THE ROLE OF ENVIRONMENTAL LIGHT EXPOSURE AND CIRCADIAN TIMING IN SEASONAL AFFECTIVE DISORDER

by

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B.S. in Psychology, Ohio State University, 2013

Submitted to the Graduate Faculty of

The Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2019

UNIVERSITY OF PITTSBURGH

THE DIETRICH SCHOOL OF ARTS AND SCIENCES

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Background: Individuals with seasonal affective disorder (SAD) experience depressive episodes in the winter that remit in the summer. The phase shift hypothesis of SAD suggests that a later sunrise in winter delays circadian phase that then leads to depression. As the circadian system is optimally sensitive to blue wavelengths, blue light exposure may be particularly important for SAD. Thus, the current study aims to investigate whether circadian phase mediates the association between blue light exposure and depressive symptoms in SAD. **Methods:** Adults (N = 90; 81% women) with varying degrees of seasonality were recruited in winter. Light was measured by an actigraphy watch with a photodiode. Depressive symptoms were measured by a clinical interview while circadian phase was estimated by both self-reported sleep-wake times and melatonin onset. **Results:** A longer duration and later timing of blue light exposure were both associated with delayed melatonin onset. Neither circadian phase, nor blue light exposure was associated with depressive symptoms in the full sample. When women were analyzed separately, a relatively advanced circadian phase mediated the relationship between reduced blue light exposure centered in the afternoon and greater depressive symptoms. **Discussion:** Our results contrast previous reports that a relative delay in circadian phase is associated with greater depressive symptoms. In the full sample, this association was not present and when the data were analyzed separately for women, more advanced phase was associated with greater depression. Thus, future studies recruiting more men are necessary to determine whether gender influences the relationship between phase and depressive symptoms in SAD.

TABLE OF CONTENTS

1.0 INTRODUCTION 1

1.1 SAD AND LATITUDE 2

1.2 THE DIRECT PATHWAY AND SAD 3

1.3 THE INDIRECT PATHWAY: CIRCADIAN ENTRAINMENT 4

1.4 EXTERNAL DESYNCHRONY IN NON-SEASONAL DEPRESSION 8

1.5 INTERNAL DESYNCHRONY IN NON-SEASONAL DEPRESSION 10

1.6 THE PHASE SHIFT HYPOTHESIS OF SAD 12

1.7 LIGHT THERAPY FOR THE TREATMENT OF SAD 15

1.8 BIOLOGICAL VULNERABILITIES IN SAD 17

1.9 LIGHT EXPOSURE IN SAD 19

1.10 RELEVANCE OF WAVELENGTH 21

1.11 HYPOTHESES AND STUDY AIMS 23

2.0 RESEARCH DESIGN AND METHODS 25

2.1 PARTICIPANTS 25

2.2 MEASUREMENTS 27

2.2.1 Light exposure 27

2.2.2 Seasonality 27

2.2.3 Depressive symptoms 28

2.2.4 Phase of entrainment 28

2.2.5 Circadian phase 29

2.2.6 Sleep variables 29

2.3 PRELIMINARY ANALYSES OF DATA 30

2.3.1 Timing and duration of light above threshold 31

2.4 PRIMARY ANALYSES 33

2.4.1 Covariates 33

2.5 ANCILLARY AIMS 34

2.5.1 DLMO 34

2.5.2 White light exposure 34

3.0 RESULTS 35

3.1 PARTICIPANTS 35

3.2 DEPRESSIVE SYMPTOMS 37

3.3 SLEEP AND CIRCADIAN VARIABLES 37

3.4 LIGHT EXPOSURE VARIABLES 38

3.5 PRIMARY AIMS 39

3.6 ANCILLARY AIMS 42

3.6.1 DLMO 42

3.6.2 White light exposure 44

3.7 POST HOC ANALYSES 47

3.7.1 Women-only sample 47

4.0 DISCUSSION 50

4.1 LIMITATIONS 53

4.2 FUTURE DIRECTIONS 54

APPENDIX A: ACTIWATCH CLEANING PROTOCOL 55

APPENDIX B: MSF_{SC} CALCULATION 59

APPENDIX C: HOURLY LIGHT EXPOSURE BY CIRCADIAN AND CLOCK TIME ANALYSES OF LIGHT DATA 60

APPENDIX D: R SCRIPTS USED TO CALCULATE LIGHT DATA AND SLEEP VARIABLES 68

BIBLIOGRAPHY 78

LIST OF TABLES

Table 1. Criteria for establishing group membership 26

Table 2. Comparing various studies that report the correlation between MSFsc and DLMO..... 29

