Psychiatry Research 246 (2016) 492–499

Contents lists available at ScienceDirect

Psychiatry Research

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

Pupillary response abnormalities in depressive disorders

Scott A. Laurenzo[a], Randy Kardon[b,e], Johannes Ledolter[e,f], Pieter Poolman[b,e], Ashley M. Schumacher[a], James B. Potash[a], Jan M. Full[b,e], Olivia Rice[b,e], Anna Ketcham[b,e], Cole Starkey[b,e], Jess G. Fiedorowicz[a,c,d,*]

[a] Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, United States
[b] Department of Ophthalmology, Roy J. and Lucille A. Carver College of Medicine, United States
[c] Department of Internal Medicine, Roy J. and Lucille A. Carver College of Medicine, United States
[d] Department of Epidemiology, College of Public Health, United States
[e] Iowa City Veterans Affairs center for Prevention of Visual Loss, Department of Veterans Affairs Hospital, United States
[f] Tippie College of Business, The University of Iowa, Iowa City, IA 52242, USA

ARTICLE INFO

Keywords:
Major depressive disorder
Pupillometry
Seasonality
Bipolar disorder

ABSTRACT

Depressive disorders lack objective physiological measurements to characterize the affected population and facilitate study of relevant mechanisms. The melanopsin-mediated light signaling pathway may contribute to seasonal variation and can be measured non-invasively by pupillometry. We prospectively studied changes in melanopsin-mediated pupillary constriction in 19 participants with major depressive disorder (MDD) and 10 control across the summer and winter solstices. The melanopsin-mediated response, as measured by the pupil's sustained constriction six s after a high intensity blue light stimulus, was marginally attenuated in those with MDD relative to controls (p=0.071). The participants with MDD unexpectedly showed a significantly reduced transient pupillary response to low intensity red (p=0.011) and blue light (p=0.013), but not high intensity red and blue light. Sustained pupillary constriction in response to high intensity blue light was more pronounced with increasing daylight hours (p=0.037) and was more strongly related to objectively measured versus estimated light exposure. Melanopsin-mediated impairments in pupil response may serve as a biological marker for vulnerability to depression in low light conditions. Assessment of these and other responses to light stimuli, such as response to low intensity light, may be useful for the study of the neurobiology of MDD and related mood disorders.

1. Introduction

The Global Burden of Disease Study found MDD to be the fourth leading cause of disability worldwide, following lower respiratory tract infections, diarrheal diseases, and perinatal disorders (Ustün et al., 2004). Depressive disorders have a 16% lifetime prevalence in the United States (Kessler et al., 2003) and are associated with occupational and psychological disability (Judd et al., 2000, 2008). The heritability, calculated as 0.37, for unipolar depressive disorders is moderate (Sullivan et al., 2000), but genome-wide association studies have been limited in their ability to link specific genes with increased risk for major depression (Ripke et al., 2013). This indicates there are no single causal genes that by themselves lead to depression, and thus, the development of major depressive disorder is multifactorial. Therefore, research aimed at identifying intermediate phenotypes or endophenotypes is valuable (Glahn et al., 2012), especially considering major depressive disorder currently lacks any reliable, objective, or quantifiable biomarker.

SAD is a current diagnostic subtype of major depressive disorder, defined in the DSM-V as recurrent major depressive disorder with the extra diagnostic criterion "with seasonal pattern," (Association, 2013) and has a lifetime prevalence of 2.6% (Levitt and Boyle, 2002). Some studies found higher prevalence of SAD at higher latitudes, suggesting at least some individuals are vulnerable to developing a disordered mood in response to the environmental stress of changing light (Imai et al., 2003; Kegel et al., 2009), but prospective studies show a lack of diagnostic stability for SAD (Leonhardt et al., 1994; Sakamoto et al., 1995; Schwartz et al., 1996; Thompson et al., 1995). In the longest follow-up study to date, seasonality was not stable from one decade to the next, yet a winter predominance for depression was confirmed (Cobb et al., 2014). The episodic and multifactorial nature of mood disorders renders such studies based on clinical features challenging. A quantifiable biological measure to assess vulnerability to seasonal exacerbation in mood disorders would provide advantages compared

* Corresponding author at: Department of Psychiatry, Roy J. and Lucille A. Carver College of Medicine, United States.

http://dx.doi.org/10.1016/j.psychres.2016.10.039
Received 25 May 2016; Accepted 19 October 2016
Available online 21 October 2016
0165-1781/ Published by Elsevier Ireland Ltd.

to clinical interviews that rely on the timing of episodes. The pupillary light reflex, measured with pupillometry, has the potential to be one such measure, as it can assess melanopsin-mediated physiologic changes in response to a bright blue light at the peak wavelength sensitivity of melanopsin pigment.

Studies of melanopsin gene variation and seasonal affective disorder suggest a potential relationship between melanopsin-mediated retinohypothalamic tract pathways and SAD (Roecklein et al., 2012, 2013b). The retinal circuitry for transmitting environmental light signals used in chronobiological functions has recently been found to involve melanopsin, a photopigment found in intrinsically photosensitive retinal ganglion cells (ipRGCs) (Guler et al., 2008; Kawasaki and Kardon, 2007). These cells may be indirectly activated by rod and cone photoreceptors or directly activated by intrinsic melanopsin pigment. LeGates and colleagues have provided compelling evidence for the induction of depression-like symptoms in mice by shortening the photoperiod (7 h light/dark cycle) mediated through ipRGCs (LeGates et al., 2012). In healthy humans, the pupillary light reflex has also shown varying responsiveness in relation to changes in seasonal light (Münch et al., 2016).

