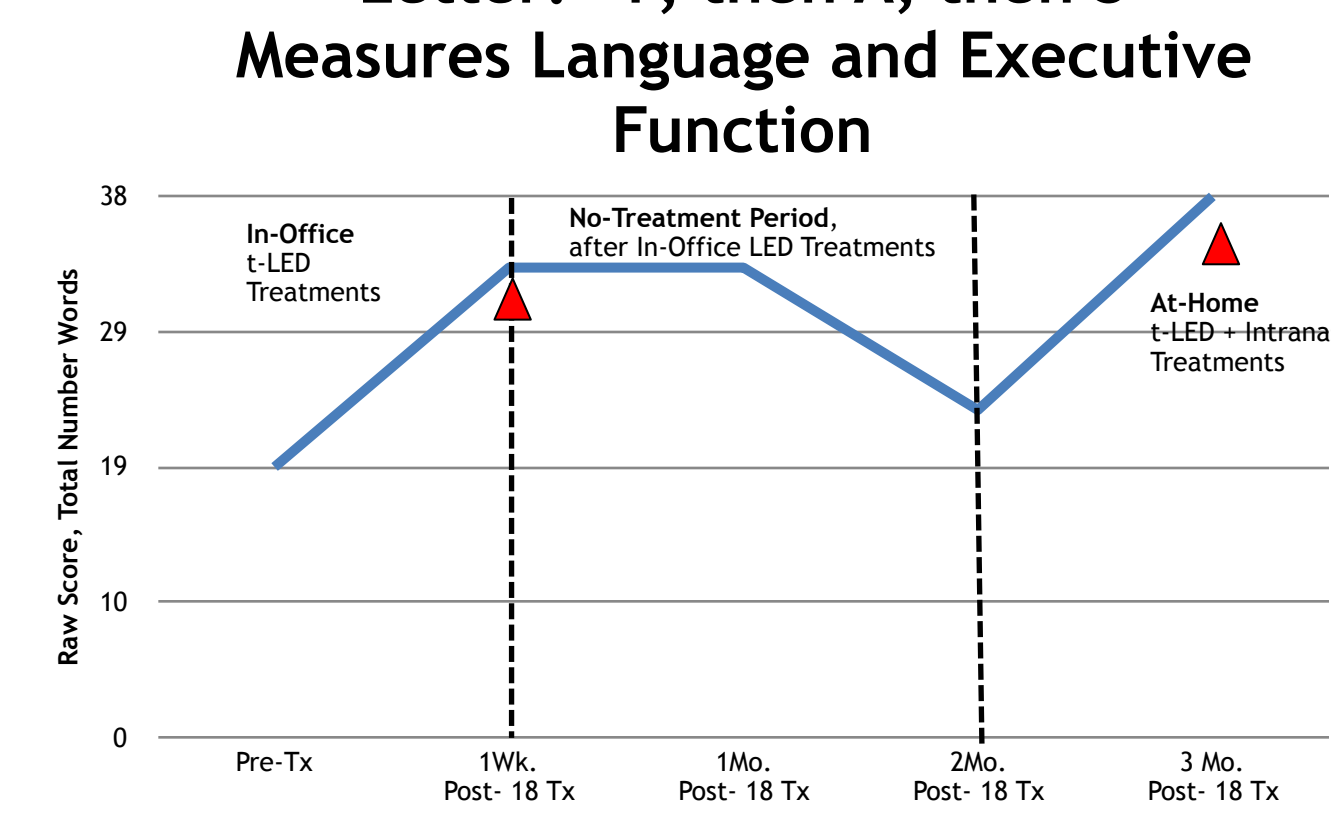
Case 1, continued

D-KEFS, Color-Word Interference Test (Stroop) Measures Executive Function



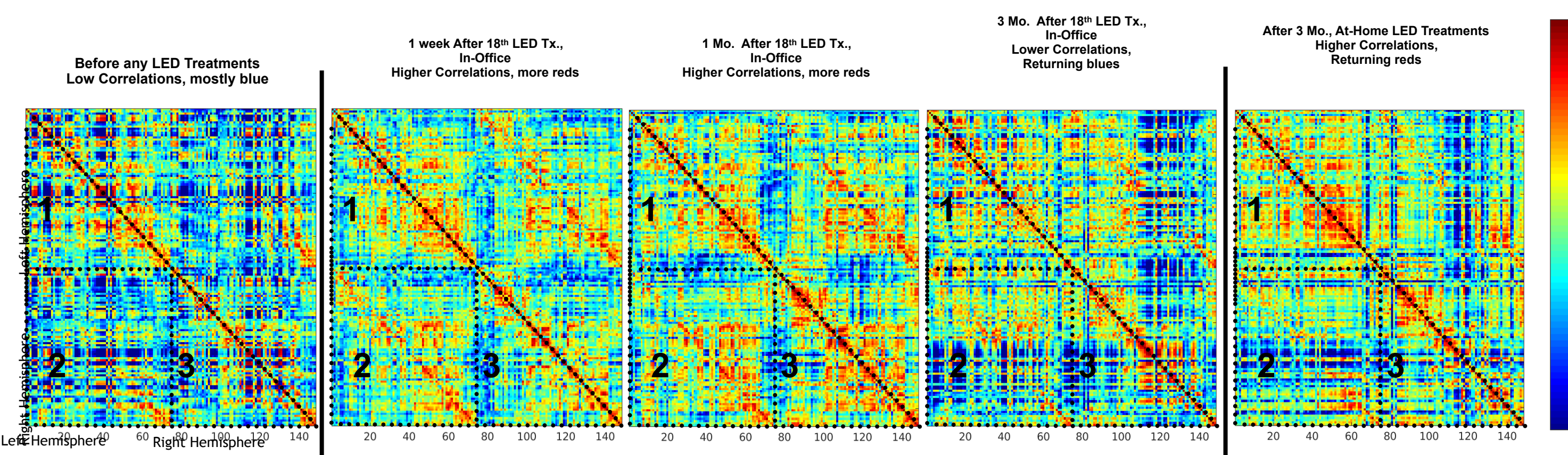
Controlled Oral Word Association Test Name in 1 minute, as many words as possible, that begin with a specific Letter: F, then A, then S

Measures Language and Executive Function



Resting-state functional-connectivity MRI

Eyes open, fixated on a white cross-hair, on black background (7-min; 3T Philips, Achieva MRI). Head motion was restricted with cushioning. **Whole Brain Analysis:** The analysis was repeated with 148 cortical ROIs generated by