Table 3. Demographic and descriptive statistics of entire sample by group 36

Table 4. Model of blue light timing and duration predicting depressive symptoms 40

Table 5. Models of blue light timing and duration predicting circadian phase 41

Table 6. Models of circadian phase predicting depressive symptoms..... 41

Table 7. Demographic and descriptive statistics by group in subsample with DLMO 43

Table 8. Model of white light timing and duration predicting depressive symptoms 45

Table 9. Model of white light timing and duration predicting circadian phase..... 45

Table 10. Model of blue light timing and duration predicting depressive symptoms in women . 47

Table 11. Model of blue light timing and duration predicting circadian phase in women..... 48

Table 12. Models of circadian phase predicting depressive symptoms in women..... 48

Table 13. Summary of findings including effect sizes and p-values..... 49

Table 14. Model of white light exposure from 10:00 – 11:00am predicting depressive symptoms 67

Table 15. Models of white light exposure from 10:00 – 11:00am predicting circadian phase..... 67

LIST OF FIGURES

Figure 1. Circadian variables 5

Figure 2. The phase response curve 6

Figure 3. Internal and external desynchrony 8

Figure 4. Relationship between depression and phase angle of melatonin and sleep onset 14

Figure 5. The melanopsin sub-sensitivity model 19

Figure 6. The theoretical model 24

Figure 7. MLiT and SD MLiT for a single SAD participant 32

Figure 8. Correlations between thresholds of blue light and circadian phase 39

Figure 9. Correlations between thresholds of blue light and circadian phase 46

Figure 10. Flow chart to determine sleep onset 55

Figure 11. Group hourly blue light exposure by (A) clock time and (B) time since wake 64

Figure 12. Group hourly blue light exposure by (A) clock time and (B) time since wake for a subsample of participants with DLMO 65

Figure 13. Hourly white light exposure by (A) clock time and (B) time since wake 66

1.0 INTRODUCTION

One in ten people will experience a mood disorder in their lifetime (Kessler et al., 2005). Depression is one of the leading causes of occupational disability (Murray & Lopez, 1997) and costs the United States $36.6 billion each year (Lépine & Briley, 2011; Kessler et al., 2006). Given the enormity of this public health concern, efforts to understand the etiology of depression are critical for its treatment and prevention.

Nearly 10-20% of individuals with depression exhibit a seasonal pattern of symptoms, referred to as seasonal affective disorder (SAD; Magnusson et al., 2000). Most commonly, individuals with SAD present with depressive symptoms in the winter that remit in the spring (Lewy et al., 1982; Rosenthal et al., 1983). In contrast to non-seasonal depression, individuals with SAD report greater atypical depressive symptoms such as hypersomnia, fatigue, hyperphagia, and carbohydrate craving (Rosenthal et al., 1984; Wirz-Justice et al., 1986; Thompson & Isaacs, 1988; Garvey et al., 1988; Lingjaerde et al., 1999; Rosenthal et al., 1984). In the general population, another 20% report seasonal patterns in food consumption, energy, sleep and mood without meeting criteria for a major depressive episode (Kasper et al., 1989). These individuals that react to changes in the season without developing depression are classified as sub-syndromal SAD (S-SAD; Rastad et al., 2005). Since SAD and S-SAD symptom onset tracks seasonal changes, environmental factors such as climate are thought to be involved in SAD etiology.

