

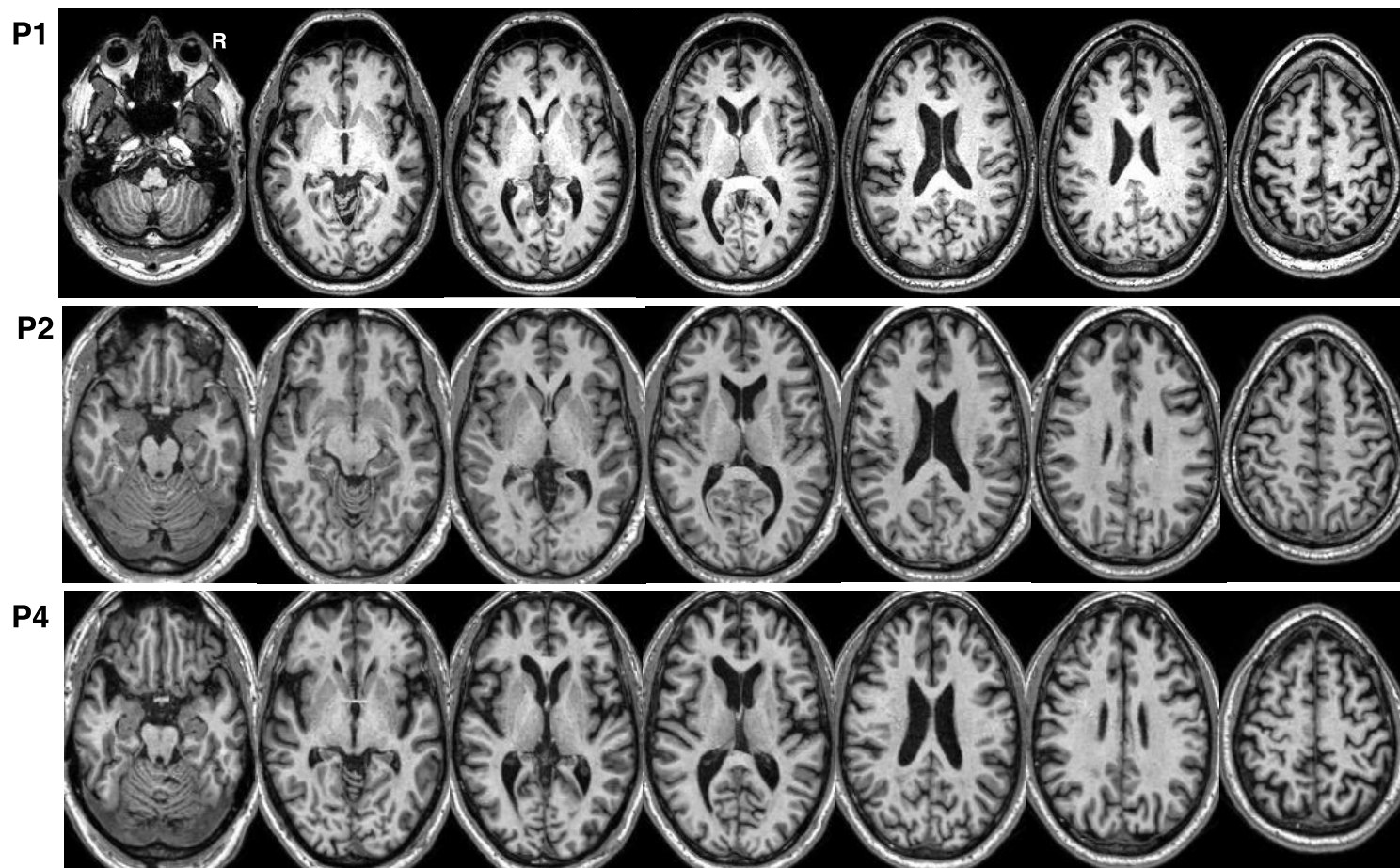
SUPPLEMENTARY MATERIALS

Transcranial Photobiomodulation Treatment: Significant Improvements in Four Ex-Football Players with Possible Chronic Traumatic Encephalopathy

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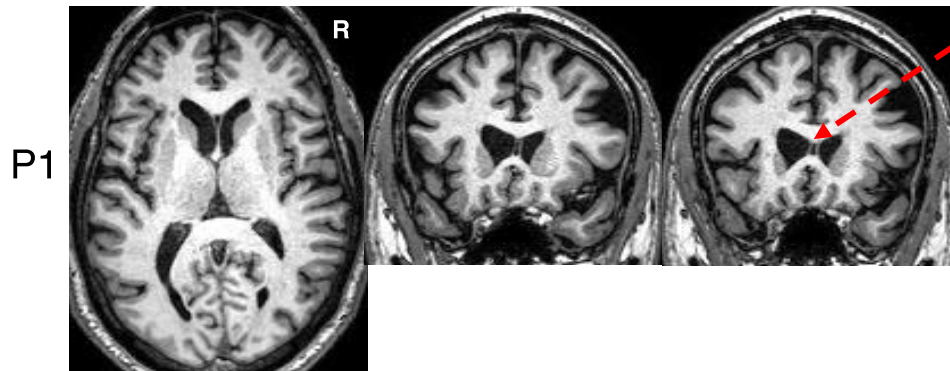
Supplementary Figure 1. Structural MRI scans, T1-weighted axial views.



P1 (65 years), P2 (55 years), and P4 (74 years). Deep sulci, widespread cortical atrophy present, especially P1 and P4. No focal lesions.

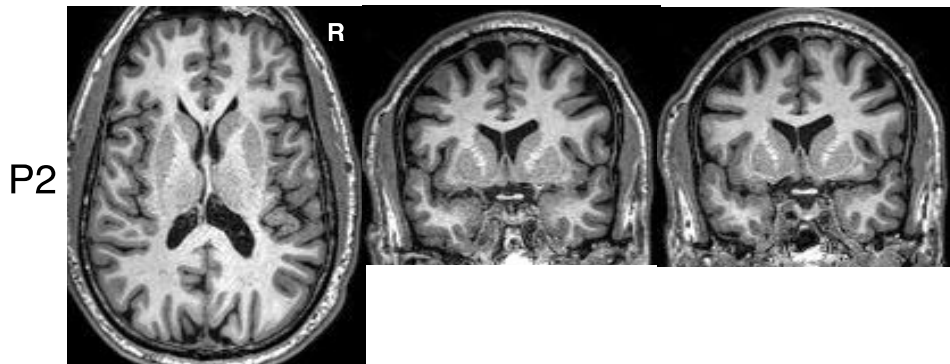
See also Supplementary Figure 2, where coronal views show a cavum septum pellucidum was present for P1 and P4.

