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The post illumination pupil response is reduced in seasonal affective disorder

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ABSTRACT

Individuals with seasonal affective disorder (SAD) may have a decreased retinal sensitivity in the non-image forming light-input pathway. We examined the post illumination pupil response (PIPR) among individuals with SAD and healthy controls to identify possible differences in the melanopsin signaling pathway. We also investigated whether melanopsin gene (*OPN4*) variations would predict variability in the PIPR. Fifteen SAD and 15 control participants (80% women, mean age 36.7 years, S.D.=14.5) were assessed in the fall/winter. Participants were diagnosed based on DSM-IV-TR criteria. Infrared pupillometry was used to measure pupil diameter prior to, during, and after red and blue stimuli. In response to blue light, the SAD group had a reduced PIPR and a lower PIPR percent change relative to controls. The PIPR after the blue stimulus also varied on the basis of *OPN4* I394T genotype, but not *OPN4* P10L genotype. These findings may indicate that individuals with SAD have a less sensitive light input pathway as measured by the PIPR, leading to differences in neurobiological and behavioral responses such as alertness, circadian photoentrainment, and melatonin release. In addition, this sensitivity may vary based on sequence variations in *OPN4*, although a larger sample and replication is needed.

1. Introduction

Seasonal affective disorder (SAD) accounts for approximately 10–20% of outpatients with recurrent depression (Magnusson and Partonen, 2005). Treatment of this large segment of depressed individuals may be improved with a better understanding of the etiology of SAD. Although the pathophysiologic mechanisms underlying SAD remain unknown, one hypothesis postulates a seasonal variation in retinal subsensitivity (Reme et al., 1990; Hebert et al., 2002). Retinal subsensitivity to light is suggested by many of the phenomena observed in SAD including: the regular winter timing of depressive episodes, a lengthened melatonin release profile during longer winter nights (Wehr et al., 2001), the utility of light therapy as an antidepressant treatment (Rohan et al., 2009), and retinal electrophysiology research (reviewed below). Individual differences in retinal signaling may explain retinal subsensitivity (Wehr et al., 2001). Specifically, retinal subsensitivity in SAD may result from the absence of a seasonal change in retinal sensitivity found in healthy controls, such that the retina fails to become more sensitive to the low light levels of winter. In contrast to previous studies, the pupillometry method in the present study is designed to isolate the response of melanopsin-containing, intrinsically photosensitive retinal ganglion cells (ipRGC), which are the primary class of photoreceptors entraining the circadian clock. A polymorphism in the melanopsin gene has been associated with increased risk of SAD, suggesting that the melanopsin gene may be etiologically significant in SAD (Roecklein et al., 2009).

In addition, melanopsin-driven processes have significant overlap with SAD symptomatology. Melanopsin cells in the retina project to multiple areas in mammals (Do and Yau, 2010), and if these projections are conserved in humans, they would include areas involved in circadian regulation (suprachiasmatic nuclei, intergeniculate leaflet), energy homeostasis (lateral hypothalamus), and sleep regulation (ventral supraventricular zone, preoptic nucleus; Hattar et al., 2002; Hannibal and Fahrenkrug, 2004; Hattar et al., 2006). Circadian, energy, and sleep processes are either involved in the symptoms of SAD (e.g., fatigue), or hypothesized to be etiologically significant in SAD.

Given the overlap between SAD symptomatology and melanopsin-driven processes, we hypothesized that retinal subsensitivity in SAD may be mediated at least in part by melanopsin containing ipRGCs. Theoretically the ipRGC sensitivity in SAD could be lower than that of healthy individuals, such that the

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environmental irradiance levels in winter may fall below this threshold, leading to depression. The present study measures melanopsin cell sensitivity in individuals with SAD compared to non-depressed controls.

Melanopsin containing ipRGCs project from the retina to the suprachiasmatic nucleus, which serves as a circadian clock, and have a peak sensitivity of ~482 nm when measured in vitro (Provencio et al., 2000; Lucas et al., 2001; Hattar et al., 2002; Berson et al., 2002; Gooley et al., 2003; Dacey et al., 2005) and peak sensitivity of 482 nm when measured in vivo (Gamlin et al., 2007; Markwell et al., 2010). In addition to entraining the circadian clock, ipRGCs are involved in the pupil light reflex, in which the pupil constricts and redilates in response to light. The pupil area in melanopsin knockout mice after 1 min of blue light is much larger (i.e., less constricted) than that of wild-type mice (Hattar et al., 2003; Lucas et al., 2003). Using primate cell recording techniques, Gamlin et al. (2007) and Dacey et al. (2005) demonstrated that, unlike rods and cones, ipRGCs have a sustained response after removal of the light source. This results in continuing constriction of the pupil after light off and is called the post-illumination pupil response (PIPR). The PIPR is intrinsic to melanopsin-containing ipRGCs (Gamlin et al., 2007). Therefore, the magnitude of the PIPR response to blue light reflects the sensitivity of the melanopsin pathway (Gamlin et al., 2007). The PIPR then provides an elegant way to isolate the contributions of ipRGCs from those of rods and cones. The PIPR has been measured in a range of healthy and clinical populations (Gamlin et al., 2007; Kawasaki and Kardon, 2007; Kardon et al., 2009, 2011; Kankipati et al., 2010, 2011; McDougal et al., 2010; Feigl et al., 2011, 2012; Park et al., 2011; Kawasaki et al., 2012), and the present design is based in part on the methods in these studies. However, the PIPR has yet to be measured in SAD.

