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Transcranial Laser Stimulation as Neuroenhancement for Attention Bias Modification in Adults with Elevated Depression Symptoms

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ABSTRACT

Background: Low-level light therapy (LLLT) with transcranial laser is a non-invasive form of neuroenhancement shown to regulate neuronal metabolism and cognition. Attention bias modification (ABM) is a cognitive intervention designed to improve depression by decreasing negative attentional bias, but to date its efficacy has been inconclusive. Adjunctive neuroenhancement to augment clinical effectiveness has shown promise, particularly for individuals who respond positively to the primary intervention.
Objective/hypothesis: This randomized, sham-controlled proof-of-principle study is the first to test the hypothesis that augmentative LLLT will improve the effects of ABM among adults with elevated symptoms of depression.
Methods: Fifty-one adult participants with elevated symptoms of depression received ABM before and after laser stimulation and were randomized to one of three conditions: right forehead, left forehead, or sham. Participants repeated LLLT two days later and were assessed for depression symptoms one and two weeks later.
Results: A significant three-way interaction between LLLT condition, ABM response, and time indicated that right LLLT led to greater symptom improvement among participants whose attention was responsive to ABM (i.e., attention was directed away from negative stimuli). Minimal change in depression was observed in the left and sham LLLT.
Conclusions: The beneficial effects of ABM on depression symptoms may be enhanced when paired with adjunctive interventions such as right prefrontal LLLT; however, cognitive response to ABM likely moderates the impact of neuroenhancement. The results suggest that larger clinical trials examining the efficacy of using photoneuromodulation to augment cognitive training are warranted.

Introduction

Individuals with depression experience biased cognitive processes that are theorized to facilitate the onset and maintenance of their symptoms [1]. Biased attention toward depression-relevant stimuli has been observed in clinical depression [1,2] and has been linked with vulnerability for clinical worsening [3–5]. In recent years, a growing number of techniques have set out to ameliorate negative cognitive biases with the goal of decreasing depression symptomatology.

One such technique is known as attention bias modification (ABM). ABM attempts to shift negatively biased attention in favor of more adaptive patterns of attention [6], which is theorized to decrease the cognitive and affective symptoms associated with depression [7]. ABM has been shown to decrease symptoms of anxiety by decreasing attention for threatening stimuli [8–10]. In depression, however, the results are less consistent. Previous research using ABM in individuals with clinically relevant depression showed greater decreases in symptoms compared to those who received no training [11–13]. However, meta-analyses quantifying the influence of ABM on depression symptoms have shown variable results and small effect sizes [10,14]. Considering the strong theoretical and empirical support linking attention biases to depression,

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there is a compelling rationale to augment ABM in order to improve its potential efficacy.

Neuroenhancement is a field that utilizes pharmacological or neuromodulatory interventions to improve cognitive capabilities [15]. This technique aims to directly influence cognitive systems either through the activation of adaptive processes or the inhibition of maladaptive ones. Though it is extensively researched in healthy individuals [16,17], neuroenhancement offers considerable promise as an adjunctive clinical intervention, particularly when cognitive systems are implicated in the etiology of the disorder [15,16].

Critically, recent findings suggest that improvement associated with adjunctive neuroenhancement may be contingent on the individual's response to the primary intervention. In studies using adjunctive neuroenhancement such as d-cycloserine, yohimbine, and methylene blue, clinical improvement at follow-up was greatest for participants who showed the most improvement from exposures [18–21]. In contrast, neuroenhancement may lead to a worsening of clinical outcomes following an unsuccessful treatment session (e.g., an exposure session where end state fear remained high) [20,21]. These findings suggest that neuroenhancement may augment learning that takes place during the intervention, even if the learning was not necessarily therapeutic. As such, indicators of treatment response during the primary intervention should be considered a key moderator when investigating neuroenhancement outcomes.

A promising new option for adjunctive neuroenhancement is low-level light therapy (LLLT) using near-infrared transcranial lasers or light emitting diodes (LEDs). LLLT is a non-invasive intervention shown to regulate neuronal function in cell cultures, animal models, and clinical conditions [22]. The primary photoneuromodulation mechanism of action of LLLT is increased mitochondrial cytochrome oxidase [23], a respiratory enzyme that is commonly reduced in disorders involving cognitive impairment and decreased cognitive reserve [24–28]. Up-regulating cytochrome oxidase through neuroenhancement has been shown to improve oxygenation and metabolic efficiency in the brain [29,30], which stimulate ATP production and facilitate neuronal energy production [31–33]. Consequently, techniques that increase cytochrome oxidase, such as LLLT and methylene blue, have been shown to improve cognition in mice and rats [33,34] as well as in humans [35–37].

