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Guest Editorial

Traumatic Brain Injury: A Major Medical Problem That Could Be Treated Using Transcranial, Red/Near-Infrared LED Photobiomodulation

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Traumatic Brain Injury: Severity of the Problem

Three traumatic brain injuries (TBIs) occur every minute in the United States. TBI is a major medical problem worldwide.[1] More than 5,000,000 Americans are living with TBI-related disabilities with an annual cost of $60–76.5 billion.[1,2] Nonpenetrating, mild TBI (mTBI) is the most common type (75%). mTBI is defined by loss of consciousness (LOC) lasting ≤30 min (or no LOC), and with a period of altered mental status (amnesia/confusion) lasting up to 24 h. Persistent cognitive problems occur in 5–22% of cases.

Sports-related concussion or mTBI, followed by cognitive dysfunction are of increasing concern both in males and females.[3] With each successive concussion, there is a cumulative effect,[4] including a prolonged period of recovery and progressively increased risk for re-injury.[5] Blast TBI caused by an improvised explosive device (IED) is the signature injury of soldiers returning from Iraq and Afghanistan.[6] It is estimated that 28% of patients with combat-related mTBI also have clinical levels of post-traumatic stress disorder (PTSD) symptoms.[7]

Approximately 53% of individuals with TBI also report sleep disturbances.[8] Poor sleep disrupts the clearing of metabolites from the brain, including β-amyloid and other potentially neurotoxic waste products that accumulate during periods when a person is awake.[9]

Persistent neuroinflammation may be a mechanistic link between TBI and potential for later development of neurodegenerative disease, including Alzheimer's disease (AD).[10,11] Increased microglial activity may persist for a long time post-TBI.[12] Chronic traumatic encephalopathy (CTE), a progressive tau protein-linked neurodegenerative disease, is believed to develop (at least in part) from repeated head trauma.[13] Symptoms include cognitive dysfunction, progressive irritability, suicidal ideation, and dementia. It may develop years after the original head trauma occurred. CTE has also been documented in United States military veterans exposed to blast injury in Iraq and Afghanistan.[14]

Structural CT or MRI brain scans show no focal brain abnormalities with nonpenetrating mTBI, although abnormalities in the white matter axons, important for connecting areas of brain cortex, can be observed on special diffusion tensor imaging MRI scans.[15] The frontal lobes, including medial and lateral prefrontal cortex areas that are important for normal cognitive function, are especially vulnerable to damage following rapid acceleration/deceleration and twisting, for example, whiplash in a motor vehicle accident (MVA), concussive blast force, or even direct impacts to the head.[14,16] Loss of brain interconnectivity from axonal damage produces the cognitive, emotional, and behavioral problems observed following TBI.[17]

In healthy controls, specific brain networks have been identified that function in a temporally coherent, correlated manner, even during the ''resting state'' (when no task is being performed).[18,19] The cortical brain areas that comprise a specific brain network may be located in areas close to each other, or further away. These brain networks are studied in the MRI scanner while the participant is simply at rest, looking at a fixation point for 5–7 min. These resting-state functional connectivity MRI scans (rs fMRI) have shown abnormalities in TBI cases in specific brain networks critical for cognitive function.[20–22] These networks have very low-frequency, coherent oscillations in the frequency range of 0.01–0.08 Hz. The general features appear to also be present in the brains of monkeys and small animals.[23]

There are three, highly specialized brain networks important for cognition that have been observed to be dysregulated on rs fMRI scans in TBI. The first of these is the default mode network (DMN), which consists of: (1) anterior areas in the medial frontal lobes [medial prefrontal cortex (mPFC)]; (2) posterior areas in the medial parietal lobes [precuneus and posterior cingulate cortex (precun/PCC)] and in posterolateral areas in the lateral parietal lobes (angular gyri); and (3) deep, medial temporal lobes/

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hippocampal areas.[19] In order for normal cognitive function to occur, the DMN, particularly the medial posterior portion (precun/PCC) needs to *de-activate*, so that a different network can *activate*, for example, the central executive network (CEN). The CEN is the second network that can be affected. The CEN consists of the dorsolateral prefrontal cortex areas and the intraparietal sulcus areas. Abnormality in the DMN (with *failure to de-activate*) has been observed in multiple studies with mTBI cases.[20–22] The third network affected in mTBI cases is the salience network (SN).[24] The SN controls the DMN, and the SN consists of the anterior insulae, the presupplementary motor areas (preSMAs), and the dorsal anterior cingulate cortex (dACC) areas. The SN is critical for normal executive function and inhibition.[25,26] The cerebral cortex in the anterior parts of the SN (preSMAs and dACC) help to promote inhibitory control (*de-activation*) of the posterior parts of the DMN (precun/PCC), particularly during tasks that require *inhibition* and *rapid switching* for success. The SN is important for signaling the need to change behavior.[27] Patients with mTBI (and PTSD) often present with diminished control of inhibition.[28]

