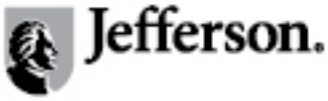

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Review

Melanopsin, photosensitive ganglion cells, and seasonal affective disorder☆

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ABSTRACT

In two recent reports, melanopsin gene variations were associated with seasonal affective disorder (SAD), and in changes in the timing of sleep and activity in healthy individuals. New studies have deepened our understanding of the retinohypothalamic tract, which translates environmental light received by the retina into neural signals sent to a set of nonvisual nuclei in the brain that are responsible for functions other than sight including circadian, neuroendocrine and neurobehavioral regulation. Because this pathway mediates seasonal changes in physiology, behavior, and mood, individual variations in the pathway may explain why approximately 1–2% of the North American population develops mood disorders with a seasonal pattern (i.e., Major Depressive and Bipolar Disorders with a seasonal pattern, also known as seasonal affective disorder/SAD). Components of depression including mood changes, sleep patterns, appetite, and cognitive performance can be affected by the biological and behavioral responses to light. Specifically, variations in the gene sequence for the retinal photopigment, melanopsin, may be responsible for significant increased risk for mood disorders with a seasonal pattern, and may do so by leading to changes in activity and sleep timing in winter. The retinal sensitivity of SAD is hypothesized to be decreased compared to controls, and that further decrements in winter light levels may combine to trigger depression in winter. Here we outline steps for new research to address the possible role of melanopsin in seasonal affective disorder including chromatic pupillometry designed to measure the sensitivity of melanopsin containing retinal ganglion cells.

Contents

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1. Introduction

The recently described melanopsin light input pathway may contribute to our understanding of seasonal affective disorder (SAD). SAD involves recurrent depressive episodes in the fall or winter months with remission or a change to mania or hypomania in the spring (Rosenthal et al., 1984). SAD is common and pervasive, affecting 0.8–2.2% of the North American population (Lam and Levitt, 1999). Three evidence-based treatments exist (i.e., antidepressant medications, light therapy, and psychotherapy), but not all SAD patients respond fully to these treatments. Incorporating research on melanopsin has the potential to improve our understanding of the etiology of SAD by identifying a link between gene variations, biomarkers, and risk for depression, and also to suggest new and individually tailored treatments.

The role of melanopsin in SAD has not been thoroughly explored, although the rationale for further investigation is strong. The regular winter recurrence of episodes, seasonal biological changes, and the benefit of light therapy for SAD suggest that its etiology is rooted in abnormal responses to light. Shorter photoperiods in winter may trigger SAD in susceptible individuals, analogous to other mammalian seasonal responses. An abnormal response to light may be mediated by abnormal retinal signaling (Wehr et al., 2001), termed the retinal subsensitivity hypothesis of SAD (Hebert et al., 2002). Such hypotheses were conceived prior to the description of melanopsin and its role in circadian, neuroendocrine and neurobehavioral processes. Abnormal retinal responses to light could be due to differences in the retinohypothalamic pathway, comprised of retinal ganglion cells that contain the photosensitive protein melanopsin. Some SAD patients differ from controls based on sequence variation in the melanopsin gene (Roecklein et al., 2009). Additionally, those variations are associated with seasonal changes in sleep timing and chronotype (Roecklein et al., 2012). Although melanopsin variations may hypothetically be the physiological basis underlying the retinal subsensitivity hypothesis, other possibilities are discussed as well.

Below, we briefly summarize the neurobiology and function of the melanopsin system, which has recently been reviewed by others (e.g., Do and Yau, 2010). Although the implications of the melanopsin system for human eye disease and human sleep and cognitive performance have been described elsewhere (e.g., Kawasaki and Kardon, 2007), this review focuses on the potential role of melanopsin in SAD and possible treatment implications.

1.1. Circadian, neuroendocrine and neurobehavioral responses to light

The discovery of melanopsin confirmed that rods and cones are not the only photoreceptors involved in circadian, neuroendocrine, and neurobehavioral responses to light (Provencio et al., 1998). Melanopsin is found in intrinsically photosensitive retinal ganglion cells (ipRGCs), which are photosensitive even when input from rods and cones is pharmacologically blocked (Berson et al., 2002; Hattar et al., 2002; Gooley et al., 2001). Although melanopsin is found in only 2% of ganglion cells, their dendrites form a "photoreceptive net" across the retina (Berson et al., 2002; Hattar et al., 2002; Gooley et al., 2001; Provencio et al., 2002). Additionally, melanopsin cell responses increase with light intensity with a high threshold, and they are slow to initiate and terminate nerve impulses, qualities making them ideal for measuring gross environmental light levels rather than forming crisp images (Berson et al., 2002, 2010; Dacey et al., 2005; Pu, 2000). Melanopsin signaling pathways, as established in animal models, have complex inputs from bipolar, amacrine, rod, and cone cells, and multiple projections (Do and Yau, 2010). If conserved in humans, the retinorecipient areas that may be important in SAD include the suprachiasmatic nucleus (SCN) and intergeniculate leaflet (circadian regulation), the lateral hypothalamus (energy homeostasis), and the ventral subparaventricular zone and preoptic nucleus (sleep promotion and regulation; Graham et al., 2008; Hannibal and Fahrenkrug, 2004; Hattar et al., 2002, 2006).

