

Transcranial Photobiomodulation Improves Cognitive Performance in Young Healthy Adults: A Systematic Review and Meta-Analysis

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Abstract

Background: Transcranial photobiomodulation (t-PBM) is a noninvasive modality that may improve cognitive function in both healthy and diseased subjects.

Objective: This systematic review and meta-analysis addresses the question of whether t-PBM improves cognitive function in healthy adults.

Methods: We searched MEDLINE using PubMed, EMBASE, SCOPUS, Web of Science, and Cochrane Library up to March 2019. We also searched ProQuest and Google Scholar databases for unpublished material. The search was limited to articles on the procognitive effects of t-PBM in healthy adults. The initial search resulted in 871 studies, of which nine publications met our criteria for inclusion and exclusion. Seven studies were performed on young, healthy subjects (17–35 years), and two studies were conducted on older (≥ 49 years), normal subjects. A meta-analysis was performed on six full-text publications whose subjects were young adults.

Results: t-PBM administration improved cognition-related outcomes by an 0.833 standardized mean difference (SMD; 95% confidence interval (CI): 0.458–1.209, 14 comparisons) in young, healthy participants. Funnel plotting revealed asymmetry, which was validated using Egger's ($p=0.030$) and Begg's regression ($p=0.006$) tests. However after reanalysis, this asymmetry disappeared in the attention subgroup, but not in the memory subgroup. The trim-and-fill analysis indicated two studies were lacking required data. Thus, the effect size was adjusted from an SMD of 0.761 (95% CI: 0.573–0.949) to 0.949 (0.779–1.120). The overall quality score of the studies was modest.

Conclusions: We demonstrated a significant, beneficial effect of t-PBM on cognitive performance of young, healthy individuals; however, the heterogeneity of the data was high. This could be due to the modest quality or to the low number of included studies, or to the differences between the various subdomains assessed. These shortcomings should be meticulously addressed before concluding that t-PBM is a cognitive-enhancing intervention in healthy individuals.

Keywords: transcranial photobiomodulation, cognition, memory, learning, attention, healthy adults

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Introduction

THE SIGNIFICANT IMPACT of various cognitive enhancement strategies has been demonstrated in the scientific literature.¹ Mounting evidence suggests that these interventions may help maintain cognitive performance, and preserve the quality of life and independence of both young and older adults. With the introduction of novel technologies, namely computers and videogames, these interventions or strategies could be readily applied to both the young and older populations.^{2,3} Among these novel approaches, the potential of photobiomodulation (PBM) has been underestimated.

PBM, also known as low-level light/laser therapy (LLLT), has been proposed to be a noninvasive modality that stimulates many different biological processes.⁴ Lately, transcranial PBM (t-PBM) has gained increased attention as a novel approach to stimulate the physiological functions of the brain.^{5,6} Mechanistically, at the appropriate light irradiance and fluence, photons at red (600–670 nm) and near-infrared (NIR; 800–1100 nm) wavelengths are absorbed by the cytochrome c oxidase (CCO) in neuronal mitochondria, leading to an increased synthesis of adenosine triphosphate (ATP), along with photodissociation of nitric oxide (NO), yet levels of reactive oxygen species remain comparably low.⁷ After passing through the scalp and the skull, the red/NIR photons can also affect cerebral blood vessels and subsequently increase cerebral blood flow (CBF), due to the vasodilation triggered by the release of NO.⁸

Both experimental^{9–11} and clinical research^{12–14} suggests that t-PBM improves cognitive function in the diseased brain. t-PBM has also shown promising results for cognitive enhancement in healthy individuals.^{15,16} Human studies have demonstrated that t-PBM using low powers of light from both lasers or light-emitting diodes (LEDs) emitting specific wavelengths of red and NIR light can potentially increase the oxygen consumption and metabolic activity in the frontal cortex, which may subsequently lead to improved cognitive performance in several domains.^{17–20}

Systematic reviews and meta-analyses are meant to be careful, scientific syntheses of current data to inform the decision making of clinicians and researchers. On one hand, systematic reviews are inherently a qualitative assessment as they typically report a series of findings and address the question of whether scientific discoveries are coherent and able to be generalized over various populations and settings. On the other hand, meta-analyses, by offering a quantitative summary of findings, can more precisely estimate the overall treatment effects and exposure risks.²¹ Our systematic review and meta-analysis addresses whether t-PBM improves cognitive function in young and older healthy adults.

