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Beneficial Effects of Transcranial Light Emitting Diode (LED) Therapy on Attentional Performance: An Experimental Design

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Abstract

Background: Transcranial light therapy (TCLT) is a new noninvasive interventional method, which applies red to near infrared spectrum laser or light emitting diode (LED) source on the head, transcranially. This spectrum can penetrate the skull and could improve the brain pathological conditions and cognitive functions. Despite relative advantages of the LED upon laser sources, TCLT research has been limited on the beneficial effects of LED source on human cognitive performances.
Objectives: This study aimed at investigating the effectiveness of the TCLT with LED source on brain attentional performance as an important cognitive ability.
Methods: This experimental intervention study was conducted in Tabriz, Iran, from September to October 2016. The study samples were selected by the convenience sampling method. Thirty-four healthy individuals (age: 18 to 24; 17 males and 17 females) were randomly assigned to sham (n = 17) or real intervention (n = 17) groups. We applied 850 nm LED with irradiation energy density 60 J/cm^2 upon the frontal cortex, the brain region involved in attentional activities. Before and after TCLT, participants completed a cognitive task (Level-1 of parametric Go/No-task), which measures attentional performance.
Results: Our results revealed improvement of efficiency score as the main parameter of attentional performance in the real intervention group versus sham-TCLT group. The interaction of group $\times$ time was significant (P = 0.004). Mean change of the efficiency score was higher in the real intervention group (mean = 4.6 $\pm$ 3) than the sham group (mean = 0.8 $\pm$ 3) after TCLT (P = 0.001).
Conclusions: Applying the TCLT by LED source over the PFC, promotes attentional performance as an important cognitive function.

Keywords: Low-Level Light Therapy, Light-Emitting Diode, Attention, Cytochrome Oxidase

1. Background

Sustained attention, as 1 of the brain higher-level cognitive functions, describes human ability to focus on a task during a period of time (1). This cognitive ability could be vital in some daily activities such as driving (2). Sleep deprivation and using drugs could decrease sustained attention performance in healthy subjects (3). This cognitive function may also be impaired in aging and some pathologic conditions, including, neurodegenerative and affective disorders, cerebrovascular and metabolic diseases, and substance misuse (4-7). The right frontal pole of the cortex or right prefrontal cortex (PFC) is involved in sustained attention (8). Activation of this region reflects the brain capacity to vigilance and attention (9, 10). It implies that augmenting the neural cells of the PFC with appropriate non-invasive therapeutic methods, such as transcranial low-level light therapy (TCLT), could improve attentional performance (10-12).

Transcranial low-level light therapy is an emerging non-invasive therapeutic technology, which irradiates low power red to near infrared wavelength in the range of 650 to 1100 nm of the electromagnetic spectrum over the intended area of the scalp. This light spectrum can penetrate to the brain parenchyma for modulation of the neuronal processes of the target tissue (11, 13, 14). Studies suggested that TCLT induces a wide range of biological changes because of its non-thermal effects (15-17). It can regulate neural functions (13, 18), modulate gene expression (19), and protect cells from death after ischemic stroke (20) and neurotoxicity (21). It can also promote the cell's energy production (22) by increasing mitochondrial respiration (23, 24). An increase in the brain cerebral blood flow has also been observed after light irradiation (25). Recent evidence suggested that TCLT could improve brain functions in animal models, and also in human subjects. Therapeutic effects of the TCLT were reported in psychological conditions such as various types of anxiety, depression (17, 22, 26), phobia, and post-traumatic stress disorder (24, 26). Light therapy,

also as a non-invasive medication, could improve neurological scores in parkinson disease (PD) (27, 28), traumatic brain injury (TBI) (13, 29, 30), and alzheimer disease (AD) (31, 32). Promotion of higher order cognitive abilities also occurs after light therapy. It has been shown that TCLT over the forebrain promotes executive function, learning and, memory in individuals with cognitive impairment and healthy conditions (8, 12, 17, 22, 24, 26).

Light irradiation may be delivered from the laser source or light emitting diode (LED) device. Application of the LED has some advantages over a laser source. The laser produces collimated and fully coherent irradiation, hence its application to the target organs may cause relatively high-level temperature and subsequent thermal tissue injuries (17). Unlike laser, LED beams are not completely collimated, so they produce insignificant amounts of heating or damage in exposed tissues (15, 17). In addition, LED has been considered as a safe device by the American food and drug administration (FDA) for human trials, even for clinical and home application (15, 33).

Despite relative advantages of the LED upon a laser source, almost all human experimental studies have been focused on laser TCLT. Only a few case reports or pilot studies were devoted to transcranial LED therapy on the human population. These studies have observed the therapeutic effect of the LED device in clinical conditions. However, to the best of our knowledge there are no experimental studies on the effectiveness of LED-TCLT on brain functioning. In addition, in a recent computational modeling study, Yue et al. (2015) questioned the penetration depth of the LED source and suspected its effectiveness on human brain functions (34). Therefore, it seems that further studies are needed to verify the beneficial effect of the LED source upon human brain functioning.

2. Objectives

This study was the first experimental study, which aimed at investigating the effectiveness of a single session of LED irradiation in healthy individuals by assessing sustained attention performance.

3. Methods

3.1. Research Design

This study was an experimental intervention study, conducted at the University of Tabriz, Tabriz, Iran, (September to October 2016).

In a convenience sampling method, a total of 39 healthy undergraduate students, invited from the governmental university of Tabriz (department of psychology), were included in the study. The volunteers were asked to complete an information questionnaire including their name, age, dominant hand, telephone number, and history of the neurological or psychological disease. Five individuals were excluded because of left-handedness and medication consumption, and finally, eligible healthy students were entered in the study.

The final sample size was 34 (17 males and 17 females with age ranging from 18 to 24), which was calculated based on the pilot survey ($n = 12$, $M_1 = 4.7$, $M_2 = 1.0$, $SD_1 = 2.9$, $SD_2 = 3.2$, and effect size = 1.21), and according to a formula related to mean comparison of the 2 groups by the G*power Freeware (v. 3.1.9.2) (35). Alpha and Beta were considered as 0.05 and 0.2, respectively. For more details refer to Figure 1.

Simple random allocation strategy was used to assign the participants to the study groups, using a random number list. Each individual in the study had an equal chance of being in either the sham or real intervention group.

3.2. Ethical Considerations

The protocol was approved by the regional ethical committee of Tabriz University of Medical Sciences (permit no: IR.TBZMED.RCE.1395.687; date of issue, 26th of September 2016(. Informed consent was obtained from participants before starting the session. It included information on the procedure, device, and their safety. Participants noticed that they may be assigned to the real intervention or the sham-TCLT group and they could inquire the invention after study completion. It was emphasized that they could end the session whenever they intended. All the questionnaires were coded for the sake of confidentiality.

3.3. Inclusion and Exclusion Criteria

The inclusion criteria were normal or corrected vision, normal audition, and right-handedness with light pigmentation (white skin), as skin pigmentation could effect the light absorption (8). The exclusion criteria were history of neurological or psychological disorders, taking drugs that effected the neural system, and having a high rate of errors in doing the task (8, 36).

3.4. Sustained Attention Task

According to the purpose of the present study, we used the Parametric Go/No-Go level-1 (PGNG) task as a novel neuropsychological task, which measures sustained attention. The PGNG task has the ability to distinguish deficit in sustained attention from other cognitive domains. The task has high internal validity and strong reliability. It has been well supported for convergent and construct validity and

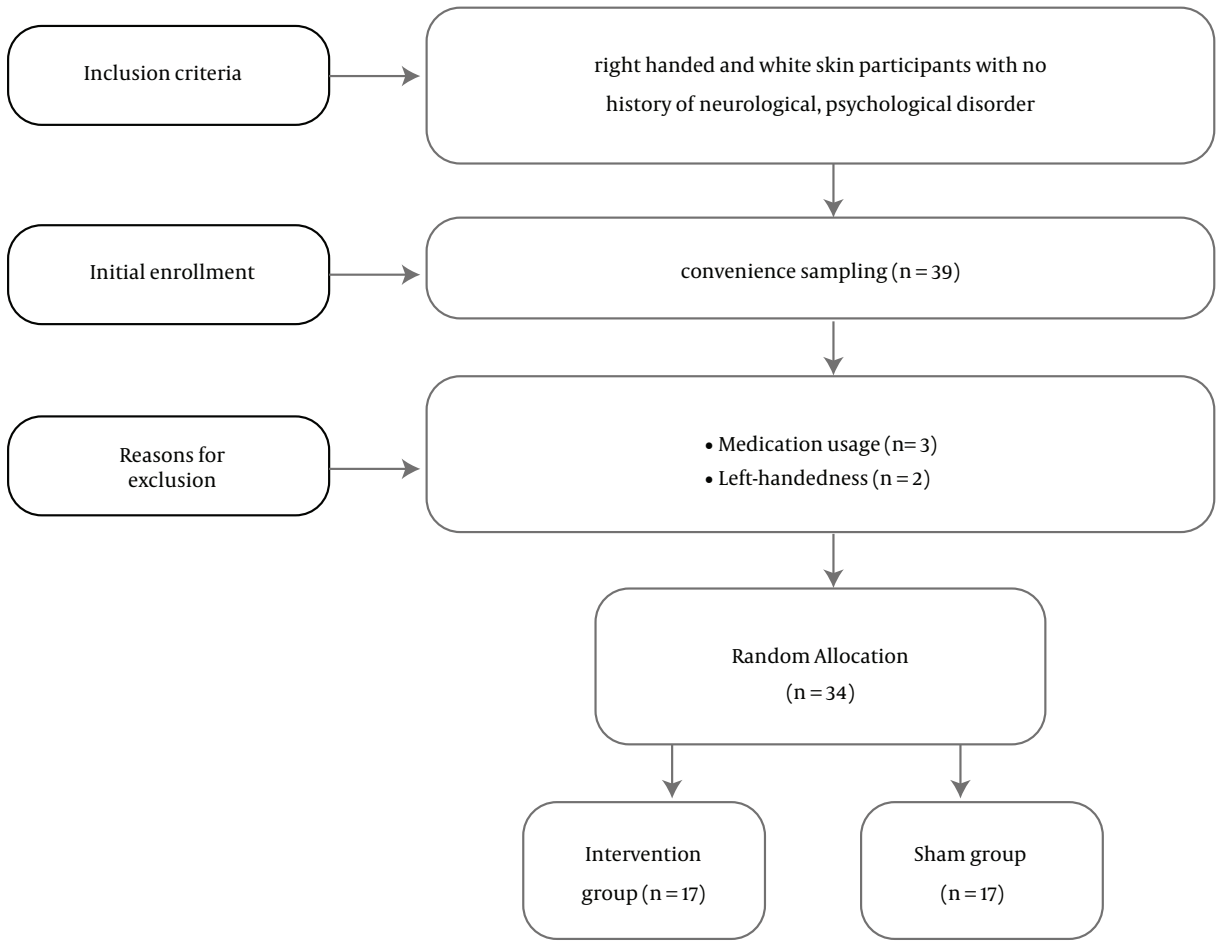


Figure 1. Flowchart of the Study Design

could be successfully performed on adolescents of different age to measure sustained attention in the healthy and clinical population. It is notable that limited learning effect is 1 of the characteristics of the PGNG task (37, 38).

3.5. Parametric Go/No-Go Task Design

A sequence of black color letters (a, b, j, l, r, s, t, x, y, z), in Times New Roman font (size 40), was presented for 500 ms with no inter-stimulus interval by the DMDX software (version 5.1.3.4) (39). Participants were asked to press the space-bar with the index finger whenever x, y or z were appearing on the screen, regardless of the order (Figure 2).

The PGNG task can assess 3 dependent neuropsychological variables: Reaction Time to Target (RTT), the Percentage of Correct Trials (PCT), and Efficiency Score (ES). The RTT is the average response time to correct trials (in milliseconds). The RTT can present the participants' processing speed in multiple target search. The PCT is computed by dividing the number of correct answers by the total number of possible targets. It can assess sustained attention and set maintenance. The ES can balance the reaction time to accuracy with the following formula:

$$ES = (PCT/RTT) \times 100$$

According to the formula, participants with rapid and accurate response to the target (lower RTT score and higher PCT score) have higher ES. The ES is an index of individuals' attentional performance as an important cognitive ability (37, 38).

3.6. Intervention Procedure

3.6.1. Pre-Intervention Procedure (PGNG task)

The data collection procedure in this study was accomplished by an expert observer. Participants were asked to complete the PGNG task before the TCLT intervention. They sat in front of the TFT LCD screen with distance of about 0.5 meters. They avoided any distractor such as electronic

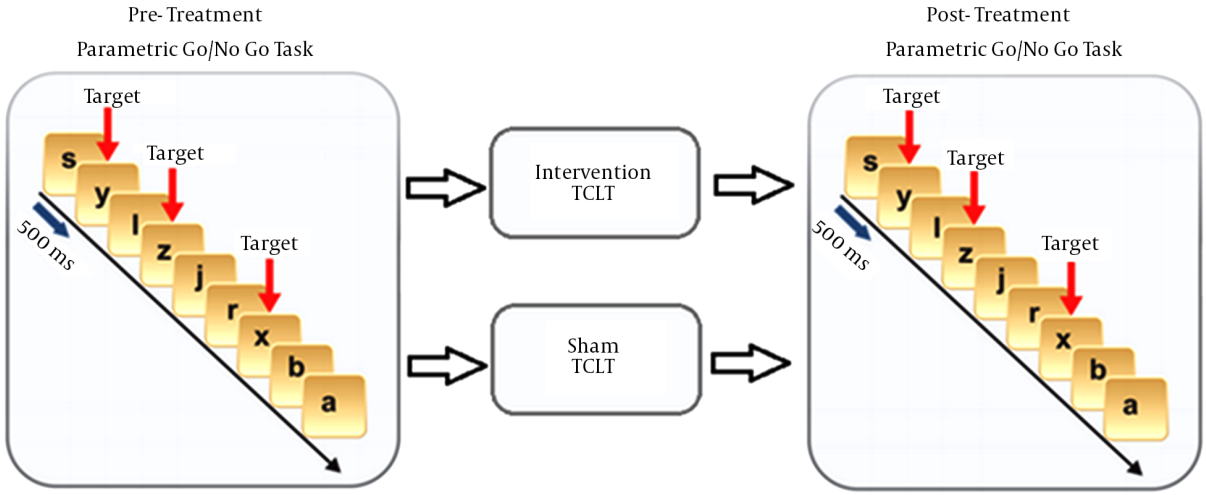


Figure 2. The Parametric Go/ No-Go Task Administration

devices to concentrate on the instructions. Before starting the PGNG task, participants were asked to practice 30 example trials of the task for familiarization with the procedure. They then completed the task in 1': 30" (37).

3.6.2. Intervention Procedure (Instrument, Dose, and Calibration)

One square super-luminous multi-LED array source with 20 cells was used (Iranbargh, Tehran, Iran) for TCLT in this study. The dimensions of the LED were 14 mm × 10 mm with 400 mW total radiation power. The device was calibrated before the experiment (Iranbargh, Tehran, Iran). The power density was 285 mW/cm^2 and energy density was 60 J/cm^2 (8). The wavelength of the LED was 850 nm (40, 41). Light was emitted by the LED source continuously for 2.5 minutes on the right frontal pole of the cortex (Fp2, according to the EEG 10 to 20 system), which is responsible for sustained attention (8, 42).

The sham group received the same procedure as the real intervention group, yet, they received only a 5-second light irradiation for each 1-minute of the treatment on the frontal cortex. This amount of irradiation was the 1/12th cumulative dose of energy density, which was received by the real intervention group (8).

3.6.3. Post-Intervention Procedure (PGNG Task)

Immediately after TCLT treatment, participants were asked again to complete the PGNG task similar to the pre-intervention procedure.

3.7. Data Preparation

All 3 dependent measures of the PGNG task were extracted from the raw data by the Matlab software (v: R2016a). It is important to note that response time to the target stimulus was faster than 200 ms (quick response or fast impulsiveness) or longer than 1000 ms in each trial, and was not included in calculating the mean of RTT.

3.8. Statistical Analysis

The normality of the data was checked by the Kolmogorov-Smirnov test. The ES in the pre- and post-intervention conditions were distributed normally in both real intervention and sham-TCLT groups (P values > 0.1). To analyze the data, repeated-measures analysis of variance (ANOVA) was used. The Greenhouse-Geisser correction was used because of the violation of sphericity assumption. The group of assignment (real intervention/sham-TCLT) and gender (male/female) were considered as between subject factors, and time (pre TCLT/post TCLT) as the within-subject factor. Interaction of group × time was assumed to indicate the effect of TCLT. The significance level was set at 0.05. All analyses were based on the per-protocol approach. The subjects fully accomplished the study and there were no missing data.

