

# Transcranial light-emitting diode therapy for neuropsychological improvement after traumatic brain injury: a new perspective for diffuse axonal lesion management

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**Abstract:** The cost of traumatic brain injury (TBI) for public health policies is undeniable today. Even patients who suffer from mild TBI may persist with cognitive symptoms weeks after the accident. Most of them show no lesion in computed tomography or conventional magnetic resonance imaging, but microstructural white matter abnormalities (diffuse axonal lesion) can be found in diffusion tensor imaging. Different brain networks work together to form an important part of the cognition process, and they can be affected by TBI. The default mode network (DMN) plays an important central role in normal brain activities, presenting greater relative deactivation during more cognitively demanding tasks. After deactivation, it allows a distinct network to activate. This network (the central executive network) acts mainly during tasks involving executive functions. The salience network is another network necessary for normal executive function, and its activation leads to deactivation of the DMN. The use of red or near-infrared (NIR) light to stimulate or regenerate tissue is known as photobiomodulation. It was discovered that NIR (wavelength 800–900 nm) and red (wavelength 600 nm) light-emitting diodes (LEDs) are able to penetrate through scalp and skull and have the potential to improve the subnormal, cellular activity of compromised brain tissue. Based on this, different experimental and clinical studies were done to test LED therapy for TBI, and promising results were found. It leads us to consider developing different approaches to maximize the positive effects of this therapy and improve the quality of life of TBI patients.

**Keywords:** traumatic brain injuries, diffuse axonal injury, low-level light therapy, neurologic manifestations, post-concussion syndrome, quality of life

## Current impact of traumatic brain injury (TBI) for public health policies

In the US, there occur 50,000 deaths annually from TBI, with the majority of those on the scene. Of an annual emergency room attendance of 1.1 million, there are 235,000 hospitalizations from nonfatal TBI. Recently, there has been an increase in TBIs presenting to the emergency department by 14%.<sup>1,2</sup>

Despite most of the victims of TBI recovering satisfactorily, some studies estimated higher rates (some with the considerable rates of 70%–90%) of these patients presenting with psychological or neurological symptoms weeks or months after the original head trauma<sup>3</sup> and 5%–22% of them persisting with these cognitive problems after these initial weeks.<sup>4</sup> Most of these patients present with mild TBI associated with normal computed tomography (CT) findings and no post-traumatic amnesia, and they

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normally present with complete resolution of post-traumatic symptoms within 1 month. However, ~30% of those with mild TBI and post-traumatic amnesia have persistent post-traumatic symptoms, and a significant number at 1-year post-injury have decreased functional outcome and disability.<sup>5</sup> The current data indicate that ~124,000 (43.1%) of people discharged with TBI from acute hospitalizations developed TBI-related long-term disability.<sup>6</sup> The definition of disability was given broadly, including inability or considerable difficulty in performing the activities of daily living, presenting post-injury symptoms, which prevented people from doing things they intended to do, and poor cognitive and mental health levels on standard measures focused on the findings from a previous population-based study.<sup>7</sup>

Despite these relevant rates, it is important to emphasize that they are likely underestimated, once they depend on hospitalizations only, and they do not include TBI treated in other settings or for which treatment was not sought.<sup>6</sup>

## Relationship of TBI, neuropsychological disorders and radiological features

Neuropsychological disorders include sleep problems (in 53% of patients),<sup>4</sup> irritability, apathy<sup>8</sup> and even diseases such as depression, obsessive-compulsive disorder (OCD) and anxiety syndromes.<sup>8-10</sup> Other common symptoms include headaches, balance problems, dizziness, fatigue and memory and attention difficulties.<sup>10</sup> This constellation of physical, emotional and cognitive symptoms is included in formal diagnostic criteria for post-concussion syndrome.<sup>10</sup> These presentations affect every aspect of an individual's life, such as education, potential employment opportunities and even social and family relationships.<sup>11</sup>