Materials and Methods

Search strategy

Bibliographic databases (i.e., MEDLINE through PubMed, EMBASE, SCOPUS, Web of Science, and Cochrane Library) were searched electronically for studies on the effects of t-PBM on the cognitive performance of healthy individuals through the keywords “low-level light therapy,” “laser therapy,” “phototherapy,” “near-infrared laser,” “transcranial laser,” “photobiomodulation,” “transcranial,” “cognition,” “attention,” “learning,” “memory,” and “executive func-

tion.” ProQuest and Google Scholar databases were also searched for unpublished material. Two independent researchers screened the title, abstract, and (whenever needed) the full text of the articles, and judged the searched materials against the inclusion and exclusion criteria. In case of any disagreement, a third independent researcher was called upon to decide on the inclusion of a contested article. There were no restrictions based on date of publication. However, our search was limited to studies performed in human subjects and to publications written in English. Therefore, animal, *ex vivo*, or *in vitro* studies were not included.

Inclusion and exclusion criteria

All clinical trials, whether presented in full or in conference articles assessing the effects of t-PBM on the cognitive performance of healthy young or older individuals were included. Studies performed on animals and *ex vivo* or *in vitro* (primary cultures or cell line) were excluded. Also, non-English language publications and studies conducted on unhealthy or diseased individuals were excluded from our review and meta-analysis. Studies that had used other diagnostic or therapeutic procedures, such as transcranial magnetic stimulation (TMS), which might alter brain excitability were also excluded. The primary outcomes of our study were cognition-related behavioral outcomes, including measures of attention, memory, learning, and executive function.

Data extraction

The author, publication year and type, number of participants, age, cognitive domain, light source/wavelength, operation mode, output power (W), irradiance (mW/cm²), irradiation time (min), fluence (J/cm²), energy (J), beam spot area (cm²), total area exposed (cm²), irradiation site, number of treatment sessions, neuropsychological tasks, and outcome(s) were extracted. Quality measures, and measures to assess and control study biases were also extracted from the included studies. Further, the number of participants in each group, the standard deviation, or the standard error of the mean were extracted from the studies. However, the time of outcome evaluation was not extracted from the studies. In case more than one experiment was conducted within the same study, each experiment was regarded as a separate study and included in the meta-analysis. However, when neurobehavioral measures were repeated in the same group of participants, only the last evaluation data were extracted from the study. Because most of the presented data in studies were geographically reported, we used Universal Desktop Ruler software, version 2.9 to extract the mandatory data.

Assessment of methodological quality of studies

The methodological attributes of the selected studies, including the measures of internal validity (e.g., performance, selection, detection, and attrition biases) and other measures of study quality, such as reporting quality and power, were evaluated using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This tool identifies the risk of bias in human subject research at different steps, such as: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.²²

Statistical analyses

All analyses were performed through Comprehensive Meta-Analysis Software (CMA) version 3. Due to the heterogeneity of the data, the random effects model was used to pool the data statistically. However, because of the homogeneity of the data in the attention subgroup, the fixed effects model was used in this domain. The outcome of this study was the overall effects of t-PBM on cognition-related behavioral outcomes. Funnel plotting,²³ Egger's regression,²⁴ Begg's regression, and Duval and Tweedie's nonparametric trim-and-fill approach²⁵ were used for the assessment of publication bias.²⁶ The chi-square test and the Higgins I2 test were applied to evaluate heterogeneity.²⁷

Results

General study characteristics

A total of 871 studies were identified during the initial systematic search, of which nine publications met our criteria for inclusion and exclusion. Seven studies were conducted in young healthy subjects, and two in older, normal subjects. Eight publications were full-text articles, and one publication was a conference article. Meta-analysis was performed on six full-text articles whose study subjects were young. Due to the very few studies in older subjects, the meta-analysis could not be performed for this age group (Fig. 1).