1.2. Gene variations and human behavior

We have reported melanopsin gene (*OPN4*) associations in two populations. In a study of 220 individuals, those with the TT genotype at P10L (rs2675703) had a 5.6 times increased risk of SAD (Roecklein et al., 2009). This association was retested in a healthy sample to remove the effect of mood disorder symptoms. In 268 healthy individuals, the effects of P10L TT genotype and day length interacted to predict earlier bedtime when individuals were assessed on shorter days, and later bedtime when individuals were assessed on longer days (Roecklein et al., 2012). If replicated, and found in SAD as well, these data may indicate a specific etiological relationship between P10L, changes in sleep timing, and SAD. To date, however, these are the only two SNP-association studies showing a link between melanopsin and SAD in the first study, and between melanopsin and seasonal changes in sleep timing in the second study. Replication, and other studies designed to evaluate the role of melanopsin in SAD are needed. Such studies will greatly benefit from the basic science literature describing the functions of melanopsin and melanopsin containing cells.

1.3. Functions of melanopsin

Functions that are controlled by photic stimulation of the melanopsin system include the pupil light reflex, circadian photoentrainment, sleep regulation, acute suppression of plasma melatonin, and acute effects of light on cognitive performance, although the expression of these functions varies between humans

Table 1
Summary of melanopsin findings in human research.

Authors	Year	Participants	Findings
Thapan et al.	2001	22 Healthy individuals	459 nm light maximally suppressed melatonin release
Brainard et al.	2001	72 Healthy individuals	446–477 nm most effective in suppressing nighttime melatonin release
Lockely et al.	2003	16 Healthy individuals	460 nm light more effective than 555 nm for phase shift and melatonin suppression
Phipps-Nelson et al.	2003	16 Healthy individuals	10,000 lx light (fluorescent) reduces subjective sleepiness and improves psychomotor performance compared to dim 1000 lx (incandescent)
Cajochen et al.	2005	10 Healthy men	460 nm light more effective than 550 nm light for melatonin suppression, alerting response, and responses of body temperature and heart rate
Zaidi et al.	2007	2 Visually impaired individuals	480 nm peak sensitivity for melatonin suppression, phase shifts, acute increase in alertness, pupillary constriction, and stimulus detection
An et al.	2009	12 Healthy individuals	458 nm more effective than 550 nm light for cognitive functioning and arousal level, 458 nm light produced larger effects at nighttime
Roecklein et al.	2009	130 SAD 90 healthy controls	rs2675703 (P10L) T/T variation higher in SAD than controls
Gamlin et al.	2007	2 Healthy men	Sustained post-stimulus pupilloconstriction (PIPR) maximally sensitive to 482 nm
Brainard et al.	2008	26 Healthy individuals	460 nm light optimal for melatonin suppression
Mure et al.	2009	12 Healthy individuals	Sustained pupil constriction and PIPR maximally sensitive to 460–480 nm, evidence for melanopsin bistability
Revell et al.	2010	12 Healthy men	479 nm light more effective for melatonin suppression, but cognitive performance more sensitive to other wavelengths indicating involvement of multiple photoreceptors
Kankipati et al.	2010	37 Healthy individuals	PIPR evident in response to 470 nm but not 623 nm stimulus
Gooley et al.	2010	48 Healthy individuals	Melatonin suppression tests indicate that melanopsin is primarily responsive to long duration, high irradiance stimuli
McDougal and Gamlin	2010	6 Healthy individuals	Cone photoreceptors adapt over 30 s, and rods do not respond at high irradiances, such that long-duration high irradiance stimuli induce melanopsin responses
Kankipati et al.	2011	16 Glaucoma patients 19 matched controls	PIPR lower in glaucoma patients compared to matched controls, PIPR decrease correlates with glaucomatous neuropathy
Kardon et al.	2011	32 Retinitis pigmentosa (RP) patients 43 healthy controls	RP patients had a more pronounced PIPR compared to controls
Zele et al.	2011	11 Healthy individuals	PIPR maximally evident at CT 15, ~2 hr 40 min prior to DLMO
Gagne et al.	2011	10 SAD 10 healthy controls	SAD and controls did not differ in ERG after 1 h red or blue stimulus, ERGs were lower after blue in both groups
Gagne and Hebert	2011	12 SAD 11 healthy controls	ERG decrease after 10,000 lx 1-hour exposure in summer and winter in SAD but not controls, did not differ by wavelength
Roecklein et al.	2012	234 Healthy individuals	rs2675703 (P10L) T/T variation interacts with photoperiod to predict chronotype and sleep timing

SAD: seasonal affective disorder. PIPR – post-illumination pupil response. DLMO – Dim light melatonin onset. See Section 3.5 regarding studies on blue or blue-enriched light therapy in SAD.

and other mammals. In general, melanopsin knockout mice (*Opn4*$^{-/-}$) show impairment in many of these measures, indicating that ipRGCs are important for encoding light intensity for animal biological and behavioral responses (Hattar et al., 2003). Some or all of these functions may be relevant to human mood disorders, especially the effects on sleep and cognitive performance. Selected findings from the past decade of human research related to melanopsin phototransduction and physiology are summarized in Table 1.

