NeuroImage 139 (2016) 37–43

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Bright-light intervention induces a dose-dependent increase in striatal response to risk in healthy volunteers

Julian Macoveanu [a,b,c,*], Patrick M. Fisher [b,d], Martin K. Madsen [b,d,e], Brenda Mc Mahon [b,c,d,e], Gitte M. Knudsen [b,d,e], Hartwig R. Siebner [a,e,f]

[a] Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Denmark
[b] Center for Integrated Molecular Brain Imaging, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[c] Psychiatric Center Copenhagen, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[d] Neurobiology Research Unit, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark
[e] Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark
[f] Department of Neurology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 3 February 2016
Revised 13 June 2016
Accepted 14 June 2016
Available online 16 June 2016

Keywords:
Bright-light intervention
Ventral striatum
Seasonal affective disorder

ABSTRACT

Bright-light interventions have successfully been used to reduce depression symptoms in patients with seasonal affective disorder, a depressive disorder most frequently occurring during seasons with reduced daylight availability. Yet, little is known about how light exposure impacts human brain function, for instance on risk taking, a process affected in depressive disorders.

Here we examined the modulatory effects of bright-light exposure on brain activity during a risk-taking task. Thirty-two healthy male volunteers living in the greater Copenhagen area received 3 weeks of bright-light intervention during the winter season. Adopting a double-blinded dose-response design, bright-light was applied for 30 minutes continuously every morning. The individual dose varied between 100 and 11.000 lx. Whole-brain functional MRI was performed before and after bright-light intervention to probe how the intervention modifies risk-taking related neural activity during a two-choice gambling task. We also assessed whether inter-individual differences in the serotonin transporter-linked polymorphic region (5-HTTLPR) genotype influenced the effects of bright-light intervention on risk processing.

Bright-light intervention led to a dose-dependent increase in risk-taking in the L_A/L_A group relative to the non-L_A/L_A group. Further, bright-light intervention enhanced risk-related activity in ventral striatum and head of caudate nucleus in proportion with the individual bright-light dose. The augmentation effect of light exposure on striatal risk processing was not influenced by the 5-HTTLPR-genotype.

This study provides novel evidence that in healthy non-depressive individuals bright-light intervention increases striatal processing to risk in a dose-dependent fashion. The findings provide converging evidence that risk processing is sensitive to bright-light exposure during winter.

Introduction

Seasonal affective disorder (SAD) is a subtype of depressive disorders where depression begins and ends at about the same times every year (American Psychiatric Association, 2013). In the majority of affected patients, SAD starts in the fall and continues into the winter months. SAD manifests as anhedonia, depressed mood, irritability, changes in appetite and sleeping patterns, a symptomatology shared with other affective disorders (Rosenthal et al., 1984). In patients with fall-onset SAD, bright-light intervention (BLI) has successfully been used to alleviate depressive symptoms in SAD and other affective disorders (Golden et al., 2005; Pail et al., 2011; Terman and Terman, 1999). Additionally, BLI during winter has been shown to decrease measures of distress also in healthy individuals without season-dependent symptoms (Partonen and Lönnqvist, 2000). In healthy volunteers, acute and repeated bright light exposure during winter may modify neural processing of emotional stimuli (Fisher et al., 2014; Vandewalle et al., 2010). We recently demonstrated dose-dependent effects of BLI on threat-related amygdala and prefrontal reactivity (Fisher et al., 2014).

Experimental research in psychology and economics has linked depressive symptoms with decreased risk-taking behavior (Eisenberg

* Corresponding author at: Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Kettegaard Alle 30, DK-2650 Hvidovre, Denmark.
E-mail address: julian.macoveanu@gmail.com (J. Macoveanu).

http://dx.doi.org/10.1016/j.neuroimage.2016.06.024
1053-8119/

et al., 1996; Kramer and Weber, 2012; Smoski et al., 2008). Patients suffering from SAD showed a stronger preference for safe financial choices relative to individuals without SAD (Kramer and Weber, 2012). The decreased risk-taking behavior was only expressed during winter and was associated with depression symptoms. Kamstra et al. (2003) showed that the amount of daylight through the fall and winter correlate with stock market investments and related returns. Higher latitude markets in both hemispheres showed a more pronounced season-dependent effect and stock returns change. The neural mechanisms underlying effects of changes in daylight availability on risk taking remain, however, to be clarified.

Seasonal variations in light exposure have been linked to changes in serotonergic signaling, neurotransmitter system commonly associated with affective disorders including SAD (Kalbitzer et al., 2010; Lambert et al., 2002; Praschak-Rieder and Willeit, 2012), and recently linked to risk-related decision making and reward processing (Macoveanu et al., 2013a, 2013b). A polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR) has been associated with seasonality in both major depression disorder patients and general population (Praschak-Rieder et al., 2008; Ruhé et al., 2009). The serotonin transporter binding in striatum, a central brain structure in reward- and risk-related behavior, was found to show a negative correlation with the amount of daylight with a peak occurring in midwinter as an endophenotype of the low-expression genotype (S) (Kalbitzer et al., 2010). Since the S-allele predisposes to higher impulsivity (e.g. Curran et al., 2005; Retz et al., 2008), it is possible that risk-taking behavior may be modulated by the individual 5-HTTLPR genotype.

