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Singular and combined effects of transcranial infrared laser stimulation and exposure therapy: A randomized clinical trial

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ABSTRACT

This RCT will test whether transcranial infrared laser stimulation (TILS) administered immediately following standard exposure therapy enhances the retention of fear extinction for naturally acquired pathological fear. A second aim is to investigate the efficacy of TILS as a stand-alone intervention for reducing pathological fear. Participants with elevated fear in any one of the following four domains: (a) fear of enclosed spaces, (b) fear of contamination, (c) fear of public speaking, or (d) fear of anxiety (i.e., anxiety sensitivity) will be recruited from introductory psychology classes and the greater Austin community. Participants displaying marked fear responding will be stratified on baseline fear responding and fear domain and randomized to one of four treatment arms: (1) Exposure + TILS, (2) Exposure + sham TILS, (3) TILS alone, or (4) Sham TILS alone. We anticipate that TILS will enhance exposure therapy outcome relative to sham TILS and that this enhancement effect will be most pronounced for (a) those displaying higher baseline fear responding, and (b) those showing greater fear reduction during exposure. Study rationale as well as additional predictions and clinical implications are discussed.

1. Introduction

Repeated exposure to fear-provoking targets is the most potent strategy in the treatment of anxiety-related disorders [1,2]. However, some patients do not respond to exposure-based treatments, and among those who do, a sizeable minority display a return of fear [3]. These data underscore the need to develop strategies for enhancing exposure therapy, as well as identifying alternative cost-effective interventions for pathological anxiety. By translating findings from animal models of fear extinction experiments to human populations, researchers are testing the use of cognitive enhancers to augment the neural mechanisms that underlie exposure therapy (see [4] for a review). So far, the most promising cognitive enhancers investigated have been orally administered pharmacological agents (e.g., D-cycloserine and methylene blue) [5, 6, 7]. However, these agents have three inherent drawbacks: (a) they are contraindicated with certain medical conditions, (b) they can interact with other drugs increasing risk of toxicity, and (c) they produce side effects.

Transcranial photobiomodulation of the brain, a form of red to near-infrared photo stimulation, has recently been proposed as a metabolic and cognitive enhancing alternative to pharmacological agents (see [8] and [9] for a review). TILS is safe, non-invasive, and produces no side-effects [9]. Research with rodents suggests that photobiomodulation enhances the retention of fear extinction learning and prevents fear renewal [10]. There is considerable evidence that TILS functions by donating photon energy to copper ions within the photoaccepting terminal enzyme of the mitochondrial respiratory chain: cytochrome oxidase [11, 12]. By upregulating cytochrome oxidase activity, TILS improves oxygen consumption, cerebral blood flow, and neuronal metabolic capacity [10]. Photobiomodulation's effects are optimized when stimulation occurs in brain regions with heightened energy demands [10], such as the ventromedial prefrontal cortex (vmPFC) after extinction [10, 13]. Exciting work utilizing sophisticated broadband near-infrared spectroscopy (bb-NIRS) with humans measured increased cytochrome oxidase concentrations in vivo during and after a brief administration of TILS to the PFC, further validating a mitochondrial mechanism of action [14]. Although promising, this technology has yet to be tested in conjunction with extinction-based therapy in human clinical trials.

Preliminary research also suggests that TILS alone can lead to cognitive and emotional improvements. TILS has been shown to facilitate sustained attention [15], executive function [15,16], and mood [15] in healthy subjects and improved attention bias modification (ABM) for sub-clinically depressed individuals [17]. Regarding more severe clinical populations, one uncontrolled study reported a decrease in symptoms of depression and anxiety after photo stimulation to the right and

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Table 1
Exposure procedures.

Fear domain description	
Fear of enclosed spaces	Participants will complete 6, 5-min trials in which they lie supine within a tightly enclosed wooden chamber.
Fear of contamination	Participants will complete 10, 4-min trials in which they touch a mixture of dirt, dead insects, and hair with both hands.
Fear of public speaking	Participants will complete 10, 3-min public speeches with 3 people observing, while standing behind a podium.
Anxiety sensitivity	Participants will complete 6, 10-s inhalations of a mixture of 35% CO_2/65%O_2 to induce bodily sensations of anxiety.

left dorsolateral prefrontal cortices (dlPFC) [18]. Psychological benefits after photobiomodulation were attributed to an increase in regional cerebral blood flow (rCBF). TILS alone merits further investigation in a placebo-controlled randomized trial.

Taken together, the evidence suggests that TILS could be applied towards the treatment of anxiety in two ways: (1) as a metabolic enhancing adjunct to exposure, applied to a key brain region (i.e., vmPFC) involved in the consolidation of fear extinction learning. And (2) as a stand-alone intervention, targeting the dlPFC to increase rCBF and potentially decrease anxiety symptoms.