Supplementary Figure 2. Coronal views, Cavum Septum Pellucidum present in two of the three ex-football players (P1, P4).



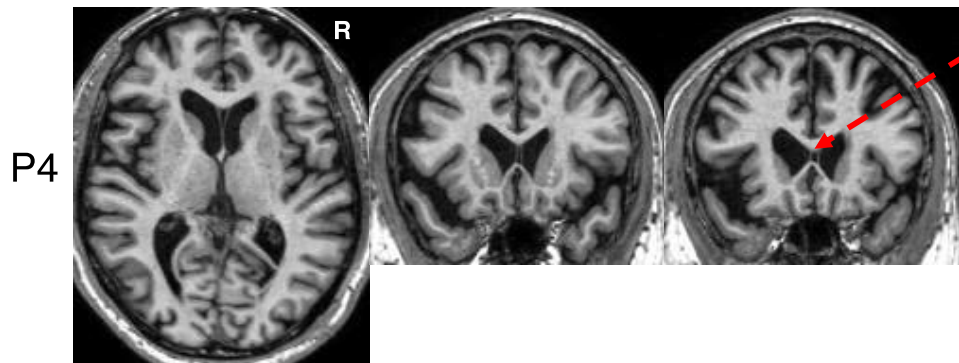
P1. Cavum septum pellucidum present.

Age at Entry into tPBM study: 65 years
Age First Exposure to Football: 10 years, Pop Warner
Years played Football: 14 years
Years played Pro-Football: 1.5, CFL
Position: Middle Linebacker
Fronto-temporal cortical atrophy



P2. Cavum septum pellucidum not present.

Age at Entry into tPBM study: 55 years
Age First Exposure to Football: 7 years, Pop Warner
Years played Football: 15
Years played Pro-Football: 0, College only
Position: Tackle, Offensive Lineman
Some fronto-temporal cortical atrophy



P4. Cavum septum pellucidum present.

Age at Entry into tPBM study: 74 years
Age First Exposure to Football: 13 years
Years played Football: 11
Years played Pro-Football: 4, NFL
Position: Defensive End, and Offensive Lineman, all positions
Fronto-temporal cortical atrophy

Supplementary Text Material 1. MRI Scan Acquisition Parameters and Analysis Programs

Image acquisition, structural and resting-state functional-connectivity MRI

All MRI scans were performed on a 3T Philips Achieva system at the Boston University Center for Biomedical Imaging. Structural MRI scans were acquired with 3D T1-Weighted (T1W) Turbo Field Echo (TFE) scans [TR/TE/flip angle/Field of view (FOV) = 6.768 ms/3.12 ms/9°/250 x 250 x 180 mm]. The resting-state functional-connectivity MRI (rs-fcMRI) scans were acquired with TR/TE/flip angle/FOV = 2999.998 ms/30 ms/80°/198.750 x 159.000 x 212.000 mm. These were acquired for each subject on each MRI visit.

Imaging data processing, rs-fcMRI

The fMRI data were processed with the HCP version 4.1.3 functional processing pipelines [1] by performing gradient and motion correction, referencing the preprocessed structural T1 space, and resampled to the MNI standard space by nonlinear registration. The fMRI timeseries were then mapped to the standard CIFTI grayordinate space and smoothed with a 2 mm FWHM Gaussian. To extract subject-level fMRI connectivity based on predefined resting state networks (RSNs), we parcellated each subject's whole brain fMRI timeseries into 718 parcels using the Cole-Anticevic Brain-wide Network Partition (CAB-NP) labels reordered by networks, which included subcortical regions and reordered the 718 parcels based on RSN definitions [2]. We then performed correlation analysis between each parcel on the parcellated timeseries, extracted the correlation coefficients in matrix formats, and averaged the correlation coefficients from all parcels within individual RSN or between RSNs to obtain a representative connectivity measure for our analysis.

Statistical analysis: Correlations between rs-fcMRI measures, and NP tests and psychosocial measures

The average connectivity measures from the RSN of interest (Salience, Central Executive, and Default Mode) were correlated with neuropsychological tests/subtests (Stroop, CVLT, COWAT, CPT, BVMT-R); and psychosocial questionnaire ratings (PTSD, BDI, PSQI, SF-MPQ, Dysexecutive Questionnaire), pre-/post- tLED, to evaluate potential relationships between resting-state functional network connectivity, and neuropsychological tests and psychosocial

questionnaire ratings, over time. Significant correlations ($p < 0.05$) were reported with the Pearson correlation coefficients (ρ) and p-values.

Image acquisition, magnetic resonance spectroscopy (MRS)

The H-MRS data were acquired by single-voxel examination in the anterior cingulate cortex and the posterior cingulate cortex. The single-voxel size was 3 x 3 x 5 cm. Spectra were obtained using a double spin-echo point-resolved spectroscopy sequence (PRESS) with the following settings: echo time, 38 ms; repetition time, 2000 ms; 1024 data points; and 128 data acquisitions. Cerebral metabolites NAA, Mi, Cr and Cho were measured.

Imaging data processing, MRS

The MR spectra were analyzed and quantified using the totally automatic robust quantitation in nuclear MR (TARQUIN) algorithm [3].

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Supplementary Text Material 2. Additional Home Treatment Information, Neuro Gamma

The Neuro Gamma LED device was used for home treatments. It is designed to treat *only five cortical nodes of the DMN*. These include the following: 1) midline, mesial prefrontal cortex (mPFC) area, located subjacent to top, center of forehead at the front hairline; 2) midline, precuneus, located subjacent to junction of the sagittal suture line with L and R lambdoid suture lines; 3) and 4) the L and R intraparietal cortices (angular gyrus areas), located subjacent to posterior/superior ear area; and 5) indirectly, the hippocampal area. The NIR, LED nasal applicator (attached to the Neuro Gamma device) was clipped into one nostril and hypothesized to deliver NIR photons to olfactory bulbs located on orbito-frontal cortex. The olfactory bulbs have direct connections to parahippocampal gyrus and hippocampal complex; the hippocampus is also part of DMN [1–3]. Use of the 40-Hz pulse rate in each diode was based on results with AD mice [4], showing approximately 41% reduction in tau deposits, and 67% reduction, amyloid- β in visual cortex only (light was shown only to the eyes). Increased phagocytosis from microglia was posited. Thus, in the present study, the 40 Hz pulse rate in the Neuro Gamma device was used to possibly help remove some p-tau deposits. Use of the red 633nm, CW, nasal LED applicator was based on reports showing red wavelength improves blood rheology [5,6], cerebral blood flow [7], and increases melatonin [8].

