Three-week bright-light intervention has dose-related effects on threat-related corticolimbic reactivity and functional coupling

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Summary

Three-week bright-light intervention significantly affected threat-related amygdala-prefrontal reactivity and functional coupling in healthy males. These first findings of bright-light effects on brain function suggest its clinical efficacy may be, in part, through modulation of this corticolimbic circuit in a manner that is moderated by serotonin signaling.

Introduction

For ~30 years, bright-light therapy has been used to treat depressive disorders, most notably seasonal affective disorder, which is characterized by seasonally emergent symptoms. Despite this, little is known about the neurobiological mechanisms underlying its effects.

• Dysfunction within a corticolimbic circuit comprising the amygdala and medial prefrontal cortex (mPFC) is implicated in the pathophysiology of depression. The response of this circuit to threat-related stimuli is altered in depressed individuals and represents a candidate circuit underlying bright-light therapy’s clinical efficacy.

• Serotonin signaling 1) modulates this circuit, 2) is also implicated in the pathophysiology of depression and 3) shows evidence of seasonal variability that is moderated by 5-HTTLPR genotype status (Fig. 1).

• Here we evaluated the effects of a clinically relevant bright-light intervention protocol on threat-related corticolimbic reactivity and functional coupling. We explored the effects of serotonin signaling by evaluating if 5-HTTLPR genotype status moderated the effects of bright-light intervention on corticolimbic reactivity and circuit function.

Methods

Participants

• 32 healthy males participated in the study where exclusion criteria included: 1) psychiatric/neurological illness, 2) substance abuse, 3) excessive light exposure during study participation and preceding autumn, 4) retinal pathology or photosensitizing medication and 5) SPQA score > 10 [2]. Data were collected from November to February, 2011 and 2012.

• To evaluate genetic effects, 5-HTTLPR tri-allelic genotype status (L’ = L, S’ = L or S) was balanced (i.e., 16 L/L vs. 16 S’ carriers).

Bright-light intervention protocol

Randomization

• Participants were instructed to sit 50 centimeters from the lamp for 30 minutes between 07:00 – 09:00 each morning. Morning intervention is consistent with extending the photo-period and clinically effective [3].

• Light dose (i.e., illuminance) was estimated by evaluating each participant’s home environment (i.e., eye-to-lamp distance, person-to-lamp angle, lamp intensity, etc.), fMRI paradigm and analysis.

• Participants completed a gender-matching faces fMRI paradigm including various blocks of angry- or fearful-faces interleaved with neutral faces (e.g., NFNANF, etc.).

• fMRI data were pre-processed and analyzed in SPMS. Task-related effects of interest (angry & fear vs. neutral faces) were evaluated for each scan session, accounting for motion and physiological measures.

• Task-reactive clusters were identified across all participants at baseline within the amygdala and mPFC. These clusters were used to define seeds for functional analysis, including 1) a 5 mm radius sphere centered at -30, -4, -18 for the left amygdala, 2) -12, 40, 18 for the mPFC and 3) -36, 18, 18 for the right amygdala.

• Light-dose effect model

• Light dose and genotype-by-light dose effects on task response and FC were evaluated using a linear model that accounts for BOLD response at baseline [4]:

\[
\text{BOLD}_D + \beta_0 + \beta_1 * \text{BOLD}_D + \beta_2 * \text{Light Dose} + \epsilon
\]

\[
\text{BOLD}_{D, S} = \text{BOLD} \text{ response at rescan & baseline, respectively; Light Dose = Light dose received (kilolux). Effect of interest in bold. Genotype-by-light dose interaction model included two additional regressors: 1) Genotype status (L’ vs. S’ carrier) and 2) Genotype-by-light dose effect (effect of interest)}.

Results

Table 1. Demographic and light intervention information

<table>
<thead>
<tr>
<th>Group</th>
<th>Sex Ratio</th>
<th>Age (yrs)</th>
<th>BMI</th>
<th>5-HTTLPR status</th>
<th>Light dose (kilolux)</th>
<th>Intervention length (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.50</td>
<td>22.5</td>
<td>24.5</td>
<td>L’ (L’ vs. S’ carriers)</td>
<td>10.9</td>
<td>24 ± 2 (16)</td>
</tr>
<tr>
<td>Rescan</td>
<td>0.50</td>
<td>22.5</td>
<td>24.5</td>
<td>L’ (L’ vs. S’ carriers)</td>
<td>10.9</td>
<td>24 ± 2 (16)</td>
</tr>
</tbody>
</table>

Table 2. Bright-light intervention and 5-HTTLPR effects on functional coupling at rescan

<table>
<thead>
<tr>
<th>Effect of interest</th>
<th>L’ carriers (N = 16)</th>
<th>S’ carriers (N = 16)</th>
<th>Left amygdala seed (5 mm radius sphere at -30, 4, -18)</th>
<th>Beta value (95% CI)</th>
<th>p = 0.03</th>
<th>mPFC seed (left) (5 mm radius sphere at -12, 40, 18)</th>
<th>Beta value (95% CI)</th>
<th>p = 0.01</th>
</tr>
</thead>
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<tr>
<td>Positive effect</td>
<td></td>
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<td>Left amygdala: 0.22 [-0.36, -0.08] p = 0.003</td>
<td>mPFC: -0.21 [-0.36, -0.06] p = 0.009</td>
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Discussion

• This is the first study to evaluate the effects of a clinically relevant bright-light intervention on brain function. We show that threat-related corticolimbic reactivity and functional coupling are significantly decreased and increased, respectively.

• Our findings implicate the effects of light exposure on this corticolimbic circuit as a key neurobiological mechanism underlying its clinical efficacy. Our study provides a framework for future studies evaluating neurobiological mechanisms mediating the responsiveness to light exposure in clinical populations.

• 5-HTTLPR genotype status significantly moderated mPFC-prefrontal functional coupling. SPM (left) outlines prefrontal region showing interaction effect with mPFC seed (inset). Functional coupling increased in S’ carriers but was unaffected in L’ individuals (right). Voxel-threshold p < 0.01, uncorrected. Cluster size = 394 voxels (p < 0.05, corrected).

References


No potential conflict of interest.