There are currently no pharmacologic treatments for the secondary injuries that follow mTBI, or for prevention of cognitive and behavioral problems associated with mTBI.[29] Cognitive behavioral therapy approaches for TBI patients attempt to maximize the patient's behavioral functioning by working with residual cognitive capacities,[30] but injured, nonfunctioning brain cells may limit their potential for success. Treatments are needed that *directly target injured brain cells* to improve the functioning of underlying brain systems (including functional connectivity in networks such as the DMN, CEN, and SN) that regulate attention, executive function, memory, emotions, and behavior.

Rationale for Applying Transcranial, Red/Near-Infrared (NIR) LED Photobiomodulation to Treat TBI

NIR wavelengths (800–900 nm) can penetrate through scalp and skull (2–3%, $\sim$1 cm).[31–33] These NIR wavelengths have the potential to improve the subnormal, cellular activity of compromised brain tissue by increasing adenosine triphosphate (ATP) production in the mitochondria,[34–36] and increasing regional cerebral blood flow.[37–39]

Application of NIR transcranial LED (tLED) has been shown to have an anti-inflammatory effect, inhibiting microglial activation.[40] There are also strong antioxidant effects (increase in mitochondrial superoxide dismutase),[41] and increase in heat-shock protein 70, a molecular chaperone that prevents mis-folding and unwanted protein aggregation, especially at the telomeres of DNA.[42] Perhaps the most important effects are the potential for increased *neurogenesis* and *synaptogenesis*, reported in small animal studies treated with NIR in the acute stage post-TBI.[43,44]

Clinical studies showing improvements in cognition (executive function and verbal memory), PTSD, and sleep, following a series of tLED treatments in chronic TBI, are promising. For example, significant improvements were reported in executive function and verbal memory, after a series of 18 red/NIR tLED treatments (500 mW, 22.2 mW/cm^2, 22.48 cm^2 per treatment area) in chronic TBI patients who began tLED at 10 months to 8 years post-TBI.[45] These cognitive tests included, in part, the Stroop (Color Word Interference) test for executive function; Trial 4 inhibition switching ($p=0.003$); and California Verbal Learning Test II, Alternating Versions, Long Delay (20 min) Free Recall ($p=0.006$). The tLED treatments may also be performed at home.[46]

Participants reported improved sleep, and fewer PTSD symptoms, if present. Post-tLED, one participant was able to write checks and pay bills for the first time since an MVA 5 years earlier. For another participant, his mTBI was caused by having been pulled into a blast furnace. His recurring nightmares of this TBI, which had lasted for 2 years, ceased post-tLED. One of the participants was still active duty military, but had been unable to return to his unit for 3 years following blast TBI. Post-tLED he returned for further evaluation by his special operations unit. These significant improvements post-tLED suggest that the NIR photon placements on the head may be affecting cortical areas in the DMN, CEN, and SN.

Resting-state fMRI scans have been obtained before and after 18 tLED treatments in left-hemisphere stroke patients with chronic aphasia. These pilot data show significantly increased correlations between pairs of cortical nodes within each of three separate networks (DMN, CEN, SN) post-tLED, along with significant increases in ''naming ability.'' These changes on rs fMRI were observed in aphasia patients treated with 26 J/cm^2 per LED cluster head placement (red/NIR, 500 mW, 22.2 mW/cm^2). Two LED cluster heads were placed simultaneously on midline nodes within the DMN (mPFC and precun/PCC), as well as on the left-hemisphere language areas (Naeser Laboratory, personal observation). These results suggest that rs fMRI studies obtained pre- and post-tLED could be supportive of tLED effects in future tLED studies with TBI.

Improved sleep (measured with wristwatch actigraphy) and improved cognition were recently reported post-red/NIR tLED or intranasal LED (iLED) in chronic TBI patients.[47] These TBI patients showed an average increase of 1 h of sleep per night at 1 week following 18 LED treatments. Red photons have been reported to increase melatonin levels.[48] It is hypothesized that some NIR photons can reach the hippocampal/lateral entorhinal cortex areas via intranasal delivery to potentially improve memory.

Results from these open-protocol, LED studies with chronic TBI patients suggest that future studies are warranted. Newly funded, sham-controlled studies with red/NIR tLED and iLED for PTSD, blast-TBI and Gulf War illness are underway at the VA Boston Healthcare System, Boston University School of Medicine, and the United States Army Research Institute of Environmental Medicine. In addition, a tLED study with acute TBI patients is underway through the Emergency Department at Massachusetts General Hospital.

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