

## Potential for Transcranial Laser or LED Therapy to Treat Stroke, Traumatic Brain Injury, and Neurodegenerative Disease

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**N**EAR-INFRARED (NIR) LIGHT PASSES readily through the scalp and skull and a small percentage of incident power density can arrive at the cortical surface in humans.<sup>1</sup> The primary photoreceptors for red and NIR light are mitochondria, and cortical neurons are exceptionally rich in mitochondria. It is likely that brain cells are ideally set up to respond to light therapy. The basic biochemical pathways activated by NIR light, e.g., increased adenosine-5'-triphosphate (ATP) production, and signaling pathways activated by reactive oxygen species, nitric oxide release, and increased cyclic adenosine monophosphate (AMP) all work together to produce beneficial effects in brains whose function has been compromised by ischemia, traumatic injury, or neurodegeneration. One of the main mechanisms of action of transcranial light therapy (TLT) is to prevent neurons from dying, when they have been subjected to some sort of hypoxic, traumatic, or toxic insult. This is probably because of light-mediated upregulation of cytoprotective gene products such as antioxidant enzymes, heat shock proteins, and anti-apoptotic proteins. Light therapy *in vitro* has been shown to protect neurons from death caused by methanol,<sup>2</sup> cyanide or tetrodotoxin,<sup>3</sup> and amyloid beta peptide.<sup>4</sup>

There is also probably a second mechanism operating in TLT; increased neurogenesis. Neurogenesis is the generation of neuronal precursors and birth of new neural cells.<sup>5</sup> Two key sites for adult neurogenesis include the subventricular zone (SVZ) of the lateral ventricles, and the subgranular layer (SGL) of the dentate gyrus in the hippocampus.<sup>6</sup> Neurogenesis can be stimulated by physiological factors, such as growth factors and environmental enrichment, and by pathological processes, including ischemia and neurodegeneration.<sup>7</sup> Adult neurogenesis (in the hippocampus particularly) is now recognized as a major determinant of brain function both in experimental animals and in humans. Neural progenitor cells in their niche in the SGL of the dentate gyrus give birth to newly formed neurons that are thought to play a role in brain function, particularly in olfaction and in hippocampal-dependent learning and

memory.<sup>8</sup> In small animal models neurogenesis can be readily detected by incorporation of bromodeoxyuridine (BrdU), injected before euthanasia, into proliferating brain cells. Increased neurogenesis after TLT, has been demonstrated in a rat model of stroke,<sup>9</sup> and in the Hamblin laboratory after TLT for acute traumatic brain injury (TBI) in mice (W. Xuan, T. Ando, et al., unpublished data). These two mechanisms of action of TLT in ameliorating brain damage (prevention of neuronal death and increased neurogenesis) have motivated studies in both animals and humans for diverse brain disorders and diseases. TLT for acute stroke is the most developed,<sup>10</sup> but acute TBI has also been shown to benefit from TLT.<sup>11</sup> These areas are reviewed further.

### Stroke

In an early study with TLT to treat acute stroke in rats, significant beneficial results were obtained whether TLT was applied in a bilateral, ipsilesional or contralesional manner.<sup>12</sup> TLT (808nm) significantly improved recovery ( $p < 0.01$ ) at 3 weeks following ischemic stroke when treated once, at 24h post-stroke (contralesional; power density, 7.5 mW/cm<sup>2</sup> to brain tissue).<sup>9</sup> The number of newly formed neuronal cells, assessed by double immunoreactivity to BrdU and tubulin isotype III, as well as migrating cells (doublecortin immunoreactivity), was significantly elevated in the ipsilesional SVZ. There was no significant difference in the stroke lesion area between control and laser-irradiated rats. The authors suggested that an underlying mechanism for the functional benefit post-TLT was possible induction of neurogenesis. Other studies have also suggested that because improvement in neurologic outcome may not be evident for 2–4 weeks in the post-stroke rat model, delayed benefits may be caused, in part, by induction of neurogenesis and migration of neurons.<sup>13,14</sup>

A recent study with embolized rabbits showed a direct relationship between level of cortical fluence (energy density, J/cm<sup>2</sup>) delivered, and cortical ATP content.<sup>15</sup> Five minutes following embolization (right carotid), rabbits were exposed

