

Transcranial LED therapy for cognitive dysfunction in chronic, mild traumatic brain injury: Two case reports

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ABSTRACT

Two chronic, traumatic brain injury (TBI) cases are presented, where cognitive function improved following treatment with transcranial light emitting diodes (LEDs). At age 59, P1 had closed-head injury from a motor vehicle accident (MVA) without loss of consciousness and normal MRI, but unable to return to work as development specialist in internet marketing, due to cognitive dysfunction. At 7 years post-MVA, she began transcranial LED treatments with cluster heads (2.1" diameter with 61 diodes each – 9x633nm, 52x870nm; 12-15mW per diode; total power, 500mW; 22.2 mW/cm²) on bilateral frontal, temporal, parietal, occipital and midline sagittal areas (13.3 J/cm² at scalp, estimated 0.4 J/cm² to brain cortex per area). Prior to transcranial LED, focused time on computer was 20 minutes. After 2 months of weekly, transcranial LED treatments, increased to 3 hours on computer. Performs nightly home treatments (now, 5 years, age 72); if stops treating >2 weeks, regresses. P2 (age 52F) had history of closed-head injuries related to sports/military training and recent fall. MRI shows fronto-parietal cortical atrophy. Pre-LED, was not able to work for 6 months and scored below average on attention, memory and executive function. Performed nightly transcranial LED treatments at home (9 months) with similar LED device, on frontal and parietal areas. After 4 months of LED treatments, returned to work as executive consultant, international technology consulting firm. Neuropsychological testing (post- 9 months of transcranial LED) showed significant improvement in memory and executive functioning (range, +1 to +2 SD improvement). Case 2 reported reduction in PTSD symptoms.

Keywords: Traumatic brain injury, treatment, cognitive dysfunction, light emitting diodes, post-concussion syndrome, sports head injury, LLLT, PTSD

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1. Introduction

1.1 Traumatic Brain Injury

Traumatic brain injury (TBI) represents a significant socioeconomic burden. In the United States, TBI incidence is 618 per 100,000 person-years^[1], and an estimated 80,000–90,000 individuals sustain long-term disabilities annually^[2]. TBI can result in neurological impairment because of immediate CNS tissue disruption (primary injury). However, surviving cells may be secondarily damaged by complex mechanisms triggered by the primary event, leading to further damage and disability^[3]. Diffuse axonal injury (DAI) has been recognized as one of the main consequences of closed-head TBI^[4, 5]. Closed-head, blast injury is currently the signature injury of veterans returning from Iraq and Afghanistan^[6-9].

Common locations for DAI are the cortical-medullary (gray matter-white matter) junction (particularly in the frontal and temporal areas), internal capsule, deep gray matter, upper brainstem, and corpus callosum^[10]. For a review of white matter pathways often involved with traumatic axonal injury, see Taber & Hurley^[11].

1.2 White matter abnormalities on diffusion tensor imaging (DTI) in post-concussive and closed-head TBI

Structural imaging with conventional CT or MRI generally does not show focal lesion sites in closed-head mild TBI (post-concussive or blast-related)^[12-14]. MR diffusion tensor imaging (DTI) is sensitive to the characteristics of water diffusion in the brain; it is used to assess microstructural integrity of white matter pathways that are especially vulnerable to the mechanical trauma of TBI^[15].

DTI has been used successfully to detect abnormalities in white matter tracts in TBI cases^[16-20]. Niogi et al.^[17] observed significantly lower fractional anisotropy (FA) values (>2.5 SD lower, than matched normal controls), in the white matter of five *a priori* regions of interest: 1) anterior corona radiata (41% of TBI cases); 2) the uncinate fasciculus (29% of TBI cases); 3) genu of corpus callosum (21%); 4) inferior longitudinal fasciculus (21%); and 5) cingulum bundle (18%).