2. Methods

2.1. Study design and objectives

This study will investigate these two applications of TILS with a four-arm randomized placebo-controlled design. Based on preliminary evidence that PFC photobiomodulation enhances fear extinction in rodent models [10], we hypothesize that participants treated with TILS to the vmPFC after exposure therapy will show greater fear reduction than participants treated with exposure and sham laser. Given the established potency of exposure therapy, we also anticipate that both groups undergoing exposure will experience greater fear reduction than those receiving TILS alone or sham laser alone. Furthermore, because of the observed anxiolytic effects of photobiomodulation of the dlPFC [18], we expect that those receiving TILS to the dlPFC will show greater fear reduction relative to those receiving sham TILS. We also anticipate that the beneficial effects of TILS will be more pronounced for individuals with higher baseline fear responding.

Moreover, based on evidence suggesting that the extinction retention effects of cognitive enhancers depend on what is actually learned during training [19, 6], we expect TILS to enhance fear extinction retention at follow-up, for subjects who report low levels of fear at the end of exposure therapy, but will show poorer fear reduction at follow-up for participants continuing to display moderate to high levels of fear at the conclusion of exposure therapy.

A further exploratory aim of this experiment is to investigate the potential treatment moderating role of specific fear domains. To our knowledge, studies investigating cognitive enhancers as adjuncts to exposure have yet to test the generality of these augmentation strategies by including a diverse range of pathological fears into a single study population. This study will address this limitation by recruiting subjects displaying marked pathological anxiety across multiple fear domains (enclosed spaces, contamination, public speaking, or bodily sensations associated with anxious arousal, i.e., anxiety sensitivity). These pathological fears will function as subclinical analogues to more severe diagnosable anxiety-related disorders such as claustrophobia, obsessive-compulsive disorder, social anxiety disorder, and panic disorder, respectively.

2.2. Participants

Undergraduate students at the University of Texas and members of the Austin community ($N = 120$) who display marked fear of any of four domains (e.g., fear of enclosed spaces, fear of contamination, fear of public speaking, or anxiety sensitivity) will be recruited for participation in this study. Inclusion criteria include: (1) 18–65 years old and (2) peak fear severity greater than or equal to 50 out of 100 on two behavioral approach tests (BATs; see measures). Participants will be fully informed about all study procedures and will be required to provide written informed consent to participate in the trial.

Exclusion criteria include: (1) insufficient phobicity (peak fear < 50 on either BAT), (2) presence of significant suicidality, (3) medication instability, (4) currently receiving exposure treatment, (5) presence of a medical condition (i.e., pregnancy, seizure disorder, respiratory disorder, cardiovascular disease) that would contraindicate participation in one or more treatment or assessment activities (e.g., 35% CO_2 inhalation challenge); see Table 1, active neurological condition (such as epilepsy or stroke).

2.3. Screening, randomization, and procedural overview

After indicating elevated fear on the online prescreen measures, participants will be considered eligible and will be invited to the lab for a face-to-face pretreatment assessment. Elevated fear will be defined as 2 standard deviations above the sample mean on the validated symptom inventories (see measures) and a score of 1 or below on a behavioral prediction item. The behavioral prediction item asks subjects to rate the probability of behavioral approach to specific feared stimuli on a scale from 0 (definitely could not) to 3 (definitely could). Upon undergoing consent procedures, participants will complete established baseline self-report measures for their respective fear domain, and will also complete one behavioral approach test in the training context (BAT-T) and one outside of the training context (BAT-G).

Participants who report a peak fear equal to or above 50 (out of 100) on both BATs will be stratified on their primary fear domain, gender, and pretreatment severity of fear (peak fear ≥75 for "severe" fear, and peak fear of 50–74 as "moderate" fear) and will be block randomized into one of four treatment arms: (1) exposure + TILS, (2) exposure + sham TILS, (3) TILS, or (4) sham TILS. Participants randomized to Arms 1 and 2 will receive TILS or sham TILS following the completion of exposure therapy. Participants randomized to arms 3 and 4 will receive TILS or sham TILS after their baseline assessment but will not receive exposure therapy. Following the actual or sham laser administration, participants will complete posttreatment assessments. Two weeks after visit 1 (pretreatment/treatment/posttreatment), participants will return to the lab for a follow-up visit. During follow-up, all participants will complete the outcome measures and a contextual memory recognition task (see measures). Finally, participants will be debriefed.

2.4. Exposure training procedure

Participants in arms 1 and 2 will complete a one-session multiple trial exposure therapy protocol consistent with previous studies in our laboratory [6, 20, 21]. Prior to treatment, participants will watch a domain specific psycho-educational video providing them with a fear extinction rationale for exposure training. The exposure session will be similar across fear domains and will consist of the following common elements: (a) non-graduated exposure to a single feared stimulus also encountered during BAT-T, (b) repeated identical trial format, (c) treatment process data collected before and after every trial, (d) and