FreeSurfer. Connectivity was calculated using Brain Connectivity Toolbox (Rubinov and Sporns, 2010). See Correlation Matrices below, for L Hemisphere, R Hemisphere and both Hemispheres.



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

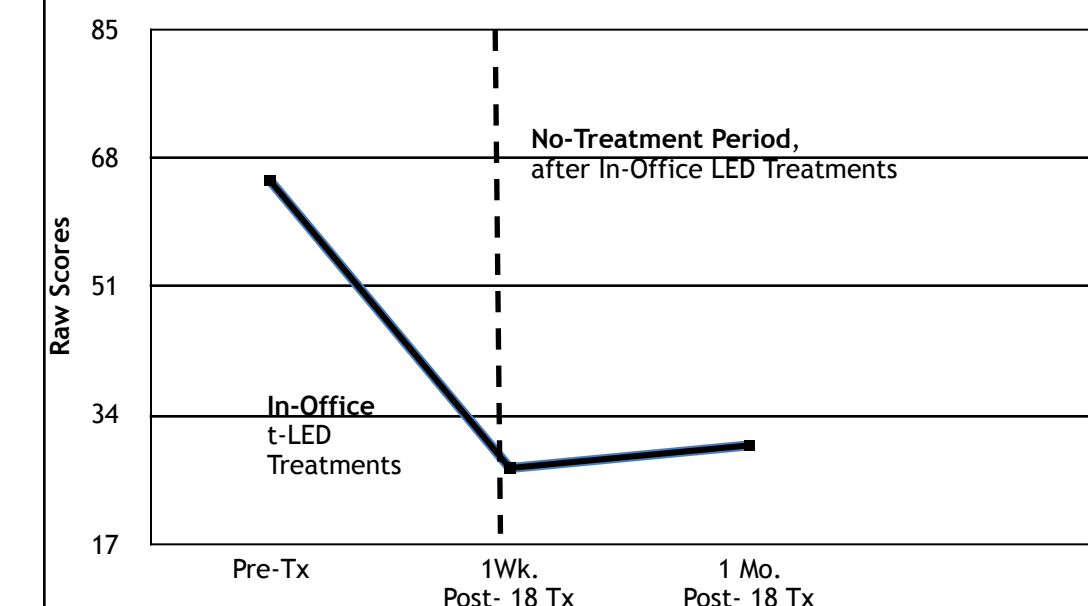
	Before LED Tx.	1 wk After In-Office LED	1 mo After In-Office LED	3 mo After In-Office LED	After 3 mo In-Home LED
Number of correlations in 1, 2 and 3 > +0.60 (%)	1127 (10)	1243 (11)	1693 (16)	1268 (12)	1443 (13)
Number of correlations in 1, 2 and 3 > +0.40 to 0.59 (%)	2082 (19)	2860 (26)	2978 (27)	2679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

