Significant Improvements in Cognitive Performance Post-Transcranial, Red/Near-Infrared Light-Emitting Diode...

Article in Journal of neurotrauma · February 2014
DOI: 10.1089/neu.2013.3244 · Source: PubMed

CITATIONS
30

READS
284

9 authors, including:

Maxine H Krengel
Boston University
46 PUBLICATIONS 722 CITATIONS

Paula Martin
Boston University
24 PUBLICATIONS 1,355 CITATIONS

Michael Hamblin
Massachusetts General Hospital
576 PUBLICATIONS 16,524 CITATIONS

Errol Baker
U.S. Department of Veterans Affairs
82 PUBLICATIONS 5,707 CITATIONS

Some of the authors of this publication are also working on these related projects:

- Phototherapy in chronic diseases View project
- Posttraumatic Seizures Following Brain Injury View project
**Title:** Significant improvements on cognitive performance post-transcranial, red/near-infrared LED treatments in chronic, mild TBI: Open-protocol study

Running title (42 characters; allowed 45): Transcranial LED therapy to treat mild TBI

Table of Contents title: (75 characters; allowed 75): Significant improvement in executive function, post-LED treatments in mTBI

All authors’ names, degrees and affiliations:

Margaret A. Naeser, PhD (Corresponding Author)
VA Boston Healthcare System (12-A)
150 So. Huntington Ave.
Boston, MA 02130 U.S.A.
Research Professor of Neurology
Boston University School of Medicine
Boston, MA
email: mnaeser@bu.edu

Ross Zafonte, DO
Department of Physical Medicine and Rehabilitation
Harvard Medical School
Spaulding Rehabilitation Hospital
Massachusetts General Hospital
Brigham and Women’s Hospital
300 1st Avenue
Charlestown, MA 02129
email: RZAFONTE@PARTNERS.ORG

Maxine H. Krengel, PhD
Clinical and Research Neuropsychologist
VA Boston Healthcare System (116B)
150 So. Huntington Ave.
Boston, MA 02130 U.S.A.
Boston University School of Medicine
Department of Neurology
email: mhk@bu.edu

Paula I. Martin, PhD
VA Boston Healthcare System (12-A)
150 So. Huntington Ave.
Boston, MA 02130 U.S.A.
email: paulak@bu.edu

Judith Frazier, RN, MEd
Research Nurse Coordinator
TBI Research Program
Spaulding Rehabilitation Hospital
79/96 13th Street
Charlestown, MA 02129
email: JFRAZIER2@PARTNERS.ORG
Michael R. Hamblin, PhD
Wellman Center for Photomedicine, Massachusetts General Hospital, BAR 414
40 Blossom Street
Boston MA 02114 USA
Harvard-MIT Division of Health Sciences and Technology
Cambridge, MA
Associate Professor
Department of Dermatology, Harvard Medical School
e-mail: hamblin@helix.mgh.harvard.edu

Jeffrey A. Knight, PhD
Staff Psychologist
National Center for PTSD
VA Boston Healthcare System (116B-2)
150 So. Huntington Ave.
Boston, MA 02130
e-mail: Jeffrey.knight@va.gov

William P. Meehan III, MD
Director, Micheli Center for Sports Injury Prevention
Director, Sports Concussion Clinic, Boston Children’s Hospital
9 Hope Avenue, Suite 100
Waltham, MA 02453
e-mail: William.Meehan@childrens.harvard.edu

Errol H. Baker, PhD
Biostatistician/Research Psychologist
Center for Healthcare Organization and Implementation Research (CHOIR)
VA Boston Healthcare System (152M)
150 So. Huntington Ave.
Boston, MA 02130
e-mail: errol.baker@va.gov

Key Words: mild traumatic brain injury; mTBI; treatment for mTBI; photobiomodulation; executive function
Abstract (250 Words)

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 ATP important for cellular metabolism. Nitric oxide is released locally, increasing regional cerebral blood flow. LED therapy is non-invasive, painless, and non-thermal (FDA-cleared, non-significant risk device). Eleven chronic, mTBI participants (26-62 Yr, 6M) with non-penetrating head injury and persistent cognitive dysfunction were treated for 18 outpatient sessions (MWF, 6 Wks), starting at 10 Mo to 8 Yr post-mTBI (MVA or sports-related; and one participant, IED blast injury). Four had a history of multiple concussions. Each LED cluster head (2.1" diameter, 500mW, 22.2mW/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 Wk, 1 and 2 Mo post- the 18th treatment. A significant linear trend was observed for the effect of LED treatment over time for Stroop test for Executive Function, Trial 3 inhibition (p=.004); Stroop, Trial 4 inhibition switching (p=.003); California Verbal Learning Test (CVLT)-II, Total Trials 1-5 (p=.003); and CVLT-II, Long Delay Free Recall (p=.006). Participants reported improved sleep, and fewer PTSD symptoms, if present. Participants and family reported better ability to perform social, interpersonal and occupational functions. These open-protocol data suggest placebo controlled studies are warranted.
Introduction

Each year in the U.S., approximately 1.7 million patients are evaluated for traumatic brain injury (TBI), including three TBIs every minute. It is estimated there are 5.3 million Americans living with TBI-related disabilities. The annual economic cost is estimated to be between $60-$76.5 billion. The majority of cases (70-85%) are in the category of mild TBI (mTBI). Most of the civilian mTBI patients recover cognitive abilities within 3 months; however, the literature reports that between 5-22% of individuals have persistent symptoms.

Cognitive dysfunction associated with sports-related mTBI is of increasing concern, both for males and females (including children). Within the past 10 years, the diagnosis of concussion in high school sports has increased annually, by 16.5%.

It is estimated that 15-40% of soldiers returning from Iraq and Afghanistan as part of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) report at least one mTBI. Closed-head, blast injury is the signature injury, and the cognitive sequelae, recovery and rehabilitation are of increasing concern. Estimates are as high as 320,000 veterans who have returned with TBI, most with mTBI. Post-traumatic stress disorder (PTSD) is also a major concern with OEF/OIF soldiers who have experienced mTBI. Thus a compelling need exists to address chronic deficits in this population.

Cases of chronic mTBI often present clinically with deficits in attention, working memory, cognitive manipulation of temporal information, and general information processing speed. The most common complaints are in attention/concentration and working memory - i.e., the ability to hold information in mind, and to manipulate it in light of incoming material. At 6 months post-injury, indices of executive function were found to predict persistence of post-concussive syndrome, in mild and moderate TBI patients. In addition to cognitive problems, these patients are often unable to re-establish family and work relationships. Due to the diffuse nature of damage, however, no single behavioral outcome measure captures the multidimensional nature of mTBI outcome.
Rationale for present study

The present study examined whether the application of red and near-infrared (NIR) light, utilizing light-emitting diodes (LED) applied directly to the head could improve cognitive function, particularly executive function and verbal memory, in chronic, mTBI patients. Photons in the red and NIR wavelengths have potential to improve subnormal, cellular activity of brain tissue that has been damaged by brain trauma.

Scalp application of red and NIR light is a new application for LED technology. Over 30 years ago, however, it was observed in human cadaver studies that red (600nm) and NIR (800-900nm) wavelengths could penetrate through scalp and skull (approximately 1cm). Two physiological changes associated with exposure of cells to red and NIR wavelengths of light are:

1) Increased production of adenosine tri-phosphate (ATP) by the mitochondria; and
2) Increased vasodilation/regional cerebral blood flow (rCBF), explained below.

The last enzyme complex (cytochrome c oxidase) of the electron transport chain within the mitochondrial membrane is a photo-acceptor for red and NIR photons. There is mitochondrial damage and dysfunction after TBI. Increased ATP production by the mitochondria improves cellular respiration, oxygenation, and function. Also, in hypoxic/compromised cells, cytochrome c oxidase is inhibited by non-covalently bound nitric oxide. When the mitochondria are exposed to red/NIR photons, nitric oxide is released and diffused outside the cell wall, promoting local vasodilation and increased blood flow. The effect of the light is non-thermal.

Multiple animal studies using mice, show significantly better recovery of motor and cognitive function after NIR transcranial low-level laser therapy when treated in the acute post-injury phase. Most of this work has suggested improved energy kinetics and decreased inflammation as possible mechanisms for acute neuroprotection. Energetics may also have a role in the chronic phase of injury. We have reported that midline and bilateral, scalp application of red/NIR LED therapy improved executive function and verbal memory in two case reports.
with chronic, traumatic brain injury.\textsuperscript{41} One TBI patient with a history of multiple concussions (retired military) who had been on medical disability for 5 months prior to transcranial LED treatments, returned to full-time employment after 4 months of nightly, home LED treatments.

We undertook a pilot, open-protocol study among patients with chronic, mTBI who received the same number of specific, transcranial LED treatments. Pre- and post-neuropsychological testing and psychological measurements were acquired out to 2 months after the last LED treatment, in order to evaluate its potential to improve chronic symptomatology.

Materials and Methods

Design

We utilized a case series design.\textsuperscript{42}

Participants

Eleven, chronic, mTBI cases with non-penetrating head injury (6M) participated. Their ages ranged from 26-62 Yr. at time of entry (mean, 44.3 Yr.; SD, 13.7) and the time post-mTBI ranged from 10 months to 8 years (mean, 38.2 Mo., SD, 29.4). Their demographics including medical history for mTBI, years of education and work status are provided in Table 1.

[Table 1]

All participants had previously been diagnosed as having mTBI, with loss of consciousness (LOC) lasting 30 minutes or less (or no LOC); and with a period of altered mental status that could include post-traumatic amnesia - "memory gaps" or confusion lasting up to 24 hours. To be included in the study, persistent cognitive problems consistent with a diagnosis of mTBI were present for at least 6 months prior to screening cognitive testing. Exclusion criteria included moderate or severe TBI; penetrating head injury; or history of craniotomy or craniectomy. Medical records were obtained, and each participant was examined by a single experienced study clinician prior to referral for screening cognitive testing. Participants were requested not to change their medications or dosages during participation in the study.
Prior to official enrollment into the study, all subjects signed IRB-approved informed consent forms approved by the Spaulding Rehabilitation Hospital, Institutional Review Board. All study procedures complied with the IRB and with The Health Insurance Portability and Accountability Act (HIPAA) standards.

Screening, Cognitive Testing

In addition to the criteria mentioned above, in order to qualify for entry into the study each participant needed to score at least 2 SD below average on one, or 1 SD below average on at least two of the following neuropsychological (NP) tests (using age and education-adjusted norms): 1) Trail Making Test, Trails A and Trails B, measuring problem-solving, thinking flexibility, and planning.\(^{43}\) 2) Controlled Oral Word Association Test (COWAT)/FAS Test, total words generated for the letters F, A and S (one minute per letter), measuring verbal fluency and categorical generative capacity.\(^{44,45}\) 3) California Verbal Learning Test-II, examining aspects of verbal learning, organization, and memory.\(^{46}\) 4) Stroop Test for Executive Function, examining attention, mental speed, mental control, inhibition and inhibition switching.\(^{47}\)

NP Tests Administered Pre-/Post- the LED Treatment Series

The participants were tested four times during participation in the study: 1) Pre-testing, within one week before the first LED treatment; 2) Post-testing, within one week after the final (18\(^{th}\)) LED treatment; 3) at 1 month after the final LED treatment; and 4) at 2 months after the final LED treatment. The tests administered at all four testing times included the following: 1) Stroop Test for Executive Function;\(^{47}\) 2) California Verbal Learning Test-II (CVLT-II) with Alternating Versions, with Short Delay Free Recall; Short Delay Cued Recall; Long Delay (20 minutes later) Free Recall; and Long Delay Cued Recall, for each testing session;\(^{46}\) 3) Delis-Kaplan Executive Function (D-KEF) - Trails Test (Delis, Kaplan, Kramer, 2001);\(^{47}\) 4) Controlled Oral Word Association Test (COWAT)/FAS Test, total words generated, for the letters F, A and S;\(^{44,45}\) and Digit Span, Forwards and Backwards, WAIS-IV.\(^{48}\) Some of the tests administered at screening were carried over to serve as pre-treatment/baseline scores at Time 1.
In order to avoid practice effects, alternating versions of the NP tests were used at the post-LED testing times, when possible. This included the CVLT-II, Alternating Versions for the 16 words presented, and the alternate form of the FAS test, using the 3 different letters B, H, and R. A consistent practice effect for repeated presentations of the Stroop test has not been demonstrated.

In addition, psychological measurements included the PTSD Checklist–Civilian (PCL-C), the Beck Depression Inventory-II (BDI), and the Visual Analog Scale (VAS) for pain (0-10, verbal report).

LED Device and LED Treatment Method

Two identical, LED Console Units were used (MedX Health, Model 1100, Toronto). Each Console Unit had three LED cluster heads. This device was FDA-cleared as non-significant risk in 2003 (FDA-cleared for home treatment, 2005). A sample LED cluster head is shown in Fig 1. Each LED cluster head had a 2.1-inch diameter (9 red diodes, 633nm, and 52 NIR diodes, 870nm were embedded into each LED cluster head); 22.48 cm² in size; 500mW total power; 22.2mW/cm² power density; continuous wave. The power output (500mW) for each LED cluster head was verified pre- and post- the LED treatments using the MedX MEDRAD200X Radiometer System.

Table 2 lists the LED cluster head placements on the head that were used at each visit (Set A for 10 minutes, followed immediately by Set B for 10 minutes), and approximate surface brain cortex areas that were impacted with the red/NIR LEDs. The LED placement loci included, in part, a proposed paradigm to target nodes within the default mode network (DMN) and the salience network (SN), areas where functional connectivity MRI studies have reported abnormalities in TBI. The LED placement loci also included dorsolateral prefrontal cortex (DLPFC), part of the central executive network (CEN). SI Fig 1 shows location of extra-cranial bone and suture landmarks on the skull, in relationship to approximate surface brain cortex.
areas. In the present study, the LED placements were hypothesized to impact the immediate subjacent, surface cortical areas, although this is unknown.

[Table2]

[SI Fig1]

At each visit, six, 2.1-inch diameter LED cluster heads were applied simultaneously for 10 minutes during Set A, and then immediately after Set A, the LED placement loci were changed, and Set B was treated for 10 minutes [energy density, 13 Joules/cm² (J/cm²) per each LED cluster head placement]. It was estimated that up to 3% (0.4 J/cm²) could reach surface brain cortex although this is unknown in humans (M. Hamblin, personal observation).^{28,55} Patients were treated in a recliner chair, and the total LED treatment time per visit was 20 minutes. The LED cluster heads were held in place with a soft nylon cap. Due to the elastic tension from the cap, the location of the LED placements did not shift during each 10-minute treatment (Fig1).

The LED therapy is non-invasive, painless and non-thermal.^{36} Each participant received 18 treatments (MWF, minimum of 48 hours between treatments), for 6 weeks.

Statistical Analyses

The effect of LED treatments over time was examined for the following NP tests: Stroop Test for Executive Function (D-KEF); CVLT-II, Alternating Versions; D-KEF Trails Test; COWAT/FAS Test; Digit Span Forwards and Backwards. The psychological measures including BDI; PCL-C; and VAS for pain were also examined. These data were analyzed in a series of univariate one-way, repeated-measures analyses of variance (ANOVA) with trend analysis to examine changes following treatment and the pattern of change over time – pre- LED, and at 1 week, 1 month and 2 months post- the 18th LED treatment (SPSS, v.20). In the few instances where there was a missing data point, the group mean for that time point was used to estimate that score. To reduce the number of dependent variables, the co-linearity of those measures was computed (see SI Table1 for all bivariate correlations). When $r \geq 0.8$, only one of that pair of variables was analyzed. In order to correct for the number of comparisons, a conservative p-
value ($p<0.025$) was adopted. As this was a pilot study, several NP tests were used in order to identify a subset of outcome measures for a future, more statistically robust controlled study.

[SI_Table1]

Results

There were no significant correlations between age or years of education, and the pre-LED scores on the NP tests or psychological measures. Results showed a significant linear trend for the effect of LED treatment over time for the following NP tests: inhibition (Stroop test for executive function, Trial 3; $F = 14.228$, $df = 1$, $p = .004$); and inhibition switching (Stroop Trial 4; $F = 16.091$, $df = 1$, $p = .003$); verbal learning and memory (CVLT-II, Total Trials 1-5; $F = 14.470$, $df = 1$, $p = .003$); and CVLT-II, Long Delay Free Recall ($F = 11.873$, $df = 1$, $p = .006$). See Fig2A-D. Pre- and post- treatment NP data for each participant are provided in SITables2-5, and SI_Fig2, SI_Fig3.

[Fig2]

[SI_Table2, SI_Table3, SI_Table4, SI_Table5]

[SI_Fig2, SI_Fig3]

No other NP measures showed a significant effect of treatment over time (SI_Fig4A,B). A trend towards significance was observed for the psychological measure of depression (BDI) at 1-week post- treatment ($F = 5.412$, $df = 1$, $p = .045$) (SI_Fig4C and SI_Table6).

[SI_Fig4 and SI_Table6]

Using PTSD criteria established by Monson,56,57 only four participants initially reported symptoms suggestive of PTSD (scores $> 36/85$; for specialized medical clinics, such as TBI or pain). All four cases showed a clinically meaningful decrease or a reliable decrease post-LED (SI_Table7).

[SI_Table7]
No significant decrease or increase in VAS Pain Scale scores across time were observed for the five participants who reported pain at pre-treatment, when scores ranged from 2 to 4.5 on a 0-10 scale ($F = 1.398, \text{df} = 1, p = .303$). Reported changes in psychosocial adjustments post-LED from the participants and families are provided in Table 3. There were no adverse events or negative side effects.

[Table3]

Case Analyses

For each participant, SITable8 shows the pre-LED scores and the amount of change at 2 months post-LED, for three NP tests and the psychological measures of depression and PTSD.

[SITable8]

Neuropsychological Tests

The *level of severity at entry* (pre-LED) for each participant was examined in relationship to the amount of change present at 2 months post-LED treatment. For Stroop, Trial 4 inhibition switching, five participants entered with pre-LED scores of -1 to -3 SD below their age- and education-adjusted norms, and all five improved by +1 to +4 SD at 2 months post-LED (SITable8). Four of the 9 participants entered with pre-LED scores of 0 or +0.5 SD (average scores for their age and education), and two of these participants improved by +1.5 and +2 SD; and two participants showed no change. Thus, 5/5 participants who entered the study with more severe deficits on Stroop, Trial 4 inhibition switching (-1 to -3 SD) improved by at least 1 SD. Only half of the participants (2/4 participants) who entered with average scores (0 to 0.5 SD) improved by at least 1 SD.

For CVLT-II, Total Trials 1-5, three of the 10 participants entered with pre-LED scores of -1 to -1.5 SD below their norms, and all three improved by +1 to +2 SD at 2 months post-LED (SITable8). Six of the 10 participants entered with pre-LED scores of 0 or -0.5 SD (average scores), and three improved by +1.5 to +3 SD; and three participants showed no change. One participant entered at the level of +1 SD, and remained at that level, post-LED (P1). Thus, 3/3...
participants who entered the study with more severe deficits on CVLT-II, Total Trials 1-5 (-1 to -1.5 SD) improved by at least 1 SD. Half of the participants (3/6) who entered with average scores (0 to -0.5 SD), improved by at least 1 SD.

For CVLT-II, Long Delay Free Recall, seven of the participants entered with pre- LED scores of -1 to -3.5 SD below their norms, and five of these improved by +1 to +3.5 SD at 2 months post- LED; two participants showed no change (SI Table 8). Two of the 10 participants entered with pre- LED scores of 0 SD (average scores), and both of these participants improved by +1 to +1.5 SD. One participant entered at the level of +1.5 SD, and remained at that level, post- LED (P1). Thus, 5/7 participants who entered the study with more severe deficits on CVLT-II, Long Delay Free Recall (-1 to -3.5 SD), improved by at least +1 SD. Also, both participants who entered with average scores (0 SD), improved by +1 or +1.5 SD. On each of the above measures, not a single participant worsened.

Multiple Concussions

There were four participants who had a history of multiple concussions. At 2 months post- LED, two participants (P8, P11) improved on Stroop, Trial 4 inhibition switching, by +1 and +4 SD. Three participants (P7, P9, P11) improved on CVLT, Total Trials 1-5 by +1.5 or +3 SD. All four improved on CVLT, Long Delay Free Recall by +1 to +2.5 SD. None of these participants with multiple concussions reported moderate or severe depression, or presence of PTSD.

Psychological Measures

Depression

On the BDI, five of the 10 participants entered the study with moderate or severe depression scores (SI Tables 6 and 8). Of these five participants, three had a reduced level of depression at 2 months post- LED (P2, P6, P10), either from a severe level to moderate; or from moderate to minimal or mild. At the 1-week post- LED testing, four participants had reported a reduced level of depression (P2, P3, P6, P10). Three of them continued to report a reduced level at 1 month and 2 months post- LED (P2, P6, P10). For P3, however, the initial reduction in depression at 1
week and 1 month from severe to moderate, reverted back to severe at 2 months post-LED. In summary, 2/5 participants remained with severe or moderate depression at 2 months post-LED.

PTSD

Four participants entered the study with PCL-C scores suggestive of PTSD (scores > 36/85; for specialized medical clinics, such as TBI or pain).\textsuperscript{56,57} Using criteria established by Monson,\textsuperscript{56,57} a clinically meaningful decrease in PTSD severity is defined as a change of 10-20 points; and a reliable decrease is defined as a change of 5-10 points. All four participants who initially reported symptoms suggestive of PTSD showed a clinically meaningful decrease or a reliable decrease post-LED; however, data were available for only three of these participants at 2 months post-LED (SITables 7 and 8). These three participants first showed reduction in PCL-C scores at 1 week (P5, P10), or at 1 month post-LED testing (P3) and those improvements were still present at 2 months post-LED. Note, P4 only had post-LED testing at 1 week; however, at that time she too reported a clinically meaningful decrease in PCL-C scores. In summary, all four participants who entered with scores suggestive of PTSD reported a reduced level of PTSD post-LED.

PTSD plus Depression

Three participants entered with PTSD plus moderate or severe depression (P3, P5, P10). All three of these participants had a reduction in PCL-C scores, as first reported at the 1 week or 1 month post-LED testing; and retained at 2 months post-LED. However, only one of these three participants (P10) also reported a reduced level of depression at 1 week, 1 and 2 months post-LED. Thus, when PTSD and depression co-occurred, the improvements post-LED were not parallel. Better results were obtained for reducing PTSD, than decreasing depression at 2 months post-LED in this small sample (SITable6 and SITable7).
Discussion

This small pilot, open-protocol study using transcranial red/NIR LED therapy noted significant improvements in executive function (Stroop, Trial 3 inhibition; and Stroop, Trial 4 inhibition switching) and in verbal learning and memory (CVLT Total Trials 1-5; and Long Delay Free Recall), in chronic, mTBI patients. These participants had experienced persistent cognitive dysfunction, ranging from 10 months to 8 years. As is common with mTBI, heterogeneity was present among the 11 participants, including four with a history of multiple concussions. These findings are discussed separately below, and possible mechanisms associated with beneficial effects post-LED are presented.

Executive Function

In the area of executive function (Stroop, Trial 4 inhibition switching) there was variability in the entry levels across our mTBI participants. For example, in 5/9 participants (56%), the pre-LED levels were at least -1 SD below average; whereas 4/9 entered with average scores (age- and education-adjusted norms). All five participants who entered with below-average scores on the Stroop, Trial 4 inhibition switching, improved by +1 to +4.5 SD at 2 months post-LED. Variability in performance on Stroop inhibition switching was also recently observed among a large number of TBI cases who were studied with resting-state functional connectivity MRI (rs-fMRI), task-oriented functional MRI (fMRI) and diffusion tensor imaging (DTI). In that study, 20/46, 43% performed poorly on the stop signal reaction time (SSRT) task, with slower response inhibition (higher SSRT). These cases with slower reaction times in the NoGo condition were observed to have failure deactivating the DMN, particularly the precuneus/posterior cingulate cortex (precu/PCC) portion. Failure to properly deactivate the DMN during cognitive tasks that require rapid shifting of attention and inhibition has also been observed in other studies with TBI cases.

For the five mTBI participants in the present study who entered with below-average Stroop
inhibition switching scores, but who also improved by at least +1 to +4.5 SD post-LED, it is possible that nodes within the SN and/or the DMN were impacted post-LED, thus improving function and/or connections among these nodes. It is also possible that the red/NIR photons affected the DLPFC as well as the ACC, both of which have been shown to be active during functional imaging studies of the Stroop effect. Further mechanistic rs-fMRI and task-oriented fMRI studies would be warranted to explore these potential relationships.

Verbal Memory

The CVLT is a verbal, working memory task where increased activation on task-related fMRI is associated with DLPFC, and/or fronto-parietal areas. In the present study, all three participants who entered with scores at least -1 SD below average on the CVLT Total Trials 1-5, improved by +1 to +2 SD at 2 months post-LED. Also, a total of 5/7 participants who entered with scores at least -1 SD below average, on the CVLT Long Delay Free Recall, improved by +1 to +3.5 SD at 2 months post-LED. Although no rs-fMRI, or task-specific fMRI studies were part of this pilot study, specific LED placements may have had a beneficial, focal effect on specific nodes within the CEN.

Summary, NP Cognitive Tests

Each participant who entered this study (regardless of severity level at entry) improved by at least +1 SD on either the Stroop and/or the CVLT post-LED therapy. For example, on the Stroop (Trial 3 or 4), 9/11 cases improved by at least +1 SD, at the maximum post-LED, testing time available (SI Table 8). Also, on the CVLT, 7/11 cases improved by at least +1 SD (SI Table 8). Each of the two participants who did not improve by at least +1 SD on the Stroop post-LED (P7, P9), did improve on the CVLT by at least +1 SD. Thus, all cases improved by at least +1 SD on either the Stroop and/or the CVLT, post-LED; and 9/11 cases improved by at least +1 SD on both the Stroop (executive function) and the CVLT (verbal memory).
Depression

There was only a trend for significant change in depression at the 1-week post-LED testing (p = .045), and not an overall linear trend effect at 2 months post-LED. A total of only 5 participants had entered the study with moderate or severe depression. The pattern of initial reduction in depression at 1-week post-LED in 4/5 of these participants (but not an overall lasting change at 1 or 2 months post-LED), is similar to results observed in the Schiffer et al. study\textsuperscript{65} with 10 severe depression cases, where depression was significantly reduced at 2 weeks post- a single, NIR LED treatment to the left and right forehead areas, but scores returned towards baseline at 4 weeks post-LED. In both the Schiffer study,\textsuperscript{65} and our study, however, the post-LED depression scores did not return to the pre-LED levels.

Potential Mechanisms

Our study suggests a potential cognitive benefit (and reduction in PTSD symptoms) post-transcranial red/NIR LED therapy in chronic mTBI. Specific underlying physiological changes that occur post-LED therapy in this patient population are largely unknown. Data from animal and cellular studies, however, would suggest increase in ATP,\textsuperscript{29,33,66,67} diffusion of nitric oxide promoting vasodilation\textsuperscript{38} and rCBF in cortical areas,\textsuperscript{31} an increase in anti-oxidants\textsuperscript{68} and decreased inflammation\textsuperscript{39,69,70} as possible supporting mechanisms for improved function in the chronic stage.

Limitations of the present study

The results of this work should be interpreted with caution. This was a small-sample, open-protocol pilot study with 11 chronic, mTBI participants; no controls were studied. Although there was heterogeneity for etiology across the 11 participants, and four had a history of multiple concussions, all met the inclusion criteria for persistent cognitive deficits (at least 6-months post-injury), as tested at entry. It is possible that these deficits present at entry could have spontaneously improved without intervention due to passage of time, alone. A recent study, however, with over 140 TBI patients has reported that the overall problems present at 2 years
post-injury (cognitive, communication, behavioral and emotional that were present in 60% of the cases) persisted even at 10 years post-injury. Thus, in a chronic mTBI group such as ours, where 6/11 were >2 years post-TBI, significant improvements in cognition would not be expected. (Each of our 11 participants improved by at least +1 SD, on the Stroop and/or the CVLT, post-LED.) The potential impact of a placebo effect in this chronic mTBI population, however, should not be underestimated. The potential for placebo to impact anxiety and symptoms of well-being is clearly present and could have impacted the post-LED test results. The unusual cognitive improvement in this chronic, mTBI sample, however, suggests further exploration of the possible efficacy of transcranial red/NIR LED therapy for TBI in a larger, controlled study would be warranted.

Conclusions

A small number of chronic, mTBI cases (n=11), with non-penetrating head injury from diverse etiologies (MVA, sports-related, work- or home accident, and blast TBI) all improved by at least +1 SD on the Stroop test for executive function, and/or verbal learning and memory on the CVLT, post-LED therapy. Group statistical analyses with linear trend analysis showed significant improvements over time (out to 2 Mo post-LED) on the Stroop test for executive function - inhibition (p<.004); inhibition switching (p<.003); and verbal learning and memory – CVLT-II, Total Trials 1-5 (p<.003); Long Delay Free Recall (p<.006). In addition, patients who had symptoms compatible with PTSD at entry into the study reported either a clinically meaningful decrease, or a reliable decrease in symptoms post-LED therapy. These results should be interpreted with caution, however, because this was a small, open-protocol study with potential for a placebo effect. Future studies with a larger number of patients, including a control arm, are needed to determine the true effect of LED therapy.

Tests recommended as primary outcome measures in future studies include the Stroop test for executive function, and the CVLT-II (Alternating Versions) for verbal memory and learning; the COWAT/FAS test should also be considered. Future studies should segregate participants
with separate mechanisms of traumatic injury, and consider including groups with and without concurrent PTSD.

The optimum transcranial LED placements, as well as optimum LED treatment parameters such as wavelength, power density, and joules/cm$^2$ delivered to the scalp should be studied. A series of fMRI studies before and after the LED treatments would help to refine the LED placements, and examine whether changes have been made post-LED therapy in the functional connectivity networks often negatively impacted with TBI, including SN, DMN and CEN. Additional task-oriented fMRI and DTI studies would also provide invaluable information regarding the possible effects of transcranial red/NIR LED in the treatment of TBI.

Acknowledgements

M. Naeser was supported by the Clinical Sciences Research and Development, Department of Veterans Affairs. M.R. Hamblin was supported by US NIH grant R01AI050875. W.P. Meehan was supported by an American Medical Society for Sports Medicine (AMSSM) Young Investigator Award and an American College of Sports Medicine-American Medical Society for Sports Medicine Foundation Award. The content is solely the responsibility of the authors and does not necessarily represent the official views of the granting institutes. The authors thank Laura Burns, MBA, for assistance with participant enrollment; Iris Monge, for the LED treatments; and Anita Saltmarche, RN, MHSc, for assistance with acquisition of the LED units and LED methodology.

Author Disclosure Statement: No competing financial interests exist.
References


http://www.ptsd.va.gov/professional/pages/assessments/ptsd-checklist.asp


Figure Legends:
Figure 1. 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. The total treatment time per visit was 20 minutes; it was painless, noninvasive and nonthermal.
Figure 2.

A  
**Stroop Test for Executive Function:**  
Trial 3, Inhibition

B  
**Stroop Test for Executive Function:**  
Trial 4, Inhibition Switching

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

D  
**California Verbal Learning Test-II:**  
Long Delay Free Recall
Figure 2. 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).
Table 1. Demographics for 11 chronic, mTBI cases treated with transcranial, red/near-infrared light-emitting diode (LED) therapy.

<table>
<thead>
<tr>
<th>ID Number</th>
<th>Age at Entry</th>
<th>Gender</th>
<th>Time post-TBI</th>
<th>Medical History for mild TBI</th>
<th>Years Ed.</th>
<th>Work Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>52</td>
<td>M</td>
<td>5</td>
<td>MVA</td>
<td>16</td>
<td>Disabled</td>
</tr>
<tr>
<td>P2</td>
<td>59</td>
<td>M</td>
<td>2 6</td>
<td>MVA</td>
<td>22</td>
<td>Partially disabled; Working only 22 hours/week at entry.</td>
</tr>
<tr>
<td>P3</td>
<td>50</td>
<td>F</td>
<td>1 8</td>
<td>Pedestrian hit by a car</td>
<td>18</td>
<td>Disabled Unable to return to work.</td>
</tr>
<tr>
<td>P4</td>
<td>26</td>
<td>F</td>
<td>1 4</td>
<td>Multiple-car MVA, hit from behind.</td>
<td>14</td>
<td>Unemployed, disabled.</td>
</tr>
<tr>
<td>P5</td>
<td>58</td>
<td>M</td>
<td>1</td>
<td>Sports injury, close-range impact. Hit in the head by a baseball.</td>
<td>16</td>
<td>Disabled</td>
</tr>
<tr>
<td>P6</td>
<td>62</td>
<td>F</td>
<td>7</td>
<td>MVA</td>
<td>12</td>
<td>Partial employment. Disabled.</td>
</tr>
<tr>
<td>P7*</td>
<td>49</td>
<td>F</td>
<td>3</td>
<td>Ski accident. History of multiple concussions and a prior stroke</td>
<td>16</td>
<td>Disabled.</td>
</tr>
<tr>
<td>P8*</td>
<td>32</td>
<td>M</td>
<td>3</td>
<td>Blast Injury. Additional IED, TBIs.</td>
<td>13</td>
<td>Disabled, Active Duty Military. Unable to return to Unit, 3 Yrs.</td>
</tr>
<tr>
<td>P9*</td>
<td>44</td>
<td>M</td>
<td>10</td>
<td>MVA. Multiple (&gt;10) concussions (falls, sports injuries, accidents).</td>
<td>16</td>
<td>Disabled.</td>
</tr>
<tr>
<td>P10</td>
<td>27</td>
<td>M</td>
<td>1</td>
<td>Industrial/work accident. Complicated mTBI, maxillo-orbital fractures with fragments into left infra-temporal fossa.</td>
<td>12</td>
<td>Disabled.</td>
</tr>
</tbody>
</table>
No craniotomy.

| P11* | 28 | F  | 8 | - | Fell off a chair. Also a concussion, 12 Yrs. prior to entry. | 18 | Working full-time. |

* History of multiple concussions
Table 2. List of LED cluster head placements on the forehead and scalp treated at each visit. Each participant received Set A, followed immediately by Set B, at each treatment session. Each LED cluster head had a 2.1-inch diameter. (See also SIFig1 showing location of external bone and suture landmarks on the skull in relationship to surface brain cortex areas.)

<table>
<thead>
<tr>
<th>Placement Order</th>
<th>LED Placement loci for each LED Cluster Head</th>
<th>Approximate, Surface Brain Cortex Areas hypothesized to be impacted with the LED Cluster Heads</th>
</tr>
</thead>
<tbody>
<tr>
<td>Set A LED Placements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>Midline of face, centered over front hairline (half of LED placement was anterior to hairline on forehead; half of LED placement, posterior to hairline).</td>
<td>L &amp; R dACC, part of SN. L &amp; R vmPFC, part of DMN.</td>
</tr>
<tr>
<td>2nd and 3rd</td>
<td>L &amp; R forehead, between eyebrow and front hairline, centered on pupil line.</td>
<td>L &amp; R orbito-frontal cortex; and most anterior, MFG areas</td>
</tr>
<tr>
<td>4th</td>
<td>Midline, superio to external occipital protuberance (half-way to vertex); and on alternate treatment days, midline, inferior to external occipital protuberance.</td>
<td>L &amp; R precuneus, with midline placement superior to occipital protuberance. Precuneus areas are part of DMN. Placement inferior to occipital protuberance was used to promote neck muscle relaxation, and treat headache pain, if present.</td>
</tr>
<tr>
<td>5th</td>
<td>Midline, vertex of the head.</td>
<td>L &amp; R SMA, and PreSMA. PreSMAs are part of SN.</td>
</tr>
<tr>
<td>6th</td>
<td>Sole of foot (proximal to toes), alternating L &amp; R on different treatment days, as well as alternating with a placement on dorsum of foot (proximal to toes), also alternating L &amp; R on different treatment days.</td>
<td>Red wavelength of low-level laser light applied to a point on the foot has been observed to increase ipsilateral, regional cerebral blood flow to occipital cortex (Siedentopf et al., 2002).</td>
</tr>
<tr>
<td>Set B LED Placements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7th and 8th</td>
<td>Immediately posterior to L &amp; R front hairline, centered on pupil line.</td>
<td>L &amp; R MFG areas, including DLPFC, part of CEN.</td>
</tr>
<tr>
<td>9th and 10th</td>
<td>L &amp; R temple areas.</td>
<td>L &amp; R IFG, possibly including L &amp; R AI, but unknown due to greater depth of AI, part of SN.</td>
</tr>
<tr>
<td>11th and 12th</td>
<td>L &amp; R posterior, superior to each ear.</td>
<td>Postero-lateral IPC, part of DMN.</td>
</tr>
</tbody>
</table>

Abbreviations: dACC, dorsal, anterior cingulate cortex; DMN, default mode network; vmPFC, ventral medial prefrontal cortex; SN, salience network; MFG, middle frontal gyrus; SMA, supplementary motor area; DLPFC, dorsolateral prefrontal cortex; CEN, central executive network; IFG, inferior frontal gyrus; AI, anterior insula; IPC, inferior parietal cortex (PPC, posterior parietal cortex), includes angular gyrus.
Table 3. Psychosocial changes post-LED, reported by participants and families.

<table>
<thead>
<tr>
<th>ID Number</th>
<th>Psychosocial Changes Post- LED</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Able to sort bills, write checks and read essays, tasks he had been unable to perform for 5 years, since the MVA.</td>
</tr>
<tr>
<td>P2</td>
<td>Able to continue work 22 hours/week, and later, full-time. Headache pain was reduced; no longer required meds for headache pain.</td>
</tr>
<tr>
<td>P3</td>
<td>Non-talkative at entry, but became quite verbal and talkative after LED Tx. Husband reported that she was &quot;better adjusted&quot; at home. BDI remained at moderate level.</td>
</tr>
<tr>
<td>P4</td>
<td>Clinically meaningful decrease in PTSD.</td>
</tr>
<tr>
<td>P5</td>
<td>Clinically meaningful decrease in PTSD. Wife reported more active around the home and was able to perform errands. Went on a job interview.</td>
</tr>
<tr>
<td>P6</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P7*</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P8*</td>
<td>Post-LED treatment series, able to return to the Military, for further evaluation.</td>
</tr>
<tr>
<td>P9*</td>
<td>Remained disabled.</td>
</tr>
<tr>
<td>P10</td>
<td>Clinically meaningful decrease in PTSD. Pre-LED treatment, the patient reported recurrent nightmares of the mTBI event. After a few weeks of LED treatments, he reported that the nightmares had stopped.</td>
</tr>
<tr>
<td>P11*</td>
<td>Prior to the Post-testing at 1 week, she was promoted to a new position, causing distress. PTSD and BDI were minimal at Pre-Tx., and at 2 months Post-LED. She reported better sleep.</td>
</tr>
</tbody>
</table>
* History of multiple concussions.
Table 1. Demographics for 11 chronic, mTBI cases treated with transcranial, red/near-infrared light-emitting diode (LED) therapy.

Table 2. Description of LED cluster head placements on the forehead and scalp (Set A and Set B).

Table 3. Psychosocial changes post-LED, reported by participants and families.
Supplemental Figure Legends:

**Supplemental Figure 1.** Approximate locations of surface brain cortex areas in relation to bone suture lines and extra-cranial landmarks on the skull (reproduction of a lithograph, Gray1197.png). In the present study, the 2.1-inch diameter LED cluster heads were placed on the forehead and scalp areas based on these surface landmarks. Source: Gray’s Anatomy of the Human Body (originally published in 1918) is now in the public domain; permission to reprint is not required.

**Supplemental Figure 2.** 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.

**Supplemental Figure 3.** Verbal Memory, California Verbal Learning Test-II, Alternating Versions, Total Trials 1-5: Graph showing pre- and post- LED test scores for each participant (SD adjusted for age and education).

**Supplemental Figure 4.** Graphs for two additional NP tests, showing no significant trend over time: A) FAS Test (p=.087); and B) Digit Span, Forwards and Backwards, Total (p=.119). C) There was a trend toward significant improvement on the psychological measure for depression (BDI) at 1 week post- the 18th LED treatment, vs. pre- LED (p=.045).
List of Supplemental Tables

**Supplemental Table 1.** Correlations among neuropsychological and psychological measures.

**Supplemental Table 2.** Executive Function - Stroop Trial 3: inhibition. Standard deviations from normative data, for each participant.

**Supplemental Table 3.** Executive Function – Stroop Trial 4: inhibition switching. Standard deviations from normative data, for each participant.

**Supplemental Table 4.** Verbal Memory - California Verbal Learning Test II, Alternating Versions, Total Trials 1-5. Standard deviations from normative data, for each participant.

**Supplemental Table 5.** Verbal Memory – Long Delay Free Recall, California Verbal Learning Test II, Alternating Versions. Standard deviations from normative data, for each participant.

**Supplemental Table 6.** Beck Depression Inventory-II. Raw scores and severity levels for each participant.

**Supplemental Table 7.** PTSD Checklist – Civilian (PCL-C) scores for each participant.
Supplemental Table 8. Summary for each mTBI participant showing the pre- LED scores, and the amount of change at 2 months post- LED.
Supplemental Figure 1. Approximate locations of surface brain cortex areas in relation to bone suture lines and extra-cranial landmarks on the skull (reproduction of a lithograph, Gray1197.png). In the present study, the 2.1-inch diameter LED cluster heads were placed on the forehead and scalp areas based on these surface landmarks. Source: Gray's Anatomy of the Human Body (originally published in 1918) is now in the public domain; permission to reprint is not required.

Supplemental Figure 2.

![Graph showing Executive Function Stroop Trial 4: Inhibition Switching](image-url)
Supplemental Figure 2. 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.

Supplemental Figure 3.

Verbal Memory
California Verbal Learning Test II, Alternating Versions, Total Trials 1-5
Supplemental Figure 3. Verbal Memory, California Verbal Learning Test-II, Alternating Versions, Total Trials 1-5: Graph showing pre- and post- LED test scores for each participant (SD adjusted for age and education).

Supplemental Figure 4.

A  
FAS Test

B  
Digit Span  
Forwards and Backwards, Total

C  
Beck Depression Inventory-II

*P = 0.046 Pre-Tx vs. Post-1 Week*
Supplemental Figure 4. Graphs for two additional NP tests, showing no significant trend over time: A) FAS Test (p=.087); and B) Digit Span, Forwards and Backwards, Total (p=.119). C) There was a trend toward significant improvement on the psychological measure for depression (BDI) at 1 week post- the 18th LED treatment, vs. pre- LED (p=.045).

Supplemental Table 1. Correlations among neuropsychological and psychological measures.

<table>
<thead>
<tr>
<th>Neuropsychological/ Psychological Measures</th>
<th>DESS Trails Test</th>
<th>FAS</th>
<th>CTrail 1 Total Trails 1-5</th>
<th>CTrail 2 Short Delay Recall</th>
<th>CTrail 2 Long Delay</th>
<th>CTrail 2 Long Delay</th>
<th>CTrail 2 Total Trails 1-5</th>
<th>Spot Trial 1 Error Naming</th>
<th>Spot Trial 2 Spot Reading</th>
<th>Spot Trial 2 Spot Reading</th>
<th>Spot Trial 4 Inhibition and Switching</th>
<th>Digit Span and Backward Total</th>
<th>Beck Depression Inventory</th>
<th>FTSD Clinician</th>
<th>Chronic TBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESS Trails Test</td>
<td>0.757</td>
<td>0.300</td>
<td>0.300</td>
<td>0.279</td>
<td>0.279</td>
<td>0.300</td>
<td>0.279</td>
<td>0.300</td>
<td>0.279</td>
<td>0.300</td>
<td>0.279</td>
<td>0.300</td>
<td>0.279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTrail 1 Total Trails 1-5</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTrail 2 Short Delay Recall</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTrail 2 Long Delay</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTrail 2 Total Trails 1-5</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot Trial 1 Error Naming</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot Trial 2 Spot Reading</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot Trial 2 Spot Reading</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spot Trial 4 Inhibition and Switching</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span and Backward Total</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTSD Clinician</td>
<td>0.277</td>
<td>0.172</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td>0.272</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: p values within parentheses
Supplemental Table 1. Correlations among neuropsychological and psychological measures.

Supplemental Table 2. Executive Function - Stroop Trial 3: Inhibition.
Standard deviations from normative data, for each participant.

<table>
<thead>
<tr>
<th>ID</th>
<th>1 Wk. Pre-Tx</th>
<th>1 Wk. Post-Tx</th>
<th>1 Mo. Pre-Tx</th>
<th>1 Mo. Post-Tx</th>
<th>2 Mo. Pre-Tx</th>
<th>2 Mo. Post-Tx</th>
<th>Change in SD from Pre-Tx 1 Wk.</th>
<th>Change in SD from Pre-Tx 1 Mo.</th>
<th>Change in SD from Pre-Tx 2 Mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>-1.0</td>
<td>2.9</td>
<td>2.9</td>
<td>2.9</td>
<td></td>
<td></td>
<td>3.9</td>
<td>3.9</td>
<td>3.9</td>
</tr>
<tr>
<td>P2</td>
<td>0.0</td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td></td>
<td></td>
<td>0.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>P3</td>
<td>0.0</td>
<td></td>
<td>2.0</td>
<td>1.0</td>
<td></td>
<td></td>
<td>0.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P4</td>
<td>-2.0</td>
<td>-1.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>0.0</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P6</td>
<td>3.5</td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td>3.5</td>
<td>3.5</td>
<td>4.0</td>
</tr>
<tr>
<td>P7*</td>
<td>0.5</td>
<td></td>
<td></td>
<td>-</td>
<td>1.0</td>
<td></td>
<td>0.0</td>
<td>-</td>
<td>0.5</td>
</tr>
<tr>
<td>P8*</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P9*</td>
<td>0.0</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
<td></td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P10</td>
<td>-3.0</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.5</td>
<td></td>
<td></td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>P11*</td>
<td>0.0</td>
<td></td>
<td>1.0</td>
<td>1.5</td>
<td></td>
<td></td>
<td>0.0</td>
<td>1.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

2 Cases improved +3.9 to +4.5 SD, at 2 Mo. Post-18 Tx. P1, P6
4 Cases improved +1 to +1.5 SD, at 2 Mo. Post-18 Tx. P2, P3, P10, P11
4 Cases 0 to +0.5 SD, at 2 Mo. Post-18 Tx. P5, P7, P8, P9
P4 no data at 2 Mo. Post-18 Tx.

* History of multiple concussions
Supplemental Table 2. Executive Function - Stroop Trial 3: inhibition. Standard deviations from normative data, for each participant.

<table>
<thead>
<tr>
<th>ID Nmbr.</th>
<th>Pre-Tx</th>
<th>1 Wk. Post-Tx</th>
<th>1 Mo. Post-Tx</th>
<th>2 Mo. Post-Tx</th>
<th>Change in SD from Pre-Tx</th>
<th>Change in SD from 1 Wk. Post-Tx</th>
<th>Change in SD from 1 Mo. Post-Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>P2</td>
<td>0.0</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>P3</td>
<td>0.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>P4</td>
<td>-2.0</td>
<td>-1.0</td>
<td>-</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>-2.0</td>
<td>-1.0</td>
<td>-1.5</td>
<td>0.0</td>
<td>1.0</td>
<td>0.5</td>
<td>2.0</td>
</tr>
<tr>
<td>P6</td>
<td>-1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>3.5</td>
<td>2.0</td>
<td>2.0</td>
<td>4.5</td>
</tr>
<tr>
<td>P7*</td>
<td>0.5</td>
<td>1.5</td>
<td>-</td>
<td>0.5</td>
<td>1.0</td>
<td>-</td>
<td>0.0</td>
</tr>
<tr>
<td>P8*</td>
<td>-3.0</td>
<td>-1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>P9*</td>
<td>0.0</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P10</td>
<td>-2.0</td>
<td>-1.5</td>
<td>0.0</td>
<td>-1.0</td>
<td>0.5</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P11*</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

4 Cases improved +2 to +4.5 SD, at 2 Mo. Post-Tx: P3, P5, P6, P8
3 Cases improved +1 to +1.5 SD, at 2 Mo. Post-Tx: P2, P10, P11
2 Cases no change, 0 SD, at 2 Mo. Post-Tx: P7, P9
P1, P4 no data at 2 Mo.

* History of multiple concussions
Supplemental Table 3. Executive Function – Stroop Trial 4: inhibition switching. Standard deviations from normative data, for each participant.

Supplemental Table 4. Verbal Memory - California Verbal Learning Test II, Alternating Versions, Total Trials 1-5. Standard deviations from normative data, for each participant.

<table>
<thead>
<tr>
<th>ID Nbr</th>
<th>1 Wk. Pre-Tx</th>
<th>1 Mo. Post-18Tx</th>
<th>2 Mo. Post-18Tx</th>
<th>Change in SD from Pre-Tx 1 Wk. Post</th>
<th>Change in SD from Pre-Tx 1 Mo. Post</th>
<th>Change in SD from Pre-Tx 2 Mo. Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>1.0</td>
<td>2.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P3</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>P4</td>
<td>-1.5</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
<td>1.5</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P7*</td>
<td>0.0</td>
<td>0.0</td>
<td>1.0</td>
<td>1.5</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P8*</td>
<td>-0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>P9*</td>
<td>0.0</td>
<td>0.0</td>
<td>1.5</td>
<td>1.5</td>
<td>0.0</td>
<td>1.5</td>
</tr>
<tr>
<td>P10</td>
<td>-1.5</td>
<td>0.0</td>
<td>0.8</td>
<td>-0.2</td>
<td>1.5</td>
<td>2.3</td>
</tr>
<tr>
<td>P11*</td>
<td>0.0</td>
<td>2.0</td>
<td>2.0</td>
<td>3.0</td>
<td>2.0</td>
<td>3.0</td>
</tr>
</tbody>
</table>

2 Cases improved +2 to +3 SD, at 2 Mo. Post-18Tx. P3, P11
4 Cases improved +1 to +1.5 SD, at 2 Mo. Post-18Tx. P5, P7, P9, P10
4 Cases 0 to +0.5 SD, at 2 Mo. Post-18Tx. P1, P2, P6, P8
P4 no data at 2 Mo. Post-18Tx.

* History of multiple concussions
Supplemental Table 4. Verbal Memory - California Verbal Learning Test II, Alternating Versions, Total Trials 1-5. Standard deviations from normative data, for each participant.

<table>
<thead>
<tr>
<th>ID</th>
<th>Pre-Tx</th>
<th>1 Wk.</th>
<th>1 Mo.</th>
<th>2 Mo.</th>
<th>Change in SD from Pre-Tx 1 Wk.</th>
<th>Change in SD from Pre-Tx 1 Mo.</th>
<th>Change in SD from Pre-Tx 2 Mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Post-18 Tx</td>
<td>Post-18 Tx</td>
<td>Post-18 Tx</td>
<td>Post-18 Tx</td>
<td>Post-18 Tx</td>
<td>Post-18 Tx</td>
</tr>
<tr>
<td>P1</td>
<td>1.5</td>
<td>2.0</td>
<td>1.5</td>
<td>1.5</td>
<td>0.5</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>P2</td>
<td>-1.0</td>
<td>-1.0</td>
<td>1.0</td>
<td>0.0</td>
<td>2.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P3</td>
<td>-2.0</td>
<td>-2.5</td>
<td>-2.5</td>
<td>-2.0</td>
<td>-0.5</td>
<td>-0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>P4</td>
<td>-0.5</td>
<td>0.0</td>
<td>-</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.5</td>
<td>-1.0</td>
<td>0.0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>P6</td>
<td>-3.0</td>
<td>-0.5</td>
<td>-1.0</td>
<td>0.5</td>
<td>2.5</td>
<td>2.0</td>
<td>3.5</td>
</tr>
<tr>
<td>P7*</td>
<td>-1.0</td>
<td>-0.5</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P8*</td>
<td>-2.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.5</td>
<td>2.0</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>P9*</td>
<td>0.0</td>
<td>-0.5</td>
<td>0.0</td>
<td>1.0</td>
<td>0.5</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td>P10</td>
<td>-3.5</td>
<td>-0.5</td>
<td>-1.0</td>
<td>-1.5</td>
<td>3.0</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>P11*</td>
<td>0.0</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>1.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

3 Cases improved +2 to +3.5 SD, at 2 Mo. Post-18 Tx: P6, P8, P10
4 Cases improved +1 to +1.5 SD, at 2 Mo. Post-18 Tx: P2, P7, P9, P11
3 Cases no change, 0 SD, at 2 Mo. Post-18 Tx: P1, P3, P5
P4 no data at 2 Mo. Post-18 Tx.

* History of multiple concussions
Supplemental Table 5. Verbal Memory – Long Delay Free Recall, California Verbal Learning Test II, Alternating Versions. Standard deviations from normative data, for each participant.

Supplemental Table 6. Beck Depression Inventory-II. Raw scores and severity levels for each participant.

<table>
<thead>
<tr>
<th>Severity Level Pre-Tx</th>
<th>1 Wk. Pre-Tx</th>
<th>1 Wk. Post-Tx</th>
<th>1 Mo. Post-Tx</th>
<th>2 Mo. Post-Tx</th>
<th>Severity Level 2 Mo. Post-Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>mild</td>
<td>15</td>
<td>12</td>
<td>28</td>
<td>18 mild</td>
</tr>
<tr>
<td>P2</td>
<td>moderate</td>
<td>20</td>
<td>19</td>
<td>15</td>
<td>15 mild</td>
</tr>
<tr>
<td>P3</td>
<td>severe</td>
<td>31</td>
<td>20</td>
<td>28</td>
<td>30 severe</td>
</tr>
<tr>
<td>P4</td>
<td>mild</td>
<td>15</td>
<td>18</td>
<td>-</td>
<td>15 no data</td>
</tr>
<tr>
<td>P5</td>
<td>moderate</td>
<td>22</td>
<td>23</td>
<td>23</td>
<td>25 moderate</td>
</tr>
<tr>
<td>P6</td>
<td>moderate</td>
<td>24</td>
<td>10</td>
<td>10</td>
<td>10 minimal</td>
</tr>
<tr>
<td>P7*</td>
<td>minimal</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>no data</td>
</tr>
<tr>
<td>P8*</td>
<td>mild</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>2 minimal</td>
</tr>
<tr>
<td>P9*</td>
<td>minimal</td>
<td>12</td>
<td>10</td>
<td>10</td>
<td>0 minimal</td>
</tr>
<tr>
<td>P10</td>
<td>severe</td>
<td>34</td>
<td>13</td>
<td>14</td>
<td>27 moderate</td>
</tr>
</tbody>
</table>
| P11*                  | minimal      | 0             | 14†           | 6             | 3 minimal                  | 0 - 13 = minimal
14 - 19 = mild
20 - 29 = moderate
30 - 63 = severe

* History of multiple concussions

† Within 2 days before the 1-Wk. Post-testing, patient was promoted to a new position at work. This was disturbing for her, at that time.

Supplemental Table 6. Beck Depression Inventory-II. Raw scores and severity levels for each participant.
Supplemental Table 7. PTSD Checklist – Civilian (PCL-C), for each participant.

<table>
<thead>
<tr>
<th>ID Number</th>
<th>1 Wk. Post-Tx (Max = 85)</th>
<th>1 Mo. Post-Tx</th>
<th>2 Mo. Post-Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>P2</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>P3</td>
<td>47**</td>
<td>47</td>
<td>38†</td>
</tr>
<tr>
<td>P4</td>
<td>47**</td>
<td>30‡</td>
<td>-</td>
</tr>
<tr>
<td>P5</td>
<td>79**</td>
<td>65‡</td>
<td>68‡</td>
</tr>
<tr>
<td>P6</td>
<td>35</td>
<td>27†</td>
<td>27†</td>
</tr>
<tr>
<td>P7*</td>
<td>19</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>P8*</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>P9*</td>
<td>24</td>
<td>17†</td>
<td>19†</td>
</tr>
<tr>
<td>P10</td>
<td>48**</td>
<td>17‡</td>
<td>17‡</td>
</tr>
<tr>
<td>P11*</td>
<td>25</td>
<td>31</td>
<td>22</td>
</tr>
</tbody>
</table>

* History of multiple concussions

** Score ≥36, suggestive of PTSD, based on case referral from specialized clinic (TBI or Pain). Source: Table 1, PTSD Checklist (PCL) July 2012 [http://www.ptsd.va.gov](http://www.ptsd.va.gov).

† Reliable decrease, compared to Pre-Tx: 5-10 points.

‡ Clinically meaningful decrease: 10-20 points. (Monson et al., 2008)
Supplemental Table 7. PTSD Checklist – Civilian (PCL-C) scores for each participant.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>ND (Trial 3, Inhibition -1)</td>
<td>+1 0 +1.5 0</td>
<td>0 0 -1 +1 20 0</td>
<td>+3 Mild Depression</td>
<td>17 0</td>
</tr>
<tr>
<td>P2</td>
<td>0 0 +1.5 0</td>
<td>0 0 -1 +1 20 0</td>
<td>0 0 -1 +1 20 0</td>
<td>+3 Mild Depression</td>
<td>17 0</td>
</tr>
<tr>
<td>P3</td>
<td>0 0 +2 -1</td>
<td>0 0 -1 +2 20 0</td>
<td>0 0 -1 +2 20 0</td>
<td>+3 Mild Depression</td>
<td>31 47** Rliable Decrease</td>
</tr>
<tr>
<td>P4</td>
<td>-2 (+1 at 1 Wk, ND, 2 Mo Post-LD)</td>
<td>-1.5 (+1.5, 1 Wk, ND, 2 Mo Post-LD) -0.5 (+0.5, 1 Wk, ND, 2 Mo Post-LD) -15</td>
<td>Mild (2, 1 Wk, ND, 2 Mo)</td>
<td>+3 Moderate</td>
<td>47** (-17, 1 Wk, Clinical Decl. ND, 2 Mo)</td>
</tr>
<tr>
<td>P5</td>
<td>-2 +2 -1</td>
<td>+1 -1 +1 20 0</td>
<td>0 0 -1 +1 20 0</td>
<td>+3 Moderate</td>
<td>79** -29 Clinical Decl.</td>
</tr>
<tr>
<td>P6</td>
<td>-1 +4.5 0</td>
<td>-3 +3.5 24 0</td>
<td>-3 +3.5 24 0</td>
<td>-14 Minimal</td>
<td>35 -6 Rliable Decrease</td>
</tr>
<tr>
<td>P7</td>
<td>0.5 0 0</td>
<td>+1.5 -1 +1 3 0</td>
<td>ND ND 19 0</td>
<td>+1 Rliable Decrease</td>
<td></td>
</tr>
<tr>
<td>P8</td>
<td>-3 +4 -0.5</td>
<td>+0.5 -2 +2 15 0</td>
<td>-13 Mild 17 +1</td>
<td>+7 Rliable Decrease</td>
<td></td>
</tr>
<tr>
<td>P9</td>
<td>0 0 0</td>
<td>+1.5 0 0</td>
<td>-12 Minimal 24 7</td>
<td>+31 Clinical Decl.</td>
<td></td>
</tr>
<tr>
<td>P10</td>
<td>-2 +1 -1.5</td>
<td>3.5 +2 34 0</td>
<td>Moderate 48** +31 Clinical Decl.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P11</td>
<td>-1 +1 0</td>
<td>+3 0 +1.5 0</td>
<td>Minimal 25 +3 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* History of multiple concussions. Abbrev: ND, no data. Change of at least 1 SD, or a reduced severity-level, at 2 Mo, post-LED, marked in bold.
** Score ≥36, suggestive of PTSD, based on case referral from specialized clinic (TBI or Pain). Source: Table 1, PTSD Checklist (PCL) July 2012, http://www.ptsd.va.gov). Compared to Pre-Tx: Clinically meaningful decrease* 0-20 points; Reliable decrease≥5-10 points (Monson et al., 2008).
Supplemental Table 8. Summary for each mTBI participant showing the pre-LED scores, and the amount of change at 2 months post-LED.