1.3.1. Pupillometry

The contribution of melanopsin to neurobehavioral responses can be distinguished from that of other photoreceptors when exposures to specific wavelengths, intensities, and durations of light are tested. The pupillary light reflex (PLR) adjusts the diameter of the pupil by light intensity, protecting the retina from damage and aiding vision. To date, human studies show that blue but not red wavelengths elicit ongoing constriction during stimulation, ongoing constriction after cessation (i.e., post-illumination pupillary response, PIPR), and that the human PLR driven by melanopsin is most sensitive to short wavelength light but may be potentiated by longer wavelengths (Gamlin et al., 2007; Kankipati et al., 2010; Kawasaki and Kardon, 2007; Mure et al., 2009). Although in rodents, melanopsin contributes about three times more to steady state pupil diameter than cones at high irradiances, rods, cones, and melanopsin cells all contribute to the PLR (Hattar et al., 2003; Lucas et al., 2003; Tsujimura et al., 2010). Although different populations of melanopsin cells exist, the M1 type intrinsically photosensitive retinal ganglion cells (ipRGCs) underlie both circadian photoentrainment and the pupillary light reflex (Schmidt et al., 2011), making it possible to make inferences about the function of one system by measuring the other. Pupillometry in humans is a potential tool for investigating "melanopsin-related disorders" (Gamlin et al., 2007). Extended duration stimuli of specific narrow band wavelengths can be used in a relatively fast and noninvasive way in human studies to isolate the functioning of melanopsin, allowing inferences about the relative sensitivity of melanopsin across diagnostic groups (Do and Yau, 2010; Kardon et al., 2011). Potential clinical applications of pupillometry are broad, from diagnosis of retinal diseases, to possibly discerning the role of melanopsin photoreception in SAD (Kardon et al., 2011; Wilhelm, 2010).

1.3.2. Circadian photoentrainment

Although the etiology of SAD has not been determined, one main hypothesis contends that SAD is due to a seasonal circadian phase disturbance, and is discussed more thoroughly below (Lewy et al., 2006). Hence, the role of melanopsin in circadian photoentrainment has implications for this hypotheses of SAD. Data indicate that, in specific conditions of photoentrainment in rodents, about 40–50% of the response is driven by melanopsin cells (Do and Yau, 2010), although it is unclear if this translates to other non-visual responses in humans. Melanopsin knockout mice, however, have only subtle changes in their circadian rhythms, indicating that rods and cones convey light information through the melanopsin

ganglion cells for entrainment. Phase shifts in rhythms of human melatonin in response to 460 nm light are two-fold greater than those in response to 555 nm light at high irradiances, indicating a primary role of melanopsin photoreception for human circadian photoentrainment (Lockley et al., 2003).

1.3.3. Melatonin synthesis

Melanopsin could also play a role in SAD through the regulation of melatonin. In both humans and animals, the pineal gland releases melatonin at night in response to darkness and signals from the circadian clock (Lewy, 2007; Nelson et al., 2010). Winter nights result in a longer duration of melatonin, which is a biological signal that triggers seasonal behaviors in mammals, such as changes in feeding and sleeping (Schibler, 2007; Workman and Nelson, 2011). Light acts to acutely suppress melatonin, and mice missing rods and cones still exhibit suppression of melatonin (Lucas et al., 1999; Panda et al., 2003), implying that melanopsin is involved in acute melatonin suppression in mice. In humans, short wavelength light between 446–477 nm is the most effective for acute suppression of melatonin, indicating a primary role for melanopsin in melatonin suppression (Brainard et al., 2001; Revell et al., 2010; Thapan et al., 2001). Cone photoreceptors, in addition, appear to contribute to human melatonin suppression at the beginning of light exposure (Gooley et al., 2010). Both early and late responses to light in humans may be therapeutically important, and optimal light therapy might employ both longer and shorter wavelengths to engage cones as well as melanopsin (Brainard et al., 2001, 2008; Gooley et al., 2010; Revell et al., 2010; Thapan et al., 2001).

1.3.4. Circannual rhythms

Many rhythms that recur annually, such as in the seasonally breeding Siberian hamster, are driven by changes in day length and the resulting increase in the duration of nightly melatonin synthesis (see Schibler, 2007 for a review). In addition to melatonin, other circadian markers of season that may also be influenced by melanopsin-mediated light input include photoperiod-dependent patterns of gene expression in rodents (Sumova et al., 2003; Tournier et al., 2003; Travnickova et al., 1996) and seasonal variations in the electrophysiological activity in the rodent central clock that encode day length (VanderLeest et al., 2007). Given the role of melanopsin in melatonin and circadian entrainment described above, seasonal rhythms driven by circadian rhythms or photoperiod would be similarly dependent on individual differences in melanopsin functioning. In healthy humans, controlled laboratory studies have shown that the melatonin rhythm as well as prolactin, cortisol, body temperature and sleep are influenced by photoperiod length (Wehr, 1991; Wehr et al., 1993). Those studies illustrated the conservation of photoperiodic responsiveness of humans, although it has been suggested that in industrialized societies, photoperiodic responses may be masked by higher ambient artificial light levels Wehr et al., 1993). In contrast, one study found no seasonal change in the nightly duration of melatonin release in controls, suggesting that only some subgroups of individuals, notably those with SAD, retained the lengthened duration of melatonin release seen in other mammals (Wehr et al., 2001).