4. Results

Demographic characteristics of the 2 groups are presented in Table 1. Descriptive values of the Go/No-Go parameters before and after TCLT in both groups are summarized in Table 2.

Table 1. Demographic Characteristics of the Two Groups

Variables	Real Intervention	Sham	P Value
Age[a]	21 ± 2	21 ± 1.7	P = 1.0[c]
Gender[b]	47	58	P = 0.4[d]
Education level[a]	14 ± 1	13 ± 0.7	P = 0.1[c]
History of psychological/neurological disorder	None	None	P = 1[d]

[a]Years expressed as mean ± SD.
[c]Independent t test.
[b]Frequency of females expressed as No. (%).
[d]Chi-square test.

Table 2. Descriptive Values of Go/No Go Parameters Before and After Transcranial Light Therapy in Both Groups[a]

Variables	ES		PCT		RTT	
	Pre	Post	Pre	Post	Pre	Post
Sham (n = 17)	18 ± 5	19 ± 4	75 ± 18	80 ± 14	414 ± 24	449 ± 17
Real intervention (n = 17)	17 ± 5	22 ± 4	73 ± 16	90 ± 11	459 ± 22	406 ± 22

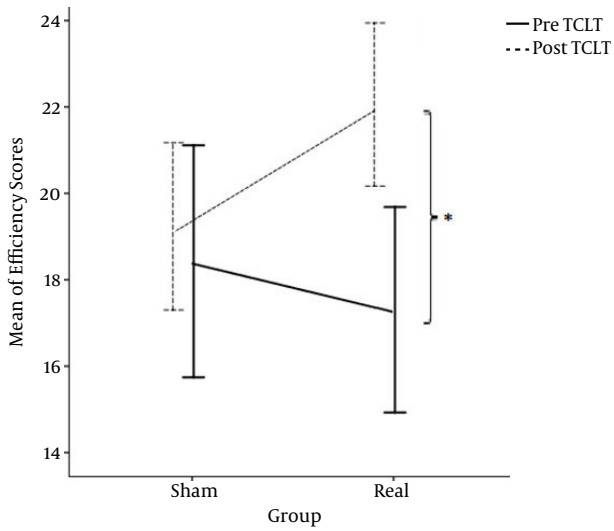
Abbreviations: ES, Efficiency Score; PCT, Percentage of Correct Trials; RTT, Reaction Time to Targets.
[a]Values are expressed as mean ± SD.

A repeated measures test was conducted to analyze the effect of TCLT on the efficiency score. The test showed a significant group × time interaction (F (1, 30) = 10.68, P = 0.003, and eta = 0.26). Post hoc comparison showed a significant increase of efficiency in the real intervention group (t = 2.20, df = 32, and P = 0.03) (Figure 3).

The main effect of group was not significant (F (1, 30) = 0.13, and P = 0.71), indicating successful random assignment of participants. Also, there was no significant difference in efficiency between males and females (F (1, 30) = 0.18, and P = 0.61). There was no significant interaction between sex and time (F (1, 30) = 0.05, and P = 0.82). Also the interaction of group × sex × time was not significant (F (1, 29) = 0.09 and P = 0.77).

Two further repeated measures ANOVAs were conducted to analyze the RTT and PCT. There was a significant interaction of time by group for RTT (F (1, 30) = 18.24, P < 0.001, and eta = 0.38). However, other interactions and main effects were not significant. Post hoc comparison only showed a significant decrease of reaction time in the real intervention group (t = -2.14, df = 32, and P = 0.04) (Figure 4A). Similar results were observed for PCT. The interaction of time by group was significant for PCT (F (1, 30) = 6.11, P = 0.02, and eta = 0.17). Post hoc comparison only showed a significant increase of correct responses in the real intervention group (t = -2.10, df = 32, and P = 0.04) (Figure 4B).