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Supplementary Table 1. List of Neuropsychological Tests; Psychosocial Function and Other Health Measures (Behavior/Mood Questionnaires).

Neuropsychological (NP) tests were administered by a PhD Neuropsychologist (MHK, JAK, or YB). Each NP testing visit lasted about one hour.

Neuropsychological (NP) Tests

1. DKEFS, Color-Word Interference (Stroop) [1]. Trials 1 – 4. Examines executive function, attention, mental speed, mental control, inhibition and inhibition accuracy. (5 minutes)
2. California Verbal Learning Test-II (CVLT-II)* [2]. Examines aspects of verbal learning, organization, and memory. (10 minutes)
3. DKEFS Trail-Making Test [1]. Trails 2 and 4. Measures problem-solving, thinking flexibility, planning [Executive Function] (5 minutes)
4. Controlled Oral Word Association Test (COWAT)/FAS Test* [3,4]. Total Words generated, for the letters, F, A and S. Measures verbal fluency, executive function, and categorical generative capacity. (3 minutes)
5. Connors' Continuous Performance Test (CPT), computerized reaction time task [5,6,7]. Measures attention, sustained attention, detectability [d prime, how well the respondent discriminates non-targets from targets, measuring difference between the signal (targets) and noise (non-targets) distributions; the greater the difference between the signal and noise distributions, the better the ability to distinguish non-targets and targets; reverse-scored so that higher raw score and *T*-score values indicate worse performance (i.e., poorer discrimination)]. (About 15 minutes)
6. Brief Visuospatial Memory Test- Revised* (BVRT-R) [8]. Examines aspects of visuospatial memory. (10-15 minutes)

*Alternate version administered at every other testing session to avoid practice effects.

Alternate versions of the NP tests were used at the post-LED testing times, when feasible. These included the CVLT II - Alternate Form [2]; and the alternate form of the FAS test, using 3 different letters, S, D, and J; and the BVRT Revised [8], which has 5 forms.

Psychosocial Function Measures: Self-rated measures assessing domains of daily activity.

1. Dysexecutive Questionnaire (DEX) [9]. A 20-item, self-administered measure of real-life strategic deficits, relevant to executive function in social contexts. (5 minutes)
2. Quality of Community Integration Questionnaire [10]. Assesses satisfaction with community functioning and satisfaction with general cognitive functioning (5 minutes)

Other Health Measures: (Total time about 10-15 minutes, varies for each participant)

1. PTSD Checklist-Military PCL-C, for civilians [11]
2. Pittsburgh Sleep Quality Index (PSQI) [12]
3. Beck Depression Inventory II [13]
4. Short Form McGill Pain Questionnaire [14]
5. Overall VAS pain rating (0-10) [15]
6. Vestibular Disorders Activities of Daily Living Scale [16]
7. Tinnitus Handicap Inventory [17]

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Supplementary Table 2. Each LED device, and specifications for tLED treatment protocols A, B, and C. FDA status for each device, is provided in Note, at end.

| | Protocol A. In-Office, red/NIR, LED Cluster Heads | Protocol B. At-Home, Neuro Gamma Device: Headframe with 4 NIR, diodes and 1 NIR, Intranasal diode attached. Plus a separate, Red Intranasal diode Device | | Protocol C. In-Office, red/NIR, LED-lined Helmet Device | |
|---|--|---|--|--|---|
| | MedX Health LED Cluster Heads* | Vielight Neuro Gamma device, Each diode Described Separately | Vielight Red, 633nm Intranasal LED Device | THOR Photomedicine LED lined helmet** Midline clusters turned on, only. Set A | THOR Photomedicine LED lined helmet** Left and Right Sides turned on, same time. Set B |
| Cluster Head Size | 2-inch diameter (22.48 cm ²) | 1 cm ² | 1 cm ² | 6.3 cm diameter (28.3 cm ²) | 6.3 cm diameter (28.3 cm ²) |
| Number of Cluster heads | 12 | 4 scalp 1 intranasal | Single diode | 5 | 10 |
| No. of diodes per cluster head | 61 | 1 | 1 | 69 | 69 |
| Wavelength, nm | 9 at 633 nm; 52 at 870 nm | 810 | 633 | 34 at 660 nm 9.1 mW & 35 at 850 nm 27.3 mW | 34 at 660 nm 7.7 mW & 35 at 850 nm 23.2 mW |
| Power Output, mW per cluster head | 500 | 1, anterior band, 75 3 each, posterior band, 100 1, intranasal, 25 | 8 | 1,265.6 | 1,075.4 |
| Power Density, mW/cm² | 22.2 | 1, anterior band, 75 3 each, posterior band, 100 1, intranasal, 25 | 8 | 41 | 35 |
| Pulse frequency, Hz | CW | 40 | CW | CW | CW |
| Pulse Duty Cycle, % | - | 50 | - | - | - |
| Total Time per session | Two, 20 min sets 40 min | 20 min | 25 min | 10 min 42 s | 12 min 36 s |
| Energy Density, J/cm² | 26 per cluster head | 1, anterior band, 45 3 each, posterior band, 60 1, intranasal, 15 | 12 | 26 per cluster head | 26 per cluster head |
| Joules per LED cluster head | 600 | 1, anterior band, 45 3 each, posterior band, 60 1, intranasal, 15 | 12 | 812.5 | 813 |
| Total Joules per treatment session | 7,200 | 240 | 12 | 4,063 | 8,130 |

*Two sequential Placement Sets: Six LED cluster heads per set, each set, 20 min; total time, 40 min. Two sets were necessary to cover the midsagittal/midline placements, as well as both sides of the head. MedX Health LED cluster heads, Joules per Treatment = 7.2 kJ; Total Joules after 18 Treatments = 129.6 kJ.

