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Transcranial, Red/Near-Infrared Light-Emitting Diode Therapy to Improve Cognition in Chronic Traumatic Brain Injury

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Abstract

Objective: We review the general topic of traumatic brain injury (TBI) and our research utilizing transcranial photobiomodulation (tPBM) to improve cognition in chronic TBI using red/near-infrared (NIR) light-emitting diodes (LEDs) to deliver light to the head. tPBM improves mitochondrial function increasing oxygen consumption, production of adenosine triphosphate (ATP), and improving cellular energy stores. Nitric oxide is released from the cells increasing regional blood flow in the brain. ***Review of published studies:*** In our previously published study, 11 chronic TBI patients with closed-head TBI caused by different accidents (motor vehicle accident, sports-related, improvised explosive device blast injury) and exhibiting long-lasting cognitive dysfunction received 18 outpatient treatments (Monday, Wednesday, Friday for 6 weeks) starting at 10 months to 8 years post-TBI. LED therapy is nonthermal, painless, and noninvasive. An LED-based device classified as nonsignificant risk (FDA cleared) was used. Each LED cluster head (5.35 cm diameter, 500 mW, 22.2 mW/cm^2) was applied for 9 min 45 sec (13 J/cm^2) using 11 locations on the scalp: midline from front-to-back hairline and bilaterally on frontal, parietal, and temporal areas. Testing was performed before and after transcranial LED (tLED; at 1 week, 1 month, and at 2 months after the 18th treatment) and showed significant improvements in executive function and verbal memory. There were also fewer post-traumatic stress disorder (PTSD) symptoms reported. ***Ongoing studies:*** Ongoing, current studies involve TBI patients who have been treated with tLED using either 26 J/cm^2 per LED location on the head or treated with intranasal only (iLED) using red (633 nm) and NIR (810 nm) diodes placed into the nostrils. The NIR iLED is hypothesized to deliver photons to the hippocampus, and the red 633 nm iLED is believed to increase melatonin. Results have been similar to the previously published tLED study. Actigraphy sleep data showed increased time asleep (on average one additional hour per night) after the 18th tLED or iLED treatment. LED treatments may be performed in the home. Sham-controlled studies with veterans who have cognitive dysfunction from Gulf War Illness, blast TBI, and TBI/PTSD are currently ongoing.

Keywords: traumatic brain injury, TBI, photobiomodulation, PBM, TBI treatment, cognitive dysfunction, light-emitting diodes, LED, postconcussion syndrome, sports head injury, PTSD, LLLT

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Introduction

Mechanisms of low-level laser (light) therapy and photobiomodulation therapy

Low-level laser (light) therapy (LLLT), now referred to as photobiomodulation therapy (PBMT) since 2015, triggers several mechanisms that have specific effects on cells and tissues. The more common light sources used today in PBM are noncoherent, light-emitting diodes (LEDs), whereas previously, coherent light from lasers was more commonly used. The wavelengths used with LEDs are the same as those used with lasers, and red (600–700 nm) and near-infrared (NIR, 800–1100 nm) regions of the spectrum are the most popular. Increased mitochondrial production of adenosine triphosphate (ATP) occurs after hypoxic/compromised cells are exposed to the red or NIR wavelengths of light.[1,2] Cytochrome-C oxidase (CCO) is the inner mitochondrial membrane-bound protein that is unit IV in the respiratory electron transport chain that can become inhibited in hypoxic cells or stressed cells. This inhibition occurs by noncovalent binding of nitric oxide to the iron and copper centers in the enzyme. When the hypoxic/stressed cells are exposed to red or NIR photons, the inhibitory nitric oxide is dissociated from CCO and is then released to diffuse outside the cells, acting to cause vasodilation and increase local blood flow.[3,4] After traumatic brain injury (TBI), the mitochondria inside brain cells (both neurons and glial cells) suffer damage and dysfunction.[5–8] Increased regional cerebral blood flow (rCBF) has been reported following transcranial application of NIR PBMT delivered to the forehead in a severe TBI patient[9] and in patients with chronic psychiatric disorders, including major depression and post-traumatic stress disorder (PTSD).[10] Both studies reported improvements in behavior.

There is a brief burst of reactive oxygen species (ROS) produced in the mitochondria inside the cells after red/NIR light is absorbed by CCO. This burst of ROS activates a number of cell signaling pathways. Because of the danger of oxidative stress to cellular homeostasis, evolution has designed a system through which ROS can activate the expression of a range of redox-sensitive genes and transcription factors such as nuclear factor-kappa B (NF-κB).[11,12] This system of redox-sensitive sensors leads to upregulation of antioxidant enzymes, small-molecule antioxidants, and a range of protective factors that prevent cell death and repair cellular damage. NF-κB also stimulates expression of genes related to cellular proliferation and migration, and also modulates production of cytokines and growth factors.[13] In small-animal studies, vascular endothelial growth factor (VEGF; a well-known factor for stimulating angiogenesis) has also been reported to enhance neurogenesis (the formation of new neurons or brain cells) in damaged brain. Neurogenesis directly improves the self-repair capacity of the brain.[14] Animal studies have shown increased VEGF and more angiogenesis after application of NIR laser therapy postmyocardial infarction, as well as after brain damage.[15] Increasing VEGF using red/NIR light could be a therapeutic target to enhance brain repair. The anti-inflammatory, anti-edema, and proangiogenic properties of PBMT taken together suggest that this form of therapy could also be effective in treating acute stroke.[13,16]

Neurogenesis is the term for differentiation of progenitor cells into newly formed neurons, and within the brain this occurs initially in the hippocampus or subventricular zone, and then, the cells migrate to the location in the brain where they are needed. Synaptogenesis is the formation of new synapses, or connections between existing neurons, and is among the most important mechanisms the brain uses to recover from acute TBI or stroke. Results from recent small-animal studies where NIR transcranial photobiomodulation (tPBM) was used to treat acute, severe TBI have supported the notion that tPBM increases neurogenesis and synaptogenesis (at least in mice). Compared to controls, there was significantly better recovery at 28 days post-TBI in mice receiving 3 daily NIR tPBM treatments (beginning at 4 h post-TBI).[17,18] The increased neurogenesis (measured by immunofluorescence staining of brain sections) was located in the subgranular layer of the dentate gyrus of the hippocampus, and in the subventricular zone at day 7. The increased synaptogenesis was located in the perilesional area of the brain (cortex) and in the subventricular zone at day 28. These results from two acute TBI studies in mice, however, suggest that NIR tPBM could be used to improve rehabilitation and recovery in patients suffering from the chronic sequelae of TBI (as well as chronic stroke patients). The potential for clinical therapies (such as tPBM) that can increase neurogenesis and synaptogenesis especially in chronic TBI patients (where neuroprotection may be too late) is intriguing.[19]

Clinical Effects Following TBI

Frequency of occurrence and cost of TBI

There are three incidents producing TBI that occur every single minute in the United States, and TBI remains a major and growing medical problem worldwide.[20] More than 5 million Americans are living with TBI-related disabilities and $\sim$1.7 million patients are evaluated annually (many in emergency rooms). The annual cost for TBI is between $60 and $76.5 billion.[20,21] Closed-head, mild TBI (mTBI), also known as concussion, is the most common (75%) manifestation of TBI in most populations. Persistent cognitive dysfunction occurs in 5–22% of mTBI cases. Cases with mTBI will have loss of consciousness (LOC) for 30 min or less (or possibly no LOC), and are also likely to have a period of altered mental status lasting up to 24 h. These altered mental states may include post-traumatic amnesia or ''memory gaps,'' drowsiness, confusion, and visual disturbances.