1.3.5. Sleep regulation

Since hypersomnia is a primary SAD symptom, the role of melanopsin in sleep regulation may be important. Extensive human research has established that light has clear effects on (1) circadian entrainment of sleep, (2) homeostatic sleep regulation, and (3) acute light-induced effects on alertness. Animal research indicates that melanopsin plays a role in some or all of this sleep regulation and physiology. Melanopsin cells project to neural regions involved in sleep regulation (Hattar et al., 2006) including the ventral lateral pre-optic area (VLPO; Hannibal and Fahrenkrug, 2004; Lu et al., 2000), and the superior colliculus (SC), which has been implicated in the photic regulation of sleep (Gooley et al., 2003; Miller et al., 1998). In nocturnal rodents, light during the dark activity phase will acutely induce sleep, but in diurnal animals and humans, short wavelength light has the expected opposite effect of increased alertness. Knockouts, however, have significantly reduced acute light-induced activation of the VLPO and SC, and do not exhibit acute sleep responses to light, or experience a delay in such responses (Altimus et al., 2008; Do and Yau, 2010; Lupi et al., 2008; Tsai et al., 2009). Melanopsin appears to be involved in the physiological basis of the homeostatic sleep drive, since melanopsin knockout mice exhibit reduced sleep duration and debt (Tsai et al., 2009).

1.3.6. Alertness

Decrements in alertness are also relevant for depression, although light has the opposite effect on nocturnal mice as in diurnal humans. In mice, darkness is alerting during the light phase, but this effect is delayed in melanopsin knockouts, indicating that melanopsin participates in driving acute alertness responses (Altimus et al., 2008; Tsai et al., 2009). These data lead to the hypothesis that a melanopsin-mediated effect on alertness may explain the role of melanopsin in SAD (Schmidt et al., 2011). Human studies have found that light causes an acute increase in cognitive performance and alertness (e.g., Badia et al., 1991; French et al., 1990), especially short wavelength light (An et al., 2009; Cajochen et al., 2005; Lockley et al., 2006; Phipps-Nelson et al., 2003; Revell et al., 2010; Zaidi et al., 2007; Figueiro et al., 2007). Based on spectral sensitivity, however, self-reported alertness ratings are driven by a combination of photoreceptors whose contributions may vary across the day (An et al., 2009; Revell et al., 2010). Although light may increase alertness by suppressing melatonin when it is released, other as yet unidentified process stimulating the ascending arousal system and cortex are likely during the day when melatonin is low (Lockley and Gooley, 2006).

1.3.7. Daily rhythm

Daily variations in melanopsin cell numbers, protein, and mRNA have been observed in animals (Gonzalez-Menendez et al., 2009; Hannibal et al., 2005; Sakamoto et al., 2004), although daily variations in melanopsin-related functions may also be due to downstream processes in the melanopsin and circadian pathways. In humans, it appears that a daily variation in the sensitivity of the melanopsin pathway occurs, as reflected by the PIPR (Zele et al., 2011), and melatonin suppression and iris constriction (Figueiro et al., 2005). Objective measures of human cognitive function in response to light are highest at night, after dusk (An et al., 2009). The mechanism behind such daily variation is likely to be due to an interaction between multiple photoreceptors, the clock, and light input (Dacey et al., 2005; Wong et al., 2007). For example, the peak period of melanopsin mRNA expression in rats increases in duration under long day length conditions and is illumination dependent (Mathes et al., 2007). It is possible that a light sensitive transcription feedback loop controls melanopsin activity (Hannibal et al., 2005), such that the effect of light on circadian, neuroendocrine and neurobehavioral processes varies by time of day. Consistent timing of measurement is therefore critical when studying behavioral responses dependent on melanopsin.

2. SAD etiology

Although biological hypotheses of SAD have been reviewed elsewhere (Lamont et al., 2007; Levitan, 2007; Rohan et al., 2009), none have yet incorporated the recent findings regarding these melanopsin-containing ganglion cells that regulate the biological and behavioral responses to light. Seasonal changes in circadian

rhythms and light responses in humans and animals can be healthy or adaptive, but individuals with SAD may experience a pathological extreme of normal human seasonal variation (Magnusson, 2000). In seasonally breeding rodents, multiple biological rhythms vary across the seasons, and such rodents may have utility as potential animal models for SAD (Workman and Nelson, 2011). There is evidence of seasonal variation in humans such as seasonal peaks in birth rates, growth rate, cortisol, testosterone, pain thresholds, alertness, sexual activity and conception, and behaviors such as crime, suicide, all cause mortality, and rape (see Roenneberg and Aschoff, 1990; Lam and Miron, 1991; Workman and Nelson, 2011). Aschoff (1981) suggests that sociocultural factors and increasing industrialization may explain a decrease in amplitude of these seasonal rhythms since the 1930s. The general U.S. population reports a winter worsening of mood, increased appetite, longer sleep duration, and decreased energy and social interaction levels in winter (Rosen et al., 1990). SAD is seen as the extreme case on a continuum of seasonal variations in mood and behavior (Kasper et al., 1989). In fact, some degree of seasonal depression may have once been adaptive as a means to save energy in winter, although wintertime decrements in activity would be less adaptive in our current environment (Eagles, 2004). Here we describe etiological hypotheses of SAD, with a focus on the possible role of melanopsin in many of the hypotheses.