The melanopsin-mediated pathway is most responsive to bright blue light with a peak sensitivity at a 485 nm wavelength, which causes a sustained contraction of the pupil even after the termination of the blue-light stimulus. This sustained contraction is called the post-illumination pupil response (PIPR), and at 6-s post-illumination, it is due to the activation of melanopsin causing sustained ipRGC signaling (Adhikari et al., 2015; Park et al., 2011). A red light stimulus will activate the melanopsin-containing retinal ganglion cells via photoreceptors without activating the melanopsin itself. Red light will cause a similar initial, transient pupillary contraction, but with a much faster subsequent dilation back to baseline size, as compared to the sustained reaction to a photopically matched intensity blue light stimulus due to the lack of melanopsin activation in ipRGCs by red light (Park et al., 2011).

The purpose of the current study is to use an innovative approach to understand the influences of light on MDD. We utilized pupillometry to characterize retinal function in individuals with mood disorders as a function of seasonal changes in daylight exposure. When the retina is exposed to 485 nm wavelength light, the melanopsin-mediated pathway is activated causing signals to travel to the suprachiasmatic nucleus via the retinohypothalamic tract and also to the midbrain resulting in the PIPR. Due to the proposed relationship between the melanopsin-mediated retinohypothalamic tract pathway and SAD (Roecklein et al., 2012, 2013b), we were interested in how the melanopsin-mediated PIPR may vary based on a person's diagnosis with seasonal depression and hours of daylight at different seasons. We suspected that those vulnerable to seasonal depressive episodes would show decreased ability to transmit light signals to the brain, which could be quantifiable by comparing pupillary light reflexes. Specifically, we hypothesized that the participants with MDD, particularly those prone to seasonal depressions, would have reduced melanopsin-mediated pupillary light reflexes (PIPR) to high intensity blue light relative to controls.

2. Methods

2.1. Sample

We recruited 19 participants between the ages of 18 and 50 with prior diagnoses of MDD based on structured diagnostic interview through prior participation at the Iowa site of the Genetics of Recurrent Early-Onset Depression II (GenRED II) study (Shi et al., 2011). Participants were recruited from the GenRED II study's participant list as they had already been well phenotyped, and assigned a research diagnosis of MDD. Participants with MDD were evaluated during two different periods a year, each within one month of either the summer or winter solstice. Within each period, they had two visits scheduled approximately two weeks apart. Study visits occurred between 1/2014 and 1/2016. Another 10 participants without major depression served as controls and underwent pupillometry assessments up to every month over the course of an entire year. Assessments were confined to the period surrounding the solstice for those with MDD to reduce participant burden.

2.2. Psychometrics

After consenting at the first scheduled visit, the MDD participants completed a structured diagnostic interview using the Depression and Seasonality Interview – Ontario (DSI-O) to confirm the mood disorder diagnosis (Schaffer et al., 2003). This same interview also included the Seasonal Physical Activity Questionnaire (SPAQ) (Magnusson, 1996), and a chronotype questionnaire, the Composite Scale of Morningness (Folkard et al., 1979). At both the summer and winter solstice appointments the participants also completed surveys to assess mood including the clinician-administered Hamilton Depression Rating Scale-Seasonal Affective Disorders Version (Williams et al., 1988). Self-reported scales included the Major Depression Inventory (Olsen et al., 2003), Patient Health Questionnaire-9 (Kroenke et al., 2001), and the Generalized Anxiety Disorder-7 (Spitzer et al., 2006). The duration and quality of sleep during both seasons were assessed using the Pittsburgh Sleep Quality Index (Buysse et al., 1989). Sun exposure during each season was examined using the Sun Exposure Questionnaire (Hanwell et al., 2010). Physical activity and light exposure were also measured utilizing the Actiwatch-L which was worn in the two weeks between visits in each seasonal period.

2.3. Pupillometry

Pupillary light reflexes were tested using a DP2000 Neuroptics binocular pupillometer (Neuroptics, Irvine, CA), which consists of an articulating arm attached to an optical head. The optical head contains two miniature video cameras and a bank of light emitting diodes, which can transmit red, green, blue, and white lights over a 5 log unit intensity range. Software allowed photopically matched light intensities to be selected for red and blue light intensities. This allowed for the comparison of rod, cone, and intrinsic melanopsin-mediated pupil response variation under conditions of low mesopic levels of adaptation. Rod responses were tested with three low intensity 1-s blue light (463 nm) stimuli given at 1 cd/m^2. Cone weighted pupil responses were tested with low intensity, 1 cd/m^2 (0 log cd/m^2), 1-s red light and high intensity red light (2.6 log cd/m^2). The intrinsic melanopsin-mediated post-illumination pupil responses at 6 s following termination of the light stimulus were tested with a 1-s bright blue light stimuli (2.6 log cd/m^2) compared to 1-s bright red light (622 nm) stimuli (2.6 log cd/m^2). The red light activated the melanopsin-containing retinal ganglion cells via the rods and cones without direct activation of the melanopsin and served as an internal control compared to the post-illumination sustained pupil response to the photopically matched bright blue light stimulus. Recordings of pupillometry data from one subject are illustrated in Fig. 1.

The recorded pupil responses were analyzed by automated software developed at the University of Iowa (Randy Kardon M.D., Ph.D. and Pieter Poolman, Ph.D.), which averaged the right and left pupil responses that are simultaneously elicited for each light stimulus. Pupil tracing during intermittent blinks were interpolated using a validated software program. The transient and sustained pupil contractions were reported as percent pupil contraction (contraction amplitude in mm divided by baseline pupil size in mm).

2.4. Statistical analysis

Analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary,