Blue light exposure increases functional connectivity between dorsolateral prefrontal cortex and multiple cortical regions

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Objective Blue light is a powerful environmental stimulus that can produce significant phase shifts in the circadian rhythm of melatonin and sleep propensity as well as acute effects on alertness of neurobehavioral performance. Here, we undertook an expansion and reanalysis of our previously published findings to examine the effect of acute blue light exposure on the strength of resting-state functional connectivity (rsFC) between a previously identified region of the left dorsolateral prefrontal cortex (DLPFC) and 106 cortical and subcortical regions.

Methods Twenty-nine healthy adults (16 men and 13 women; age 18–32 years) completed a psychomotor vigilance test (PVT) before and after a single 30-min exposure to either blue ($\lambda = 469$ nm; $n = 17$) or amber wavelength ($\lambda = 578$ nm; $n = 12$) light, immediately followed by an rsFC scan.

Results Compared with amber light, blue light exposure produced significantly greater functional connectivity between the left DLPFC seed region and 30 cortical and subcortical regions ($P < 0.05$; false discovery rate-corrected). Although neurobehavioral performance did not differ between light conditions, only those exposed to blue light showed a significant association between rsFC and sustained PVT performance. Better sustained PVT performance was associated with greater connectivity between the left DLPFC and regions associated with visuospatial awareness/motion detection (right temporo-occipital middle temporal gyrus) and memory (left hippocampus), as well as reduced connectivity in a circuit associated with cognitive rumination and distraction (left parahippocampal gyrus).

Conclusion Findings suggest that blue-wavelength light may facilitate acute alertness and improved cognitive performance through enhanced rsFC between the left DLPFC and cortical regions associated with visuospatial awareness. NeuroReport 33: 236–241 Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.

Keywords: blue light, functional connectivity, vigilance, prefrontal cortex

Introduction Light exposure has powerful effects on brain neurobiology and behavior. Many of these effects occur via specialized receptors known as intrinsically photosensitive retinal ganglion cells (ipRGCs) within the nonimage-forming visual system [1]. These ipRGCs are specifically responsive to light within the blue wavelengths (i.e. ~470 nm) and project to regions of the brain involved in regulating circadian timing (i.e. suprachiasmatic nucleus), visual processing (i.e. lateral geniculate nucleus), appetite (i.e. ventromedial hypothalamus), and limbic structures (i.e. amygdala and habenula) involved in emotion and salience detection [2]. Blue light is well known for its synchronizing and phase-shifting effects on the daily timing of circadian rhythms [3]. The timing of light is crucial to circadian rhythms, as exposure to blue light in the morning produces a subsequent phase advance in daily melatonin secretion, leading to an earlier onset of sleep and wake, whereas evening exposure delays this onset.

Although less extensively studied, blue light also has acute effects on brain function, mood, alertness, and cognitive performance. Exposure to bright light, especially in the blue wavelengths, leads to immediate improvements in mood [4,5], simple alertness [6], working memory [7], and retention of long-term verbal memory [8]. We recently demonstrated that a single 30-min exposure to blue-wavelength light (versus amber placebo light) was associated with a significant increase in subsequent functional connectivity between the right amygdala and a region of the left dorsolateral prefrontal cortex (DLPFC), within the horizontal section of the intermediate frontal sulcus (imfs-h) [9], a finding that was associated with acute declines in negative mood state [5]. Importantly, the connectivity between these two regions was bidirectional.
suggesting that information flow was significant in both directions. In that prior study, we focused on the amygdala as the seed region and found the DLPFC to be the sole target region for which amygdala connectivity was increased by blue light. Because the left DLPFC is a crucial multimodal region of the cortex that is involved in a variety of cognitive processes, we expanded our prior analysis to identify blue light–modulated cortical connectivity patterns originating from the DLPFC as the seed region. We hypothesized that blue light would increase DLPFC connectivity to regions of the cortex associated with alertness and vigilance. Further, we expected the strength of such connectivity to be associated with acute changes in neurobehavioral performance on a psychomotor vigilance test (PVT).

Methods

Participants

The participants were the same 29 right-handed, normal sleeping, healthy adults reported in our previous paper [5] and included 16 men and 13 women between the ages of 18 and 32 years (M = 21.5, SD = 2.8). While initial findings from this sample have been reported elsewhere [5,8,10], the present article presents new data that expand and build on the prior outcomes and which have not been published previously. The protocol for this project was approved by the Institutional Review Board at the University of Arizona and the U.S. Army Human Research Protections Office. All participants provided written informed consent before enrollment.