Sports-related TBI

Cognitive dysfunction from sports-related mTBI is of increasing concern both for men and for women (and is especially worrying for children).[22] Diagnoses of concussion in high school sports have increased annually by 16.5% within the past 10 years.[23] There is a cumulative effect that seems to build up in the brain with each successive concussion.[24,25] These cumulative effects include a more prolonged period of recovery, and a progressively increased risk for re-injury if the athlete continues to participate (vulnerable brain).[26,27] The verbal learning scores measured postseason in college athletes were lower than expected in 24% of those who had participated in contact sports (vs. only 3.6% participating in noncontact sports with low scores). The greater the number of head impacts the athletes had sustained during the season, the slower the reaction times were on ImPACT testing.[25] College

football players in positions such as offensive linemen are at the greatest risk of cognitive dysfunction.[28]

TBI in soldiers and veterans

Closed-head, blast injury TBI has been termed ''the signature injury'' of soldiers returning from Iraq and Afghanistan as part of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF).[29,30] Long-lasting cognitive dysfunction and methods to enhance recovery and rehabilitation continue to be of great interest to military authorities.[31] The numbers of warfighters who have returned with TBI have been estimated to be as high as 320,000.[32,33] PTSD is another major concern in soldiers who have received an mTBI, because they have a better memory of the traumatic event compared to those who sustained a more severe TBI.[34] It has been estimated that 28% of soldiers with mTBI also report clinically significant symptoms of PTSD. More severe exposures to blast and consequently worse ensuing mTBIs have been correlated with clinical levels of PTSD symptoms.[35] The incidence of co-occurrence of mTBI together with PTSD and depression is higher in military personnel than among civilians.[36]

Diffuse axonal injury and white matter abnormalities on magnetic resonance imaging scans in TBI

In many patients with closed-head mTBI, there are no detectable focal brain lesions or abnormalities that can be seen on CT or structural magnetic resonance imaging (MRI) scans.[24,37–39] However, 30% of cases without any visible damage on CT scans do in fact have abnormalities in the white matter tracts, which can be detected using diffusion tensor imaging (DTI) MRI scans.[40]

Diffuse axonal injury (DAI) also known as traumatic axonal injury is now recognized as one of the clinically important results of closed-head mTBI.[41] DAI occurs after shearing or stretching motion occurs within the brain matter, and angular forces exert deformation on axons and small blood vessels.[8,42–44] The frontal lobes of the brain (including the medial and lateral prefrontal cortex areas) are especially vulnerable to damage, when linear and angular motions, and sudden acceleration and deceleration of the head occurs. Examples of these motions of the head include whiplash sustained in a motor vehicle accident (MVA), concussive blast force, and direct impacts to the head sustained in battle.[45–47] DAI leads to impaired axonal transport, and focal axonal swelling continues to occur for several hours possibly resulting in axonal disconnection.[48] All degrees of severity of TBI can result in at least some axonal damage.[49] The reduced interconnectivity in white matter tracts results in the cognitive, emotional, and behavioral problems often observed post-mTBI.[50,51]

Development of neurodegenerative disease post-TBI

Widespread pathological alterations in tau protein and amyloid beta, long-lasting degeneration in the white matter, and prolonged neuroinflammation may be present for years after only a *single* TBI.[52,53] There may be increased microglial activity that persists for a long time after TBI,[54,55] and this persistent neuroinflammation may be a mechanistic link between having sustained a TBI in the past and the development of neurodegenerative diseases, including Alzheimer's disease (AD) in the future.[53] Damaged axons may also release increased amounts of the AD-associated protein amyloid beta, which can then go on to form plaques in the brain.[44,56,57]

There are a range of brain disorders known as ''tauopathies,'' which are characterized by pathological aggregation of the microtubule-associated protein known as tau that forms neurofibrillary or gliofibrillary tangles. Tangles are formed by hyperphosphorylation of tau, causing it to aggregate in an insoluble form. Chronic traumatic encephalopathy (CTE) is a tauopathy that is believed to develop from repeated head trauma.[58,59] Symptoms of CTE include progressive cognitive dysfunction, irritability, suicidal ideation, and eventually dementia. CTE may develop years after the original head trauma occurred; it has been reported in U.S. military veterans exposed to blast injury in Iraq and Afghanistan, in addition to occurring in American football players and boxers.[47]

Neuroendocrine disturbances post-TBI

In a recent review of neuroendocrine disturbances post-TBI,[60] it was reported that the highest incidence was observed at 1–2 years postinjury and then decreasing over time, but there was again a later increase at ≥5 years postinjury. At 1–2 years postinjury, gonadotropic insufficiency was the most common hormonal disturbance (19%), followed by somatotropic (11.5%), corticotropic (9.2%), and thyrotropic (3.4%) insufficiencies. At ≥5 years postinjury, somatotropic insufficiency increased to 24.1%, whereas corticotropic and thyrotropic insufficiencies decreased (2.5% and 0%). The authors concluded that, ''neuroendocrine disturbances are frequent even years after TBI.''[60]

Functional brain imaging in TBI

mTBI cases have been observed to display abnormal patterns of neural activation during performance of cognitive tasks combined with functional neuroimaging studies, since the first case was reported in 1999.[61] At 1 month post-mTBI, during a working memory (WM) task, there was more widespread bifrontal and biparietal activation in mTBI cases than was seen in healthy adults. There was no difference, however, in the accuracy of WM between the two groups. At 1 year post-TBI, this pattern of abnormal brain hyperactivation was still present.[62,63] At the 1 year time point, they showed no significant post-concussive symptoms, however, they still continued to show mildly slower reaction speeds compared to healthy adults.

Resting-state, functional-connectivity MRI scans in TBI

A special type of functional MRI (fMRI) scan called a resting-state, functional-connectivity MRI (rs-fcMRI) has been used to reveal specific, intrinsic neural networks that are widespread but temporally controlled (operating at very low frequencies, 0.01–0.09 Hz). These networks are detectable even when the subject is resting quietly in the MRI scanner, without being subjected to any external, task-related stimuli.[64] One of these cortical networks is called the ''Default Mode Network'' (DMN) and is made up of the mesial prefrontal cortex (mPFC); the precuneus and posterior cingulate cortex (precu/PCC); posterolateral parietal cortices (angular gyri), and medial temporal lobes including the hippocampus.[65] The DMN is most commonly shown to be activated when a person is not focused on the outside world, and the brain is at wakeful rest, such as during

daydreaming and mind wandering. The DMN in general and the precu/PCC in particular show rapid, highly reactive deactivation in normal subjects who are engaged in tasks demanding their full attention, whereas the frontoparietal dorsal attention network shows coordinated increased activation at the same time. mTBI cases, however, have shown abnormality in the activation of the DMN, particularly consisting of failure to deactivate critical cortical nodes when required to perform complex tasks.[66–69]

Two other intrinsic neural networks that are important for normal functioning of the brain during attention-requiring cognitive tasks have been observed to demonstrate abnormalities in some mTBI patients. The first of these networks is the salience network (SN).[70] One of the functions of the SN is to control the DMN. The SN comprises cortical areas, including the anterior insula (AI), the presupplementary motor area (preSMA), and the dorsal anterior cingulate cortex (dACC). The SN is important for normal executive function and for inhibition or self-control.[71–73] It functions to distinguish the most relevant among a range of internal, external, and intrapersonal stimuli to guide behavior. The brain cortex in the anterior parts of the SN (preSMA, dACC) acts to promote inhibitory control (deactivation) of the posterior parts of the DMN (precu/PCC), particularly during tasks requiring inhibition and rapid switching to complete satisfactorily. The SN regulates dynamic changes in other networks and can be said to signal the need to change behavior.[74] The second network, the central executive network (CEN), comprises the dorsolateral prefrontal cortex (DLPFC) and the intraparietal sulci.[75,76] The CEN is especially important for the performance of tasks involving executive function. The role of the CEN includes cognitive manipulation of temporal information, WM, and affects processing speed. CEN processing is involved in reasoning, problem solving, planning and execution of tasks, and effective flexibility and multi-tasking.

Cognitive dysfunction in TBI

Patients with mTBI commonly complain of problems with executive function that prevent them from completing tasks that require attention, concentration, and good WM. They will find it difficult to hold information in the front of their mind and to modify this information in light of incoming new material.[63,77,78] Measurements of executive function at 6 months post-TBI have been shown to predict the likely persistence of postconcussive syndrome after mild/moderate TBI.[79] The failure of attempts by TBI patients to re-establish satisfactory family and work relationships is one of the most distressing sequelae they complain about.[80] No single behavioral measure, however, captures the multi-dimensional nature of TBI long-term symptoms due to the diverse ways that brain damage can express itself.[81]

Sleep disturbance in TBI

In addition to the cognitive and psychosocial problems mentioned above, patterns of sleep are usually disturbed.[82–84] It has been estimated that 53% of individuals with TBI report disturbed sleep.[85] Problems in sleeping may exacerbate the symptoms of TBI,[86] including worsening neuropsychiatric symptoms (depression, anxiety, PTSD, etc.),[87] and can also interfere with full participation in rehabilitation programs.[88] The etiology of TBI-related sleep problems is currently under investigation. Reports have suggested that neurobiological factors are involved, particularly that there may be impaired functioning of the neural circuits responsible for regulation of the sleep/wake cycle.[89,90] Poor sleep patterns are also expected to disrupt the normal process by which brain metabolites, such as beta-amyloid and other potentially neurotoxic waste products that accumulate during awake time, are cleared from the brain during sleep.[91]