2.1. Circadian hypotheses of SAD

2.1.1. Phase shift hypothesis

The phase shift hypothesis proposes that SAD occurs when circadian rhythms are out of phase, shifted earlier or later, relative to the sleep/wake cycle (Lewy, 2007). This hypothesis has been defined as the difference between a marker of circadian phase (i.e., DLMO) and mid-sleep, or a misalignment in the phase angle between the circadian clock and the sleep/wake cycle. Although a majority (71%) of SAD patients have delayed rhythyms (Lewy et al., 2006), approximately half do not have significantly different rhythms compared to controls (46%; Eastman et al., 1993). This indicates that circadian misalignment alone may not explain SAD etiology. Morning light therapy (or combined morning/evening light) appears superior to evening or midday light therapy administration (Terman et al., 1989). When circadian misalignment is measured, treatment to correct misalignment is associated with decreased depression symptoms in SAD (Lewy, 2007), and the degree of change in misalignment is associated with degree of improvement (e.g., Lewy et al., 2006). It may be that subgroups of individuals with SAD have different directions and degrees of misalignment, perhaps due to different genetic predispositions. Given the role of melanopsin in circadian entrainment, and this evidence for circadian misalignment in SAD, it is not surprising that melanopsin gene variations are associated with changes in sleep timing and chronotype (Roecklein et al., 2012), although these findings have not yet been replicated.

2.1.2. Photoperiod

The photoperiod hypothesis of SAD states that longer duration of nocturnal melatonin release, due to longer nights in winter, may be a "circadian signal of change in season," triggering depression (Wehr et al., 2001). Wehr et al. (2001) tested the photoperiod hypothesis in SAD and healthy controls living in their usual environment. Individuals with SAD had longer winter melatonin release (30–48 min in men and women compared to themselves in summer), a seasonal variation not seen in healthy controls (Wehr et al., 2001). Individuals with SAD did not have a significant phase shift compared to healthy controls in winter, but time of melatonin offset and midpoint was consistent with the phase shift hypothesis (Wehr et al., 2001). It remains to be seen if regular light therapy during winter can lead to shortened duration of melatonin release in SAD, or if gene variations are associated with melatonin. In healthy individuals, there can be large individual differences in nighttime acute suppression of melatonin by light (Brainard et al., 1988). Further, evening melatonin suppression by light is more effective in winter (Owen and Arendt, 1992). Although the factors explaining these seasonal and individual differences in light suppression of melatonin are unknown, one possible explanation could be genetically mediated differences in retinal sensitivity.

2.1.3. Retinal sensitivity

The retinal subsensitivity hypothesis proposes that normal increases in retinal sensitivity in response to low light levels in winter is impaired, leading the retina to be less sensitive than necessary (Hebert et al., 2002; Reme et al., 1990). Whole retina recording measures include electroocculography (EOG), and electroretinography (ERG), under either scotopic conditions, reflecting primarily rod responses, or photopic conditions, reflecting largely cone driven responses.

2.1.3.1. Electroocculography. Two studies found lower EOG ratios in SAD, which would reflect lower electrical potential and activity if outside of the normal range (Lam et al., 1991; Ozaki et al., 1993). The first study to analyze season found that healthy individuals had higher EOG ratios in winter compared to summer, a difference not seen in SAD patients (Ozaki et al., 1995). This indicates that the up-regulation thought to be required for low winter light levels was not occurring in SAD, and that the lack of up-regulation could be pathological in SAD. In SAD patients responding to one week of winter light therapy, however, low EOG ratios did not rise to the levels seen in controls (Ozaki et al., 1993). The underlying mechanism behind EOG levels is still unclear, making conclusions difficult to draw from this type of recording.

2.1.3.2. Electroretinography. One study using scotopic ERG in response to dim white light flashes found that women with SAD had lower ERG, but men with SAD had higher ERG amplitude compared to controls, while other studies did not find this gender difference (Lam et al., 1992). Both individuals with subsyndromal seasonal affective disorder (S-SAD) (Hebert et al., 2002) and SAD (Hebert et al., 2004) had lower rod sensitivity (i.e., scotopic ERG) in winter compared to controls. This difference normalized in summer and after treatment with light therapy (Hebert et al., 2004). The photopic ERG may also be decreased in SAD in winter, and does not differ from controls after light therapy or in summer (Lavoie et al., 2009). Recently, SAD and control participants were exposed to 10,000, 100, and 5 lx light for one hour (Gagne and Hebert, 2011). A significant decrease in ERG following 10,000 lx 1 h exposures was found in both summer and winter in SAD but not controls, and is proposed as a biomarker of SAD, although the response was not specific to wavelength. In a recent study using different wavelengths, ERGs were compared between SAD and control participants after either a red or blue 1 h exposure (Gagne et al., 2011). ERGs were significantly lower after the blue stimuli, but SAD and controls did not differ. There may be other measures, such as chromatic pupillometry (e.g., the PIPR, which is primarily driven by melanopsin containing cells and not rods and cones), that are more sensitive to melanopsin cell functioning than ERG, given that melanopsin cells are only 1–2% of the ganglion cells in the retina (Provencio et al., 1998) and would contribute less to whole retina recording responses like ERG. Considering synaptic connections through bipolar cells from both rods and cones to the M1 (melanopsin type 1) cells involved in the pupillary light reflex and circadian photoentrainment (Schmidt et al., 2011), it stands to reason that deficits in the classical photoreceptors would impact melanopsin-mediated functions as well.