Materials and procedure

The light exposure devices and study procedures are described in detail in our prior papers [7,8,10] but are outlined briefly here. Following a normal night of sleep, participants arrived at the lab at 07:45 h to complete the consent process, several questionnaires, and cognitive assessments. Between 09:45 and 10:45, participants completed a second 10-min PVT. At 10:45, immediately upon completion of the light exposure period, participants were escorted to the dimly lit MRI scanner located in the room next door to undergo a series of neuroimaging scans, including a resting-state functional connectivity scan (rsFC). The scan was initiated at approximately 11:00 and continued for the next hour. Participants were then released from the session.

Neuroimaging methods

Participants reclined supine within a Skyra 3T MRI scanner (Siemens, Erlangen, Germany) to complete a series of functional MRI scans using a 32-channel head coil. Movement was restricted by comfortable padding placed around the head. T1-weighted structural MRI was first acquired with a 3D magnetization prepared rapid gradient echo sequence (time to repetition - TR/echo time - TE/flip angle = 2.1 s/2.33 ms/12°) across 176 sagittal slices (256 × 256) and a slice thickness of 1 mm (voxel size = 1 × 1 × 1 mm³). Resting-state functional (T2*) scans were acquired over 32 transverse slices (2.5 mm thickness; matrix: 88 × 84) using an interleaved sequence [TR/TE/flip angle = 2 s/25 ms/90°; 2.5 × 2.5 voxel size (i.e. with a 40% slice gap, 180 volumes; field of view = 220 mm)] over a 6-min acquisition time. During the rsFC scan, participants were instructed to relax and let their mind wander while keeping both eyes open and
Resting-state connectivity preprocessing

The CONN functional connectivity toolbox (version 17.f; www.nitric.org/projects/conn, RRID:SCR_009550) was used to analyze the rsFC data (for details, see [14]). Using the default Montreal Neurologic Institute (MNI) preprocessing pipeline, the series of 180 functional images were realigned, unwarped, slice-time–corrected, and coregistered with the segmented T1 images in accordance with standard algorithms, including noise removal with the anatomical component-based noise correction procedure method [15,16] and bandpass filtering (0.01–0.1 Hz). Outlier detection and removal of variance due to nuisance covariates (i.e. >3 SD mean global signal intensity; scan-to-scan motion exceeding 0.5 mm) were accomplished via standard regression during the first-level analysis. Images were normalized to the standard stereotaxic space of the MNI and spatially smoothed (8 mm full width at half maximum) and resliced to $2 \times 2 \times 2$ mm.

We selected 106 cortical and subcortical regions of interest (ROIs) (i.e. excluding cerebellar regions) as target ROIs from the default Harvard-Oxford Atlas (https://neuro.debian.net/pkgs/fsl-harvard-oxford-atlases.html) incorporated into the CONN Toolbox. The mean blood oxygen level dependent signal time series within each of these ROIs was calculated for use in subsequent connectivity analysis.

Functional connectivity analysis

Using a standard ROI-to-ROI approach, functional connectivity analyses were performed using the CONN toolbox [14]. This approach begins by setting a ‘seed’ region and then determining the intrinsic resting correlations between the seed region and the set of target ROIs over the course of the scan. The seed ROI was defined by the DLPFC cluster at the MNI stereotaxic coordinates $(x = -24, y = 46, z = 18, k = 90)$ identified as a correlate of the amygdala in our prior task-related study on the same data [5]. This cluster corresponds to Brodmann Area 46 and is located on the horizontal section of the left intermediate frontal sulcus (imfs-h) according to the Petrides atlas of the cerebral cortex [9]. In contrast to our prior study where the DLPFC cluster was a voxel-based outcome region, in the present study, the previously identified DLPFC cluster served as the seed region to examine connectivity with all other ROIs throughout the cerebrum. Bivariate correlation maps (Fisher-transformed) were then computed between this seed ROI and all other 106 target ROIs. Within the CONN program, we coded light condition as a between-group variable. Differences in connectivity strength between blue and amber groups were calculated, controlling for the effects of age and sex. False positives were controlled at the analysis level via false discovery rate (FDR) ($P < 0.05$; FDR correction; two-tailed test) [14]. Significant connections between the DLPFC seed and the target ROIs were then extracted as $Z$-transformed correlation coefficients and entered into a stepwise linear regression analysis in SPSS (version 28; IBM Corp, Armonk, New York, USA) to predict changes in the square root–transformed PVT lapses (see above) from pre- to postlight exposures (after controlling for age and sex).

Results

Functional connectivity

After FDR correction for multiple comparisons, the functional connectivity analysis yielded 30 significant connections between the seed region of the left DLPFC and the target ROIs that were modulated by light exposure (all $P$-values $< 0.05$, FDR-corrected). The strength of each of these connections was significantly greater within the blue versus the amber group (i.e. there were no connections that were stronger in the amber group compared with blue). These connections are depicted in Fig. 1, whereas Table 1 lists each significant connection and its associated statistics. Table 1 also lists the MNI coordinates of the centroid (i.e. geometric center) of each significantly correlated atlas-based ROI. As reported in our prior publication [5], blue light was associated with significantly greater connectivity between the DLPFC and right amygdala. However, as evident in Fig. 1, blue light also modulated connectivity between the left DLPFC and a broad range of 30 other cerebral regions, including occipital, temporal, and medial parietal areas.