1.3 Functional brain imaging studies in chronic TBI

Functional brain imaging studies have observed abnormalities in chronic TBI cases. Kato et al.^[21] observed significantly low, regional glucose metabolism (rCM) in resting PET scans, in 36 chronic TBI cases (DAI; mean age=36.3 Yr., SD=9.8; at 6-38 months post-motor vehicle accident), compared to normal controls. The TBI cases all needed continuous rehabilitation programs for cognitive sequelae. The low rCM was located in bilateral frontal lobes, temporal lobes, thalamus and right cerebellum. Full-Scale IQ (FIQ) positively correlated with rCM in bilateral medial frontal gyrus areas and right cingulate (Brodmann areas, BA 9, 24, 32). Other functional imaging studies in TBI cases have shown abnormal hypo-activation or hyper-activation in the frontal lobes^[22-27]. Two important regions within the frontal lobe that are susceptible to damage in TBI, and therefore particularly important as potential areas for treatment with transcranial low-level laser therapy (LLLT) or light emitting diodes (LEDs), are the prefrontal cortex and the anterior cingulate cortex.

Prefrontal Cortex: Activations in the prefrontal cortex areas have been reported in functional imaging studies involving diverse cognitive tasks^[28]. A prevalent view regarding the possible functional specification of these mid-dorsal regions is that they may be involved primarily in maintaining, monitoring, and manipulating information in working memory^[29]. In addition, they may also be involved in aspects of attention control, particularly sustained attention^[30, 31].

Anterior Cingulate Cortex: The anterior cingulate cortex has been implicated in cognitive processes, including divided attention, novelty detection, working memory, memory retrieval, Stroop tasks (inhibition), evaluative judgment, motivation, and performance monitoring^[28, 30-36]. It is considered an initiating or inhibiting region, in that it initiates appropriate, or suppresses inappropriate behavior^[28, 35, 37].

Chronic post-traumatic stress disorder (PTSD) cases share some of the same abnormality in neurocircuitry with the chronic TBI cases, involving the medial prefrontal cortex areas. This includes an inadequate top-down governance over the amygdala by the medial prefrontal cortex and the hippocampus^[38-40].

1.4 Background and beneficial cellular effects of low-level laser/light therapy and light emitting diodes

LLLT which includes non-thermal lasers (less than 500 mW), or even non-coherent LEDs in the red or near-infrared (NIR) wavelength range, are commonly known as cold laser, biostimulation or photobiomodulation. All types (coherent lasers or non-coherent LEDs) have been shown to produce beneficial cellular effects in controlled trials (Desmet et al.^[41], for review). LLLT is increasingly being used for tissue preservation and functional stimulation at the cellular level after various forms of injury. During LLLT, absorption of red or NIR photons by cytochrome c oxidase in the mitochondrial respiratory chain^[42] causes an increase in cellular respiration that continues for much longer than the light is present when delivered at appropriate fluence and exposure durations. Primary cellular effects include increase in mitochondrial respiration^[43], increase in ATP synthesis^[43-45], production of low levels of reactive oxygen species (ROS)^[46], modulate expression of 111 genes in a cDNA microarray study^[47], and increase nerve cell proliferation and migration^[48]. Transcranial NIR light that penetrates the scalp and skull, can significantly reduce damage from

experimentally induced stroke in rats ^[48] and rabbits ^[49], can improve the memory performance of middle aged mice ^[50], and has been shown to reduce damage from acute stroke in humans ^[51, 52]. Most recently, transcranial NIR LED applied to the left and right forehead has been observed to significantly reduce depression and anxiety in patients diagnosed with chronic major depression ^[53].

Since the mid-1960s, LLLT/LED has been used as a safe and effective therapy for many indications around the world ^[54]. Applications include wound healing, reduction of edema and inflammation, and prevention of tissue loss. It is used by orthopedists to relieve pain, treat chronic inflammation and autoimmune diseases, and used by others in sports medicine and rehabilitation clinics. It is applied directly to the respective areas (e.g., wounds, sites of injuries or tissue damage), or in some circumstances to various other points on the body (muscle-trigger points, acupuncture points) ^[55-57].

1.5 Cellular effects of LLLT/LED relevant to treatment of chronic TBI

Neurogenesis in damaged brain after TBI is not the rare event it was once thought to be ^[58]. LLLT has been effective in stimulating repair of neurons (both peripheral and in spinal cord) and could increase neurogenesis in TBI. Byrnes and colleagues ^[59] showed that adult rats that underwent a T9 dorsal hemisection, followed by treatment with an 810 nm, 150 mW diode laser showed significant improvement in axonal regeneration and functional recovery. LLLT applied in the acute stage reduces scarring and may lessen the astroglial scar that inhibits neurogenesis in the brain after TBI. In traumatized muscles in rats, LLLT has been shown to inhibit NF- κ B expression and activation (back to control levels) ^[60].

LLLT increases expression (and activation) of growth factors such as transforming growth factor- β (TGF- β) and vascular endothelial growth factor (VEGF) that may contribute to positive brain remodeling after TBI. There has been a report ^[61] that in a rat stroke model, transcranial LLLT triggered the expression of TGF- β 1 (as well as reducing NO levels). Tuby et al. ^[62] showed that in a rat heart infarcts model, LLLT significantly increased VEGF expression levels and this correlated with increased angiogenesis.

1.6 Transcranial LLLT in animal model studies of TBI and aging

In the first reported study of LLLT in a TBI animal model ^[63], mice were subjected to closed head cerebral contusion using a weight drop procedure and administered either sham or real NIR LLLT (808 nm). Administration of transcranial LLLT once, at 4 hours after injury, dramatically reduced post-injury lesion size by 90%. Neurological severity scores (modified to emphasize motor function) for the laser-treated mice were also significantly lower ($p < 0.05$) at 28 days. These data suggest that LLLT might reduce histopathology and improve cognitive, as well as motor and neuropsychological outcome after TBI.

Transcranial LLLT has improved working memory in middle-aged mice ^[50]. A daily 6-min exposure to transcranial NIR light 1072 nm for 10 days, yielded a number of significant behavioral effects on middle-aged female CD-1 mice (12-months) tested in a 3D-maze. Prior to NIR light treatment, middle-aged mice had showed significant deficits in a working memory test, and LLLT treatment reversed this deficit. Interestingly, the LLLT treated middle-aged group despite making less memory errors than sham middle-aged group, spent longer time in different parts of the maze than both the young group (3-months) and sham-middle-aged group (12-months). Young mice appeared more anxious than middle-aged mice in the first sessions of the test. The middle-aged mice treated with LLLT were more careful in their decision-making, which resulted in an overall improved cognitive performance, comparable to that of young CD-1 mice.

1.7 Transcranial LLLT in human stroke patients

Transcranial LLLT has been shown to significantly improve outcome in human stroke patients, when applied at ~18 hours post-stroke, over the entire surface of the head [20 points in the 10/20 electroencephalography (EEG) system], regardless of stroke location ^[51]. Only one LLLT treatment was administered, and 5 days later, there was significantly greater improvement in the real- but not in the sham-treated group ($p < .05$, NIH Stroke Severity Scale). This significantly greater improvement was still present at 90 days poststroke, where 70% of the patients treated with real LLLT had successful outcome, versus only 51% of controls. A NIR (808 nm) laser was used, delivering ~1 Joule/cm² of energy over the entire surface of the head.

Lampl et al. ^[51] wrote that, "Although the mechanism of action of infrared laser therapy for stroke is not completely understood...infrared laser therapy is a physical process that can produce biochemical changes at the tissue level. The putative mechanism ...involves stimulation of ATP formation by mitochondria and may also involve prevention of apoptosis in the ischemic penumbra and enhancement of neurorecovery mechanisms... What is clear is that infrared irradiation is probably delivering its effect independent of restoration of blood flow and the mechanism is probably related to an improved energy metabolism and enhanced cell viability ^[64, 65]." In a second study, with the same transcranial LLLT protocol, with an additional 656 acute stroke patients randomized for real or sham laser, similar significant beneficial results ($p < .04$) were observed for moderate and moderate-severe stroke patients (but not for mild or severe), who received the real laser protocol ^[52].

2. Treatment Methodology and Results for each chronic, TBI case

2.1 Case 1

2.1.1 Medical history, case 1

At age 59, case 1 sustained a closed-head, traumatic brain injury in a motor vehicle accident (MVA) in a large city (April, 1997). She was the driver of a small compact car, and while stopped at a red light her car was hit from behind, by a large heavy car driven at a high rate of speed. Her head snapped back, and hit a very rigid, head-rest. She was wearing a seat-belt, and did not lose consciousness. She called the police; but drove herself home. Later that evening, the increasing headache caused her to seek medical attention in an emergency room. Head X-rays and brain MRI scan were normal. She returned home with pain meds for the headache and neck pain. Brain MRI scans continued to be considered normal, even years later.

Summary of the initial 2-month period, post-MVA: She was told to stay home and rest for 2 months. She slept a great deal. She tried to return to work after 2 months, but could not function, due to confusion, inability to remember what people said to her, and inability to focus on her computer work.

She had two Master's Degrees, knew three languages and had written three books; she was a member of Mensa. She had been director of marketing and a sales development specialist for an internet marketing company. She had also taught web-design on the graduate level at a major university.

At 5 months after the MVA, she was diagnosed by a neurologist as having post-concussive syndrome and was told she might never recover, even for 5 years. She resigned from all professional work, due to cognitive dysfunction.

At 2 years post-MVA, her cognitive abilities were evaluated for several days at a rehabilitation institute. Her divergent reasoning abilities were "significantly impaired across all verbal tasks." Her "executive functioning ability was severely impaired." Executive functioning involves planning ahead, such as in a game of chess. She also had a vulnerability to emotional distress and depression (not uncommon with chronic TBI).

Summary of cognitive behavioral treatment programs, 2 - 4 years post-MVA: At 2 years post-MVA, she underwent two, 20-week Remedial Training for Cognitive Function programs with peers of similar education and background, who had similar cognitive deficits due to TBI or myocardial infarction with hypoxia to the brain. However, few of her old skills returned, no new skills were acquired, and her original disabilities remained. After completion of the second, 20-session program, she was still unable to perform any work; there was depression, and a suicidal gesture.

At 4 years post-MVA, she received further Behavioral Therapy Sessions at a rehabilitation institute in a different state. This included 39 one-hour (one-on-one) Cognitive Training Sessions followed by 39 one-hour Personal TBI Acceptance Sessions. After completion of these programs, she could work on her computer for 20 minutes at a time.

2.1.2 Transcranial LED treatments, Case 1

At 5 years post-MVA, she and her husband moved to another state, and at 7 years post-MVA, she answered an ad for "Free LED treatments for Pain." Following the MVA, she had developed painful, knee osteoarthritis. She received two,

LED treatments on both knees, one week apart. This resulted in "...a reduction of swelling by 66% and a reduction in pain by 80%." This was an FDA-cleared indication for use of the MedX Health, LED cluster head device. She then requested that the doctor place the LED cluster heads on her head, "to treat her brain."

After consultation with co-author AS at MedX Health in Toronto, the appropriate informed consent was obtained, and the transcranial LED treatments were initiated. This was an off-label use for the MedX Health, LED cluster head device.

1st transcranial LED treatment (May, 2004), 7 years post-MVA: In a doctor's office, an LED cluster head device was used with the following parameters: The unit had three, square-shaped LED cluster heads, each with a dimension of 4.4 cm x 4.4 cm (approximately 1.75 inch x 1.75 inch). A treatment area was 19.39 cm²; and each cluster head contained 49 diodes (40 NIR 870 nm diodes, 12.25 mW each, and 9 red 633 nm red diodes, 1 mW each). The total power was 500 mW ($\pm 20\%$), with continuous wave (CW). The power density was 25.8 mW/cm² ($+20\%$); 1 J = 2 sec and 1 J/cm² = 38.8 sec.

Transcranial treatment loci and parameters: Left (L) and right (R) forehead areas, 8 J/cm² to each area; the treatment time was 5 min, 10 sec per area. The patient's reaction was as follows: She drove herself home (30 minutes), then slept through dinner and most of the next day. On day 3 post- the 1st LED treatment, she had improved concentration and focus. She was able to work at her computer for 40 minutes. For the preceding 7 years post-MVA, she was able to work at her computer for only 20 minutes.

High intensity, LED treatment considerations: Only 2 to 3% of NIR energy penetration from skin on the scalp surface, is estimated to reach brain cortex 1 cm deep from the scalp or skin surface ^[66]. Also, only 0.2 to 0.3% energy penetration from scalp or skin surface is estimated to reach 2 cm deep (into the white matter) (M. Hamblin, Ph.D., personal communication). Thus, 3% of 8 J/cm² delivered to skin on L and R forehead areas, would deliver only 0.24 J/cm² to brain cortex. This is a low energy density. If there is an effect, it is unclear whether the effect might be related to: a) The photons might be reaching the grey and white matter of the brain? b) The photons might be stimulating shallow acupuncture points located on the surface of the scalp or skin? or c) There might be "systemic effects" including radiation of the extracranial blood supply, which could carry some photons into the cerebral spinal fluid via emissary veins and the arachnoid villi (discussed later) (Mary Dyson, Ph.D., personal communication).