Seven studies assessed the effects of t-PBM on attention. Also, four studies evaluated the impacts of t-PBM on

memory. Two further studies measured the effects of t-PBM on executive function. Only one study assessed the impacts of t-PBM on the learning domain of cognitive performance.

In six studies, a 1064 nm laser light source was used for t-PBM. On the other hand, two studies used an 850 nm LED light source and only one study applied a combined 633/870 nm LED cluster. The operation mode in all studies was continuous wave (CW). Other physical and treatment characteristics, such as output power, irradiance, irradiation time, fluence, beam spot area, and total area exposed are extensively summarized in Table 1. In all studies, the target of irradiation was the frontal cortex, especially the prefrontal cortex (PFC), but in one study, one of the three LED clusters was aimed at the parietal cortex (placement on Pz point on the electroencephalography [EEG] map).

Two studies applied the psychomotor vigilance task, and two studies used the Go/No-Go task to assess attention in the participants. Delayed match to sample was used in three studies to evaluate memory. Also, the Wisconsin Card Sorting Task was used in one study to assess executive function. Additionally, the category learning task was applied in one study to assess learning ability in the subjects. The interference task of verbal cognition was used to assess verbal cognition in one study. Finally, Eriksen flanker and category fluency tests were used to assess frontal-related cognitive function in one study. Eight studies used a one-session treatment schedule. However, one study performed in older adults, used a five-session schedule.

FIG. 1. Summary of included and excluded articles.

