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Effects of bright light exposure on human fear conditioning, extinction, and associated prefrontal activation

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ABSTRACT

Bright light (BL) not only regulates human emotion and circadian physiology but can also directly modulate emotional memories. Impaired fear extinction and enhanced fear acquisition and consolidation are hallmarks of fear-circuitry disorders; thus, we tested whether BL facilitates fear extinction and inhibits fear acquisition. We randomly exposed 29 healthy humans to high- (9000 lx) or low-intensity light (< 500 lx) for 15 min, near the nadir of the phase response to light, in a single-blind manner. Simultaneously with the light exposure, subjects performed fear extinction training and second fear acquisition, where a visual conditioned stimulus (CS), previously paired with an electric shock unconditioned stimulus (US), was presented without the US, while another CS was newly paired with the US. Conditioned responses (CRs) and changes in prefrontal cortex (PFC) activity were determined during encoding and delayed recall sessions. BL-exposed subjects exhibited lower extinction-related PFC activity and marginally higher acquisition-related PFC activity during light exposure than subjects exposed to control light. Twenty-four hours later, BL reduced CRs to both the extinguished and non-extinguished CSs with marginally lower extinction-related PFC activation, suggesting that BL enhanced fear extinction, while suppressing fear acquisition. Further, BL sustained tolerance to fear re-conditioning. Our results demonstrate that a single and brief BL exposure, synchronized with fear extinction and acquisition, instantaneously influences prefrontal hemodynamic responses and alleviates fear expression after 24 h. Although the specificity of BL effects deems further investigation, our findings indicate the clinical relevance of adjunctive BL intervention in exposure-based cognitive-behavioral therapy for fear-circuitry disorders.

1. Introduction

Bright light (BL) therapy is an important option for treating not only seasonal affective disorder (SAD) but also non-seasonal affective disorders (non-SADs), including major depression, antepartum depression, and premenstrual depression [1]. Since light is a major environmental zeitgeber of the human circadian system [2], the optimal dose of BL exposure entrains endogenous circadian rhythmicity (e.g., melatonin onset), which may consequently alleviate SAD and circadian rhythm sleep disorders [3, 4]. In contrast, the mechanisms by which BL therapy alleviates non-SADs remain controversial [5, 6]: BL therapy could affect circadian-related etiology involved in non-SADs or could ameliorate non-SADs through other mechanisms.

Although BL may improve mood without circadian entrainment in humans [5, 7, 8], "non-chronobiological" BL therapy has not been implemented intentionally in psychiatric practice until recently [9]. LeGates and colleagues [5] showed that in mice, altered photoperiod causes depressive behaviors and impaired cognitive performance without altering circadian rhythmicity in the suprachiasmatic nucleus (SCN) [5]. Human neuroimaging studies have suggested that light exposure immediately modulates brain responses to emotional and non-emotional stimuli in several brain areas, including limbic (amygdala and hippocampus) and higher cortical regions (dorsolateral prefrontal cortex [dlPFC], cingulate cortex, ventromedial prefrontal cortex [vmPFC], parietal cortex, and precuneus) [6, 7, 10, 11]. While these areas are not primarily involved in visual perception through classical photoreceptors or in circadian entrainment via the SCN, it remains plausible that BL activates these photoreactive brain areas in a way that facilitates affective or cognitive brain functions [6]. Intrinsically photosensitive retinal ganglion cells (ipRGCs) play a crucial role in eliciting

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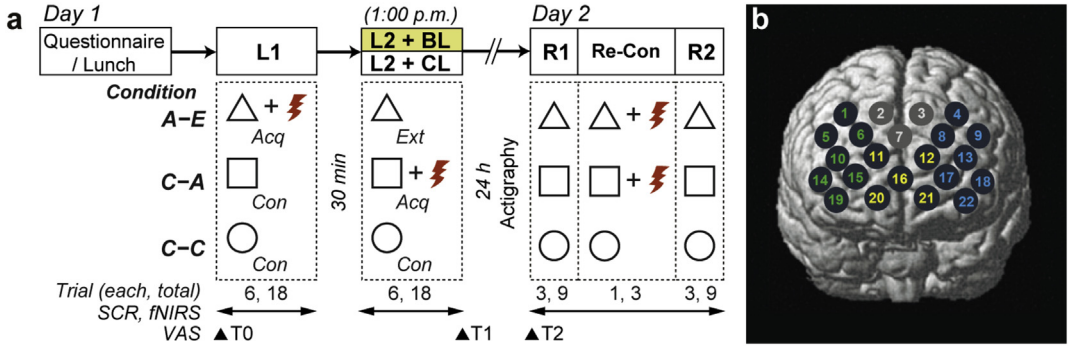

