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 it's clinical efficacy may be, in part, through modulation of this corticolimbic circuit in a manner that is moderated by serotonin signaling.

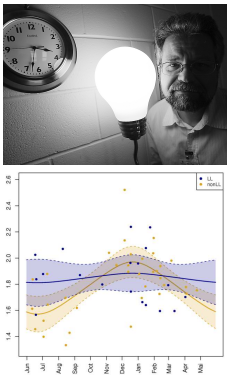
Introduction

• 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.



Figures 1 & 2. This study evaluated effects of light-intervention on brain function. Plot shows evidence that 5-HTTLPR genotype status moderates seasonal variability in serotonin transporter binding ([11C]DASB PET) [1].

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) SPAQ 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_A; S' = L_G or S) was balanced (i.e., 16 L'/L' vs. 16 S' carriers).

Bright-light intervention protocol

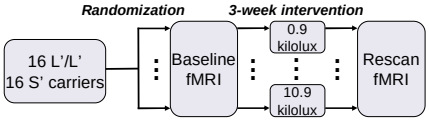


Figure 3 Study outline. Tri-allelic 5-HTTLPR status was considered for randomizing light dose. Following baseline fMRI, participants were randomly assigned to receive a three-week light intervention dose then an fMRI rescan.

• 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 varying blocks of angry- or fearful-faces interleaved with neutral faces (e.g., NFNANF, etc.).

• fMRI data were pre-processed and analyzed in SPM5. 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 amygdala and mPFC using anatomically defined ROIs (Pickatlas), correcting for multiple comparisons with AFNI 3dClustSim. Mean reactivity from clusters were extracted for baseline and rescan and effects of light dose were evaluated.

• Functional coupling (FC) reflects the correlation in voxel-level BOLD time series between brain regions within a scan session, which we interpret to reflect circuit function. We evaluated FC by separately considering three seeds (left amygdala, right amygdala and mPFC). Seeds were defined by a 5 mm radius sphere centered on maximally responsive voxel at baseline.

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]:

$$BOLD_R = \beta_0 + \beta_1 * BOLD_B + \mathbf{\beta_2 * Light\ Dose} + \varepsilon$$

$BOLD_R$ & $BOLD_B$ = BOLD 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'/L' vs. S' carriers) and 2) genotype-by-light dose (effect of interest).

Results

Table 1. Demographic and light intervention information

Datasets	*5-HTTLPR (L'L' vs. S' carrier)*	*Age (years)*	*Intervention length (days)*	*Bright light dose (kilolux)*
30*	14/16	24.3 ± 3.7	21.2 ± 2.0 (19-28)	3.4 ± 2.9 (0.1-10.9)

*Two datasets (each L'L') were excluded due to image artifact.

Negative effect on threat-related corticolimbic reactivity

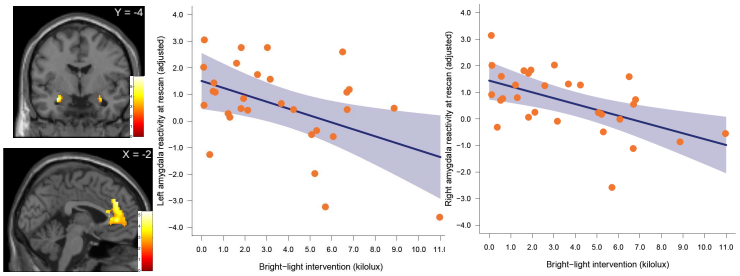


Figure 4. Corticolimbic reactivity was significantly reduced in a light-dose dependent manner. SPMs (*left*) outline task-related corticolimbic reactivity at baseline. Plots (*middle*, *right*) show significant association between left- and right-amygdala at rescan and light dose received (left amygdala: β [95% CI] = -0.26 [-0.46, -0.06] p = 0.01; right amygdala: -0.22 [-0.36, -0.08] p = 0.003; mPFC (plot not shown): -0.21 [-0.36, -0.06] p = 0.009).

Positive effect on corticolimbic functional coupling

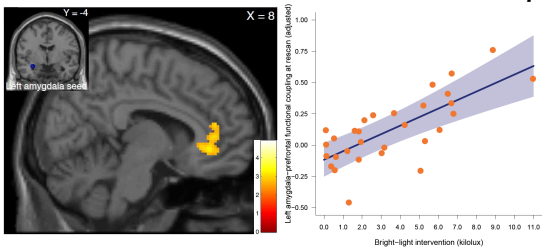


Figure 5. Corticolimbic functional coupling significantly increased in a light-dose dependent manner. SPM (*left*) outlines prefrontal region showing functional coupling with amygdala seed (*inset*) that is significantly increased proportional to light dose (*right*). Voxel-threshold p < 0.01, uncorrected. Cluster size = 938 voxels (p < 0.05, corrected).

5-HTTLPR moderates effect on prefrontal functional coupling

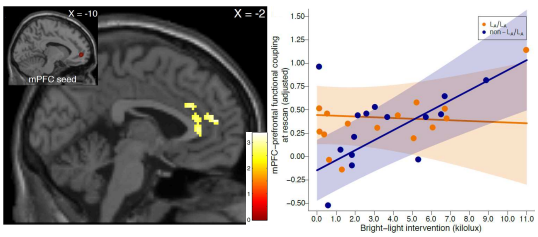


Figure 6. 5-HTTLPR genotype status significantly moderated mPFC-prefrontal functional coupling. SPM (*left*) outlines prefrontal region showing interaction effect with mPFC seed (*inset*). Functional coupling increased in S' carriers but was unaffected in L'L' individuals (*right*). Voxel-threshold p < 0.01. Cluster size = 394 voxels (p < 0.05, corrected).

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

	X, Y, Z	Z-score	Cluster size*
Bright-light intervention effects on functional coupling at rescan			
Left amygdala seed (5 mm radius sphere at -30, -4, -18)			
Positive association			
Medial prefrontal cortex	-4, 28, 0	4.11	938
mPFC seed (5 mm radius sphere at -10, 52, 0)			
Positive association			
Medial prefrontal cortex	-4, 28, -2	4.12	1594
5-HTTLPR-by-bright-light dose interaction effects on functional coupling at rescan			
mPFC seed (5 mm radius sphere at -10, 52, 0)			
Positive association			
Medial prefrontal cortex	-12, 40, 18	3.02	394

*Statistical threshold for mPFC search volume: voxel-threshold: p < 0.01, uncorrected; cluster-threshold: k > 249 voxels.

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 status significantly moderated light intervention effects on only intra-prefrontal functional coupling such that coupling was positively affected by intervention in S' carriers but not L'L' individuals. This finding would benefit from replication in an independent cohort but is notably consistent with previously hypothesized serotonergic effects on clinical efficacy of bright-light therapy.

• Developing an understanding of the neurobiological mechanisms sensitive to light intervention benefits the ability to apply this treatment strategy in relevant contexts and target clinical cohorts likely to be responsive. Our findings provide a benchmark for evaluating its effects in clinical cohorts.

References

[**1**] Kalbitzer *et al*., (2010) *Biol Psych* 67:1033-1039; [**2**] Rosenthal *et al*., (1987) *Psychobio of Bulimia* 205-228 (*book chapter*); [**3**] Terman *et al*., (2001) *Arch Gen Psych* 58:69-75; [**4**] Vickers & Altman, (2001) *BMJ* 323:1123-1124.