Figure 3. Efficiency Scores (ES) Before and After Transcranial Light Therapy in Sham and Real Intervention Groups

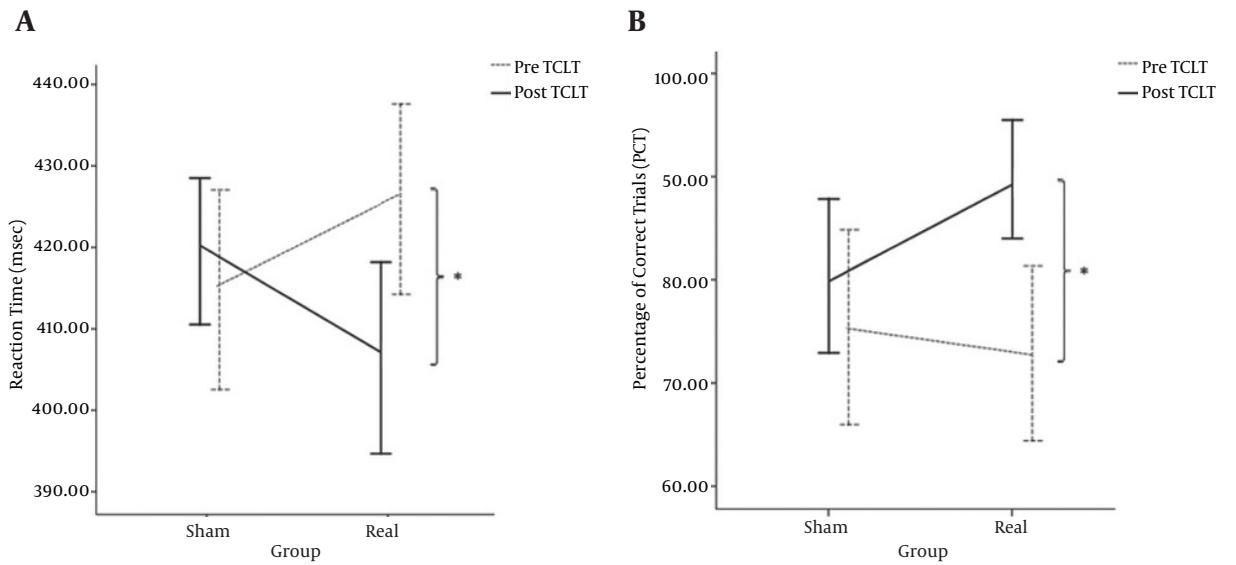


The real intervention group showed significant change for the ES after TCLT (P = 0.03) while the change in the sham group was not significant (P > 0.05). Error bars represent 95% confidence interval. *significant at 0.05.

5. Discussion

This study was the first experimental study, which investigated the effectiveness of the transcranial LED therapy on brain attentional performance. According to our

Figure 4. A, Responding Reaction Time (RTT) Before and After Transcranial Light Therapy (TCLT) in Sham and Real Intervention Groups; B, Percentage of Correct Trials (PCT) Before and After TCLT in Sham and Real Intervention Groups



The real intervention group showed significant changes in the RTT and PCT after TCLT (P = 0.04 and P = 0.04 respectively) while the changes in the sham group were not significant (P > 0.05). Error bars represent 95% confidence interval. *significant at 0.05.

results, the real intervention group responded to the task with better processing speed (decrease in RTT), lower impulsiveness, and more accuracy (increase in PCT) than the sham group. This means that a higher ES is an index of the attentional performance (37). As a result, the main finding of our study was the effectiveness of the TCLT with LED source for promotion of attentional performance.

Enhancement of attentional performance after light therapy with LED source in our study is consistent with previous studies, which illustrated the therapeutic effects of the TCLT with LED on a variety of clinical conditions and cognitive outcomes. Application of the LED source in animal modeling of the TBI revealed that the LED-TCLT could increase the recovery process after head injury (43). It has also been shown that LED light can increase neuroprotective factors and behavioral outcomes in an animal model of PD (28). The LED-TCLT could improve psychopathological conditions and cognitive functions by improving cellular oxygenation in mice (24). Effect of TCLT with LED on neurotoxicity and apoptotic changes of the cells were also investigated in animals, in vitro models. These studies revealed an increase in oxygen consumption and anti-apoptotic factors after TCLT. It could also reduce the pro-apoptotic factors and prevent cells from death (21, 40). In humans, psychological parameters of depression, anxiety, and post-traumatic stress disorder after TBI could be improved by LED (26). It could also improve occupational and social functions and cognitive performance in TBI (44). The effectiveness of the TCLT with LED has also been observed in the clinical population by increasing cerebral blood flow in vegetative state and healthy elderly females (15). However, almost all of these human studies on LED device were limited to pilot, case report or protocol study designs (11, 15, 25, 26).