Fig. 1. Experimental timeline and fNIRS probe set. **(a)** Experimental schedule. The L1 ("first learning") phase began at 12:00 a.m., in which each participant randomly performed three conditions of six trials. In each trial of the A-E condition, the participant viewed a visual stimulus (conditioned stimulus, CS; triangle) and then experienced an electric shock (unconditioned stimulus, US). In each trial of the C-A condition, the participant viewed a different visual stimulus (square), but no shock followed. In each trial of the C-C condition, the participant viewed a circle, and no shock followed. The order of figure presentations was randomized across participants throughout the phases. After a 30-min break, the L2 ("second learning") phase commenced. For the HIG, this took place under bright light (BL) exposure; for the LIG, under control light (CL) exposure. The L2 phase, like the L1, comprised three conditions of six trials. In the A-E condition, the participant received "extinction" trials, in which the triangle was shown but no shock followed. In the C-A condition, the participant received "acquisition" trials in which the square was shown and a shock to the fingers followed. In the C-C condition, the participant viewed a circle, and no shock followed ("safety" trials). The participant went home and returned on the following day. At 1:00 p.m., the R1 ("first recall") phase commenced, which comprised three conditions of three trials. In each trial, the participant was shown one of the three visual stimuli, with no CS following. The purpose of the R1 phase was to test the level of recall of the responses learned on the previous day. The *Re*-Con ("re-conditioning") phase commenced immediately and comprised three conditions of one trial each. In the A-E and C-A trial, the participant was shown a triangle and a square, respectively, and was then subjected to finger-shock. In the C-C trial, the participant was shown a circle, but no shock followed. The R2 ("second recall") phase commenced immediately and followed the same procedure as R1. Acq, acquisition; Ext, extinction; Con, control. **(b)** fNIRS probe set. Nineteen channels were arranged over three regions of interest (ROIs); left dorsolateral PFC (blue), right dorsolateral PFC (green), and frontopolar PFC (yellow). Channel locations were superimposed on a T1-weighted MRI template. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

non-visual light effects in humans and animals [12]. The ipRGCs project to various hypothalamic nuclei responsible for sleep-wake regulation, including the SCN, ventrolateral preoptic nucleus, and lateral hypothalamic area, and have been suggested to project directly to the amygdala and indirectly to the hippocampus [13]. As limbic responses to light may further modulate cortical activities, it is not surprising that BL can immediately affect emotion and cognition (e.g., alertness and memory) without involving the SCN [14–16]. Since anxiety disorders deeply involve cognitive impairments associated with limbic pathology, the above observations raise the intriguing possibility that "non-chronobiological" BL therapy could improve the psychopathology of anxiety disorders.

Impaired fear extinction, as well as enhanced conditioned fear and fear generalization, may be relevant to the pathogenesis of fear-circuitry disorders, such as specific phobias, social anxiety, panic disorders, and posttraumatic stress disorder [17, 18]. Fear conditioning involves learning an association between a neutral conditioned stimulus (CS) and an aversive unconditioned stimulus (US). After repeated CS–US pairings, exposure to the CS alone elicits a conditioned response (CR), representing a consolidated CS–US association. If a powerful fear association forms, conditioned fear responses often generalize to related stimuli and events [19]. Such fear generalization enhances maladaptive avoidance behaviors, which are a major factor in diminishing the quality of life in patients with fear-circuitry disorders. Fear extinction is a form of inhibitory learning that attenuates a previously acquired fear response [20]. Experimental fear extinction occurs through repeated presentations of the CS without the US, thus weakening the CS–US contingency that remains after successful fear extinction. This approach shares a key therapeutic feature with exposure-based cognitive-behavioral therapy (CBT), which is currently regarded as one of the most promising interventions for fear-circuitry disorders [21, 22]. The PFC plays essential roles in human fear reduction, including fear extinction, through top-down regulation of hyperactivity in limbic structures, including the amygdala [23–25]. The dlPFC and frontopolar PFC (fpPFC) may inhibit amygdala activation through connections to the vmPFC during fear extinction [26–30]. We therefore tested whether BL could facilitate fear extinction by modulating cortical activity in the dlPFC and fpPFC, which may behave as a high-order controller. Additionally, from a clinical point of view, it seems possible that, in some situations, exposure-based CBT could unintentionally sensitize fear conditioning and its generalization, thereby counteracting the mechanisms presumed to underlie its therapeutic effects [21]. Thus, we also focused on the direct effects of BL on fear conditioning and generalization to explore the feasibility of BL for clinical application in exposure-based CBT in patients with fear-circuitry disorders.

2. Materials and methods

2.1. Participants

Twenty-nine right-handed healthy volunteers (10 women and 19 men) between the ages of 20 and 25 (mean age, 21.7 years), with no history of sleep, circadian rhythm, psychiatric, neurological, or retinal disorders, participated in this study between August 2011 and February 2012. The participants were asked to maintain their regular sleep-wake schedules from 2 weeks before the study onset until the end of the study and to refrain from taking over-the-counter medications, alcohol, or caffeine from 24 h before the study onset to its end. This clinical trial was registered in the Japanese UMIN-CTR registry as UMIN000006316. All procedures followed the guidelines outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the National Center of Neurology and Psychiatry. All participants provided written informed consent prior to participation and were paid 10,000 yen for their study participation upon adherence to the experimental instructions.

2.2. Study design

Participants were randomly assigned to two groups, a high-intensity (bright) light group (HIG; $n = 14$; 5 women; mean age, 21.4 years) or low-intensity (control) light group (LIG; $n = 15$; 5 women; mean age, 22.0 years). To obtain a single-blind design, participants were told that the aim of this study was to address BL effects on fear-associated learning but were not informed that two light intensity conditions