** Two sequential Placement Sets: Total Time, Set A plus Set B, was 23 min 18 sec, per session. Note, the power output and power density varied slightly, for the different number of cluster heads turned on at the same time, 5 (Set A, midline), or 10 (Set B, both sides). THOR helmet, Joules per Treatment = 12.2 kJ; Total Joules after 18 Treatments = 219.6 kJ.

tLED, transcranial light-emitting diode; nm, nanometers; mW, milliwatts; J/cm², Joules per cm²; CW, Continuous Wave

Note: The FDA status for each LED device is as follows:

Protocol A. The MedX Health LED device is FDA cleared as non-significant risk for temporary increase in blood circulation for temporary reduction of musculoskeletal pain.

Protocol B. The Vielight Neuro Gamma device and the separate red, 633nm, Intranasal diode device are both within the low-risk device, FDA category of "General Wellness," no medical claims are made.

Protocol C. The THOR Photomedicine helmet contains LED cluster heads that are FDA cleared as non-significant risk for temporary increase in blood circulation for temporary reduction of musculoskeletal pain.

Supplementary Table 3A. P1. Results for Neuropsychological Tests, Z-Scores and Changes, for In-Office and At-Home tLED Series.

| Neuropsychological Tests | Pre-Tx | Z-Scores | | | | Changes in Z-Scores | | | | |
|---|----------|---------------------------|----------------------------|-----------------------------|---------------------|-----------------------|------------------------|-------------------------|-------------------------------|--|
| | | 1 week Post- 18 Office Tx | 1 month Post- 18 Office Tx | 2 months Post- 18 Office Tx | 3 months of Home Tx | Pre-Tx to 1 week Post | Pre-Tx to 1 month Post | Pre-Tx to 2 months Post | Pre-Tx to 3 months of Home Tx | |
| Stroop: Color Word Interference Test | | | | | | | | | | |
| Trial 3 | -1 | +0.67 | +0.33 | -0.33 | +1 | +1.67 | +1.33 | +0.67 | +2* | |
| Trial 4 | -0.33 | +1 | +0.67 | 0 | +1.33 | +1.33 | +1 | +0.33 | +1.66 | |
| California Verbal Learning Test II | | | | | | | | | | |
| Total Trials 1-5 (Max = 80) | -0.75 | -0.25 | +0.25 | +0.55 | +0.67 | +0.5 | +1 | +1.3 | +1.42 | |
| Short Delay, Free Recall (Max = 16) | -1.5 | -1.5 | -0.5 | -0.5 | -0.5 | 0 | +1 | +1 | +1 | |
| Short Delay, Cued Recall (Max = 16) | -2 | 0 | -0.5 | -1 | -1 | +2* | +1.5 | +1 | +1 | |
| Long Delay (20 min), Free Recall (Max = 16) | -1.5 | 0 | 0 | -1 | -1 | +1.50 | +1.5 | +0.5 | +0.5 | |
| Long Delay (20 min), Cued Recall (Max = 16) | -2 | -0.5 | -0.5 | -1 | -1 | +1.50 | +1.50 | +1 | +1 | |
| Controlled Oral Word Association Test (FAS or BHR) | | | | | | | | | | |
| (No Max; 60 s per Letter) | 19 words | 33 words | 33 words | 23 words | 38 words | +14 words | +14 words | +4 words | +19 words | |
| Continuous Performance Test | | | | | | | | | | |
| Correct Detections | -0.55 | +0.61 | +0.62 | -0.3 | +0.56 | +1.16 | +1.17 | +0.25 | +1.11 | |
| False Alarm Rate | +1.71 | -1.25 | -0.9 | +1.9 | -0.99 | -2.96* | -2.61* | +0.19 | -2.7* | |
| d prime | +1.12 | -1 | -1 | +1 | -1.35 | -2.12* | -2.12* | -0.12 | -2.47* | |
| Brief Visuospatial Memory Test-Revised | | | | | | | | | | |
| Trial 1 (Immediate Recall) (Max = 12) | -1.6 | -0.58 | +0.41 | -1.57 | +1.39 | +1.02 | +2.01* | +0.03 | +2.99* | |
| Total Recall (Max = 36) | -0.85 | +0.05 | +0.05 | -0.13 | +1.67 | +0.9 | +0.9 | +0.72 | +2.52* | |
| Delayed (20 min) Recall (Max = 12) | +0.33 | +1.67 | -0.12 | -1 | +1.67 | +1.34 | -0.45 | -1.33 | +1.34 | |
| Recognition Discrimination Index: (Recognition Hits minus Recognition False Alarms) | -2.36 | +0.42 | +0.42 | +0.42 | +0.42 | +2.78* | +2.78* | +2.78* | +2.78* | |

* \geq 2 SD Improvement; Tx, Treatment

Supplementary Table 3B. P1. Results for Questionnaires, Raw Scores and Changes, for In-Office and At-Home tLED Series.

| Self-rated Questionnaires Lower Scores Better, all Questionnaires | Raw Scores | | | | | Change in Raw Scores | | | |
|--|------------|---------------------------------|----------------------------------|-----------------------------------|---------------------------|-----------------------------|------------------------------|-------------------------------|-------------------------------------|
| | Pre-Tx | 1 week Post- 18 Office Tx | 1 month Post- 18 Office Tx | 2 months Post- 18 Office Tx | 3 months of Home Tx | Pre-Tx to 1 week Post | Pre-Tx to 1 month Post | Pre-Tx to 2 months Post | Pre-Tx to 3 months of Home Tx |
| PTSD Checklist- Civilian PCL-C (Max = 85) (Min = 17) | 58 | 25 | 32 | 47 | 23 | -33 | -26 | -11 | -35 |
| Beck Depression Inventory II (Max = 63) | 24 | 1 | 0 | 9 | 0 | -23 | -24 | -15 | -24 |
| Pittsburgh Sleep Quality Index Global PSQI Score (Max = 21) | 9 | 2 | 3 | 4 | 1 | -7 | -6 | -5 | -8 |
| VAS Pain Scale (0-10) | 2 | 0 | 0 | 2 | 0 | -2 | -2 | 0 | -2 |
| Short Form McGill Pain Questionnaire Over last 30 days (Max = 45) | 21 | 10 | 2 | 4 | 0 | -11 | -19 | -17 | -21 |
| Dysexecutive Questionnaire (Max = 80) | 25 | 22 | 5 | 18 | 5 | -3 | -20 | -7 | -20 |
| Tinnitus Handicap Inventory (Max = 100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vestibular Disorders ADL Scale (Max = 280) | 40 | 30 | 28 | 28 | 28 | -10 | -12 | -12 | 12 |

Tx, treatment; PTSD, Post Traumatic Stress Disorder; PCL-C, PTSD Checklist- Civilian Version; ADL, Activities of Daily Living

Supplementary Table 4A. P2. Results for Neuropsychological Tests, Z-Scores and Changes, for In-Office tLED Series only.

| Neuropsychological Tests | Pre-Tx | Z-Scores | | | Changes in Z-Scores | | |
|--|----------|---------------------------|----------------------------|-----------------------------|-----------------------|------------------------|-------------------------|
| | | 1 week Post- 18 Office Tx | 6 weeks Post- 18 Office Tx | 12 weeks Post- 18 Office Tx | Pre-Tx to 1 week Post | Pre-Tx to 6 weeks Post | Pre-Tx to 12 weeks Post |
| Stroop: Color Word Interference Test | | | | | | | |
| Trial 3 | +0.33 | +0.67 | +0.33 | +1 | +0.34 | 0 | +0.67 |
| Trial 4 | +0.33 | +0.67 | +1 | +1 | +0.34 | +0.67 | +0.67 |
| California Verbal Learning Test II | | | | | | | |
| Total Trials 1-5 (Max = 80) | -0.80 | +0.60 | +2.10 | +1.38 | +1.40 | +2.90* | +2.18* |
| Short Delay, Free Recall (Max = 16) | -1 | 0 | +1 | +2 | +1 | +2* | +3* |
| Short Delay, Cued Recall (Max = 16) | -1.50 | -0.50 | +2 | +2 | +1 | +3.5* | +3.5* |
| Long Delay (20 min), Free Recall (Max = 16) | -1.50 | +0.50 | +1.50 | +1.50 | +2* | +3* | +3* |
| Long Delay (20 min), Cued Recall (Max = 16) | -1.50 | +0.50 | +1.50 | +1.50 | +2* | +3* | +3* |
| Controlled Oral Word Association Test (FAS or BHR) | | | | | | | |
| (No Max; 60 s per Letter) | 28 words | 45 words | 52 words | 44 words | +17 words | +24 words | +16 words |
| Continuous Performance Test | | | | | | | |
| Correct Detections | DNT | -0.40 | +1.30 | DNT | - | - | - |
| False Alarm Rate | DNT | -0.40 | -0.60 | DNT | - | - | - |
| d prime | DNT | -0.67 | -1.30 | DNT | - | - | - |
| Brief Visuospatial Memory Test- Revised | | | | | | | |
| Trial 1 (Immediate Recall) (Max = 12) | -1.33 | +0.70 | -0.80 | +0.16 | +2.03* | +0.53 | +1.49 |
| Total Recall (Max = 36) | -1.40 | +0.05 | -0.24 | -0.43 | +1.45 | +1.16 | +0.97 |
| Delayed (20 min) Recall (Max = 12) | -1.86 | -0.40 | +0.10 | -0.40 | +1.46 | +1.96 | +1.46 |
| Recognition Discrimination Index: (Recognition Hits minus Recognition False Alarms) | +0.50 | +0.50 | +0.50 | +0.50 | 0 | 0 | 0 |

* \geq 2 SD Improvement; Tx, Treatment

Supplementary Table 4B. P2. Results for Questionnaires, Raw Scores and Changes, for In-Office and At-Home tLED Series.

| Self-rated Questionnaires Lower Scores Better, all Questionnaires | Raw Scores | | | | | Changes in Raw Scores | | | |
|--|------------|---------------------------------|----------------------------------|-----------------------------------|---------------------------|------------------------------|-------------------------------|--------------------------------|--------------------------------------|
| | Pre-Tx | 1 week Post- 18 Office Tx | 6 weeks Post- 18 Office Tx | 12 weeks Post- 18 Office Tx | 3 months of Home Tx | Pre- Tx to 1 week Post | Pre- Tx to 6 weeks Post | Pre- Tx to 12 weeks Post | Pre- Tx to 3 months of Home Tx |
| PTSD Checklist- Civilian PCL-C (Max = 85) (Min = 17) | 37 | 25 | 32 | 34 | 28 | -12 | -5 | -3 | -9 |
| Beck Depression Inventory II (Max = 63) | 27 | 18 | 19 | 19 | 15 | -9 | -8 | -8 | -12 |
| Pittsburgh Sleep Quality Index Global PSQI Score (Max = 21) | 7 | 5 | 5 | 5 | 5 | -2 | -2 | -2 | -2 |
| VAS Pain Scale (0-10) | 4 | 3 | 0 | 7 | 3 | -1 | -4 | +3 | -1 |
| Short Form McGill Pain Questionnaire Over last 30 days (Max = 45) | 9 | 0 | 0 | 9 | 2 | -9 | -9 | 0 | -7 |
| Dysexecutive Questionnaire (Max = 80) | 28 | 19 | 23 | 22 | 17 | -9 | -5 | -6 | -11 |
| Tinnitus Handicap Inventory (Max = 100) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vestibular Disorders ADL Scale (Max = 280) | 28 | 28 | 28 | 28 | 28 | 0 | 0 | 0 | 0 |

Tx, treatment; PTSD, Post Traumatic Stress Disorder; PCL-C, PTSD Checklist- Civilian Version; ADL, Activities of Daily Living

Supplementary Table 5A. P3. Results for Neuropsychological Tests, Z-Scores and Changes, for In-Office tLED Series.