Most brain lesions leading to these symptoms are not shown in structural CT or magnetic resonance imaging (MRI).<sup>4,12-14</sup> However, abnormalities in the white matter (diffuse axonal lesion) could be found in diffusion tensor imaging (DTI) MRI scans.<sup>13,15</sup> DTI is sensitive to detect water diffusion in the brain. Thus, DTI is used to find microstructural lesion in white matter tracts.<sup>16</sup> There are five white matter regions of interest where one can usually see lesions:

1. anterior corona radiata (41% of TBI cases),
2. uncinate fasciculus (29% of TBI cases),
3. genu of corpus callosum (21%),
4. inferior longitudinal fasciculus (21%) and
5. cingulum bundle (18%).<sup>17</sup>

Almost all the symptoms and signs following TBI are attributed to the loss of connectivity in the aforementioned tracts.<sup>12</sup>

## Physiopathology of neurophysiological disorders after TBI

Increasing focus has been directed to brain regions in which neural activity is greater during the baseline state than during an experimental task. This state is called deactivation. The finding that demonstrates such task-related relative decreases in activity across a broad range of cognitive tasks when compared with a baseline state is what reinforces the current attention to this default mode theory. Thus, the default mode network (DMN) forms an important part of the cognition process.<sup>18</sup> Disruption of the DMN is clinically important, and abnormalities are observed in various neurological and psychiatric disorders.<sup>19</sup>

The power to regulate DMN functions seems to be a central point of normal brain activity, presenting greater relative deactivation seen during more cognitively demanding tasks.<sup>20</sup> Problems associated with sustained attention after TBI, as revealed by behavioral inconsistency, are related to an increase in DMN activity.<sup>21</sup> DMN as two other highly specialized brain networks is important for cognition. Frequently, they have been seen dysregulated on resting-state functional connectivity magnetic resonance imaging (fMRI) scans in TBI.<sup>4</sup>

The DMN can be divided as follows<sup>22</sup>:

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 posterolateral areas in the lateral parietal lobes (angular gyri) and
3. deep, medial temporal lobes/hippocampal areas.

The medial posterior portion of DMN (precun/PCC) needs to deactivate for normal cognitive function to occur. Thus, a distinct network called the central executive network (CEN) is used that can activate.<sup>21</sup>

The CEN is another network involved in the cognition process and is basically composed of two areas<sup>4</sup>:

1. the dorsolateral prefrontal cortex and
2. the posterior parietal cortex (mainly intraparietal sulcus area).

The CEN is a part of network that activates during functional MRI tasks involving executive functions (as salience network [SN]). Its activity is anticorrelated with DMN function.<sup>22</sup>

The last network affected in TBI cases is the SN. It consists of three areas<sup>4</sup>:

1. anterior insulae;
2. presupplementary motor areas and
3. dorsal anterior cingulate cortex.

The SN is necessary for normal executive function and inhibition. It controls the DMN.<sup>23,24</sup>

A couple of papers studied the effects of near-infrared (NIR) light to improve cognition through inducing a brain resting state. NIR light promoted an increase in power in alpha, beta and gamma frequencies in electroencephalogram (EEG). These findings are consistent with a brain resting stage, which is implicated in improved cognition.<sup>25,26</sup>

## Principles of red/NIR transcranial light-emitting diode (tLED) photobiomodulation (PBM)

The process of using red or NIR light to stimulate or regenerate tissue is known as PBM. It was accidentally found out after the Hungarian Endre Mester tried to use laser beams (trying to repeat an experiment performed in Boston, Massachusetts) to destroy cancer that was experimentally implanted into a laboratory rat.<sup>27</sup> The ruby laser that had been built was only a tiny fraction of the power of the laser that had previously been used in Boston by McGuff,<sup>28</sup> and he observed hair regrowth and wound healing in the stimulated area where tumor had been implanted.<sup>27</sup>

More than 30 years ago, it was also observed in cadaver studies that NIR (wavelength 800–900 nm) and red (wavelength 600 nm) LEDs are able to penetrate through scalp and skull (2%–3%, ~1 cm)<sup>29,30</sup> and have the potential to improve the subnormal, cellular activity of compromised brain tissue.