Electroretinography (ERG) is an another tool that has been used to assess retinal sensitivity in SAD. ERG records electrical responses at the corneal surface to measure the function of retinal cells such as rods (scoptic) or cones (photopic), but not retinal ganglion cells. Photoreceptor (and bipolar cell) sensitivity is assessed by the measure log *K*, which is a calculation of the intensity of light that evokes half of the maximum (Vmax) rod or cone response. Using this measure, Lavoie et al. (2009) found that rods were less sensitive in SAD patients compared to controls during winter measurements. They also showed that the Vmax amplitudes of both rods and cones were reduced in SAD patients compared to controls. Most interestingly, all three of these measures were normalized in SAD following light therapy treatment (Lavoie et al., 2009). Decreased rod sensitivity seems to be a state marker for depression in SAD, as Gagne and Hebert (2011) also found that rods had decreased sensitivity in SAD during winter, which normalized during the summer. While studying the effects of light history on retinal sensitivity, Gagne and Hebert (2011) identified a possible trait marker for SAD. In participants with SAD, exposure to bright light for 1 h prior to scoptic measurement caused a decrease in Vmax during winter and summer measurements (Gagne and Hebert, 2011). Because ipRGCs are most sensitive to blue light, Gagne et al. (2011) compared retinal responses of SAD and control participants after exposure to red or blue light. In response to blue light, both groups had a decrease in an ERG measure that is driven by ON-bipolar cells and Muller cells. These data reviewed here support a role for retinal subsensitivity in SAD, but do not assess the specific contribution of ipRGCs. Given the relatio nship between SAD, retinal subsensitivity, and gene polymorphisms in melanopsin, we hypothesize that ipRGCs specifically will be less sensitive in SAD participants than in controls when measured using a unique pupillometry measure specific to ipRGCs.

The present study was designed to specifically test the sensitivity of ipRGCs in SAD using a melanopsin-specific pupillometry test. M1-type melanopsin cells are directly involved in the pupillary light reflex as well as in circadian photoentrainment (Schmidt et al., 2011). Hence, impairment in one process (i.e., pupil constriction) may reflect impairment in the other processes mediated by M1 cells (i.e., photoentrainment). Although rods and cones also contribute to circadian photoentrainment (Provencio, 2011), melanopsin cells drive 40–50% of the response (Do and Yau, 2010). Because melanopsin cells are such a large component of the pathway implicated in retinal subsensitivity in SAD, it is important to investigate whether there may be a decrease in melanopsin cell sensitivity. Therefore, in the present study, we compared individuals with SAD and controls on the melanopsin-driven PIPR. We also examined differences in the PIPR by melanopsin gene (*OPN4*) sequence variations. Although others (i.e., Higuchi et al., 2013) have found that the steady-state pupil diameter varies as a function of melanopsin gene variation I394T, this will be the first test of the melanopsin-specific PIPR in SAD with both the P10L and I394T melanopsin gene variations.

2. Methods

2.1. Participants

Participants age 18–65 were recruited from the greater Pittsburgh, Pennsylvania metropolitan area through community advertising (latitude 40°26′N). The institutional review board of the University of Pittsburgh approved this study, and participants gave informed consent and received compensation. None of the participants reported a history of psychotic or bipolar disorder, sleep disordered breathing, narcolepsy, or current substance use disorder. All participants were studied during the fall or winter months in 2011 and 2012 while individuals in the SAD group were in a Major Depressive Episode.

2.2. Clinical assessments

SAD group participants met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; APA, 2000) criteria for unipolar Major Depressive Disorder With a Seasonal Pattern according to the Structured Clinical Interview for DSM-IV Axis I Disorders-Research Version (SCID-I; First et al., 2002). Participants also completed the Modified Seasonal Pattern Assessment Questionnaire (M-SPAQ; Blouin et al., 1992; Rosenthal et al., 1984), the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorder version (SIGH-SAD; Williams et al., 1992), and the Beck Depression Inventory, Second Edition (BDI-II; Beck et al., 1996). Inclusion criteria for the SAD group were (1) a diagnosis of MDD-SP based on the SCID, (2) a SIGH-SAD score of >19 total, >9 on the HAM-D subscale, and >4 on the atypical subscale which defines an SAD episode (Terman et al., 1990), and (3) a Global Seasonality Score (GSS) from the M-SPAQ of >11, endorsing "feeling worst" in January and/or February (with or without other months) but not July and/or August, and perceiving seasonal changes as at least a "moderate" problem (Kasper et al., 1989). Inclusion criteria for the control group were (1) no history of mood disorder based on the SCID, (2) scores below episode criteria listed above on the SIGH-SAD, (3) a GSS of 8 or 9 and endorsing "no problems" with seasonal changes on the M-SPAQ, or GSS <8 (Kasper et al., 1989), and (4) BDI-II score <10.

2.3. Stimuli

Lights of equal corneal irradiance (13.7 log Photons/cm^2/s) were presented for 30 s ON, and 120 s OFF. Retinal irradiance was calculated to account for age-related decreases in lens transmission and pupil diameter during the stimulus. Using age and pupil diameter during stimulus presentation, retinal irradiance was calculated for each participant. Stimuli were turned on and off electronically using a commercially available remote receiver and E-Prime 2 software (Psychology Software Tools, Inc., Pittsburgh, PA). Round light emitting diode bulbs (Super Bright LEDs; St. Louis, MO) were placed behind an 8.5″ diameter mylar diffuser (Speedotron, Chicago, IL) at a distance of 17″ from the eye (~29° of the visual field; lenses were not used to focus the stimulus on a point in the retina). The LED lights were presented to both eyes, and pupil responses were measured in the left eye in all subjects, so the consensual response was not used. Stimuli are 22.68 nm (467.7 nm blue light) and 15.78 nm (632.9 nm red light) full-width half-maximum (FWHM), and absolute corneal irradiance was measured at the approximate location of the participants' eye in the headrest with a 50-micron width aperture