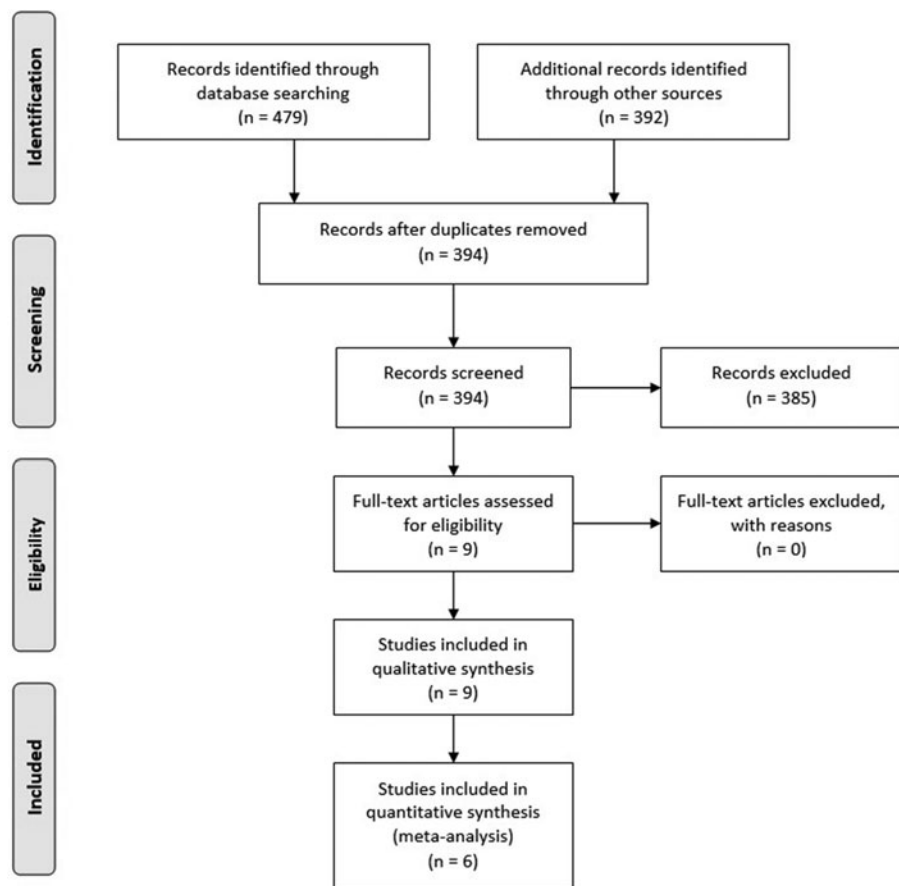


TABLE 1. SUMMARY OF STUDIES ON THE PROCOGNITIVE EFFECT OF TRANSCRANIAL PHOTOBIO-MODULATION IN HEALTHY INDIVIDUALS

Study (year)	Participants (n)	Age	Cognition domain	Light source/wavelength	Operation mode	Output power (W)	Irradiance (mW/cm ²)	Irradiation time (min)	Fluence (J/cm ²)	Energy (J)	Beam spot area (cm ²)	Total area exposed (cm ²)	Irradiation site	Number of treatment sessions	Neuropsychological tasks	Outcomes
Barrett and Gonzalez-Lima (2013) ¹⁶	Healthy young volunteers (40)	18–35 years old	Attention and memory	Laser/1064 nm	CW	3.4	250	8 (4/site)	60/site	816/site	12.56	25.12 (12.56×2 sites)	2 sites; Medial and lateral to the Fp2 point	1	PVT and DMS	Significant improvement of both attention and memory
Blanco et al. (2015) ⁴³	Healthy young volunteers (30)	Mean age = 20.4 years	Executive function	Laser/1064 nm	CW	3.4	250	8 (4/site)	60/site	816/site	12.56	25.12 (12.56×2 sites)	2 sites; Lower and upper portion of right lateral forehead at Fp2 and F4	1	The Wisconsin Card Sorting Task	Improvement of executive function
Hwang et al. (2016) ⁴⁴	Healthy young volunteers (60)	18–30 years old	Attention and memory	Laser/1064 nm	CW	3.4	250	8 (4/site)	60/site	816/site	13.60	25.12 (12.56×2 sites)	2 sites; Medial and lateral to the Fp2 point	1	PVT and DMS	Significant improvement of both attention and memory
Moghadam et al. (2017) ⁴¹	Healthy young volunteers (34)	18–24 years old	Attention	LEDs/850 nm	CW	0.4	285	2.5	60	60/site	1.4	1.4	1 site; Right frontal pole at Fp2	1	Level-1 of parametric Go/No-Go task	Promotion of attentional performance
Blanco et al. (2017) ¹⁵	Healthy young volunteers (118)	17–35 years old	Learning	Laser/1064 nm	CW	3.4	250	8 (4/site)	60/site	816/site	13.60	25.12 (12.56×2 sites)	2 sites; Right frontopolar at Fp2 point and right frontal at F4 and F8	1	Category learning task	Enhancement of learning-related cognitive function
Fink et al. (2018) ²⁰	Healthy young volunteers (40)	Mean age = 19.0 years	Verbal cognition	Laser/1064 nm	CW	3.4	250	8	120/site	1632/site	NR	NR	1 site; Left prefrontal cortex	1	Interference task of verbal cognition	No effect
Jahan et al. (2019) ²	Healthy young volunteers (30)	Mean age = 21.2 years	Attention	LEDs/850 nm	CW	0.4	285	2.5	60	60/site	1.4	1.4	1 site; Right frontal pole at Fp2	1	Go/No-Go task	Beneficial effects on attentional performance
Vargas et al. (2017) ¹⁷	Healthy old volunteers (12)	49–90 years old	Attention and memory	Laser/1064 nm	CW	3.4	250	8 (4/site)	60/site	816/site	13.60	25.12 (12.56×2 sites)	2 sites; Medial and lateral to the Fp2 point	5	PVT and DMS	Significant improvement of both attention and memory
Chan et al. (2019) ³⁹	Healthy old volunteers (30)	Mean age = 66.2 years	Frontal-related cognitive function	LEDs/633 + 870 nm	CW	2.994 (3×0.998)	44.4	22.5 (7.5/site)	20/site	449/site	67.44 (3×22.48)	67.44 (3×22.48)	3 sites; Left frontopolar at Fp1 and right frontopolar at Fp2 and Pz	1	Eriksen flanker and category fluency tests	Significant improvements in their action selection, inhibition ability, and mental flexibility

CW, continuous wave; DMS, delayed match-to-sample; LEDs, light-emitting diodes; PVT, psychomotor vigilance task.