2.1.4. Sleep

Most individuals with SAD (80%) report hypersomnia (Kaplan and Harvey, 2009). Despite reports of hypersomnia, studies have not been able to identify changes in sleep architecture and sleep regulation specific to SAD. Although some studies find no differences in homeostatic drive, some evidence suggests a deficiency in the homeostatic drive in SAD (Cajochen et al., 2000). Reports of hypersomnia may also reflect a desire for more sleep as a result of disrupted sleep (Kaplan and Harvey, 2009). When measured actigraphically, individuals with SAD had decreased sleep efficiency, daytime inactivity, greater time in bed, and a phase-delay compared to healthy controls, but showed no increase in actual time spent asleep (Winkler et al., 2005). Home actigraphy and/or polysomnography may help distinguish increased time in bed from increased total sleep time in those reporting hypersomnia (Kaplan and Harvey, 2009). Another important aspect of sleep in SAD may be the timing of sleep, and resultant effects on circadian phase. In healthy individuals, sleep durations of 9 h and later morning wake times (3 h later) led to a significant phase delay in the timing of dim light melatonin onset (Burgess and Eastman, 2006). When healthy individuals in the same study slept 6 h and woke at their regular workday time, a phase advance was observed, indicating the importance of morning wake time and light exposure for circadian entrainment. Perhaps individuals with SAD are most similar to those in the 9 h sleep condition, and are phase delayed as a result, suggesting an interaction between circadian entrainment and sleep.

2.1.5. Neurotransmitters

The role of neurotransmitters including serotonin and dopamine (DA) has been investigated in SAD. Variations in DA related genes, such as the D4 receptor gene variation (*DRD4* VNTR), are associated with SAD, specifically with eating behavior, carbohydrate craving, and body mass index (Levitan et al., 2004, 2006). Because DA is additionally involved in modulating retinal sensitivity and neurobiological responses to light, it is possible that SAD etiology could be explained by variations in dopaminergic signaling (Levitan, 2007), independently of melanopsin phototransduction. Future studies may investigate an association between reduced ERG in SAD, as described above, and the *DRD4* variation in SAD (Levitan, 2007). More complex interactions between DA, melanopsin, and retinal sensitivity are possible given that DA is involved in light and dark adaptation in the retina (Levitan, 2007; Witkovsky, 2004), melatonin can inhibit DA release, and DA can inhibit melatonin production in the retina (Cahill and Besharse, 1991). DA agonists in the retina cause increased melanopsin mRNA expression (Sakamoto et al., 2005), suggesting the possibility that DA variations may impact melanopsin signaling through regulation of *OPN4* mRNA expression. DA also may modulate ipRGC signaling (Van Hook et al., 2012), and ipRGCs appear to project to dopaminergic intraneurons in the retina, thereby contributing to visual signaling (Zhang et al., 2012). Hypodopaminergic states in the retina could change DA mediated signaling in cones (Witkovsky, 2004), and given the contribution of cone signaling to melanopsin containing ganglion cells (Schmidt et al., 2011), it is theoretically possible that DA gene variations could impact melanopsin cell functioning through cone-driven processing. Although disruptions in serotonergic neurotransmission are likely to represent an underlying vulnerability in SAD (e.g., Neumeister et al., 2001), it is less likely that serotonin would interact with melanopsin signaling or retinal sensitivity. The neurotransmitter hypothesis of SAD has been well described elsewhere (Neumeister et al., 2001).

2.1.6. Hyperphagia

Individuals with SAD are more likely to report increased appetite, food intake (i.e., hyperphagia), weight gain, and carbohydrate craving. Further, 17–26% of those diagnosed with SAD present with a comorbid eating disorder diagnosis, particularly Bulimia Nervosa (BN) (Lam et al., 2001). Interestingly, in women with comorbid SAD and BN, light therapy led to a decrease in binge/purge episode frequency, but was more effective in alleviating mood symptoms (Lam et al., 2001). Although light therapy may improve mood, which in turn decreases eating symptomology, it is also possible that increased light levels directly affect eating behavior through modulation of hypothalamic pathways involved in metabolic and energy homeostasis or via circadian physiology. Neuroanatomical studies have demonstrated that melanopsin cells project to the lateral hypothalamus, a region involved in regulating energy homeostasis, suggesting that light may have direct effects on eating and/or metabolism (Hattar et al., 2003).

2.1.7. Interactions

Individual differences in light sensitivity could be a function of retinal sensitivity, the sensitivity of the circadian clock to light, reduced light input, or a combination of these factors. Circadian variations in the sensitivity of melanopsin signaling are likely to reflect a complex feedback loop between central and retinal clocks (Hastings et al., 2003; Zele et al., 2011). For example, an individual with SAD may have decreased melanopsin sensitivity, which may only be an issue in winter when environmental light levels are lower and input is decreased. The complexity of the system is increased considering that environmental factors interact with biological factors.

2.2. Environment

The environmental trigger for SAD is most likely the change in the daily light/dark cycle due to a change in season or latitude (Rosenthal et al., 1984). The temporal sequence of symptom onset in SAD is most closely linked to photoperiod than other climatic variables (e.g., minutes of sunshine, global radiation, cloud cover; e.g., Young et al., 1997). In England, not only are actimetrically-measured light levels higher in summer overall, but evening blue light is 3 times higher in summer compared to winter (Thorne et al., 2009). Research shows that individuals with SAD, however, receive the same amount of winter light compared to controls (Guillemette et al., 1998), and more in summer compared to controls (Graw et al., 1999). Therefore, individuals with SAD may be more sensitive to seasonal changes in natural light decreases in winter, or more vulnerable to this natural seasonal change (Guillemette et al., 1998).