Pharmacologic treatments for TBI

Trials of pharmacologic interventions for TBI have been largely unsuccessful.[92] There are some drugs available that can be used for the systemic changes and increased intracranial pressure associated with moderate and severe TBI, but there have been few controlled systematic clinical trials of pharmacologic agents for treatment of cognitive impairment, and those have been largely unsuccessful.[93] There was a large clinical trial (Citicoline Brain Injury Treatment Trial [COBRIT]) for moderate and severe TBI, which evaluated citicoline (cytidine 5′-diphosphocholine).[81] Citicoline had previously demonstrated some efficacy as a neuroprotective agent to mitigate secondary damage occurring after stroke, and in some smaller TBI studies.[81] Results from the COBRIT study in 2012 showed that the use of citicoline did not result in any improvement in functional or cognitive status compared with placebo after 90 days.[94]

At the present time, there are no accepted pharmacologic treatments for secondary injury that occurs after mTBI, or for the prevention of cognitive and behavioral problems commonly suffered by TBI patients.[95,96] Further research is required to test cholinesterase inhibitors where there is some preliminary evidence that suggests improvement in difficulties with attention, and some mixed results for effects on memory.[80] No conclusions can be drawn concerning the use of drugs to improve executive dysfunction post-TBI.[80,93]

McAllister et al. tested whether bromocriptine (a dopamine D2 receptor agonist) had any effects on the functioning of WM in mTBI patients.[97] Bromocriptine administration improved WM in normal healthy controls, but had no effects on TBI patients. Neuroimaging studies showed that mTBI patients were not able to activate the correct cortical regions to accomplish specific WM tasks. These results also suggested that mTBI patients may have had changes in their normal response to the neurotransmitter dopamine. However, McAllister et al. found opposite results in a different study using guanfacine (an alpha-2 adrenergic receptor agonist).[98] In this study, guanfacine was found to selectively improve WM performance in mTBI patients, but had no effects in healthy subjects. In the mTBI group, increased activation was observed in a region of the cortex responsible for task-specific WM. Guanfacine may therefore be a promising agent that could be used for testing hypotheses regarding the neural mechanisms of cognitive dysfunction after mTBI.

Cognitive and behavioral rehabilitation therapies for TBI

At present, there is only some limited evidence that cognitive and behavioral therapy (CBT) can be used to improve executive function after TBI.[31,99,100] Executive dysfunction remains a real obstacle to rehabilitation of brain-injured patients.[101] CBT attempts to improve the

executive functioning of TBI patients by encouraging neuroplasticity and rewiring of brain networks. However, the injured, nonfunctioning brain cells that remain present long term would be expected to limit the success of CBT. PBM is a treatment that directly targets injured brain cells and may improve the function of basic brain networks (including functional connectivity in the DMN, SN, and CEN). These networks regulate attention, executive function, memory, emotions, and behavior. Since there are no generally accepted effective treatments to improve cognitive function in individuals with TBI, including both veterans and nonveterans, serious consideration should be given to testing transcranial red/NIR PBMT.

Review: Previously Published Transcranial PBM Studies to Improve Cognition in TBI

Case reports: transcranial LED treatment performed at home to improve cognitive function in chronic mTBI

Naeser et al. reported two chronic mTBI cases where cognitive function improved following home-based tPBM treatment with red/NIR transcranial LED (tLED).[102] The LED clusters were applied to areas of the forehead and scalp, including locations at the midline and bilateral frontal, temporal, and parietal areas. Each red/NIR LED cluster head (MedX Health) measured 5.35 cm in diameter and had a total power output of 500 mW consisting of 61 individual diodes (9 at 633 nm and 52 at 870 nm). The power density was 22.2 mW/cm^2, and a dose (energy density) of 13 J/cm^2 continuous wave (CW) was delivered to the scalp from each LED cluster head applied for 9 min 45 sec. This dose to the forehead was estimated to deliver 0.4 J/cm^2 to the surface of the brain cortex.

Patient 1 (a 59-year-old female) was a professor of web design who sustained an mTBI in an MVA and began to receive tLED treatments 7 years after that accident. At that time, before she received any tLED treatment, her ability to sustain any attention (e.g., computer work) lasted for only 20 min. After eight weekly tLED treatments (initially performed in-office by a clinician), her ability to sustain attention on the computer increased to 3 h. She later commenced nightly tLED treatments at home, which she continued to perform daily for at least 5 years. She reported that if she stopped the treatments for more than 2 weeks, she regressed and her symptoms reappeared.

Patient 2 (a 59-year-old female) was a high-ranking, retired military officer who had sustained her most recent closed-head mTBI before beginning the tLED treatments, after falling onto concrete from a swing. She had a history of sports-related and military mTBIs. Her structural MRI scan obtained within a few months before the tLED treatments displayed frontoparietal atrophy, which was deemed moderate for her age. Before initiating tLED, she had been off work on medical leave for 5 months. After 4 months of nightly tLED treatment at home, her medical disability was no longer necessary. She returned to work full-time taking a position as a consultant with an international technology-consulting company. After 9 months of tLED treatments, her neuropsychological testing results showed significant improvement (+1 standard deviation [SD]) in measures of executive function (inhibition, inhibition accuracy) and (+2 SD) in tests for memory. She also showed a reduction in symptoms of PTSD. She reported that if she stopped daily treatment for more than 1 week, her symptoms reappeared. Both P1 and P2 continued to carry out home treatments with tLED for at least 5 years; neither of them reported any adverse events or negative side effects. At present, P1 has been lost to follow-up, while P2 continues with home treatment.

Open-protocol, group study: tLED treatment to improve cognition in chronic mTBI

Naeser et al. reported results from a pilot open-protocol trial that contained a larger number of chronic mTBI patients and was designed to test whether tLED could improve cognitive function if a systematic treatment protocol was utilized.[103] Eleven chronic mTBI patients participated in the study (ages 26–62 years, six males, five females). All participants had sustained closed-head brain trauma and suffered from persistent cognitive dysfunction. The mTBI had occurred between 10 months and 8 years ago and most were MVA- or sports-related TBIs, while one participant had sustained an improvised explosive device blast injury. Four subjects had a history of multiple concussions. Subjects were treated by a clinician for 18 outpatient sessions (3× per week, Monday, Wednesday, Friday, for 6 weeks), Each LED cluster head (same as described above) was applied for 9 min 45 sec on each of 11 scalp placements to deliver 13 J/cm^2. The locations of the LEDs were the midline of the head from front-to-back hairline, and bilaterally on the frontal, parietal, and temporal areas. Six LED cluster heads were applied to the head at the same time and held in place with a home-made soft nylon cap. Each participant was treated in a sitting position in a recliner chair. The LED placements were chosen to cover the cortical brain networks located in the DMN, SN, and CEN. It was hypothesized that these locations would lead to increased ATP in the hypoxic/compromised cells and to improved rCBF in these critical areas of the brain. Neuropsychological testing was performed at baseline (pretreatment) and at 1 week, 1 month, and at 2 months (after the final18th tLED treatment).

Results. A statistically significant linear trend was observed for the effects of tLED treatment measured over time, using the following tests: (1) the Stroop test (color word interference) for Executive Function, Trial 3 measuring inhibition ($p = 0.004$); (2) the Stroop test Trial 4 measuring Inhibition Switching ($p = 0.003$); (3) the California Verbal Learning Test (CVLT) II, Alternating Versions, Total Trials 1–5 ($p = 0.003$); and (4) the CVLT-II, Long Delay (20 min) Free Recall ($p = 0.006$) (Fig. 1). Further, participants reported improved sleep and fewer PTSD symptoms, if these were present (Fig. 2). Both participants and family members reported improved social interactions with family and occupational colleagues.

Review: Ongoing Current Studies

tLED treatments to improve sleep and cognition in chronic TBI

Bogdanova et al. at the VA Boston Healthcare System have been studying the effects of tLED treatments on sleep and cognitive function in patients with chronic moderate TBI.[104] Two patients (one male and one female) who had sustained a moderate TBI and suffered from persistent cognitive dysfunction that had been documented with scores of at

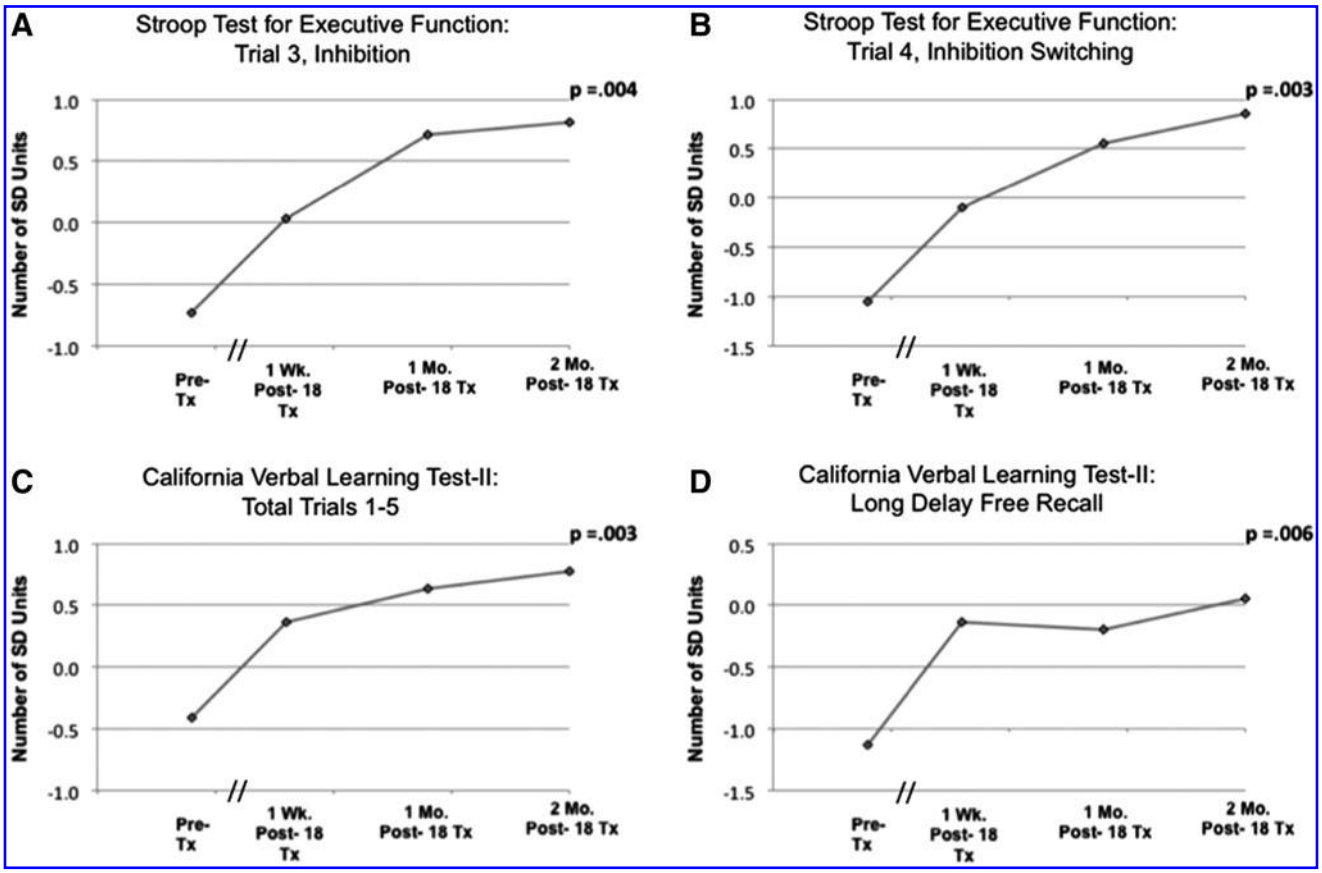

FIG. 1. Graphs showing a significant linear trend over time for the effect of tLED treatments on specific neuropsychological tests. **(A)** Stroop (color-word interference test) for Executive Function: Trial 3, Inhibition ($p = 0.004$); **(B)** Stroop, Trial 4 Inhibition Switching ($p = 0.003$); **(C)** CVLT-II, Alternating Versions, Total Trials 1–5 ($p = 0.003$); and **(D)** CVLT-II, Long Delay (20 min) Free Recall ($p = 0.006$). Reprinted with authors' permission, Naeser et al.[103] Also, reprinted from Naeseret al.[131] CVLT, California Verbal Learning Test; tLED, transcranial LED.

least 2 SD below average on a single neuropsychological test, or 1 SD below average on two different neuropsychological tests measuring executive function and memory, were treated. Each subject received 18 sessions of tLED therapy (Monday, Wednesday, and Friday for 6 weeks, with at least 48 h elapsing between sessions). An actigraphy system (Philips, Actiwatch 2) was used to record the sleep data for 1 week before treatment and for 1 week after completion of treatment. Both subjects showed marked improvement in sleep patterns, displaying an average increase of 1 h of sleep per night, after completion of

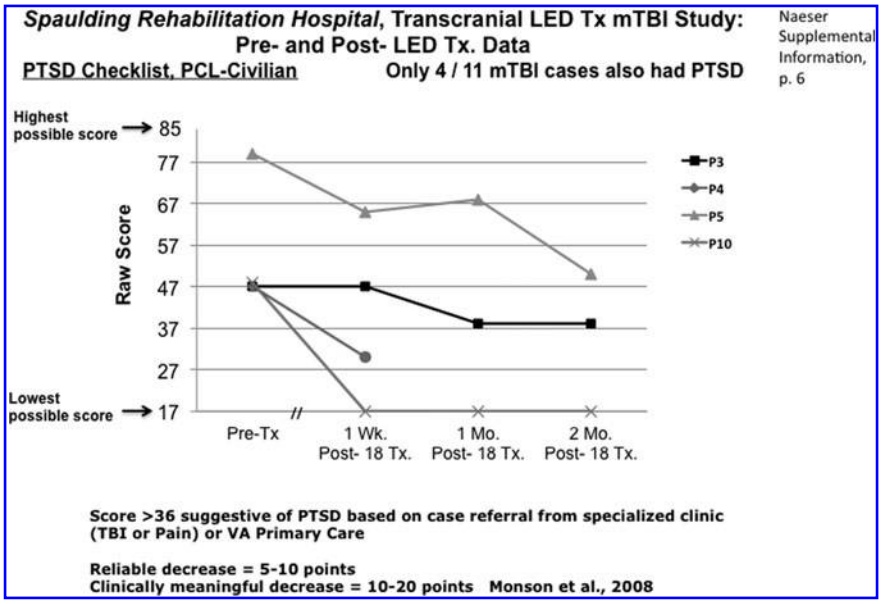

FIG. 2. Four of the 11 mTBI cases treated in the study by Naeser et al. also had PTSD. All four cases showed a clinically meaningful or reliable decrease in symptoms of PTSD, after the transcranial red/NIR LED treatment series. Source: Data are graphed from Naeser et al.[103] Also, reprinted from Naeser et al.[131] mTBI mild traumatic brain injury; NIR near-infrared; PTSD, posttraumatic stress disorder.

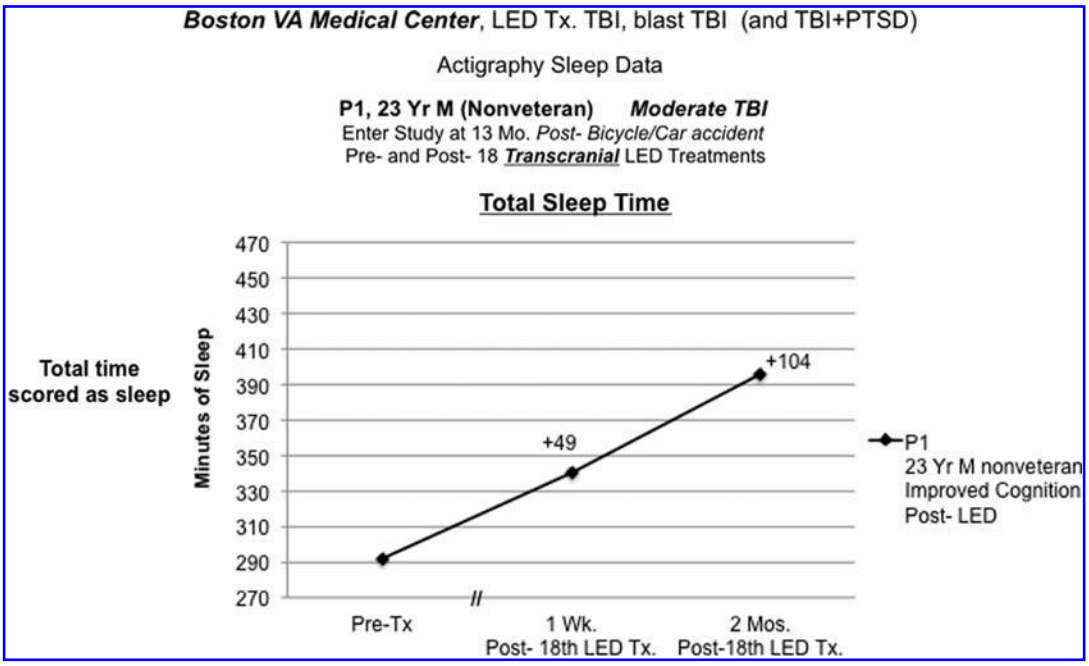

FIG. 3. Time spent asleep, increased by about 1 h after 18 transcranial red/NIR LED treatments. The Actigraphy watch was worn 24/7 for 1 week pre-tLED, and again at 1 week and 2 months post-tLED. This individual with moderate TBI also improved on executive function and verbal memory. Source: Bogdanova et al.[104] Also, reprinted from Naeser et al.[131]

the treatment series compared to before the treatment started. P1 also showed an improvement in executive function, verbal memory, and sleep efficiency. P2 also showed improvements in measures of PTSD symptoms on the PTSD checklist-Military version (PCL-M) and depression (Hamilton depression scale). No adverse events were reported (Figs. 3–6).