| Neuropsychological Tests | Pre-Tx | Z-Scores | | Changes in Z-Scores | | |
|--|----------|---------------------------|----------------------------|-----------------------|------------------------|--|
| | | 1 week Post- 18 Office Tx | 1 month Post- 18 Office Tx | Pre-Tx to 1 week Post | Pre-Tx to 1 month Post | |
| Stroop: Color Word Interference Test | | | | | | |
| Trial 3 | -2 | -3 | -0.33 | -1 | +1.67 | |
| Trial 4 | -1 | -1.67 | -0.33 | -0.67 | +0.67 | |
| California Verbal Learning Test II | | | | | | |
| Total Trials 1-5 (Max = 80) | -1.25 | -0.12 | +0.90 | +0.25 | 2.15* | |
| Short Delay, Free Recall (Max = 16) | -2 | -0.5 | -0.50 | +1.50 | +1.50 | |
| Short Delay, Cued Recall (Max = 16) | -2 | -1 | +0.50 | +1 | +2.50* | |
| Long Delay (20 min), Free Recall (Max = 16) | -1.50 | -0.50 | 0 | +1 | +1.50 | |
| Long Delay (20 min), Cued Recall (Max = 16) | -1.50 | -1 | 0 | +0.50 | +1.50 | |
| Controlled Oral Word Association Test (FAS or BHR) | -1.94 | -1.04 | -2.03 | +0.90 | -0.09 | |
| (No Max; 60 s per Letter) | 23 words | 33 words | 22 words | +10 words | -1 word | |
| Continuous Performance Test | | | | | | |
| Correct Detections | +2.60 | +1.78 | +1.10 | +0.82 | +1.50 | |
| False Alarm Rate | -0.12 | -1.30 | -1.50 | -1.18 | -1.38 | |
| d prime | -0.48 | -1.33 | -2.50 | -0.85 | -2.02* | |
| Brief Visuospatial Memory Test-Revised | | | | | | |
| Trial 1 (Immediate Recall) (Max = 12) | -1.33 | -1.33 | -1.33 | 0 | 0 | |
| Total Recall (Max = 36) | -2.32 | -2.32 | -1.57 | 0 | +0.75 | |
| Delayed (20 min) Recall (Max = 12) | -2.35 | -1.37 | -1.37 | +0.98 | +0.98 | |
| Recognition Discrimination Index: (Recognition Hits minus Recognition False Alarms) | -2.95 | -1.22 | -1.22 | +1.73 | +1.73 | |

* \geq 2 SD Improvement; Tx, Treatment

Supplementary Table 5B. P3. Results for Questionnaires, Raw Scores and Changes, for In-Office tLED Series.

| | Raw Scores | | | Changes in Raw Scores | |
|--|------------|---------------------------|----------------------------|----------------------------------|-----------------------------------|
| | Pre-Tx | 1 week Post- 18 Office Tx | 1 month Post- 18 Office Tx | Pre-Tx to Post- 1 week Office Tx | Pre-Tx to Post- 1 month Office Tx |
| Self-rated Questionnaires Lower Scores Better, all Questionnaires | | | | | |
| PTSD Checklist- Civilian PCL-C Max = 85) (Min = 17) | 65 | 27 | 30 | -38 | -35 |
| Beck Depression Inventory II (Max = 63) | 28 | 15 | 12 | -13 | -16 |
| Pittsburgh Sleep Quality Index Global PSQI Score (Max = 21) | 9 | 6 | 7 | -3 | -2 |
| VAS Pain Scale (0-10) | 7 | 3 | 5.5 [‡] | -4 | -1.5 [‡] |
| Short Form McGill Pain Questionnaire Over last 30 days (Max = 45) | 34 | 4 | 6 [‡] | -30 | -28 [‡] |
| Dysexecutive Questionnaire (Max = 80) | 33 | 4 | 4 | -29 | -29 |
| Tinnitus Handicap Inventory (Max = 100) | 52 | 20 | 16 | -32 | -36 |
| Vestibular Disorders ADL Scale (Max = 280) | 62 | 39 | 30 | -24 | -32 |

Tx, treatment; PTSD, post traumatic stress disorder; PCL-C, PTSD Checklist-Civilian Version; ADL, Activities of Daily Living

[‡]Discontinued two narcotic pain medications

Supplementary Table 6A. P4. Results for Neuropsychological Tests, Z-Scores and Changes, for In-Office tLED Series.

| Neuropsychological Tests | Pre-Tx | Z-Scores | | Changes in Z-Scores | | |
|---|----------|----------------------------|-----------------------------|-------------------------|--------------------------|--|
| | | 1 month Post- 18 Office Tx | 5 months Post- 18 Office Tx | Pre- Tx to 1 month Post | Pre- Tx to 5 months Post | |
| Stroop: Color Word Interference Test | | | | | | |
| Trial 3 | -0.33 | +0.33 | +0.67 | +0.66 | +1 | |
| Trial 4 | 0 | 0 | -1.67 | 0 | -1.67 | |
| California Verbal Learning Test II | | | | | | |
| Total Trials 1-5 (Max = 80) | -0.12 | -0.50 | -0.75 | -0.38 | -0.63 | |
| Short Delay, Free Recall (Max = 16) | -1 | -1 | -2.50 | 0 | -1.50 | |
| Short Delay, Cued Recall (Max = 16) | -1 | -1.50 | -2.50 | -0.50 | -1.50 | |
| Long Delay (20 min), Free Recall (Max = 16) | -2.50 | -1 | -1.50 | +1.50 | +1 | |
| Long Delay (20 min), Cued Recall (Max = 16) | -2.50 | -1.50 | -1.5 | +1 | +1 | |
| Controlled Oral Word Association Test | | | | | | |
| (FAS or BHR) | -1.4 | -0.74 | -0.33 | +0.66 | +1.07 | |
| (No Max; 60 s per Letter) | 25 words | 33 words | 38 words | +8 words | +13 words | |
| Continuous Performance Test | | | | | | |
| Correct Detections | -0.30 | +1.30 | +1.5 | +1.60 | +1.80 | |
| False Alarm Rate | +0.60 | -0.40 | +0.25 | -1 | -0.35 | |
| d prime | +0.30 | -0.25 | +0.40 | -0.55 | +0.10 | |
| Brief Visuospatial Memory Test-Revised | | | | | | |
| Trial 1 (Immediate Recall) (Max = 12) | -1.42 | N/A | N/A | - | - | |
| Total Recall (Max = 36) | -1.89 | N/A | N/A | - | - | |
| Delayed (20 min) Recall (Max = 12) | -1.67 | -0.03 | N/A | +1.64 | - | |
| Recognition Discrimination Index: (Recognition Hits minus Recognition False Alarms) | 0.40 | N/A | N/A | - | - | |

Tx, Treatment

Supplementary Table 6B. P4. Results for Questionnaires, Raw Scores and Changes, for In-Office tLED Series.