2nd transcranial LED treatment (May, 2004), 7 years post-MVA: One week later, in the doctor's office, the high intensity, LED cluster head device was used again, on the same loci with the same treatment parameters. Her husband drove her to and from the appointment. She had no return of excess sleepiness. She continued to have improved concentration and focus, and was able to work at her computer for 40 minutes at a time during the week.

Weeks 3 - 8 of transcranial LED treatments (1x/week) in the doctor's office: The following treatment loci were used: L and R forehead; midline at hairline; L and R temples, 8 J/cm² per area (0.24 J/cm² to cortex). The treatment parameters were gradually increased from 8 J/cm² (5 min, 10 sec) per area, up to 20 J/cm² (12 min, 54 sec) per area. She had no return of excess sleepiness and she continued to have improved concentration and focus. **After 8 weeks, she was able to work at her computer for 3 hours at a time.**

After 7 months of LED treatments, 1x/week in the doctor's office, in January 2005, **she obtained a home treatment unit** with a single LED cluster head (7 years, 9 months post-MVA). This was an off-label use for the MedX Health, single cluster head device. This LED cluster head device had the following parameters: The circular-shaped, cluster head had a diameter of 53.45 mm (2.1 inches). A treatment area was 22.48 cm²; and the cluster head contained 61 diodes (52 NIR 870 nm diodes, and 9 red 633 nm diodes, 12-15 mW each). The total optical output power was 500 mW ($\pm 20\%$), CW. The power density was 22.2 mW/cm² ($\pm 20\%$); 1 J = 2 sec and 1 J/cm² = 45 sec. She treated 6 spots per night, 10 min per area; 13.3 J/cm² per area (estimated 0.4 J/cm² to brain cortex).

The treatment loci that she used on herself at home (and continues to use) include the L and R forehead areas; the L and R temple areas; the midline at front hairline area (combined with foot areas, see below); the L and R areas posterior-superior to the ears (likely the angular gyrus areas, which seemed to help her to remember what she had read); the L and R base of skull areas (which seemed to remove the extreme sensitivity of the L scalp area that had bothered her when her hair was being cut there); and the center, top of her head (which she reports seemed to help improve her ability to do

math). Her preferred amount of treatment time per area has been 10 min, CW; 13.3 J/cm² per area (0.4 J/cm² to brain cortex). She has preferred to treat at bedtime, as this LED treatment protocol improves her sleep. She treats 6 scalp areas per night, and the locations vary each night. After 3.5 years, she also added some acupuncture points on sole of the foot - Kidney 1^[67]; or top, base of toes - Ba Feng (an area which increases relaxation). At the time of this report (January 2010), she has continued to treat herself with this basic home treatment protocol for 5 years.

She has observed that she needs to treat herself almost daily. If she stops the transcranial LED treatments for >2 weeks, she slowly regresses and her focus and attention become compromised. She then cannot work for hours on her computer, and her balance becomes poor.

As is common with chronic TBI, she has fallen sometimes, since the MVA. This includes two falls in the home since acquiring the LED home treatment unit. She feels that using the LED cluster head, transcranially, as soon as possible after a fall, helps her to recover faster.

When re-starting transcranial LED treatments after a break, she starts with a shorter treatment time and lower J/cm². A shorter, initial treatment time with the circular, LED cluster head would be 6 min per area; 8 J/cm² (0.24 J/cm² to brain cortex), building up to the preferred treatment time of 10 min per area; 13.3 J/cm² (0.4 J/cm² to brain cortex). She reports that after resuming a few weeks of transcranial LED treatment (following a break of more than 2 weeks), she thinks that she improves "beyond her previous maximum cognitive/functional plateau."