Our findings is in contrary to that of Yue et al. (2015), which suspected a penetration depth of 850 nm LED (34), while cadaveric models advocated cortical absorption of photons in the near infrared wavelength (15). This conflict may be due to the difference in the study design and instruments, which were used. Yue et al. conducted a computational modeling by utilizing a single LED emitter (34). However, the present study was an actual human experiment with multi-LED array. The multi-LED array device could produce more localized irradiation and effective penetration depth.

Several possible mechanisms have been suggested for the effectiveness of the TCLT on brain functions. It has been suggested that cytochrome oxidase of the mitochondria in brain cells would be activated by the TCLT at a wavelength of 650 to 1100 nm. This spectrum could increase the production of the adenosine triphosphate (ATP), as well as Nitric Oxide (NO) (13, 14, 24, 45, 46). In other words, light therapy increases metabolic capacity and energy production in the cells. It could also enhance brain focal perfusion

by increasing cerebral blood flow due to the release of NO (13, 15). As many cognitive dysfunctions and neurodegenerative diseases are sensitive to brain hypo-perfusion and metabolic deficiency (24), it is proposed that improvement of attentional performance in the present study was due to an increase in energy production and focal cerebral blood flow (47).

This study is comparable to the first experimental study on the effectiveness of TCLT with the laser. Barret and Gonzalez-lima (2013), evaluated the effect of the TCLT with a low-level laser source over the PFC in healthy volunteers (8). They showed that a single session of TCLT with a laser source (1064 nm and 60 J/cm^2) on the right PFC could modulate emotional score, memory, and sustained attention (8, 36). Similarly, our study, using LED source with 850 nm and 60 J/cm^2 , could induce beneficial alterations on attentional performance. A wavelength of 850 nm, however, seems to be more favorable than 1064 nm, as it has been shown that this wavelength of irradiation is more effectively absorbed by mitochondria (40).

5.1. Strengths and Limitations

The advantage of the present study was the task used for measurement of attentional performance. The PGNG provides an exclusive assessment of sustained attention in a shorter duration and with lower learning effect compared to other attentional tasks (37, 38). In addition, no side effect was reported by the subjects during and 1 hour after the intervention, as expected according to the literature (15, 17).

There were some limitations in our study. Although this study showed the effectiveness of TCLT with LED source on attentional performance, however, single session application of TCLT limits generalizability of this finding to clinical settings. Therefore, future studies are needed to investigate the everlasting effects of LED light on human brain and the effects of dose fractionation across several sessions.

5.2. Conclusion

In summary, the promotion of attentional performance in this study showed that TCLT with LED device is an effective, safe, and a cost-benefit method for the modulation of the brain function in healthy subjects.

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Footnotes

Authors' Contribution: Study concept and design, Hasan Sabouri Moghadam, Mohamad Ali Nazari, Ali Jahan, Javad Mahmoudi, and Hasan Sabouri Moghadam; Acquisition, Analysis and interpretation of data, Ali Jahan and Hasan Sabouri Moghadam; Drafting of the manuscript, Javad Mahmoudi, Ali Jahan, and Hasan Sabouri Moghadam; Critical revision of the manuscript for important intellectual content, Javad Mahmoudi, Mohamad Ali Nazari, and Ali Jahan; Statistical analysis, Ali Jahan; Administrative, technical, and material support, Javad Mahmoudi and Ali Jahan; Study supervision: Hasan Sabouri Moghadam and Mohamad Ali Nazari.

Conflict of Interest: We had no conflicts of interest in the authorship or publication of this manuscript.

Implication for Health Policy/Practice/Research/Medical Education: Transcranial low-level light therapy by LEDs could improve attentional performance in healthy individuals. Clinical trials researches to evaluate effectiveness in clinical conditions are warranted.

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