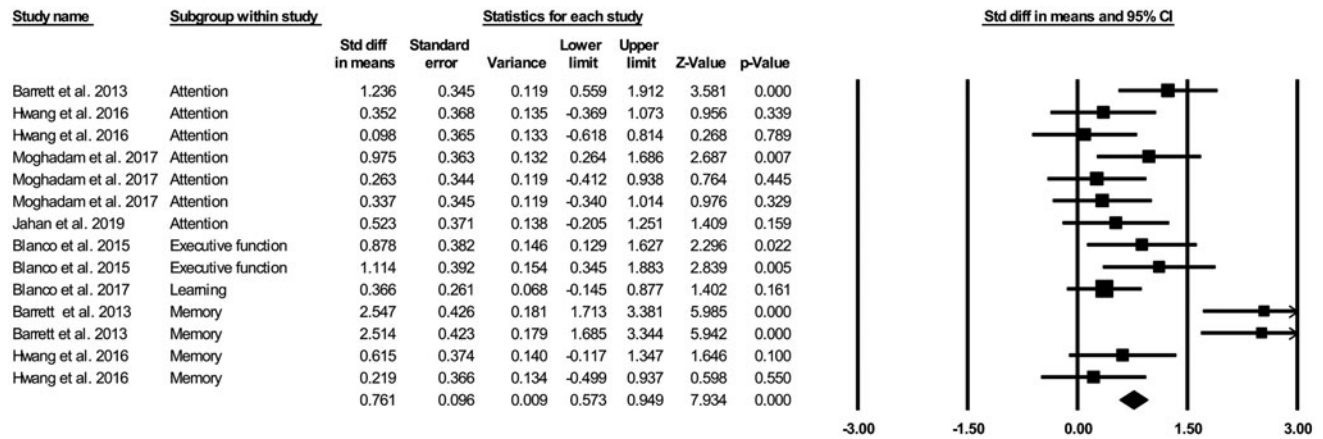


FIG. 2. Forest plot of SMD of the included comparisons in the meta-analysis. Black diamond represents the pooled SMD. Squares indicate the SMD in each study, where square sizes are inversely proportional to the standard error of the SMD. Horizontal lines signify 95% CI. CI, confidence interval; SMD, standardized mean difference.

All studies showed positive effects of t-PBM on various domains of cognition. Nevertheless, one study (conference article) did not show any effects of laser therapy on cognitive performance.

Global estimates of improvement in the neurobehavioral scores

Overall, t-PBM administration in young healthy participants improved cognition-related outcomes by 0.833 standardized mean difference (SMD; 95% confidence interval (CI): 0.458–1.209, 14 comparisons; Fig. 2).

Our analysis showed significant heterogeneity between the included studies ($\chi^2=51.094$, $I^2=74.557$, degree of freedom [df]=13, $p=0.000$). However, the heterogeneity was apparently due to the heterogeneous nature of included domains and their related tasks. Accordingly, the analyses

were reperformed for both attention and memory subgroups. Reanalysis revealed no heterogeneity between attention data studies ($\chi^2=8.217$, $I^2=26.985$, $df=6$, $p=0.223$); but, for the memory subgroup heterogeneity between studies persisted ($\chi^2=28.872$, $I^2=89.609$, $df=3$, $p=0.000$).

Overall, the funnel plot revealed asymmetry (Fig. 3), which was validated using Egger’s ($p=0.030$) and Begg’s regression ($p=0.006$) tests. The trim-and-fill analysis indicated two theoretically missing studies. Thus, the effect size was adjusted from an SMD of 0.761 (95% CI: 0.573–0.949) to 0.949 (0.779–1.120).