Intranasal (only) LED treatments to improve sleep and cognition in chronic TBI

A pilot open-protocol study, using only intranasal LED (iLED) on chronic mTBI patients, is in progress at the VA Boston Healthcare System.[105] Two small iLEDs (one

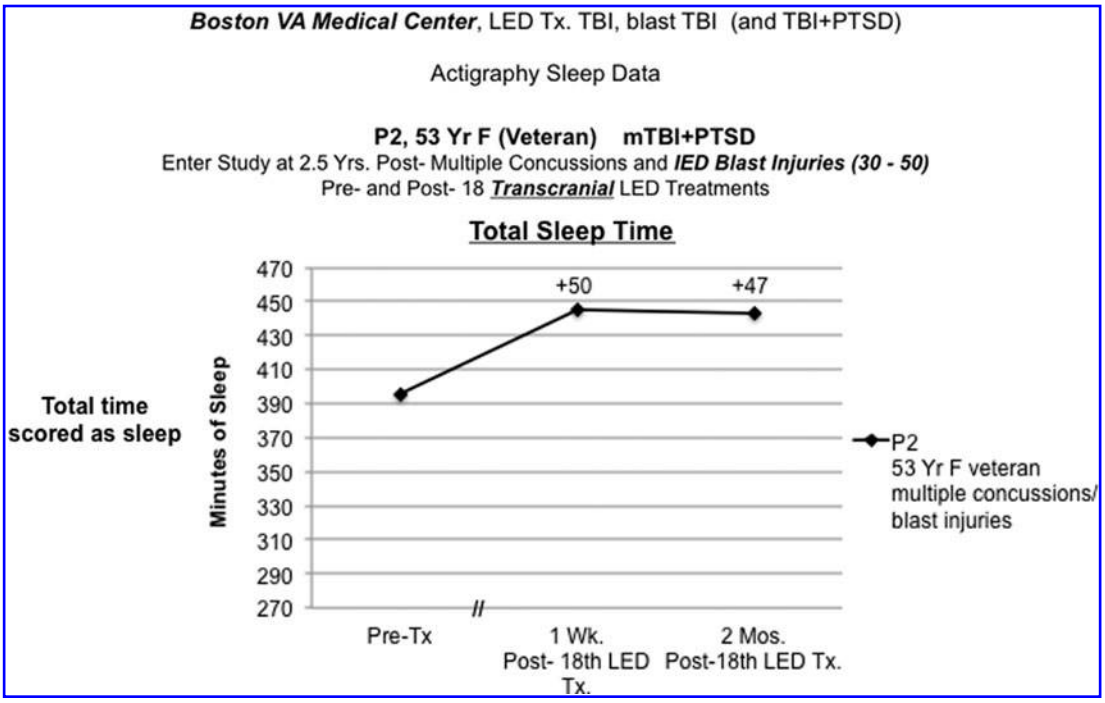

FIG. 4. Time spent asleep, increased by about 1 h after 18 transcranial red/NIR LED treatments. The Actigraphy watch was worn 24/7 for 1 week pre-tLED, and again at 1 week and 2 months post-tLED. This woman also had reduced symptoms of PTSD and depression post-tLED (see Figs. 5 and 6). Source: Bogdanova et al.[104] Also, reprinted from Naeser et al.[131]

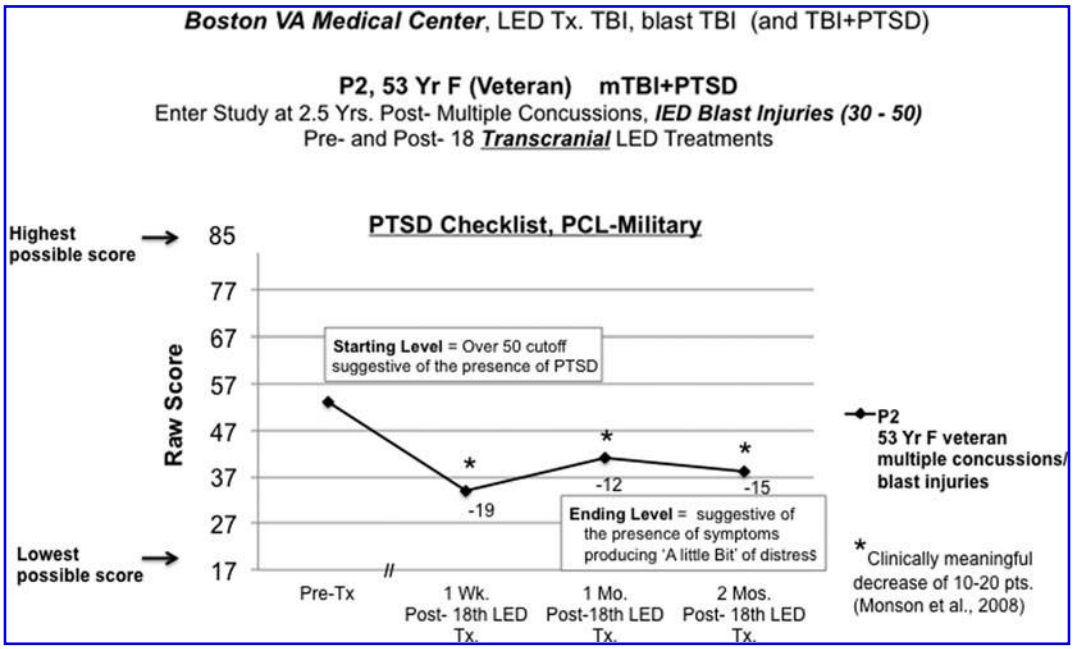

FIG. 5. Reduced PTSD symptoms after 18 transcranial red/NIR LED treatments. The changes showed a clinically meaningful decrease in PTSD symptoms at 1 week and 2 months post-tLED, compared to pre-tLED. Source: Bogdanova et al.[104] Also, reprinted from Naeser et al.[131]

clipped into each nostril) were used at the same time for 25 min. The parameters for each intranasal diode device (Vielight) are as follows: the red 633 nm intranasal diode is 8 mW total power, CW; beam spot size on contact, 1 cm^2; power density, 8 mW/cm^2; with the estimated energy density delivered to the nasal mucosa over 25 min being 12 J/cm^2 (Fig. 7). The NIR 810 nm intranasal diode pulsed at 10 Hz is 14.2 mW total power; beam spot size on contact, 1 cm^2; power density, 14.2 mW/cm^2; with estimated energy density to nasal mucosa in 25 min, 10.65 J/cm^2. Each iLED device is noninvasive, painless, and nonthermal. Each device is powered by a single AA battery

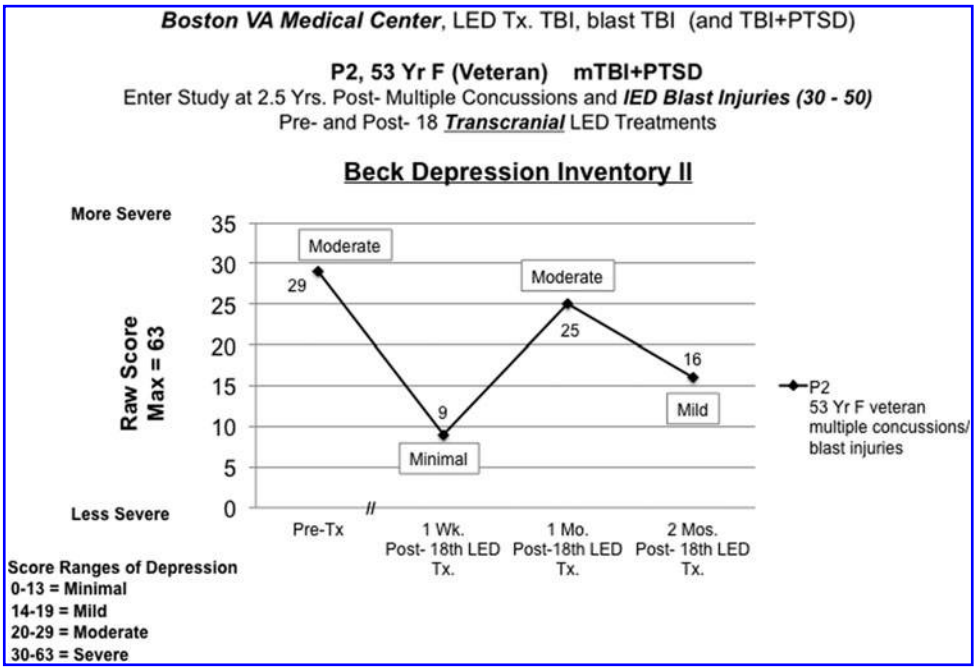

FIG. 6. Reduced levels of depression after 18 transcranial red/NIR LED treatments in this woman veteran with mTBI+PTSD. Pre-tLED, the depression level was rated as moderate. The depression level was rated as minimal at 1 week after the 18th treatment. Although the depression returned to moderate at 1 month after the 18th tLED treatment, it was rated as only mild at 2 months after the last tLED treatment. Results might have been more consistent if she had access to LED devices for home treatment.[102] Source: Bogdanova et al.[104] Also, reprinted from Naeser et al.[131]