The neurobiological mechanisms modulated by bright-light exposure are largely unknown. Given the considerable clinical overlap between SAD and other affective disorders, these psychiatric conditions may share a common mechanistic framework. The clinical effects of BLI may therefore be mediated through modulation of similar neural processes in these affective disorders. The psychological processes dysfunctional in depressed patients have been associated with altered function of specific brain systems such as prefrontal cortex, striatum, amygdala and hippocampus (Belzung et al., 2014). Specifically, recent data from a meta-analysis in major depression disorder indicated a reduced striatal response when anticipating or receiving monetary reward (Zhang et al., 2013). Treatment with selective serotonin reuptake inhibitors (SSRIs) may have a mood-normalizing effect in depressed patients by increasing the response to positive stimuli or decreasing the response to negative stimuli in the emotional network (Ma, 2014). In line with these findings, patients with major depression show reduced activation of the ventral striatum during gain and loss anticipation compared with controls before, but not after SSRI treatment (Stoy et al., 2012).

The insights on the neurobiological mechanisms responsive to BLI in non-clinical cohorts are critical in understanding how light affects normal neural processes without being confounded by clinical symptoms and may serve as benchmark for evaluating intervention effects in future studies investigating depressive disorders with or without seasonal patterns. In this fMRI study, we examined how BLI during winter impacts on risk-related neural processes in healthy individuals that show no significant seasonal influence on mood or depression symptoms. We were particularly interested in testing whether BLI would change the sensitivity of the ventral striatum to risk because the ventral striatum is consistently involved in risk-related neural processes (Macoveanu et al., 2013a, 2013b) and has been shown to be sensitive to antidepressant treatment both in healthy (Ma, 2014) and depressed volunteers (Stoy et al., 2012). We predicted that BLI would increase the response of ventral striatum to risky choices in a dose-specific manner. Based on previously reported effects on the seasonal variation of serotonin transporter levels (e.g. Kalbitzer et al., 2010), we further explored interactive effects of bright-light dose with the 5-HTTLPR status.

Methods

Participants

Seventy healthy male volunteers from the Copenhagen region were recruited via online advertisements and received modest financial compensation. The inclusion criteria were: 1) 18 to 45 years of age, 2) 18 to 30 body mass index (a body mass index of 30 represents the inferior limit of obesity), 3) no history of alcohol/drug abuse, 4) no history of psychiatric/neurological illness, 5) no excessive light exposure during study participation and preceding autumn (e.g., sun tanning or traveling), 6) no retinal pathology, 7) not taking photosensitizing medication, 8) Seasonality Pattern Assessment Questionnaire score <11 (Rosenthal et al., 1987), and 9) no overt depressive symptoms. The inclusion criteria did not take into account the individual chronotype and sleep quality. Status for the tri-allelic 5-HTTLPR polymorphism (i.e., L_A, L_G, S alleles) within the *SLC6A4* gene was determined from saliva samples as previously described (Madsen et al., 2016). Out of the 70 genotyped participants, two age-matched groups of 15 L_A/L_A and 17 non-L_A/L_A participants (i.e., S/S, $S/L_{A\ or\ G}$ or L_A/L_G alleles) were selected to be included in this functional MRI study. Prior to inclusion, adherence to the screening criteria was assessed in a clinical interview with the investigators, and participants received detailed information on the study. The 32 included participants underwent neurological and medical examination including blood test screening performed by a trained physician. The study was conducted between November 2010 and February 2011 and between November 2011 and February 2012. Written and oral informed consent was acquired from all participants. The research protocol was approved by the Ethics Committee of Copenhagen and Frederiksberg, Denmark (H-1-2010-091; amendments: 28633, 30043).

Study design and bright-light intervention

The BLI protocol was described in detail in Fisher et al. (2014). The study did not include a placebo arm due to difficulties in designing a "placebo light intervention" that is matched in terms of subjectively perceived light exposure. Instead, the protocol used a 30-minute BLI in all subjects with a variable light-dose, in order to identify how the magnitude of light dose correlates with the task-related brain response. The individual light-exposure dose ranged randomly between 100 and 11.000 lx, with L_A/L_A and non-L_A/L_A participants evenly represented across the light-dose range. The lamps (Smifa Healthcare, Solroed Strand, Denmark) emitted full-spectrum white light at variable dose. Participants were instructed to sit at 50 cm in front of the lamps for 30 min between 7:00 am and 9:00 am, independent of the individual chronotype, every morning for 3 weeks. The received light dose was estimated by measuring the illuminance of each lamp with a luxmeter (Elma 1335; Elma Instruments, Farum, Denmark) and the lamp-to-eye distance within the participant's home environment, where light intervention was administered (measured distance from lamp: mean ± SD = 71.4 cm ± 30.8; median, range = 58.5 cm, 36–170). The intervention criteria were based on recent SAD treatment guidelines (Pail et al., 2011). Bright-light intervention around sunrise is consistent with an extension of the photoperiod and previous studies reported that morning administration is particularly effective in relieving SAD symptoms in clinical cohorts (Lewy et al., 1998; Terman et al., 2001). Daily mobile phone message reminders aided compliance to the bright-light protocol. Participants were asked to make daily records of the intervention in a logbook, and they were further enquired about the amount of time spent outside during daytime (daylight exposure).

Participants and researchers were blinded to the bright-light dose received throughout the study. Immediately before and after the BLI, the volunteers took part in a whole-brain fMRI session during which they performed a dual-choice card gambling task and an emotional processing task reported in Fisher et al. (2014). The time of the fMRI investigations