RESULTS

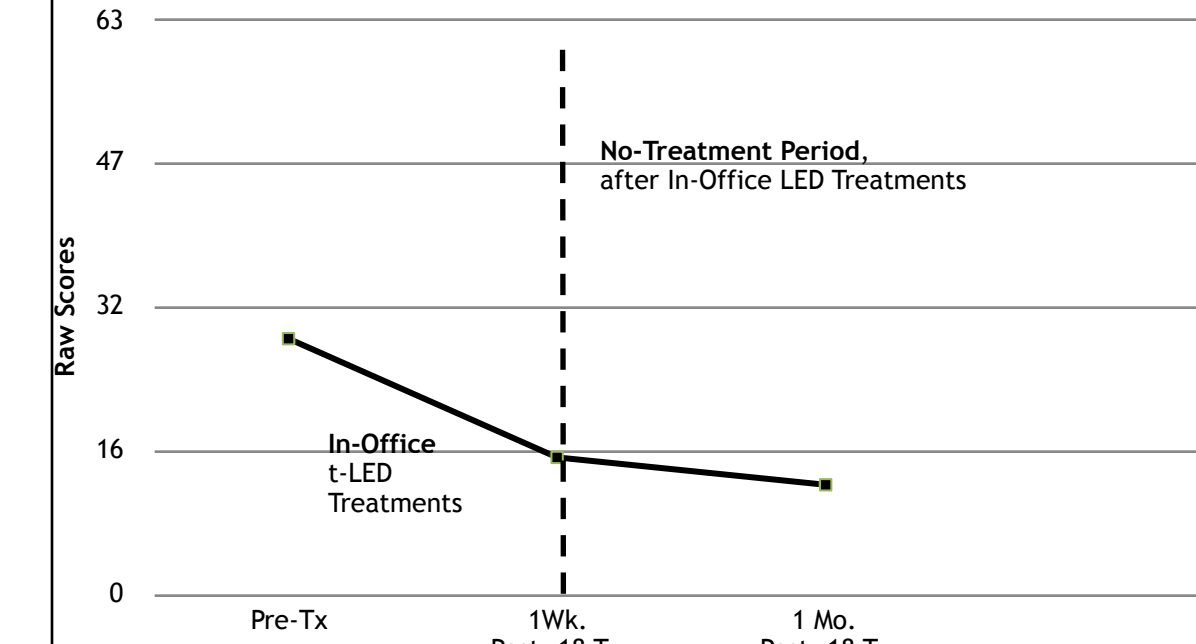
Case 2

Case 2 received 18 **In-Office** t-LED treatments with Thor, LED Helmet, lined with red/NIR diodes.