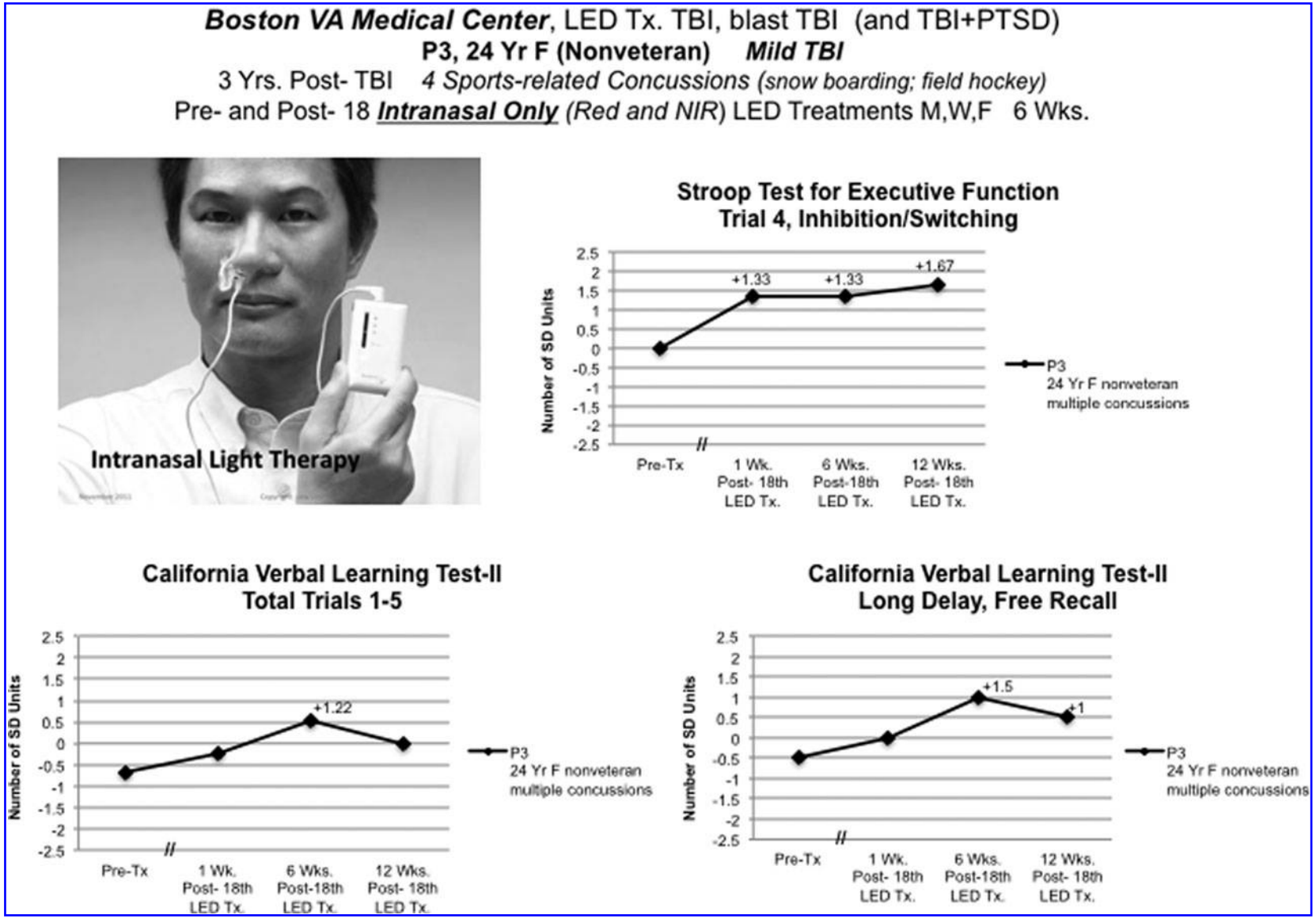

FIG. 7. Improvements in executive function and verbal memory after the 18th intranasal LED treatment in this 24-year-old female who had a history of four mTBIs. Improvements were +1 SD or more on these tests at 1, 6, and/or 12 weeks after the 18th intranasal LED treatment. Source: Bogdanova et al.[105] Also, reprinted from Naeser et al.[131]

(1.4 V); each battery is changed after 10 h of use (about 20 iLED treatments).

We hypothesize that some NIR photons that are delivered into the nose can reach medial temporal lobe structures, including the hippocampus and the adjacent perirhinal, entorhinal, and parahippocampal areas. The red photons are hypothesized to improve blood rheology[106] and possibly to improve sleep by increasing melatonin.[107] Subjects are treated three times per week for 6 weeks, with at least 48 h between treatments. The pre- and post-iLED testing is on the same schedule as described above for tLED.[103,104]

Up to the present time, a single mTBI participant (24-year-old female) who had sustained four sports-related concussions (two during snowboarding and two during field hockey) has received the complete iLED treatment series. The results measured after the iLED series were similar to those found in our tLED study.[103] Significant improvements were observed in tasks measuring executive function and verbal memory (Fig. 7), as well as attention and verbal fluency. Improvements were sustained for 1, 6, and 12 weeks after the final 18th iLED treatment. At 1 week after the 18th iLED treatment, the average total time asleep had increased by 61 min per night (Fig. 8), and her sleep efficiency (total sleep time divided by total time in bed) had increased by 11%. At 12 weeks post-iLED, her sleep efficiency was 5% higher than that measured at baseline. At that 12-week time point, she reported no longer having to use the sleeping pills that she had previously used on a regular basis. It is conceivable that if she had been provided with the opportunity to use self-administered home treatments with the iLEDs, her sleep patterns could have continued to improve even more. There were no adverse events or negative side effects.

Discussion

The overall results from the aforementioned open-protocol PBM studies designed to improve cognitive function in chronic mTBI patients include significant improvements in measures of executive function, in verbal learning, and in memory.[102–105] In the study by Naeser et al., the mTBI cases had suffered from persistent cognitive dysfunction for periods ranging from 10 months to 8 years.[103] As is often found in chronic mTBI patients, there was considerable heterogeneity among the 11 individual cases.[81] The series included four individuals with a history of multiple concussions.

Executive function and its relationship to the DMN and the SN

In the study by Naeser et al., there was variability in the baseline scores among the mTBI cases with regard to their ability to perform executive function tasks. For example, in the Stroop test Trial 4 (Inhibition Switching) considered to be the most difficult of the executive function tasks, 5/9 cases (56%) had baseline levels that were at least 1.0 SD below average, whereas 4/9 had average scores (adjusted for age and education norms).[103] All five patients who started with below-average scores improved by between +1 and +4.5 SD measured at 2 months after the tLED treatment series.

In an MRI study reported by Bonnelle et al., there was variability observed in performance in the Stroop Inhibition Switching test among a large number of TBI cases who were examined using rs-fcMRI, fMRI, and DTI scans.[70] In that study, 20/46 (43%) patients performed poorly on the ''stop-signal reaction task'' (SSRT) showing slower response inhibition (longer SSRT response times). The cases with slower