2.1.3 Overall results, case 1

After almost 6 years of transcranial LED treatments (and the patient continues to treat herself at home), she reports the following improvements: She is able to perform computer work for 3 hours at a time. She reports that her "decision-making and verbal memory are incredibly better." She has not had any formal, neuropsychological follow-up testing. She reports "improved self-awareness of both limitations and successes, as well as improved inhibition of inappropriate behavior and angry outbursts." She also continues to treat the osteoarthritis pain in her knees in the mornings, when pain is present, using the LED cluster head.

She notes there are some remaining cognitive problems. She still cannot multi-task as well as she would like. She still needs to make notes, to be sure all things are accomplished, however, her overall quality of life is much improved (now age 72, and 13 years post-MVA). She continues to take the drug, Concerta, which she had begun several years before starting the transcranial LED treatments.

2.2 Case 2

2.2.1 Medical history, case 2

Case 2 is a 52 year-old R-handed woman, who referred herself for neuropsychological evaluation and potential transcranial LED treatments in March 2009. She requested evaluation because she noticed changes in her cognitive functioning over the preceding two years, with exacerbation over the preceding four to five months (since October 2008). She holds a Bachelor's degree and had a distinguished military career as a high-ranking officer; and after 20 years of service, she retired. After retirement, she worked full-time as an executive consultant for an international, technology consulting firm and was managing well in that position.

She has a history of multiple concussions without loss of consciousness. Some concussions were associated with contact and extreme sports in college (rugby and sky diving); and others with civilian traumas or military-related events during deployment.

In 2007, she fell backwards from a swing, hitting the back of her head on concrete. This is the single concussion where she lost consciousness. She was alone at the time, and does not know the duration of loss of consciousness (likely, several minutes). Soon after this event, she noticed the onset of subtle changes in her cognitive functioning, with problems concentrating and staying on task. In October 2008 she felt that her cognitive functioning was deteriorating, and she could no longer multi-task. She went on medical disability status.

In December 2008, medical evaluations were performed. An EEG showed right temporal lobe slowing (monorhythmic), without epileptiform activity. An MRI showed a slightly larger, left frontal horn than right; and bilateral, deep prominent sulci were present throughout, especially in the high frontal and parietal cortex areas. No intra- or extra-axial lesions were seen and there was no evidence of acute infarction; no enhancing lesions were demonstrated with contrast. A toxicology screen was carried out, and a high mercury level of 1.2 µg/g (reference <0.80) was observed. The nickel level was 0.40 µg/g (reference <0.30).

Brief neuropsychological testing was performed in January/February 2009 with a cognitive screening test. She scored below the 2nd percentile on reaction time, complex attention, and cognitive flexibility. Psychomotor speed was in the low, to low-end of average range (9th to 24th percentile). The memory domain was in the above-average range (over the 74th percentile). She was described as having a pattern consistent with attention deficit disorder (ADD), with superimposed TBI. She has also been diagnosed with post-traumatic stress disorder (PTSD), associated with civilian and military traumas.

She received additional, more comprehensive neuropsychological testing in March 2009, prior to beginning transcranial LED treatments. This evaluation showed deficits in executive functioning including working memory, processing speed, and cognitive flexibility that are consistent with frontal lobe dysfunction. It was not possible to distinguish whether these deficits "were long-standing and related to ADHD, or to what extent they may be caused or exacerbated by recent neurological and/or emotional factors." She was considered to be a very bright woman whose current neuropsychological evaluation likely underestimated her true level of cognitive ability and potential. Her medications include Lexapro (since 2002, but discontinued in June, 2009), Provigil, Ritalin (30 mg per day, initiated in June, 2009), Armour thyroid replacement, liquid glutathione, and twice weekly vitamin B injections.

The neuropsychological test scores from March 2009 are described in more detail later, when compared to those following nine months of transcranial LED treatments (December 2009). In July 2009, after four months of LED treatments, she returned to full-time work as an executive consultant with the same international, technology consulting firm (her employer prior to October, 2008). She continues with employment there, as of January 2010. She also continues with nightly, transcranial LED treatments at home (explained below).

2.2.2 Transcranial LED treatments, case 2

In March 2009, case 2 began transcranial LED treatments with 3 cluster heads (2.1" diameter with 61 diodes each – 9x633nm, 52x870nm; 12-15mW per diode; total 500mW; 22.2 mW/cm²). She purchased an LED console unit that contained 3 LED cluster heads, so that 3 local areas on the scalp could be treated at once. During each treatment, the cluster heads were placed on the skin/scalp over bilateral frontal, parietal, and temporo-parietal areas. (The scalp hair was parted under each LED cluster placement, but not removed.) It is estimated that 3% of the infra-red photons delivered on the skin/scalp reach a tissue depth of 1 cm^[66].