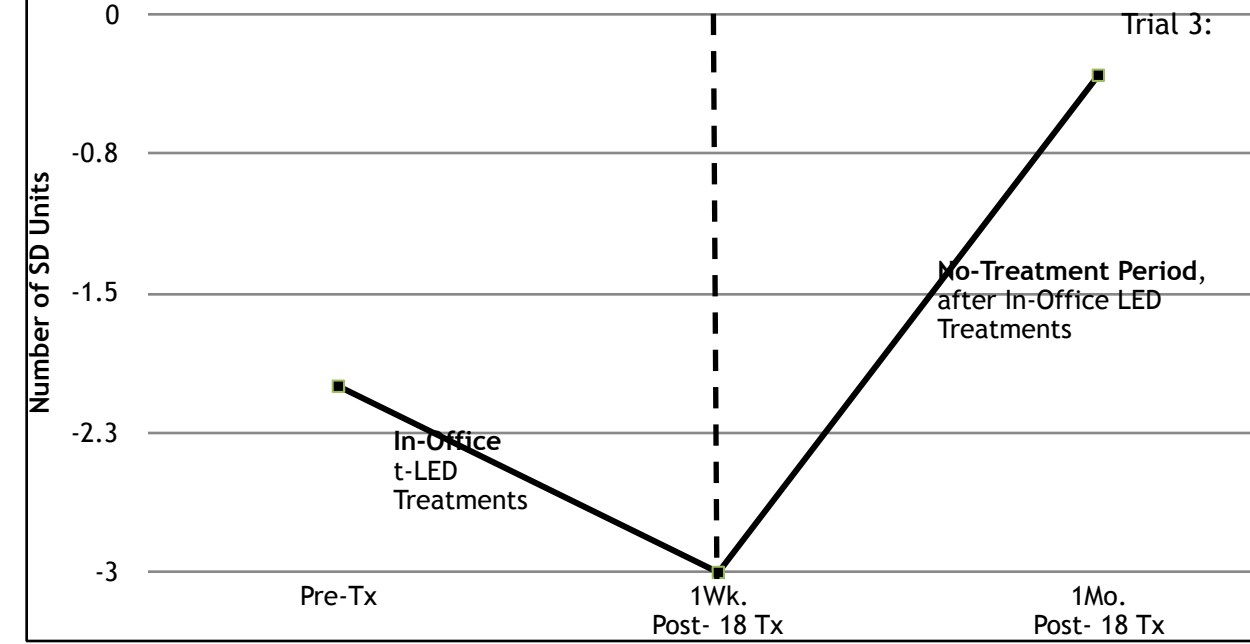
Emotional Outbursts, PTSD Post-traumatic Stress Disorder Checklist - Civilian. Lower scores = Fewer emotional outbursts