2.3. Summary

Given the reliance of circadian, neuroendocrine and neurobehavioral physiology on environmental light, and the roles of these functions in SAD, we hypothesize that winter environmental light input triggers a susceptibility to low light levels. Since all individuals living at high latitudes are exposed to seasonal changes in photoperiod, predispositions must explain why only some develop SAD. Future research is needed to determine if abnormal retinal sensitivity may constitute year-round or winter-only changes in retinal sensitivity, or it may be that certain individuals are less sensitive to RHT input centrally. One possibility is that low light levels in the winter may fall below a threshold in either melanopsin-specific, or general retinal sensitivity, which is required for euthymic functioning. Such a threshold may be biologically mediated by individual differences in the circadian photoreceptor system as a whole, or melanopsin functioning specifically. Such individual differences in retinal sensitivity may have consequences for central nervous system targets involved in circadian, neuroendocrine and neurobehavioral functions, leading

Table 2
Summary of future directions in research.

Study descriptions
Pupillometry designed to isolate the sensitivity of melanopsin cells (i.e., Post Illumination Pupil Response; PIPR)
Consider time of assessment, circadian phase of participant, season and/or photoperiod
Adjust for age-related changes in lens density
Review methodological considerations (Wilhelm, 2010)
Carefully chose duration, intensity (irradiance) and wavelength given specific experimental questions
Evaluate the blue-light hazard over the duration of exposure typical in light therapy for SAD
Test whether pupillometry or variations in genes involved in circadian entrainment can predict response to light therapy
Determine if long wavelengths prior to broad-spectrum light therapy can potentiate response in light therapy

Notes: See Section 3 for elaboration.

to symptoms typically seen in SAD such as sleep and eating changes as well as circadian phase shifts.

3. Future directions

The potential relationship between melanopsin, light, and SAD has been under-explored, in general. Table 2 details the following recommendations for areas of future research. With our recent and growing understanding of melanopsin containing ipRGCs, and the hypothesis for how melanopsin may play a role in seasonal depression, the next step is to describe a method of action for assessing the model with hypothesis testing. To date, much of the research on melanopsin physiology, especially as it might relate to seasonal variations, has been on healthy animals, and healthy humans, and very little in SAD, highlighting the need for future studies in healthy humans, those with SAD, and possibly in animal models of SAD (Workman and Nelson, 2011). Importantly, the contributions of ipRGCs to mood in humans, or animal models of depression, have not yet been described at the level of detail known for other ipRGC contributions (Schmidt et al., 2011). In testing whether or not melanopsin photoreception mediates seasonal variations in responses to light in SAD, critical issues include the nature of light stimuli, measurement of responses, and study design issues. Specifically, pupillometry designed to isolate the sensitivity of melanopsin cells from rods and cones, which has been employed in studies of retinal pathology, may lead to breakthroughs in our understanding of SAD.

3.1. Methodological considerations

Variables to consider in pupillometry include time of assessment, patient age, stimulus background and intensity, eye of exposure versus recording, sufficient spatial and temporal resolution in pupillometry recording equipment, and careful analysis of outcome data including appropriate handling of amplitude, blinks, and multiple observations per participant (Wilhelm, 2010). In addition, factors affecting the autonomic nervous system such as noise, arousal level, cognitive load, and medications should be controlled (Markwell et al., 2010). The effect of light stimuli on the retina can be affected by head movements, blinks, pupil constriction, and light transmission through the ocular media (Brainard et al., 1997, 2001; Gaddy et al., 1993). As the human lens ages, transmission of short wavelengths of light is reduced (Brainard et al., 1997; Lerman, 1987), so efforts to control for these age effects are necessary. Given that the sensitivity of the human visual system differs from the circadian system, it is currently more useful to quantify irradiance or photon density within a specified band of wavelengths rather than illuminance (An et al., 2009; Brainard et al., 2001; Gooley et al., 2010). Illuminance measures reflect the wavelength sensitivity of the human visual system to light and can significantly misrepresent photic input for nonvisual responses. A number of nascent models have proposed a basis for light measurement related to circadian, neuroendocrine and neurobehavioral responses. For example, the recently described "melanopic" photometric measure of light intensity predicts melanopsin-driven pupil and circadian responses to polychromatic light in mice with only ipRGC photoreceptors (rd/rd cl mice; Enezi et al., 2011).

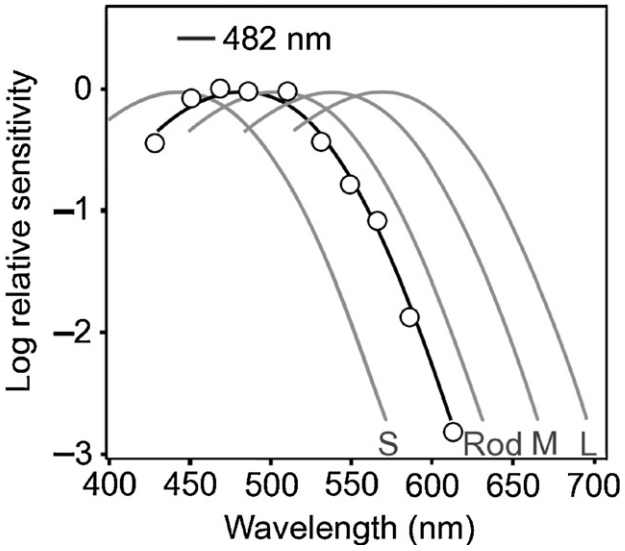

Fig. 1. Responsivity of melanopsin compared to other photopigments. *Notes*: Log relative sensitivity scaled to fit an A1-based photopigment nomogram identifying 482 nm as the wavelength at which melanopsin-containing ganglion cells are most sensitive in the non-human primate. S – short, M – medium, and L – long wavelength cone cells.