On the other hand, this asymmetry disappeared in the attention subgroup, but not in the memory subgroup, after reanalysis. This was validated through Egger’s ($p=0.674$ for attention, and $p=0.000$ for memory) and Begg’s regression ($p=1.000$ for attention, and $p=0.089$ for memory) tests.

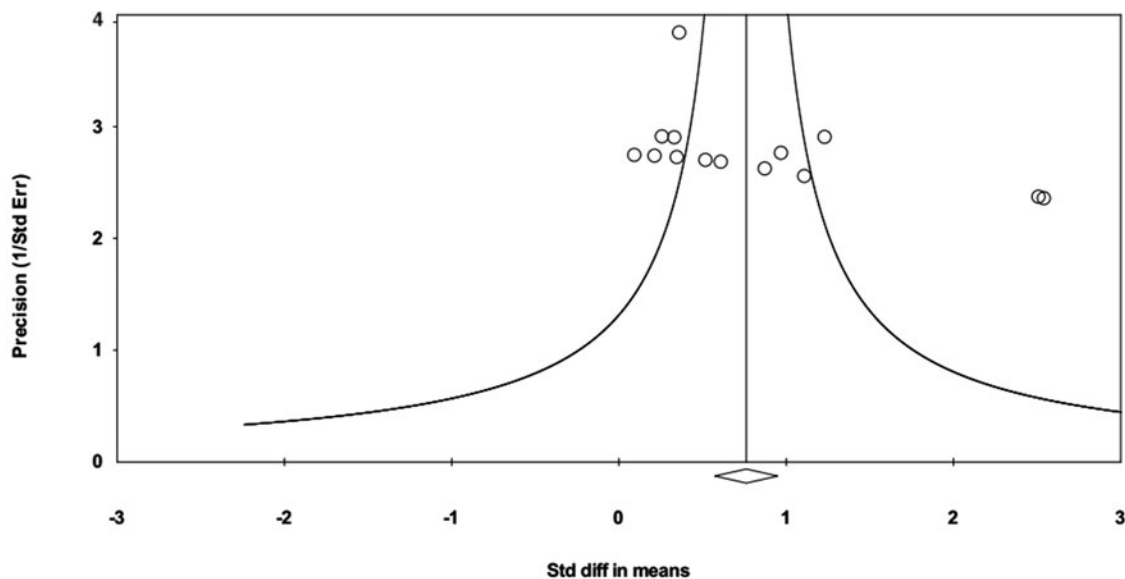


FIG. 3. Evidence of publication (reporting) bias. Funnel plot of precision by SMD; in case of no bias, the points should look like a symmetrical inverted funnel. SMD, standardized mean difference.

Study quality

On the one hand, all of the included studies had apparently complete outcome assessment and were not subject to selective reporting bias. On the other hand, only two and three studies had participants and personnel blinded to the nature of experiments and allocation concealment, respectively. Randomization of the participants was performed in six studies. Conference articles were not assessed by this checklist. Accordingly, the overall quality score of the studies was modest (Table 2).

Discussion

Our results showed a significant improvement of cognitive outcomes using t-PBM in young healthy individuals; however, the overall heterogeneity of data was high. The study design and the chosen cognitive subdomain were found to affect the cognition-related outcome scores; in fact t-PBM significantly improved the attention-related outcomes without marked heterogeneity. The heterogeneity of data in the memory subdomain remained high. This could be due to the low number of published studies or to the medium quality of the included data.

Overall, these results support the potential for a single session of t-PBM (CW mode) with red/NIR wavelengths to improve cognition-related neurobehavioral scores. However, these findings should be treated with some caution due to the limitations of the included studies.

Mechanistic insights into the observed effects

All studies conducted a single session of t-PBM and performed neuropsychological tasks accordingly, except Vargas et al.¹⁷ who administered t-PBM chronically once a week for 5 weeks. The underlying mechanisms of the procognitive effects of an acute session of t-PBM have not been completely elucidated yet; however, some possible mechanisms have been proposed.