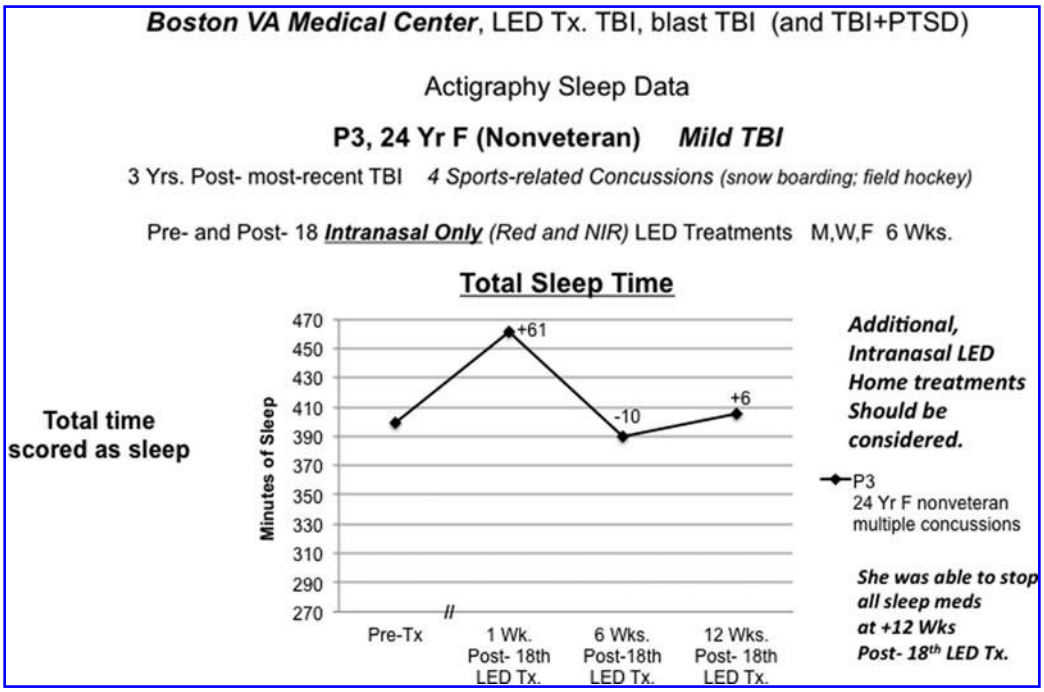

FIG. 8. Time spent asleep increased by about 1 h after 18 intranasal red/NIR LED treatments. The Actigraphy watch was worn 24/7 for 1 week before intranasal LED, and again at 1, 6, and 12 weeks after the 18th intranasal LED treatment. The gains made at 1 week after the intranasal treatments (but not sustained at 6 and 12 weeks after the last intranasal treatment) might have been sustained if she had had access to the intranasal LEDs for home treatment. Source: Bogdanova et al.[105] Also, reprinted from Naeser et al.[131]

reaction times in the NoGo condition were observed to have poor ability to deactivate the DMN, especially the precu/PCC portion of the DMN. Other components of the DMN, including the mPFC and the left hippocampus, were also observed to have less deactivation. The loss of the ability to deactivate the DMN during performance of cognitive tasks that require rapid shifting of attention and inhibition has also been reported in several other studies using fMRI to test TBI patients.[66–69]

The study by Bonnelle et al. also reported abnormalities detected in the SN among their TBI cases.[70] These SN abnormalities were prominent in those cases who failed to deactivate the precu/PCC during the SSRT. The SN (consisting of the AI, preSMA, and dACC) regulates activity in the DMN. It was also reported that failure to deactivate precu/PCC during the SSRT was correlated with the amount of damage sustained by white matter connecting the cortical nodes within the SN. This was shown by significantly lower values of fractional anisotropy (FA) measured using DTI in the SN white matter tract connecting the right AI to the preSMA and the dACC. These authors observed a significant linear correlation between the FA values of the rAI-preSMA/dACC tract with the amount of precu/PCC activation that remained during the stopping phase of the test ($r=-0.472$, $p<0.0005$). They observed that during the Stroop color/word interference test for executive function[108] that ''the FA within the rAI-preSMA/dACC tract (corrected for age and whole-brain white matter damage) was significantly correlated with the inhibition/switching versus combined color naming and word reading contrast score (Spearman one tailed $r=-0.265$ $p=0.029$ $n=52$).''[70] No other neuropsychological measures were correlated with activation/deactivation in the SN.

There were five mTBI cases in the study by Naeser et al.,[103] who started with below-average Stroop Inhibition Switching scores, and who showed good improvements (+1 to +4.5 SD). It is possible that the red/NIR light from the LED cluster heads that had been placed on the midline location of the heads of these subjects reached the cortical nodes within the SN and/or the DMN, thus improving the function of these nodes and/or increasing functional connectivity between these nodes. These changes in the DMN and SN, which could have been caused by physiological changes produced by tPBM such as increased cellular ATP or focal increases in rCBF, are discussed later in the Possible Mechanisms and Cellular Changes Post-red/NIR tLED section.

tLED and fMRI research conducted in the Naeser laboratory on patients with chronic left-hemisphere stroke has observed locally increased activation after 18 transcranial red/NIR LED treatments in targeted cortical areas using fMRI scans.[109] These studies with chronic stroke patients suggest that the exact LED locations on the surface of the scalp do have a focal effect on the brain, particularly directly beneath the LED placement locations. Although no rs-fcMRI or task-related fMRI studies were conducted during our pilot studies in chronic mTBI cases, the specific LED placements chosen may have had a beneficial focal effect on specific cortical nodes within the SN and the DMN as described in more detail below.

Specific tLED scalp placements that may affect specific cortical nodes in the SN and DMN. We chose scalp placements to deliver light to specific cortical nodes within the SN as follows: (1) the placement of the tLED on the midline of face, centered on the upper forehead and the front hairline, was designed to target the left and right dACC cortical nodes within the SN; (2) the tLED placement on the midline of the vertex of the head was designed to target the left and right preSMA cortical nodes within the SN; and (3) the tLED placements on the left and right temple areas were designed to reach the AI within the SN. The effectiveness of this strategy, however, is uncertain due to the greater depth of the AI beneath the scalp surface.

We chose scalp placements to deliver light to specific cortical nodes within the DMN as follows: (1) the tLED location on the midline of face, centered on the upper forehead and the front hairline, was designed to target the left and right mPFC cortical nodes within the DMN; (2) the tLED location on the midline of the scalp, above the external occipital protuberance (and half-way toward the vertex), was designed to target the left and right areas of the precuneus (high parietal), which are components of the precu/PCC nodes within the DMN; and (3) the tLED locations above and behind each ear were designed to target the left and right posterolateral inferior parietal areas of the cortex (angular gyrus). These areas are also nodes within the DMN.

Appropriate increased activation in the CEN (as explained below) is hypothesized to contribute to improved behavior in executive function measured by the Stroop test. Increased activation in the CEN, however, depends on appropriate decreased activation in the precu/PCC, which is part of the DMN. Improvements in communication between these two networks are therefore likely to have taken place as a result of tPBM.

Verbal learning and memory, and its relationship to the CEN

The CVLT is a verbal task of WM, where increased activation during task-related fMRI scans has been observed to occur in the DLPFC areas and/or the frontoparietal areas.[110,111] WM has also been associated with the function of the CEN using rs-fcMRI scans.[72] The CEN is a frontoparietal network consisting primarily of the DLPFC and the posterior parietal cortex (PPC).[75] In addition to WM, the CEN has also been associated with other high-level cognitive functions such as planning, decision-making, and attention.[76] During WM tasks such as the CVLT, activation should be increased within the CEN, while the DMN should be deactivated. Ideally, there should be a coordinated toggling of activation back and forth between these two networks.

Specific tLED placements that may affect specific cortical nodes within the CEN. As mentioned above, no rs-fcMRI or task-specific fMRI scans were included in our pilot studies with the mTBI cases. Nevertheless, we believe that the specific tLED placements chosen may have had a beneficial local effect on cortical nodes within the CEN. These locations could be as follows: (1) the tLED locations immediately above the left and right front hairline located on a line directly up from the pupils were designed to target the areas of the DLPFC and (2) the tLED locations positioned above and behind each ear were designed to target the inferior parietal cortex/posterior parietal areas of the cortex (IPC/PPC, angular gyrus). Each of these frontal and parietal LED locations corresponds to specific cortical nodes within the CEN.

Depression

Only five of the chronic mTBI patients started the study with moderate or severe depression. There was a trend for significant improvement in the depression score at the 1-week time point after the tLED series ($p = 0.045$), but this significant improvement was not found at 2 months post-tLED. The pattern of initial reduction in depression scores at 1-week post-tLED in 4/5 of these cases (but not an overall sustained change at 1 or 2 months post-tLED) is similar to the results found by Schiffer et al.,[10] who reported on 10 cases of severe depression. Schiffer et al. found that depression scores were significantly reduced at 2 weeks after a single application of NIR tLED to the left and right forehead. However, depression scores tended to return toward baseline after 4 weeks. In the studies by Schiffer et al. and Naeser et al., the depression scores of the majority of the patients did not completely drop back to the baseline levels.[10,103] Many articles have reported that there is downregulation of the process of neurogenesis occurring in the hippocampus in patients with major depression.[112] The possible role of tLED (or iLED) in the upregulation of neurogenesis in the hippocampus requires further study. Our results, taken together with those of Schiffer et al., suggest that continued ongoing tLED treatments may be necessary to produce sustained long-lasting improvements in depression.

PTSD and relationship to DMN and SN

Impaired response inhibition has been reported in veterans who suffer from PTSD combined with mTBI (and even in those with mTBI without PTSD).[113] More errors on NoGo trials were reported in both these groups compared to controls. In the tLED study by Naeser et al., four of the mTBI cases had baseline PCL-C scores (PTSD-Civilian checklist) that were suggestive of PTSD, and three out of these four cases also had Stroop Trial 4 Inhibition Switching scores that were at least 2 SD below average (P4, 5, 10; the fourth case, P3, started with an average score). At the end of treatment, all four of these PTSD cases showed a ''reliable'' or ''clinically meaningful'' decrease in PTSD symptoms (Fig. 2.). Moreover, all four of these cases improved by between +1 SD and +2 SD on the Stroop Trial 4 Inhibition Switching.[103] Therefore, improvements in inhibition could also explain reductions in the severity of the PTSD symptoms as well as improvements in cognitive function.

Patients with PTSD have been found to display abnormalities within the DMN.[114,115] For example, Sripada et al. reported ''reduced functional-connectivity within the DMN (between DMN seeds and other DMN cortical nodes) including rostral ACC/vmPFC; and increased connectivity within the SN (between insula seeds and other SN cortical nodes) including the amygdala.''[114] Moreover increased connectivity between networks was reported, as some DMN seeds showed increased connectivity with regions of the SN, including the insula, and conversely, SN seeds exhibited increased connectivity with regions of the DMN, including the hippocampus. These results suggested that there was some ''threat-sensitive circuitry'' operating in PTSD patients, even in task-free conditions. Loss of equilibrium between large-scale networks responsible for salience detection (environmental monitoring) versus internally focused thought may be associated with PTSD.[114] In the study by Naeser et al., the reduced PTSD symptoms may have been associated with improved modulation between these two important intrinsic networks (DMN and SN).[103] Future neuroimaging studies using rs-fcMRI in patients with PTSD may be able to show possible changes in neuromodulation between the DMN and SN after tLED application.

Menon has proposed there is a ''triple network model of aberrant saliency mapping and cognitive dysfunction'' that can occur in patients with both neurological and psychiatric disorders.[76] The three intrinsic brain networks referred to by Menon are the DMN, SN, and CEN. Naeser et al. proposed that the improvements in cognitive function occurring after tLED might be due to strengthening of the functional connections between cortical nodes in these three intrinsic networks.[103] The cortical nodes within these intrinsic networks have an especially high demand for energy (glucose, oxygen, and ATP) to maintain their proper function.[64] If PBM was able to deliver enough red/NIR photons to the mitochondria within the neurons making up these critical cortical nodes, then defective functional connectivity among these networks may have improved.

Stevens et al. investigated 12 different resting-state, functional-connectivity networks in 30 mTBI cases (13–136 days postinjury).[116] These authors reported abnormal functional connectivity in every brain network examined, including those concerned with visual processing, motor limbic functions, and numerous circuits believed to underlie executive function. Some of these functional connections were decreased and others were increased in mTBI cases, compared with controls. ''Postconcussive symptom severity was linked to abnormal regional connectivity within nearly every brain network identified, particularly the anterior cingulate.''[116] We believe that one of the most important tLED locations may be the one located on the midline, centered over the front hairline and the upper forehead, designed to target the dACC of the SN, and the mPFC of the DMN. Other very important LED locations are likely to include the high-parietal, midline precuneus area (DMN), and the DLPFC area (CEN), located posterior to the front hairline, on a line up from the pupil of each eye.

Weak connections among cortical nodes within intrinsic networks in chronic TBI

It has been reported in results from several rs-fcMRI studies on TBI patients that the three intrinsic networks (DMN, SN, CEN) continue to be present after TBI, but their connections are found to be weak.[68,117–119] Some of the abnormal, or weak, functional connections may persist for months, or even years post-TBI.[120] Menon has suggested that weak connections within and between these network nodes could compromise the dynamic interaction of these core networks, all of which can result in abnormal neurological and psychiatric behavior.[76]

Possible mechanisms and cellular changes post-red/NIR tLED

There are some specific biochemical mechanisms and cellular and physiological changes that occur in tissues after delivery of red/NIR photons that may be relevant to the brain cortex and subjacent white matter areas.

(1) ATP production by the mitochondria is increased after exposure to red/NIR photons,[1,2] especially in

hypoxic/compromised cells. Considering the constant high demands for energy characteristic of the intrinsic networks (DMN, SN, CEN),[64] increased ATP production would be highly relevant.

(2) Increased vasodilation and improved rCBF in surface cortical areas have been observed in tPBM. Animal studies using transcranial NIR PBM to treat acute TBI[121] have suggested that CCO within the mitochondria releases bound nitric oxide, which diffuses it outside the cell, promoting focal vasodilation.[3] Two human clinical trials have reported increased rCBF in areas of the brain beneath the locations on the forehead where the light is delivered.[9,10] Increased rCBF has also been observed in chronic stroke, where differences were observed in activation patterns on fMRI scans after bilateral application of tLEDs versus only ipsilesional application.[109]

(3) PBM can cause an increase in antioxidant production. PBM can activate redox-sensitive transcription factors, including NF-κB. Mitochondrial superoxide dismutase, a powerful antioxidant, is one of the most upregulated genes after NF-κB activation.[122] Another gene whose expression is increased after NF-kB activation is heat-shock protein 70 that has also been shown to be neuroprotective.[123]

(4) PBM is well known to be highly effective in decreasing inflammation.[124] For example, Khuman et al. reported that NIR tPBM used to treat acute TBI in mice led to reduced microglial activation demonstrating an anti-inflammatory effect.[121] Several reports[125] in different animal models, as well as *in vitro*, have demonstrated that PBM can reduce expression of cyclooxygenase-2 (COX-2) and thereby reduce prostaglandin synthesis.[126,127]

(5) PBM has been shown to stimulate neurogenesis in mice with acute TBI.[18] This neurogenesis was found in the two key sites in the mouse brain that also apply for adult human neurogenesis,[128] including (a) the subgranular layer of the dentate gyrus in the hippocampus and (b) the subventricular zone of the lateral ventricles. It is now known that neurogenesis persists in the adult mammalian brain (as opposed to its major role in fetal brain development) and can be further stimulated by physiological factors, such as growth factors, aerobic exercise, and environmental enrichment. Neurogenesis occurs more after ischemia and brain injury.[129]

(6) In the same mouse model of acute TBI, PBM was found to upregulate expression of Synapsin-1 in the cortex adjacent to the damaged area. Synapsin-1 is a characteristic marker for the process of synaptogenesis.[17] Synaptogenesis describes the process of formation of new synaptic connections between existing neurons, and is also known as neuroplasticity. It is highly important for recovery and rehabilitation of patients who have suffered brain damage after TBI or stroke. A clue to the mechanism of the increase in synaptogenesis after PBM was the finding of increased expression of brain-derived neurotrophic factor (BDNF). BDNF is considered to be a highly important mediator that governs not only brain repair after injury but also optimum brain functioning in many fields of cognition.

(7) Sleep may be improved. In our pilot studies at the VA Boston Healthcare System, quantitatively improved sleep was observed in these subjects using actigraphy. Improved sleep was observed after application of tLED treatments,[104] as well as after application of iLED only.[105]

Conclusions

We believe that large-scale, sham-controlled studies are warranted, both in acute and chronic TBI patients. If the behavioral results reported above can be replicated, and if supportive fMRI studies can be obtained, then perhaps a wider range of patient populations (e.g., dementia/AD) could be treated with red/NIR tLED and/or iLED therapies. Indeed, significant improvements ($p < 0.03$) in cognition were recently reported in a small number of chronic moderate dementia cases following 12 weeks of treatment with 810 nm tLED plus iLED, applied to only the cortical nodes in the DMN.[130] If treatment with tPBM can be initiated earlier post-TBI (even in the acute setting), the prevention of long-term cognitive dysfunction developing in TBI patients could also be possible.

Future Studies

Additional pilot clinical studies with tLED are being carried out at the VA Boston Healthcare System. Dr. Jeffrey Knight at the National Center for PTSD has received VA funding to carry out a pilot study using real versus sham tLED to see whether PBM can reduce symptoms of PTSD and improve cognitive function in veterans who had suffered TBI. Dr. Yelena Bogdanova is conducting a similar study of real versus sham tLED and iLED to improve sleep and cognition in veterans who have sustained TBI. Dr. Margaret Naeser is conducting a trial with VA funding to test whether real versus sham tLED and iLED can improve cognitive function in veterans suffering from Gulf War Illness. Dr. Carole Palumbo is testing the ability of tLED and iLED applied to active duty soldiers who have suffered blast TBI with funding from the Army Medical Department Advanced Medical Technology Initiative. Dr. Palumbo is an investigator at the U.S. Army Institute of Environmental Medicine.

Author Disclosure Statement

No competing financial interests exist.

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