Currently, PBM is accepted as a therapeutic tool for infected, ischemic and hypoxic wounds and also presents positive effects in healing, reducing edema and inflammation, relieving pain, treating chronic inflammation and autoimmune diseases and recovering from ischemic heart disease and even attenuating the degeneration of optic nerve.<sup>31,32</sup> There are multiple studies for other pathological processes as TBI in course.<sup>4,27,33,34</sup>

Optimal therapeutic intervention was characterized by wavelengths within the far-red to NIR range (630–1064 nm) along with a minimal energy density of 4 J/cm<sup>2</sup>.<sup>35</sup> These wavelengths and energy density were proven to be effective at stimulating biological processes, and they act by four main actions:

1. Increasing adenosine triphosphate (ATP) production in the mitochondria.<sup>36,37</sup> Which happens due to cytochrome c oxidase (CCO) increased effect. CCO absorbs light photon and avoids nitric oxide (NO) inhibitory effect on itself. Thus, the mitochondrial membrane potential is

increased; there will be more oxygen consumed, as soon as more glucose is metabolized and more production of ATP happens.<sup>36</sup>

2. Increasing regional cerebral blood flow.<sup>37,38</sup>
3. An anti-inflammatory effect by inhibiting microglial activation and also strong antioxidant effects (increase in mitochondrial superoxide dismutase).<sup>39,40</sup>
4. Signaling mediators and activation of transcription factors that cause changes in protein expression that last for some considerable time and explain long-lasting effect.<sup>28</sup>
5. Increasing neurogenesis and synaptogenesis (described in small animal studies treated with NIR in the acute-stage post-TBI).<sup>34,40</sup>

Besides these biological effects, the role of heating during transcranial laser therapy to influence the cognitive improvement results had not been investigated. To address this potential confounding factor, a recently published paper<sup>41</sup> studied 11 patients in whom a heat generator produced the same time-dependent temperature alteration curve which the transcranial laser system produced at the same forehead location. A monitor was used to evaluate hemodynamic and metabolic changes in the forehead tissue near the thermal stimulation site before, during and after the heat stimulation. The results showed that CCO of the forehead tissue was not modified for this heat stimulation, and oxyhemoglobin changes were observed in comparison with laser stimulation. The authors concluded that heat was not responsible for cerebral hemodynamics and metabolic changes during transcranial laser therapy.<sup>41</sup>

The differentiation of a progenitor cell into a neuron is called neurogenesis. It usually occurs in the subventricular zone and hippocampus. It is not such a rare event in the brain as we once thought it was.<sup>42</sup> The formation of new synapses is the process called *synaptogenesis*. It is one of the brain recovery mechanisms after TBI.<sup>43</sup> NIR transcranial photobiomodulation (tPBM) was used to treat mice with acute severe TBI in current small studies, and these studies have supported the notion that tPBM increases neurogenesis and synaptogenesis. Beginning the protocol 4 h post TBI, they found that there was a significantly better recovery at 28 days post TBI in mice receiving NIR tPBM treatments thrice daily when compared to controls. The neurogenesis was noted to be increased when measured by immunofluorescence staining of brain sections.<sup>44</sup>

The respiratory mitochondrial enzyme CCO is the primary infrared photoacceptor in cells. Its increased activity after PBM is followed by increased hemoglobin oxygenation, explaining its role on neuromodulation.<sup>45</sup>

The brain imaging technique established compared to functional MRI is functional NIR spectroscopy (fNIRS),

which uses 700–900 nm light.<sup>46</sup> The estimated mean of penetration depth (5% remaining intensity) of NIR light through the scalp and skull is  $23.6 \pm 0.7$  mm.<sup>47–49</sup> Penetration also depends on the anatomical region of the skull and wavelength.<sup>50,51</sup> Wavelength is the most important parameter that governs the depth of penetration of laser light into tissue. Living tissues' absorption and scattering coefficients are higher at lower wavelength; thus, NIR light penetrates more deeply than red light and so on.<sup>52</sup> In tPBM application, NIR light is frequently used on the forehead (penetration is easier – no hair, longer wavelength).<sup>27</sup>

The clinical effects of PBM were tested in many studies. A controlled study with 20 patients (and >20 patients for the control group) using low-level laser stimulation (1024 nm wavelength) could demonstrate enhancement in sustained attention and short-term memory.<sup>53</sup>

With a similar approach, another paper was published using a low-level laser therapy with a specific wavelength (1024 nm) in 15 controlled patients. Its results suggested that transcranial laser stimulation improves executive function and may have exciting potential for treating neuropsychological disorders deficits.<sup>54</sup>

Two types of category learning structures have been studied: rule based and information integration. These category learning structures are related to two dissociable neural systems, and both rely on the network of brain regions: a reflective system (optimal for rule-based structures and highly reliant on processing on prefrontal cortex) and a reflexive system (optimal for information integration and reliant on processing on striatum). Testing the effects of transcranial infrared laser stimulation on these systems, it was found that prefrontal rule-based learning was improved as compared to placebo, but the same did not happen for striatum information-integration learning as compared to placebo.<sup>45</sup>

## Experimental and clinical studies with red/NIR tLED for TBI

The first described TBI animal model treated with tLED therapy was done with mice, which were subjected to head cerebral contusion and received 808 nm NIR/red light-emitting diode (LED). Only one tLED session 4 h after the injury reduced a considerably size of the post-injury area by 90%, and neurological severity scores were significantly lower at 28 days for laser-treated mice.<sup>55</sup> Mice receiving 6 min daily tLED session for 10 days reverted deficits in working memory tests.<sup>56</sup>

An open protocol with PBM in a two-case study with tLED designed to improve cognitive function in chronic mild

TBI patients also found considerable improvements in verbal learning, executive function and memory.<sup>17</sup>

Increasing the number of patients with chronic mild TBI, the same author of the previous quoted study published positive results for 11 patients submitted to 18 outpatient sessions, starting at 10 months to 8 years post TBI. Each LED cluster head (5.35 cm diameter, 500 mW, 22.2 mW/cm<sup>2</sup>) was applied during 10 minutes to every 11 scalp placements (13 J/cm<sup>2</sup>). Improvements were evidenced in executive function and sleep and fewer post-traumatic stress disorders.<sup>57</sup>

Other series of two patients submitted to 18 red/NIR tLED treatments (500 mW, 22.2 mW/cm<sup>2</sup>, 22.48 cm<sup>2</sup> per treatment area) in chronic TBI patients (who began tLED at 10 months–8 years post TBI) showed improvements in cognition (mainly executive function and verbal memory).<sup>58</sup>

Resting state fMRI scans have been obtained before and after 18 tLED treatments (26 J/cm<sup>2</sup> per LED cluster head placement red/NIR, 500 mW, 22.2 mW/cm<sup>2</sup>) in left-hemisphere stroke patients with chronic aphasia, which showed significant increases in “naming ability” and significantly increased correlations between pairs of cortical nodes within each of three separate networks (DMN, CEN, SN) post tLED.<sup>4</sup>

Another study using a high-power NIR laser (10–15 W at 810 and 980 nm) to treat a moderate TBI patient through 20 NIR applications over a 2-month period showed decreased headache, depression, anxiety and insomnia, whereas cognition and quality of life improved, accompanied by changes in the single-photon emission computed tomography (SPECT) imaging.<sup>59</sup> A summary of these studies is given in Table 1.

It is important to emphasize that these clinical studies with LED therapy for TBI were neither controlled nor randomized. Thus, their conclusion may simply be due to chance. Randomized, controlled studies are necessary for further conclusions.