Although LLLT has FDA approval for peripheral pain management, it is growing in popularity as a brain research tool [35]. Specifically, LLLT with transcranial laser targeting the right prefrontal cortex has been shown to enhance sustained attention compared to sham LLLT [36], and LLLT with transcranial LEDs targeting the prefrontal cortex has been shown to decrease depression symptoms up to four weeks following treatment, although clinical studies to date have not used a sham control [38]. These findings suggest that LLLT may be an inexpensive, non-invasive, and promising neuroenhancement technique. Considering that hypoactivity in the prefrontal cortex has been associated with negative attentional bias [39–42], and considering that LLLT has been linked to increased cytochrome oxidase activity, improved cognitive function, and decreased negative affect [35,43], there is strong reason to believe that LLLT to the prefrontal cortex could improve the efficacy of ABM.

This proof-of-principle study uses LLLT with transcranial laser stimulation of the prefrontal cortex as an adjunctive neuroenhancement intervention with the goal of improving depression-related ABM outcomes. Participants completed ABM before and after a randomly-assigned session of right prefrontal LLLT, left prefrontal LLLT, or sham LLLT, then provided follow-up depression assessments over the ensuing two weeks. Administering LLLT separately from ABM is logistically necessary since laser safety regulations require participants to close their eyes and wear dark glasses during laser stimulation. However, it also allows us to assess each individual's responsiveness to ABM independently from the influence of LLLT. Participants with adaptive attention bias change immediately before LLLT were expected to benefit from subsequent neuroenhancement. Such a finding would be consistent with the idea that neuroenhancement augments learning that occurs during the primary intervention and would also provide important information about who is likely to benefit from ABM with LLLT augmentation. This study could be used to lay the groundwork for larger, more robust neuroenhancement trials using clinically depressed participants.

Materials and methods

Participants

Fifty-one adults with elevated symptoms of depression (31 female, mean age = 19.37, SD = 3.05) were recruited from the undergraduate research pool at the University of Texas at Austin. Participants who reported active neurological condition (e.g. stroke or epilepsy) were excluded from the study. Participants received course credit in exchange for their participation.

Racial and ethnic distribution in the sample was as follows: 24% Hispanic, 59% Caucasian, 23% Asian, 6% African-American, 4% American Indian or Alaska Native, 2% mixed race, and 6% unspecified. All participants provided written informed consent after receiving a complete description of the study.

Procedure

Participants were recruited based on their score on the Center for Epidemiologic Studies – Depression Scale (CES-D) from a prescreening questionnaire. Participants completed two study sessions scheduled to begin exactly 48 hours apart. The first session began with a CES-D (to confirm CES-D > 16 at the start of the experiment) and a demographic questionnaire, while session two only required the CES-D. In both sessions, participants then completed (in order) a negative bias assessment via the dot-probe task, one block of ABM, the LLLT session, an additional block of ABM, and a final negative bias assessment. Participants then completed follow-up CES-D questionnaires at one and two week intervals following enrollment (see Fig. 1 for a depiction of study design).

LLLT was administered after and before blocks of ABM since the precise timing of optimal neuroenhancement with LLLT is currently unknown. Certain neuroenhancement mechanisms, e.g. transcranial magnetic stimulation, provide peak benefit when administered in advance of or simultaneous to the target task [17]. Other neuroenhancement mechanisms, particularly those that modulate cytochrome oxidase, yield optimal clinical impact when administered after the target task [20,21,43]. Simultaneous ABM/LLLT is unfeasible due to laser safety regulations requiring participants to keep their eyes closed and wear dark glasses during laser stimulation, but the current study design increases the probability of neuroenhancement through one of the proposed mechanisms.

Two participants were unable to attend their second study session but did complete follow-up CES-D questionnaires. As a result, these participants were only included in analyses that use depression symptoms as an outcome measure.[1] All study procedures and assessments were approved prior to participant enrollment by the Institutional Review Board of the University of Texas at Austin.

[1] Removal of these participants would not have significantly impacted the direction or significance of the subsequent analyses.