Behavioral correlates

The blue and amber groups both showed a significant increase in transformed lapses from the first ($M = 2.79$, SD = 2.18) to the second ($M = 3.64$, SD = 2.06) administration of the PVT, $F(1,26) = 16.22$, $P < 0.001$, suggesting a general reduction of vigilance performance over the half-an-hour session. There was no significant main effect of light group or interaction between light group and testing session. Nonetheless, it was still of interest to determine whether the strength of brain connectivity was differentially associated with performance changes in the two groups. Accordingly, the 30 individual values reflecting the strength of connectivity between the DLPFC and each significant ROI were entered stepwise as predictors into a linear regression analysis with changes in PVT lapses over the half-an-hour of light exposure as the outcome variable. Analyses were run for the blue and amber groups separately, with age and sex forced into the equation at the first step. As shown in Table 2, reductions in lapses (i.e. improvement of psychomotor vigilance performance) within the blue light group were predicted by a linear combination of three DLPFC connections, including reduced connectivity with the left parahippocampal gyrus (L PHG) and increased connectivity with the right
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occpital-temporal region of the middle temporal gyrus and left hippocampus (L Hippo) ($R^2 = 0.910$, adjusted $R^2 = 0.865$, $P = 0.00006$). In contrast, connectivity strength was not significantly associated with PVT lapses for the amber group.

Discussion
Consistent with our hypothesis, we found that a single 30-min exposure to blue light was associated with subsequently greater functional connectivity between a previously identified region of the left DLPFC and 30 ROIs within the temporal, parietal, and occipital lobes compared with an equal period of amber light exposure. In contrast, amber light was not associated with any increased connectivity among these ROIs relative to blue light. Moreover, we found that functional connectivity between the left DLPFC and three distinct brain regions, including the L PHG, right middle temporal gyrus, and L Hippo, was associated with sustained or improved neurobehavioral performance on the PVT within the blue light group but not the amber light group. Together, these preliminary findings suggest that short-duration exposure to blue-wavelength light can acutely influence cortical network activation, which is associated with measurable neurobehavioral changes.

The present findings build on early task-related MRI work by Vandewalle and colleagues [17] who showed that exposure to blue light during a working memory task increased immediate activation of the L Hippo and left middle frontal gyrus, and recent work out of our lab showing that blue light increased subsequent activation of the left DLPFC and left middle temporal gyrus, among other regions, during a working memory task [7]. While some studies have suggested that the observed brain changes produced by blue light are associated with improvements in cognitive performance [7], others have not found such improvements [18] or suggested the possibility that acute blue light exposure reduces the amount of brain activation necessary to accomplish an equivalent level of performance (i.e. neural efficiency) [10]. Our findings build on this prior task-related fMRI work by suggesting that blue light also enhances the resting functional connectivity between the left DLPFC and numerous brain regions throughout the cortex and limbic system. These findings also clarify prior work that showed that regular daily exposures to the same blue light stimulation used here also produce significant long-term changes in functional connectivity [19], brain structure [20], cognitive performance, and sleep-wake patterns [21]. Overall, these findings suggest that acute light exposure, particularly in the blue wavelengths, can serve as a modulator of brain functioning and connectivity [22].

Despite the significantly greater functional connectivity seen for acute blue light exposure relative to amber, we did not observe any significant difference in PVT performance change between groups overall. We did find, however, that the association between functional connectivity and
behavioral changes in PVT performance differed between light conditions—connectivity was significantly associated with vigilance changes for the blue group but not the amber group. Notably, improved vigilance performance in the blue group was associated with greater connectivity changes for the DLPFC and the L Hippo, which comprise a network involved in ruminative thinking [25]. Together, these findings tentatively suggest that blue light exposure acutely facilitates performance via enhanced connectivity among brain systems involved with spatial attention, motion perception, and working memory, as well as reduced connectivity with systems involved in potentially distracting cognition. These findings should be considered preliminary because the seed region was identified in an earlier analysis of these data. However, the findings align well with prior work suggesting that blue light may enhance brain function and connectivity. Future work will need to more extensively elucidate the mechanisms underlying these apparent effects.

**Conclusion**

Thirty minutes of blue light exposure enhanced rsFC between the left prefrontal cortex and numerous cerebral regions compared with an equivalent period of amber light, a finding that was associated with better sustained vigilance performance within the blue light group. Blue light exposure appears to increase acute brain connectivity within networks relevant to attention, working memory, and visual spatial awareness.
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Conflicts of interest
There are no conflicts of interest.

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