On the one hand, medial and left inferior frontal cortices are believed to control higher-order cognitive functions.²⁸ On the other hand, both regional CBF and frontal lobe metabolic activity are considered necessary for normal cognitive function.²⁹ Also, NO is a well-known vasodilator, which mediates the regulation of CBF, most likely through improving the vessel extensibility and resistance.³⁰ During t-PBM, NO is

released from its binding sites in the neuronal CCO through a photodissociation process⁷ and consequently improves CBF in the respective areas.⁸ Also, t-PBM using a 1064 nm laser increases oxidized CCO concentrations and cerebral oxygenation in the frontal cortex.³¹ It is noteworthy that the observed beneficial impacts of t-PBM on the cerebral hemodynamics and metabolism are not due to any laser-induced heating effects on the scalp.³² Further, it has been proposed that red LEDs at 627 nm act on cerebral superficial blood vessels and alters the elasticity and resistance of the cerebrovascular endothelium, at least partly through the NO pathway.¹⁹

In addition, it has been revealed that the electrical activity of the brain changes throughout the cerebral cortex during t-PBM.³³ It was shown that t-PBM (1064 nm laser, output power of 2.2 W, a beam spot area of 13.6 cm², irradiance of 160 mW/cm², fluence of 105.6 J/cm², for 11 min) applied to the right forehead increased the power density of the alpha band and a small portion of the beta band in healthy subjects.³³ Laser-induced increase in alpha band power was also dose dependent so that the most robust activation was observed between 8 and 10 min (77–96 J/cm² on the scalp) after initiation of t-PBM session. This study suggested that desynchronization of alpha and beta waves and subsequent neuromodulation of an ipsilateral, fronto-parieto-occipital network and also a contralateral parieto-occipital network at the alpha frequency may in part explain the improved cognitive functions following t-PBM.^{33,34}

Improved mitochondrial function and ATP production, reduced oxidative stress, reduced apoptosis, and neuroinflammation are other mechanisms that might be responsible for the long-lasting procognitive effects of red/NIR t-PBM.^{9,35}

t-PBM characteristics

Cassano et al.³⁶ used simulation modeling and reported that t-PBM with 810 nm LEDs (irradiance of 300 mW/cm², a total exposed area of 28.4 cm², for 5 min) on the F3 or F4 EEG points, delivered a peak fluence of 1.72 J/cm² to the dorso-lateral PFC (dlPFC). Moreover, a peak fluence of 0.82 J/cm² was achieved at ventromedial PFC (vmPFC) using the same treatment strategy for transcranial irradiation of the Fp1-Fpz-Fp2 points.³⁶ A cortical fluence range of 0.3–3 J/cm² was reported to be a sufficient photoneuromodulatory dose,³⁷ which effectively improves frontal lobe oxygenation¹⁸ and CCO levels in healthy individuals.³¹ Similarly, the physical

TABLE 2. METHODOLOGICAL QUALITY ASSESSMENT OF THE INCLUDED PUBLICATIONS IN THE DATA SYNTHESIS BASED ON COCHRANE STUDY QUALITY CHECKLIST

Study (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Complete outcome data	Nonselective reporting	Other bias
Barrett and Gonzalez-Lima (2013) ¹⁶	+	–	–	+	+	?
Blanco et al. (2015) ⁴³	–	–	+	+	+	?
Hwang et al. (2016) ⁴⁴	+	+	–	+	+	?
Moghadam et al. (2017) ⁴¹	+	+	–	+	+	?
Blanco et al. (2017) ¹⁵	+	–	–	+	+	?
Vargas et al. (2017) ¹⁷	–	–	–	+	+	?
Chan et al. (2019) ³⁹	+	–	+	+	+	?
Jahan et al. (2019) ⁴²	+	+	–	+	+	?
Total	6	3	2	8	8	–

+, observed; –, negated; ?, unknown.

and treatment parameters applied in almost all of the included studies were nearly the same as those considered by Cassano et al.³⁶ In the included studies, the stimulation sites were the left and right vmPFC, corresponding to Fp1 and Fp2. The F4 and F8 sites that were also the target of t-PBM refer to the right dlPFC and right lateral frontal area, respectively.