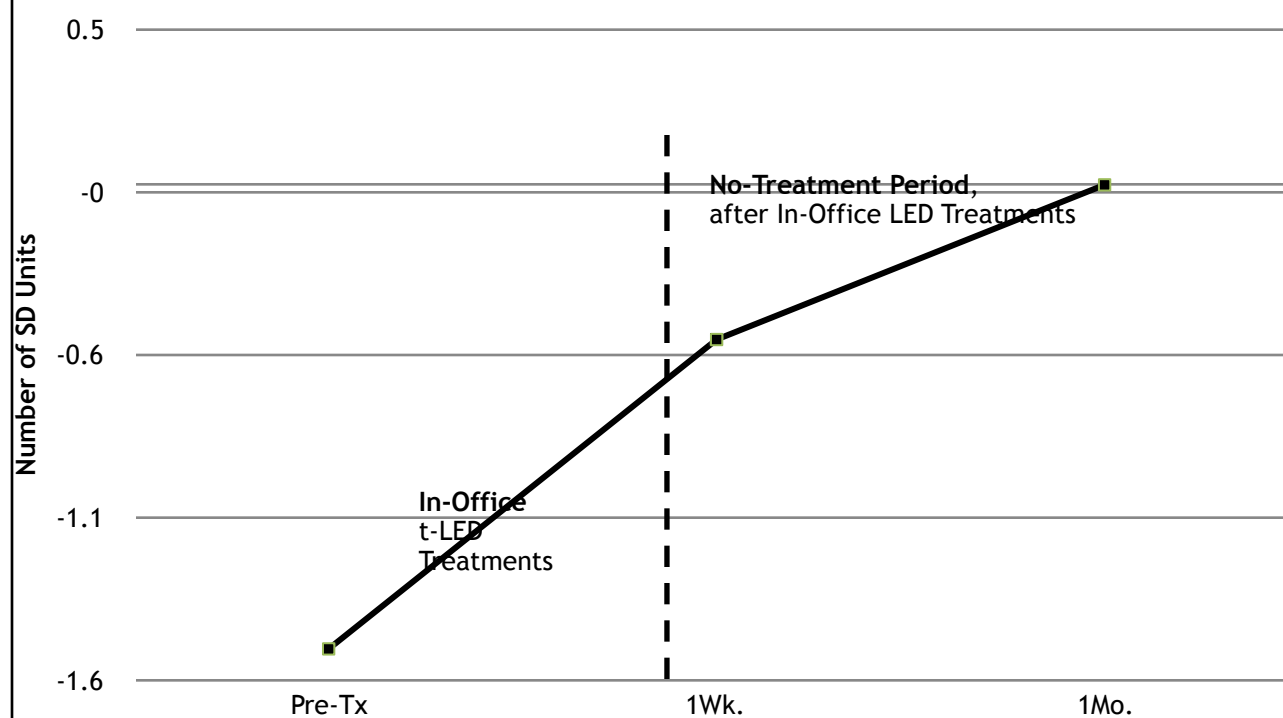
Beck Depression Inventory - II Lower Scores = Less Depression



D-KEFS, Color-Word Interference Test (Stroop), Measures Executive Function



California Verbal Learning Test: Long Delay Free Recall Remember 16 words, 20 minutes later



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

- Pre-LED Pain Meds:**
 - 2 Narcotics – 2 types of oxycodone
 - 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: Default Mode Network (DMN) is dysregulated in Chronic Pain and in Opioid Addiction (Garland et al., 2013).

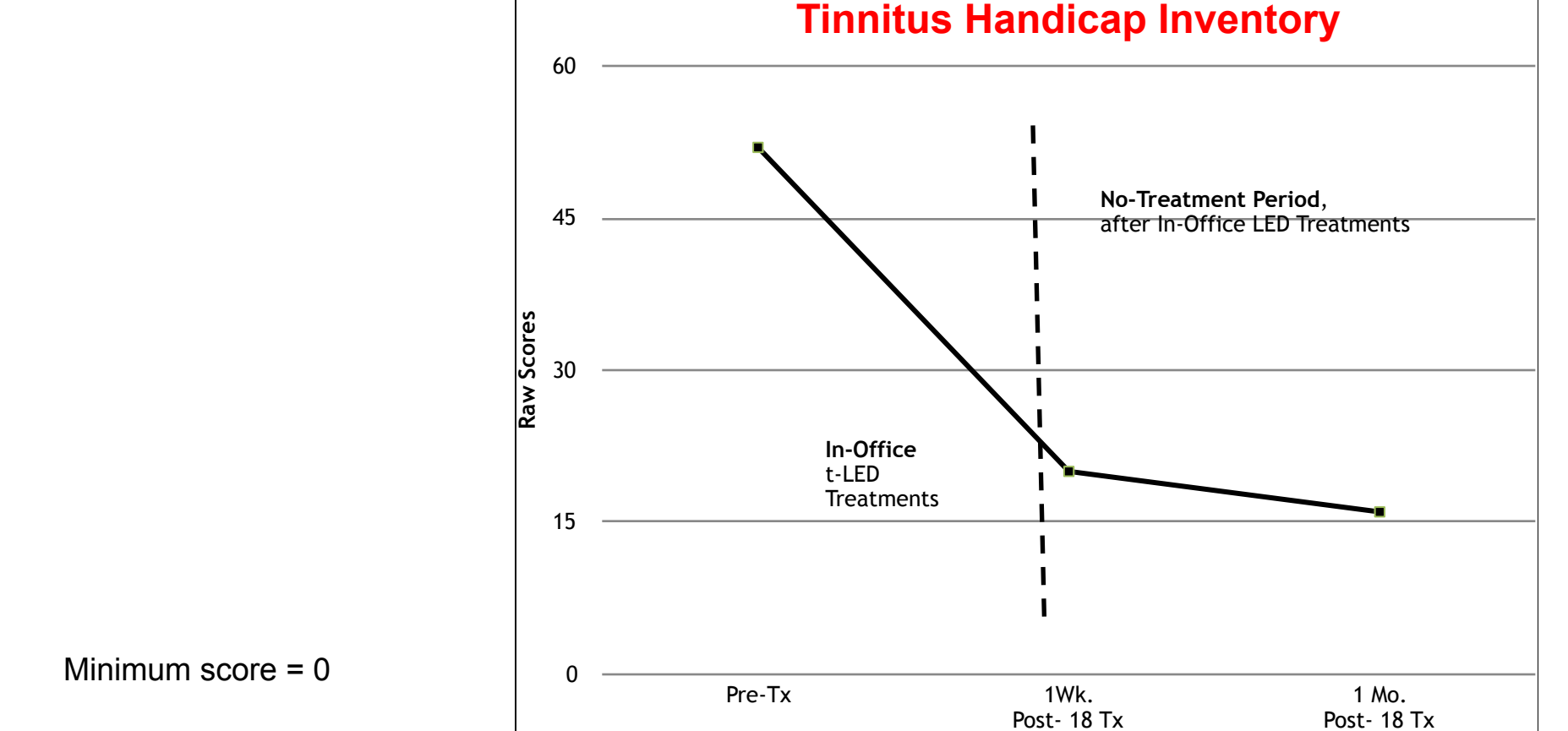
The DMN was treated with the Red/Near-infrared LEDs, that line the Thor Helmet.