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to 2 min of NIR TLT using 808-nm laser on skin surface, posterior to bregma at midline. Three hours later, the cerebral cortex was excised. Use of continuous wave (CW) TLT (7.5 mW/cm<sup>2</sup>, 0.9 J/cm<sup>2</sup>) resulted in a 41% increase in cortical ATP. Use of 100-Hz pulsed wave (PW) TLT (37.5 mW/cm<sup>2</sup>, 4.5 J/cm<sup>2</sup>) resulted in a 157% increase in cortical ATP. Surprisingly, the increased cortical ATP level of 157% was higher than that measured in naive rabbits that had never suffered stroke. The authors suggested in future studies, greater improvement might be achieved by optimizing length of treatment, and mode of treatment (PW, perhaps at 100 Hz).

TLT has been shown to significantly improve outcome in human acute stroke patients, when applied at ~18 h post-stroke, over the entire surface of the head (20 points in 10/20 EEG system) regardless of stroke location.<sup>16–18</sup> Significant improvements ( $p < 0.04$ ) were observed in the moderate and moderate-severe stroke patients only ( $n = 434$ ), who received the real laser protocol (vs. sham), but not in severe stroke patients.<sup>17</sup>

To date, there are no TLT studies to treat chronic stroke patients. The use of laser light to stimulate acupuncture points on the body (instead of needles) to treat paralysis in chronic stroke patients (>10 months post-stroke onset) has resulted in similar levels of improvement, following a series of 20 or 40 laser (or needle) treatments.<sup>19–21</sup> A 20-mW, 780-nm, CW laser with 1-mm diameter aperture (Unilaser, Denmark) was used (51–103 J/cm<sup>2</sup> per point). Overall, 5/7 (71.4%) of the patients showed improvement, with an increase of 11–28% in isolated, active range of motion for shoulder abduction, knee flexion, and/or knee extension. The two patients who showed no improvement had severe paralysis, with results similar to TLT results with severe, acute stroke patients.<sup>17</sup> Therefore, stroke patients with paralysis improved when the paralysis was not severe, although a reduction in spasticity has been observed in severe cases (M.A.N., personal observation). Stroke patients with only mild or moderate hemiparesis (including only hand paresis) appear to have the best potential for improvement. On brain CT scan, these mild-moderate cases have smaller areas of infarction adjacent to the body of the lateral ventricle, than those with severe paralysis in whom the lesion is often adjacent to the body of the lateral ventricle, closer to the SVZ, possibly impeding potential for neurogenesis. Depth of white matter lesion appears to be more important regarding potential for recovery than is the overall size of the cortical lesion.<sup>19–22</sup> (See also: [www.bu.edu/naeser/acupuncture](http://www.bu.edu/naeser/acupuncture))

## TBI

Each year, an estimated 1.7 million people sustain a TBI.<sup>23</sup> Patients with mild TBI (mTBI) have problems with poor memory and cognition at 6 months post-TBI, and for years afterwards. In 2000, the direct medical costs and indirect costs (including lost productivity from TBI) totaled an estimated \$60 billion in the United States.<sup>24</sup> There is a great need for effective treatment to promote cognitive recovery, but no standard, empirically validated interventions are available.<sup>25</sup>

Mild TBI from single and multiple events (often blast-related) is the most frequent type of brain injury experienced by Operation Enduring Freedom and Operation Iraqi Freedom military personnel.<sup>26</sup> Diffuse axonal injury<sup>27</sup> is often

observed in anterior corona radiata and fronto-temporal regions.<sup>28</sup> Cognitive problems result from tissue damage in the prefrontal cortex and anterior cingulate gyrus within the frontal lobes.

TLT has been used to treat acute TBI in animal models.<sup>11</sup> Mice were subjected to closed-head injury (CHI) using a weight drop procedure, and 4 h post-CHI, either sham, or real NIR TLT (200 mW, 808 nm) was administered on the skull (skin incision made) 4 mm caudal to the coronal suture line, on the midline (2 min, 1.2–2.4 J/cm<sup>2</sup>, 10 or 20 mW/cm<sup>2</sup>). After 5 days the motor behavior was significantly better ( $p < 0.05$ ) in the laser-treated group. At 28 days post-CHI, the brain tissue volume was examined. The mean lesion size in the laser-treated group (1.4%, SD 0.1) was significantly smaller ( $p < .001$ ), than in the control group (12.1%, SD 1.3). Additional TLT animal studies in acute TBI have produced beneficial effects, including the balance of IL-1 $\beta$ , TNF- $\alpha$ , and IL-6, thereby preventing cell death;<sup>29</sup> and using either 665-nm or 810-nm TLT (36 J/cm<sup>2</sup>) was highly effective in improving the neurological performance of mice for 4 weeks post-CHI.<sup>30</sup>

In humans, two chronic, mTBI cases showed improved cognition following a series of TLT treatments with red/NIR LED cluster heads.<sup>31</sup> These were applied to midline, and bilateral forehead/scalp areas (hair not shaved off, but parted, under each 2-inch diameter 500-mW cluster head). Each cluster head contained 52, 870-nm diodes and 9, 633-nm diodes (12–15 mW each diode); 22.2 mW/cm<sup>2</sup>; 13.3 J/cm<sup>2</sup> at skin, estimated 0.4 J/cm<sup>2</sup> at 1 cm deep (at cortex). Case 1 (66-year-old woman) began TLT treatments at 7 years after closed-head TBI (car accident). Pre-LED, she could focus sustained attention on her computer for only 20 min. After 8 weekly LED treatments, her sustained computer time increased to 3 h. To date, she has treated herself at home, almost daily for 6 years, and maintains her improved cognition (she is now 72 years of age). Case 2 (52-year-old woman) is a military officer who had a history of repeated closed-head traumas. Brain MRI showed fronto-parietal atrophy. She was medically disabled for 5 months before TLT. After 4 months of nightly TLT at home, she returned to work full time as an executive consultant at an international technology consulting firm and was able to discontinue receiving medical disability payments. Neuropsychological tests performed after 9 months of TLT showed significant improvement (+1, +2 SD) in memory (immediate and delayed recall), and in cognition (executive function, inhibition, and inhibition accuracy). Case 2 also showed improvement in post-traumatic stress disorder (PTSD) symptomatology.

Mechanisms that may be associated with improved cognition in the mTBI cases treated with TLT include:

1. Increase in ATP, which would increase cellular respiration and oxygenation in hypoxic, compromised cells.
2. Acupuncture points treated along the Governing Vessel (GV) acupuncture meridian, located in part, along the mid-sagittal suture line. These points, GV 16 (inferior to occipital protuberance), GV 20 (vertex), and GV 24 (near center-front hairline) have been used historically to help treat patients in coma,<sup>32</sup> and with stroke.<sup>33</sup>
3. Red/NIR TLT that may have irradiated the blood via the valveless, emissary veins located on the scalp surface, but were interconnecting with veins in the supe-

rior sagittal sinus (Mary Dyson, personal communication). Direct, *in vitro*, blood irradiation with red-beam laser has been observed to improve erythrocyte deformability (flexibility) and rheology.<sup>34 35</sup>

4. A possible increase in regional cerebral blood flow (rCBF), specifically to the frontal lobes, as was observed in the recent NIR TLT study to treat major depression.<sup>36</sup>

### Neurodegenerative Diseases

There was a recent study of TLT having significant beneficial effects in a transgenic mouse model of Alzheimer's disease (AD).<sup>37</sup> Another study<sup>38</sup> obtained some benefit in a transgenic SOD1 mouse model of familial amyotrophic lateral sclerosis. Light therapy for Parkinson's disease (PD) has been studied in an *in vitro* model of PD human mitochondrial cybrid "cytoplasmic hybrid" neuronal cells,<sup>39</sup> and in a clinical study of 70 patients in Russia.<sup>40</sup> The realization that impaired neurogenesis plays an important role in depression<sup>41</sup> suggested that TLT could have beneficial effects in patients with major depression and anxiety, and this was confirmed in a pilot clinical trial with 10 subjects receiving a single TLT to the forehead.<sup>36</sup>

TLT may be thought to be just in its infancy, but we believe the stage is set for rapid growth, especially in view of the massive and continuing failure of clinical trials of pharmaceuticals for many brain disorders. As the population continues to age, and the epidemic of degenerative diseases of aging such as AD and other dementias continues to grow, TLT may make a real contribution to patient health. The LED technology is not expensive (<\$5,000 for a unit with three LED cluster heads). A TLT protocol with LEDs has potential for home treatment. Additional controlled studies with real and sham, transcranial low-level laser therapy and LED are recommended.

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