| | Raw Scores | | | | Changes in Raw Scores | | |
|--|------------|---------------------------|----------------------------|-----------------------------|------------------------|------------------------|-------------------------|
| | Pre-Tx | 1 week Post- 18 Office Tx | 1 month Post- 18 Office Tx | 5 months Post- 18 Office Tx | Pre- Tx to 1 week Post | Pre-Tx to 1 month Post | Pre-Tx to 5 months Post |
| Self-rated Questionnaires Lower Scores Better, all Questionnaires | | | | | | | |
| PTSD Checklist- Civilian PCL-C (Max = 85) (Min = 17) | 33 | 25 | 17 | 22 | -8 | -16 | -11 |
| Beck Depression Inventory II (Max = 63) | 7 | 3 | 0 | 2 | -4 | -7 | -5 |
| Pittsburgh Sleep Quality Index Global PSQI Score (Max = 21) | 8 | 8 | 5 | 6 | 0 | -3 | -2 |
| VAS Pain Scale (0-10) | 4 | 5 | 3.5 | 5 | +1 | -0.5 | +1 |
| Short Form McGill Pain Questionnaire Over last 30 days (Max = 45) | 22 | 4 | 10 | 10 | -18 | -12 | -12 |
| Dysexecutive Questionnaire (Max = 80) | 19 | 15 | 15 | 10 | -4 | -4 | -9 |
| Tinnitus Handicap Inventory (Max = 100) | 14 | 38 | 6 | 10 | +24 | -8 | -4 |
| Vestibular Disorders ADL Scale (Max = 280) | 44 | 30 | 30 | 35 | -14 | -14 | -9 |

Tx, treatment; PTSD, post traumatic stress disorder; PCL-C, PTSD Checklist-Civilian Version; ADL, Activities of Daily Living

Supplementary Table 7. Repeated measures ANOVAs for Behavior/Mood Questionnaires, four Ex-Football Players as a Group, Pre- /Post- tLED.

| | | TIME | | |
|--|---|-------------|---------------------|----------------------|
| | | Pre- | Post- 1 week | Post- 1 month |
| PCL-C PTSD | Mean | 48.25 | 25.5 | 27.75 |
| | SD | 15.65 | 1 | 7.23 |
| | N | 4 | 4 | 4 |
| | Pre-/Post- 1 week | | p<0.056 | |
| | Pre-/Post- 1 month | | | p<0.050 |
| | Within-Subject Effect TIME, F=8.55 | | | p<0.017 |
| BDI Depression | Mean | 21.75 | 9.25 | 7.75 |
| | SD | 10.01 | 8.5 | 9.39 |
| | N | 4 | 4 | 4 |
| | Pre-/Post- 1 week | | p<0.051 | |
| | Pre-/Post- 1 month | | | p<0.036 |
| | Within-Subject Effect TIME, F=11.254 | | | p<0.009 |
| Short Form, McGill Pain Questionnaire | Mean | 21.5 | 4.5 | 4.5 |
| | SD | 10.21 | 4.12 | 4.44 |
| | N | 4 | 4 | 4 |
| | Pre-/Post- 1 week | | p<0.037 | |
| | Pre-/Post- 1 month | | | p<0.028 |
| | Within-Subject Effect TIME, F=11.796 | | | p<0.008 |
| Pittsburgh Sleep Quality Index | Mean | 8.25 | 5.25 | 5 |
| | SD | 0.957 | 2.5 | 1.63 |
| | N | 4 | 4 | 4 |
| | Pre-/Post- 1 week | | p<0.134 | |
| | Pre-/Post- 1 month | | | p<0.041 |
| | Within-Subject Effect TIME, F=4.958 | | | p<0.054 |

Supplementary Table 8. Correlations between **Saliency Network** Average Functional Connectivity, with Neuropsychological Test Scores, and Behavior/Mood Questionnaire Ratings across all time points, Pre- and Post- tLED, for each case.

| | P1 | | P2 | | P4 | |
|--|-----------|------------|-----------|------------|-----------|------------|
| | p | rho | p | rho | p | rho |
| Neuropsychological Tests | | | | | | |
| Stroop Trial 3 | 0.018 | 0.939 | 0.008 | 0.992 | 0.215 | 0.945 |
| Stroop Trial 4 | 0.020 | 0.934 | 0.479 | 0.521 | 0.635 | -0.543 |
| CVLT total trials | 0.589 | 0.329 | 0.658 | 0.342 | 0.226 | -0.938 |
| CVLT short delay free recall | 0.997 | -0.003 | 0.259 | 0.741 | 0.635 | -0.543 |
| CVLT short delay cued recall | 0.359 | -0.529 | 0.525 | 0.475 | 0.423 | -0.788 |
| CVLT long delay free recall | 0.165 | 0.726 | 0.460 | 0.540 | 0.228 | -0.936 |
| CVLT long delay cued recall | 0.109 | 0.794 | 0.460 | 0.540 | 0.228 | -0.936 |
| COWAT | 0.105 | 0.798 | 0.771 | 0.229 | 0.216 | 0.943 |
| CPT False alarm rate | 0.030 | -0.914 | NaN | NaN | 0.474 | -0.735 |
| CPT d prime | 0.038 | -0.899 | NaN | NaN | 0.790 | -0.324 |
| BVMT-R immediate recall | 0.228 | 0.657 | 0.312 | 0.688 | NaN | NaN |
| BVMT-R total recall | 0.245 | 0.640 | 0.633 | 0.367 | NaN | NaN |
| BVMT-R delayed recall | 0.173 | 0.717 | 0.676 | 0.324 | NaN | NaN |
| BVMT-R recognition discrimination index | 0.167 | 0.723 | NaN | NaN | NaN | NaN |
| Behavior/Mood Questionnaires, Ratings | | | | | | |
| PTSD | 0.008 | -0.964 | 0.874 | -0.126 | 0.275 | -0.725 |
| BDI | 0.056 | -0.869 | 0.485 | -0.515 | 0.222 | -0.778 |
| PSQI | 0.049 | -0.880 | 0.469 | -0.531 | 0.681 | -0.319 |
| SF-MPQ | 0.366 | -0.523 | 0.665 | 0.335 | 0.008 | -0.992 |
| DEX | 0.529 | -0.379 | 0.487 | -0.513 | 0.320 | -0.680 |

Significant correlations are in red.

CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test (letters FAS, alternating letters BHR); CPT, Continuous Performance Test; PTSD, Post-traumatic Stress Disorder Checklist, Civilian; BDI, Beck Depression Inventory II; PSQI, Pittsburgh Sleep Quality Index, Global PSQI Score; SF-MPQ, Short Form, McGill Pain Questionnaire; DEX, Dysexecutive Questionnaire; NaN, no available number.