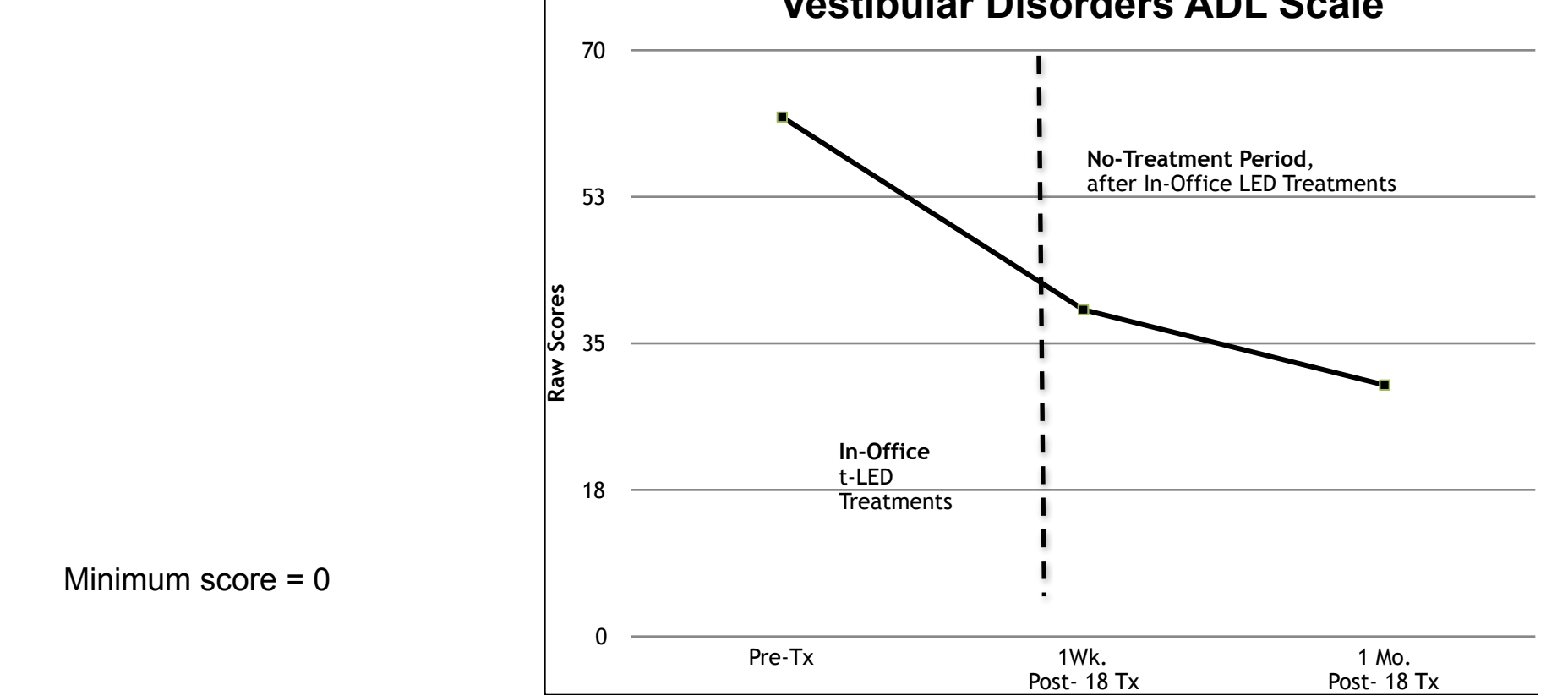
RESULTS

Case 2, continued

Maximum score = 100



Maximum score = 280



White arrows show that red 660nm, and 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** (Shimizu et al., 2018, Photomedicine and Laser Surgery).

See also, white arrows in figure below, from Shimizu et al., 2018. The peak, NIR wavelengths were 700-900nm.

Tinnitus Study from Japan Near-infrared, Application to Neck

Photomedicine and Laser Surgery
Volume 36, Number 6, 2018
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Change of Tinnitus with Xenon Phototherapy of the Stellate Ganglion

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TABLE 1. TINNITUS HANDBOOK 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	33.8±4.7*	4.3±0.4	3.0±0.3*
Severe	21	78.3±2.7	4.4 5.8 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.

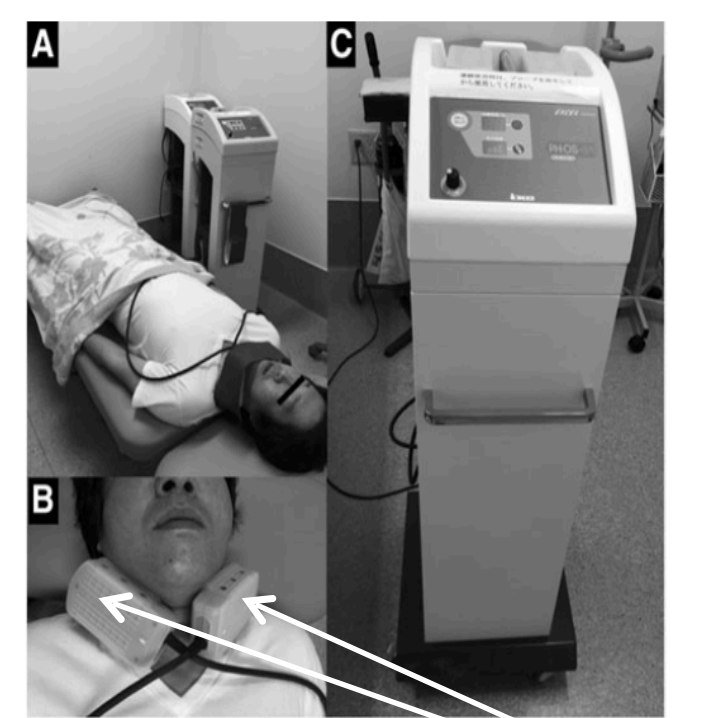


FIG. 1. Treatment was performed in a supine position (A). XPSG probes were placed around stellate ganglion region (B). Appearance of xenon phototherapy device (C). XPSG, xenon phototherapy of the stellate ganglion.

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.**

- 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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