Evidence suggested that only 2% of 1064 nm laser light could pass through the supraorbital frontal skull at Fp2 point.¹⁶ Light transmission percentages of 0.5% and 2.1% for the frontal skull were also reported for LED light at 633 and 830 nm wavelengths, respectively.³⁸ In all of the enrolled studies, except one,³⁹ the scalp fluence of 60 J/cm² per site was applied for 1064 nm laser and 850 nm LED light. Based on the aforementioned light penetration data, it could be assumed that an ~ 1.2 J/cm² light dose was received by cortical neurons in those studies. However, in one study,³⁹ the authors used a scalp fluence of 20 J/cm² per site for combined 633/870 nm LED light. Thus, it is expected that a fluence of 0.1–0.4 J/cm² reached the cortical surface which is close to the neurostimulatory range.

Whether noncoherent LED light is as effective as coherent laser light for PBM purposes is a matter of debate.⁴⁰ In three studies,^{39,41,42} which used LED clusters, the beneficial effects on the various cognitive domains were qualitatively similar to those of laser t-PBM studies.^{15–17,43,44} Therefore, it might be suggested that light coherence is not necessarily needed for achieving effective procognitive outcomes. Of note, LED arrays are less expensive than lasers; moreover, flexible LED devices can be integrated into helmets for t-PBM application. Besides, wearable LED arrays with a large active area could provide a cost-effective device for ambulatory frontal lobe photostimulation.

Study quality

We applied the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials to assess the internal and external validity of the included articles. Our previous studies have revealed that articles that possess low methodological quality were predisposed to overestimating effect sizes.²⁶ Accordingly, the quality of the articles assessed in this meta-analysis was only modest, and importantly strategies to reduce publication bias and increase quality, such as blinding of participants/personnel to the nature of experiments and allocation concealment were rarely reported or performed. Significant heterogeneity between studies was also present, which could be attributed to the difference between the assessed subdomains and to the low number of studies. However, this should be considered with caution, as the heterogeneity may indicate the existence of other factors (e.g., t-PBM parameters) that influence the impacts observed. The identification of these putative, hidden factors will further help researchers to design higher-quality studies, necessary to investigate t-PBM as a procognitive strategy.

Potential limitations

Our meta-analysis had some inevitable shortcomings; thus, the findings of this study should be considered with caution. First, this study was an observational study, which was performed on existing datasets, so our findings should only be regarded as a hypothesis. Second, as the methodological quality of the included articles was not high, our

results may have overestimated and overstated the effect sizes, or vice versa. Third, our meta-analysis may also be subject to publication bias.

Conclusions

Cognitive enrichment strategies exert a protective effect against subsequent development of dementia later in life. t-PBM, as an emergent cognitive enhancing modality, has shown promising results in the improvement of cognitive function both in young and older healthy adults. Our study confirmed these effects in young healthy individuals; however, due to the limited number of studies on older subjects, we could not adequately investigate the older adults. Also, significant heterogeneity was found between studies, which could stem from either modest quality of included studies or from differences between the assessed cognitive subdomains. The low number of included studies may also affect the reliability of our findings. These shortcomings should be meticulously addressed before concluding that t-PBM is an effective cognitive-boosting intervention in healthy individuals.

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Author Disclosure Statement

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San Clemente, CA; Varuna Biomedical Corp. Incline Village, NV; Niraxx Light Therapeutics, Inc., Boston, MA; Dr Hamblin has been a consultant for Lexington Int, Boca Raton, FL; USHIO Corp, Japan; Merck KGaA, Darmstadt, Germany; Philips Electronics Nederland B.V.; Johnson & Johnson, Inc., Philadelphia, PA; Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany; Dr Hamblin is a stockholder in Global Photon, Inc., Bee Cave, TX; Mitonix, Newark, DE. The other authors have no conflicts of interest to disclose.

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