Safety of PBM was tested in different studies. One of the first concerns was the cortical temperature during stimulation. A rabbit study in which NIR laser therapy (continuous wave energy 15 J/cm<sup>2</sup> at 808 nm wavelength) was applied for 10 min showed a cortical temperature increase under the laser probe by 0.8°C–1.8°C during treatment.<sup>60</sup> Human studies were also performed to test the safety of this therapy, and no adverse events could be related to PBM.<sup>61,62</sup> These studies and others describe no short- or long-term detrimental effects.<sup>17,57,58</sup> Low-level laser system (PBM) is registered in the Food and Drug Administration, and adverse effects described are ocular injuries, electrical shock and unintended cell damage.<sup>17,57,63</sup>

Table 1 Studies involving PBM for TBI

Reference (year)	Subject	Condition	$\lambda$ (nm)	Power (W)	Power density (mW/cm <sup>2</sup> )	Energy density (J/cm <sup>2</sup> )	Duration	Main outcome
Oron et al <sup>55</sup> (2007)	Mice	TBI model	808	0.2	10 and 20	1.2–2.4	2 min (unique)	Significant changes in neurological severity score from 5 up to 28 days after TBI. Lesion volume of the laser-treated mice was significantly lower (1.4%) than that of the nontreated group (12.1%)
Wu et al <sup>56</sup> (2010)	Mice	TBI model	660, 810 and 980	–	150	36	4 min (unique)	Mice with moderate to severe TBI had a significant improvement in neurological severity score over the course of the follow-up, and histological examination of the brains at sacrifice revealed less lesion area compared to untreated controls.
Naaser et al <sup>17</sup> (2011)	2 patients	TBI	9 red 633-nm diodes and 52 NIR 870-nm diodes	0.5	150	13.3	17 min weekly during 8 months	Improvement in executive function (inhibition, inhibition accuracy) and memory, as well as reduction in post-traumatic stress disorder
Naaser et al <sup>57</sup> (2014)	11 patients	TBI	9 red 633-nm diodes and 52 NIR 870-nm diodes	0.5	22.2	13	18 sessions (3 times per week during 6 weeks)	Improved sleep and fewer post-traumatic stress disorder
Bogdanova et al <sup>58</sup> (2014)	2 patients	TBI		0.5	22.2	13	18 sessions (3 times per week during 6 weeks)	Improved executive function, verbal memory, sleep efficiency and depression
Henderson and Morris <sup>59</sup> (2015)	1 patient	TBI	810 and 980	10–15	–	–	20 sessions during 2 months	Decreased depression, anxiety, headache and insomnia, whereas cognition and quality of life improved. Neurological function appeared to improve based on the changes in the SPECT by quantitative analysis

**Abbreviations:** PBM, photobiomodulation; TBI, traumatic brain injury; NIR, near-infrared; min, minute; SPECT, single-photon emission computed tomography.

## Conclusion

It is essential to have a rehabilitation plan, considering the morbidity due to TBI, preferably multi-professional, in order to get the maximum degree of recovery of neuropsychological activities. tLED therapy is an interesting approach to this, since it allows researchers to study the activity of the human brain in real time and finally to guide the patient's brain to plastic changes.<sup>64</sup>

There are different approaches for treatment of neuropsychological symptoms after TBI beyond PBM. Pharmacological treatments target the modulation of major neurotransmitter systems – dopaminergic, serotonergic, noradrenergic, acetylcholinergic and glutamatergic. Serotonin reuptake inhibitors act for depression secondary to TBI. Modulation of the dopaminergic system improves alertness, attention and cognitive processing speed. Cognitive and memory impairments may reflect the disruption of cholinergic function, and the effects of anticholinergic agents support this contention.<sup>65</sup>

Repetitive transcranial magnetic stimulation (rTMS) induces changes in cortical excitability, leading to reorganization of the network responsible for impaired function.<sup>64</sup> Some studies have found cognitive improvements after rTMS.<sup>66</sup> Transcranial direct current stimulation is another therapy for TBI rehabilitation based on brain excitability modulation via low-amplitude (0.5–2 mA) direct current through the scalp, and Demirtas-Tatlidede et al demonstrated its role in the facilitation of several cognitive domains.<sup>67</sup>

There is still a lot to understand and study about this new technology (PBM), but it is undeniable that its results are interesting so far. There are many questions that need to be elucidated such as duration of treatment, when to start and if all TBI patients should be treated or only a few of them depending on their characteristics. Answers like these may only be available after randomized clinical trials. However, the displayed data demonstrate that tLED therapy may be considered as a promising treatment for improvement in the quality of life of TBI patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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