Supplementary Table 9. Correlations between **Central Executive Network** Average Functional Connectivity, with Neuropsychological Test Scores, and Behavior/Mood Questionnaire Ratings across all time points, Pre- and Post- tLED, for each case.

| | P1 | | P2 | | P4 | |
|--|--------------|---------------|-----------|------------|-----------|------------|
| | p | rho | p | rho | p | rho |
| Neuropsychological Tests | | | | | | |
| Stroop Trial 3 | 0.097 | 0.809 | 0.060 | 0.940 | 0.134 | 0.978 |
| Stroop Trial 4 | 0.128 | 0.769 | 0.399 | 0.601 | 0.554 | -0.644 |
| CVLT total trials | 0.577 | 0.339 | 0.584 | 0.416 | 0.145 | -0.974 |
| CVLT short delay, free recall | 0.754 | -0.194 | 0.176 | 0.824 | 0.554 | -0.644 |
| CVLT short delay, cued recall | 0.314 | -0.572 | 0.403 | 0.597 | 0.342 | -0.859 |
| CVLT long delay, free recall | 0.011 | 0.956 | 0.416 | 0.584 | 0.148 | -0.973 |
| CVLT long delay, cued recall | 0.009 | 0.960 | 0.416 | 0.584 | 0.148 | -0.973 |
| COWAT | 0.274 | 0.610 | 0.752 | 0.248 | 0.136 | 0.977 |
| CPT False alarm rate | 0.057 | -0.866 | NaN | NaN | 0.555 | -0.644 |
| CPT d prime | 0.079 | -0.835 | NaN | NaN | 0.870 | -0.202 |
| BVMT-R immediate recall | 0.329 | 0.557 | 0.466 | 0.534 | NaN | NaN |
| BVMT-R total recall | 0.508 | 0.397 | 0.720 | 0.280 | NaN | NaN |
| BVMT-R delayed recall | 0.546 | 0.365 | 0.665 | 0.335 | NaN | NaN |
| BVMT-R recognition discrimination index | 0.106 | 0.797 | NaN | NaN | NaN | NaN |
| Behavior/Mood Questionnaires, Ratings | | | | | | |
| PTSD/PCL-C | 0.060 | -0.863 | 0.952 | 0.048 | 0.253 | -0.747 |
| BDI | 0.032 | -0.909 | 0.540 | -0.460 | 0.285 | -0.715 |
| PSQI | 0.092 | -0.816 | 0.499 | -0.501 | 0.086 | -0.914 |
| Short Form, McGill Pain | 0.292 | -0.593 | 0.588 | 0.412 | 0.812 | -0.188 |
| DEX | 0.428 | -0.467 | 0.615 | -0.385 | 0.243 | -0.757 |

Significant correlations are in **red**.

CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test (letters FAS, alternating letters BHR); CPT, Continuous Performance Test; PTSD, Post-traumatic Stress Disorder Checklist, Civilian; BDI, Beck Depression Inventory II; PSQI, Pittsburgh Sleep Quality Index, Global PSQI Score; SF-MPQ, Short Form, McGill Pain Questionnaire; DEX, Dysexecutive Questionnaire; NaN, no available number.

Supplementary Table 10. Correlations between **Default Mode Network** Average Functional Connectivity, with Neuropsychological Test Scores, and Behavior/Mood Questionnaire Ratings across all time points, Pre- and Post- tLED, for each case.

| | P1 | | P2 | | P4 | |
|--|-----------|------------|-----------|------------|-----------|------------|
| | p | rho | p | rho | p | rho |
| Neuropsychological Tests | | | | | | |
| Stroop Trial 3 | 0.863 | -0.108 | 0.079 | 0.921 | 0.535 | -0.667 |
| Stroop Trial 4 | 0.856 | -0.113 | 0.350 | 0.650 | 0.115 | 0.984 |
| CVLT total trials | 0.690 | -0.246 | 0.461 | 0.539 | 0.524 | 0.680 |
| CVLT short delay, free recall | 0.172 | -0.718 | 0.251 | 0.749 | 0.115 | 0.984 |
| CVLT short delay, cued recall | 0.782 | 0.172 | 0.469 | 0.531 | 0.328 | 0.870 |
| CVLT long delay, free recall | 0.329 | 0.558 | 0.278 | 0.722 | 0.522 | 0.682 |
| CVLT long delay, cued recall | 0.637 | 0.290 | 0.278 | 0.722 | 0.522 | 0.682 |
| COWAT | 0.789 | -0.166 | 0.467 | 0.533 | 0.534 | -0.668 |
| CPT False alarm rate | 0.707 | -0.232 | NaN | NaN | 0.775 | -0.345 |
| CPT d prime | 0.793 | -0.163 | NaN | NaN | 0.460 | -0.750 |
| BVMT-R immediate recall | 0.929 | 0.056 | 0.102 | 0.898 | NaN | NaN |
| BVMT-R total recall | 0.500 | -0.404 | 0.279 | 0.721 | NaN | NaN |
| BVMT-R delayed recall | 0.632 | -0.293 | 0.384 | 0.616 | NaN | NaN |
| BVMT-R recognition discrimination index | 0.963 | -0.029 | NaN | NaN | NaN | NaN |
| Behavior/Mood Questionnaires, Ratings | | | | | | |
| PTSD/PCL-C | 0.967 | 0.026 | 0.490 | -0.510 | 0.990 | 0.010 |
| BDI | 0.865 | -0.107 | 0.190 | -0.810 | 0.941 | 0.059 |
| PSQI | 0.824 | 0.139 | 0.197 | -0.803 | 0.855 | -0.145 |
| Short Form, McGill Pain | 0.972 | 0.022 | 0.907 | -0.093 | 0.576 | 0.424 |
| DEX | 0.702 | -0.236 | 0.173 | -0.827 | 0.242 | 0.758 |

CVLT, California Verbal Learning Test-II; COWAT, Controlled Oral Word Association Test (letters FAS, alternating letters BHR); CPT, Continuous Performance Test; PTSD, Post-traumatic Stress Disorder Checklist, Civilian; BDI, Beck Depression Inventory II; PSQI, Pittsburgh Sleep Quality Index, Global PSQI Score; SF-MPQ, Short Form, McGill Pain Questionnaire; DEX, Dysexecutive Questionnaire; NaN, no available number