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3.2. Chromatic pupillometry

Because current measures of retinal function like ERG measure electrical activity across the entire retina, the effect of relatively sparse melanopsin cells may be quite low unless stimuli are carefully designed to reflect melanopsin responses. For example, the post-illumination pupil response (PIPR) is likely to be predominately mediated by melanopsin cells as opposed to rods or cones, leading to methods designed to elicit melanopsin responses (Park et al., 2011). Studies using monochromatic light stimuli may want to approach 460 nm as opposed to 480 nm to optimally stimulate melanopsin-driven responses, as 460 nm is the wavelength maximally driving sustained melanopsin driven pupil responses to long duration stimuli (McDougal and Gamlin, 2010; Mure et al., 2009), as well as prolonged exposures for acute melatonin suppression (Brainard et al., 2001; Thapan et al., 2001). The spectral profile of photoreceptors (i.e., rods, cones, and ipRGCs) in the primate retina is shown in Fig. 1, demonstrating that narrow bandwidth stimuli are needed to minimize "bleed-through" of a stimulus intended to stimulate only ipRGCs. In SAD, it is more likely that sustained light input, from the environment across the day, is more etiologically significant than brief stimuli. In addition, it may be more ecologically valid to use polychromatic light stimuli when evaluating circadian, neuroendocrine and neurobehavioral responses. Finally, cones appear to provide strong early input and subsequently adapt, while melanopsin cells provide sustained input during continuous illumination without evidence for adaptation (Dollet et al., 2010; Gooley et al., 2010). In mice, rods appear to play a large role in

circadian photoentrainment, in addition to cones, so it is important to consider rod contributions when trying to isolate the responses of ipRGCs (Altimus et al., 2010).

3.3. Assessment timing

Beyond careful control of stimuli parameters, the timing of light experiments is critical because of the existence of circadian variations in melanopsin cell sensitivity. As described above, melanopsin cells display a daily variation in a number of factors that may affect sensitivity (Gonzalez-Menendez et al., 2009; Hannibal et al., 2005; Sakamoto et al., 2004; Zele et al., 2011). It is not yet known if efforts to standardize timing across participants should be based on the timing of first light exposure at awakening, or based on circadian time. Each would imply different means of controling for variables known to influence melanopsin functioning including circadian time, previous light exposure, and current environmental photoperiod.

3.4. Blue light hazard

Concerns have been raised about the safety of both experimental and therapeutic light exposures (Gagne et al., 2011; Reme et al., 1996; Terman, 2009). Since light devices vary in their spectral composition, it is always prudent to assure light dosages given to the human eye fall within safe exposure limits. According to national and international standards, one of the defined risks of photochemical retinal injury, the blue light hazard, is highest between 400 and 500 nm (ACGIH, 2010; ANSI, 2005, ICNIRP, 1997). Researchers can use the published standards to calculate the safe limit of duration and irradiance for stimuli (Brainard et al., 2001, 2008; Glickman et al., 2006; West et al., 2011). Values for absolute irradiance and wavelength of a light source can be determined with a spectrophotometer. Measured irradiance then should be integrated using a blue-light hazard weighting function. Standards are based on exposure durations from 1 ns to 8 h (ACGIH, 2010; ANSI, 2005, ICNIRP, 1997). Since light therapy for SAD is typically used daily during fall and winter for 30–60 min, it is within the dosimetric range of these standards. Absolute irradiance measurements also permit experimenters to determine the photon density at each wavelength from a light source, critical for accurately interpreting the physiological, behavioral and therapeutic responses to light (Revell et al., 2010). Hence, it is important for SAD researchers to provide detail on the spectrum and irradiance of their light sources (Anderson et al., 2009; Revell et al., 2010; West et al., 2011).

3.5. Optimizing light therapy for SAD

The discovery and characterization of the melanopsin pathway triggered interest in using lights with wavelengths centered around the blue portion of the visible spectrum, or broad bandwidth light with increased intensity in the blue-appearing wavelengths. Studies have established that blue or blue-enriched lights at significantly lower light irradiances, yield similar rates of improvement in SAD as traditional bright white light therapy units (Anderson et al., 2009; Glickman et al., 2006; Meesters et al., 2011; Strong et al., 2009), and are able to phase advance rhythms (Smith et al., 2009). Outstanding questions include whether the melanopsin cells are primary in mediating light therapy's effects, and whether it may be possible to potentiate the effects of light therapy by using long wavelength light first (Gooley et al., 2010; Mure et al., 2009; Rollag, 2008). Furthermore, it is possible that gene variations could be used to predict the timing, duration, risk of side effects, and potential benefit of light therapy, opening the door to individualized treatment prescriptions in the future.

3.6. Conclusions

The new research on melanopsin and the circadian, neuroendocrine and neurobehavioral repsonses to light has provided an opportunity to understand the physiology behind individual differences in responses to seasonal changes in light levels. It appears that melanopsin sequence variations may increase risk for mood disorders with a seasonal pattern. Further, seasonal variations in sleep and chronotype may be mediated by different thresholds of melanopsin-based sensitivity to light. Both of these SNP-association studies, however, deserve replication. Determining if the melanopsin pathway is involved in mood and sleep disorders may help improve treatment outcomes by determining the time, duration, and wavelength for optimal light therapy. In addition, it may be possible to identify subgroups of individuals with SAD for whom melanopsin functioning may or may not be important, allowing for individually tailored treatment prescriptions.

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