The duration of treatment for each LED placement was gradually increased over a 4-week period. During the first week, the LED cluster heads were applied daily for 7 min per local placement (7 min = 9.3 J/cm² at scalp, estimated 0.279 J/cm² to brain cortex). Following the first treatment (performed in the afternoon) she was sleepy for the next several hours. During the second week, the LED cluster heads were applied nightly (at bedtime), for 8 min per local placement (8 min = 10.6 J/cm² at scalp, estimated 0.319 J/cm² to brain cortex). During the third week, the LED cluster heads were applied nightly, for 9 min per local placement (9 min = 12 J/cm² at scalp, estimated 0.36 J/cm² to brain cortex). During the fourth week and each week thereafter, the LED cluster heads were applied nightly, for 10 min per local placement (10 min = 13.3 J/cm² at scalp, estimated 0.4 J/cm² to brain cortex). In addition to the local, transcranial LED placements, one additional placement was used on the sole of the foot (acupuncture point Kidney 1) during each home treatment. This is an acupuncture point that has been used historically, to help reverse coma and improve mentation^[67]. There were no negative side effects reported.

2.2.3 Neuropsychological test results, pre- and post- transcranial LED treatments, case 2

On the Stroop test, a color-word interference test ^[68], there was significant improvement on condition 3, showing improved inhibition (this task requires naming the ink color in which discrepant color words are printed). There was a change of +2 SDs from a score of -1.5 SD below the mean for this test (9th percentile, March 2009) to a score of +0.5 SD above the mean (63rd percentile, December 2009). There was also a significant improvement on condition 4, showing improved inhibition accuracy (this task requires switching back and forth between naming the ink colors and reading the words). There was also a change of +2 SDs from a score of -1.5 SD below the mean for this test (9th percentile, March 2009) to a score of +0.5 SD above the mean (63rd percentile, December 2009). These scores reflect significant improvement (+2 SDs) in the area of executive functioning, inhibition and inhibition accuracy.

On the Wechsler Memory Scale - Revised ^[69] there was significant improvement on logical memory passages, where the examinee repeats two paragraphs (one at a time) read aloud by the examiner, both immediately, and after a 30-minute delay. Inquiry regarding recognition of facts within each story follows the delayed recall. In March 2009, immediate recall was in the 83rd percentile, and in December 2009, the 95th percentile, reflecting a +1 SD improvement. In March 2009, delayed recall was in the 83rd percentile, and in December 2009, the 99th percentile, reflecting a +2 SD improvement. These scores show a +1 SD and a +2 SD improvement in the area of memory.

There were no significant changes on the following tests: 1) The Hooper Visual Organization Test ^[70]; she continued to score in the high-average range (92nd percentile) for this. 2) The Boston Naming Test ^[71]; she scored in the 84th percentile (59/60) for this test at both times. 3) The Lafayette Grooved Pegboard test ^[72].

In December 2009, she participated in an interview with co-author (JK), a clinical neuropsychologist specialized in PTSD regarding her history of exposure to psychologically traumatic events and **related PTSD symptoms**. As is true for many people who suffer a physical injury leading to a TBI, the index event also qualifies diagnostically for PTSD as a psychological trauma. The clinical effects can manifest in difficulties modulating memories, emotions and physiological reactivity that develop to personal internal and environmental cues. Managing these reactions can be further impaired by an overlapping, or multiple overlapping, TBIs ^[73]. Prior to a course of transcranial LED treatments, she was having noticeable difficulties employing the appropriate level of social behavior, with the appropriate level of emotional intensity in social and work milieus. Her sleep was disrupted and less regular. After a few months of transcranial LED treatments, she noticed that she had improved levels of self-awareness, self-monitoring and self-regulation in social and work settings. Her sleep was improved and impulsivity to react with irritation and anger were reduced.

3. Discussion

3.1 Possible mechanisms of transcranial LED treatments

The specific mechanisms of action of red and NIR LED therapy to treat cognitive dysfunction in chronic, mild TBI are unknown. The primary mechanism put forth in the Lampl et al. ^[51] study with human, acute stroke patients was an increase in ATP at the cellular level ^[64, 65], where the photons were utilized by mitochondria in compromised gray or white matter cells (likely more so in cells that were hypoxic). The significant, beneficial effect after only one, transcranial LLLT treatment was present at 5 days post-treatment, and this continued out to 90 days post-treatment in the stroke patients ^[51]. The increase in ATP would have had many beneficial effects, including an increase in cellular respiration and oxygenation.

An additional possible mechanism involved with improved cognition following transcranial LED treatments is consideration of the vascular route between extracranial and intracranial blood vessels via the emissary veins (Mary Dyson, Ph.D., personal communication). These are valve-free veins that traverse cranial apertures (foramina) and make connections between the intracranial venous sinuses and the extracranial veins including those of the scalp (Gray's Anatomy, 37th edition, pp.804-805 and p.571, Fig.5.22) ^[74]. Since the emissary veins are valveless, blood flow between the intra- and extracranial venous components is reversible. Since arachnoid villi (sites where the cerebrospinal fluid diffuses into the blood stream) project into the intracranial venous sinuses, particularly the superior sagittal sinus which is so superficial that it grooves the skull, it is possible that irradiating the scalp can affect not only the intracranial blood but also the cerebrospinal fluid (CSF), potentially producing systemic effects when the scalp is treated with LLLT and other types of phototherapy. Of more importance than photons reaching the CSF is that cells and molecules modified by the photons reaching them while they are in the superficial veins of the scalp will reach the intracranial veins (e.g., the

superior sagittal sinus and the CSF via the arachnoid granulations) without the need for the photons to reach these deep structures directly, another example of an indirect systemic effect of photons ^[75].

Another possible mechanism is an increase in regional cerebral blood flow (rCBF) to the prefrontal cortex and anterior cingulate gyrus. The improved scores in memory and executive functioning (particularly inhibition and inhibition accuracy) post- the LED treatments in case 2 in our current report, suggest improved function in these prefrontal cortex brain areas which are often compromised in the chronic TBI population (see Section 1.3 for a review of functional imaging studies in TBI). It is not possible to know whether changes have occurred in these regions in our two cases, without fMRI studies performed pre and post- a series of transcranial LED treatments.

A change in rCBF is possible, however, as other studies have shown increases in blood circulation including in the hands of patients with Raynaud's phenomenon ^[76, 77], in skin flaps ^[78], and in healthy skin ^[79] following LLLT/LED treatment. In the recent Schiffer et al. ^[80] transcranial LED study to treat major depression in 10 cases, an increase in mean rCBF (measured with NIR spectroscopy, INVOS system) was observed across hemispheres at the frontal pole area during the real condition vs. the sham condition, although the change did not reach statistical significance ($p = 0.16$). In that study, following one transcranial LED treatment with 810 nm (250 mW/cm², 60 J/cm²) for 4 minutes each, to F3 and F4 (10-20 EEG system) there was a significant improvement in the Hamilton Depression and the Hamilton Anxiety ratings at 2 weeks post- LED treatment (and at 4 weeks, but less so) in the 10 cases with major depression. Those results are relevant to the present study, because 3/10 cases in that study also had PTSD. Some improvements observed in case 2 (with PTSD) in the present study, may be related to her report of less anxiety following the transcranial LED treatments. In turn, this may be related to possible increased rCBF to prefrontal cortex, as was observed with the cases in the Schiffer et al., 2009 study. In the present study, case 1 reported improved self-awareness of both limitations and successes, and case 2 reported that impulsivity to react with irritation and anger were reduced. Both of these cases reported improved sleep. No negative side effects were reported.

In summary, results from our two TBI cases, and previous transcranial LLLT/LED studies with stroke patients and major depression cases, suggest that further, controlled research with this methodology is indicated. The optimal treatment parameters require further study. Transcranial LED may be an inexpensive, noninvasive treatment (suitable for home treatments) to improve cognitive ability in TBI, as well as to reduce symptom severity in PTSD. It is recommended that future studies include detailed pre- and post- neuropsychological testing, as well as functional brain imaging and DTI scans, to better understand any physiological changes that may take place post- transcranial LLLT/LED treatments.

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