1.1 SAD AND LATITUDE

In contrast to non-seasonal depression, the prevalence of SAD increases at more extreme latitudes, suggesting an involvement of climatic factors (Reviewed in Mersch et al., 1999). The two most obvious factors that vary by latitude are day length (i.e., photoperiod) and temperature. Indeed, a number of studies find that while a shorter photoperiod and lower temperatures both correlate with greater SAD prevalence, a shorter photoperiod is consistently the strongest predictor of SAD onset (Rosenthal et al., 1984; Wirz-Justice et al., 1986; Potkin et al., 1986; Molin et al., 1996; Young et al., 1997). However, there is also variation between cities located at similar latitudes, such as New York City (40.7°N) and Capri, Italy (40.6°N), which have SAD prevalence rates of 4.7% and 2.0% respectively (Terman 1988; Muscettola et al., 1995). Cloudy cities report higher rates of SAD (Potkin et al., 1986) and could account for differences in prevalence among cities with comparable latitudes. This association between latitude, cloudiness, and SAD prevalence suggests that environmental light exposure may play a role in the etiology of SAD.

Research has established that light is not only involved in vision, but also modulates a variety of non-visual functions. Light can influence various psychological and physiological processes that are disrupted in depression, including sleep (Chang et al., 2015; Cajochen et al., 1992; Carrier & Dumont 1995), alertness (Chang et al., 2015; Daurat et al., 1996), and mood (Bedrosian & Nelson 2013). Light can modulate depressive symptoms by either the direct or indirect pathway, as detailed below.

1.2 THE DIRECT PATHWAY AND SAD

Both the direct and indirect pathways require photoreception to occur in the retina. The retina contains three types of photoreceptors: rods, cones, and intrinsically photosensitive retinal ganglion cells (ipRGCs; Provencio et al., 1998; Berson et al., 2002; Hattar et al., 2002). Rods and cones are primarily involved in visual processing, while ipRGCs are primarily involved in non-visual functions (Panda et al., 2003; Hattar et al., 2003; Van Gelder et al., 2001). ipRGCs have direct projections to various brain regions and are collectively referred to as the direct pathway. The direct pathway includes brain regions involved in emotion (i.e., lateral habenula and medial amygdala), arousal (i.e., subparaventricular zone), and sleep homeostasis (i.e., ventral lateral preoptic area; Hattar et al., 2006; Hattar et al., 2002), all of which are dysregulated in depression. Thus, anatomical evidence suggests that reduced light exposure can lead to depressive symptoms by providing less ipRGC input to critical brain regions.

Preliminary studies indicate that light exposure can quickly alter mood by presumably stimulating the direct pathway. Light exposure is capable of quickly improving mood in non-depressed and mildly depressed individuals alike (Goel & Etwaroo, 2006; Virk et al., 2009). Bright light treatment can also prevent reduced mood after tryptophan depletion in mildly seasonal, non-depressed women (Aan Het Rot et al., 2008). The direct pathway is therefore implicated in these fast-acting changes in mood that occur in response to light exposure. However, more research is necessary to determine whether these direct behavioral responses to light are robust and clinically meaningful.

1.3 THE INDIRECT PATHWAY: CIRCADIAN ENTRAINMENT

In contrast to the direct pathway, light can also affect mood indirectly by shifting circadian rhythms. In addition to other brain regions, ipRGCs project to the suprachiasmatic nucleus (SCN), which controls the timing of circadian rhythms within the body. Circadian rhythms influence a variety of physiological, behavioral, and psychological processes including mood (reviewed in McClung, 2015), sleep (Fisher et al., 2013), activity (Pickard & Turek, 1982), and eating behaviors (O'Reardon et al., 2004). As all of these processes are disrupted in depression, the indirect pathway may mediate the effect of light exposure on depressive symptoms in SAD. More specifically, the timing of circadian cycles may be particularly relevant for SAD etiology.

The timing of circadian rhythms is assessed by measuring a specific point on the oscillation. As circadian rhythms fluctuate across the day, they exhibit peaks and troughs, such as the core body temperature minimum, that are used to mark the relative timing of that rhythm. The timing of a given circadian marker is referred to as circadian phase (Figure 1A). Circadian phase can shift to an earlier (i.e., phase advance; Figure 1C) or later time (i.e., phase-delayed; Figure 1D) in response to environmental cues. In other words, a phase advance indicates that each marker within a given oscillation occurs earlier than it did on the previous day.

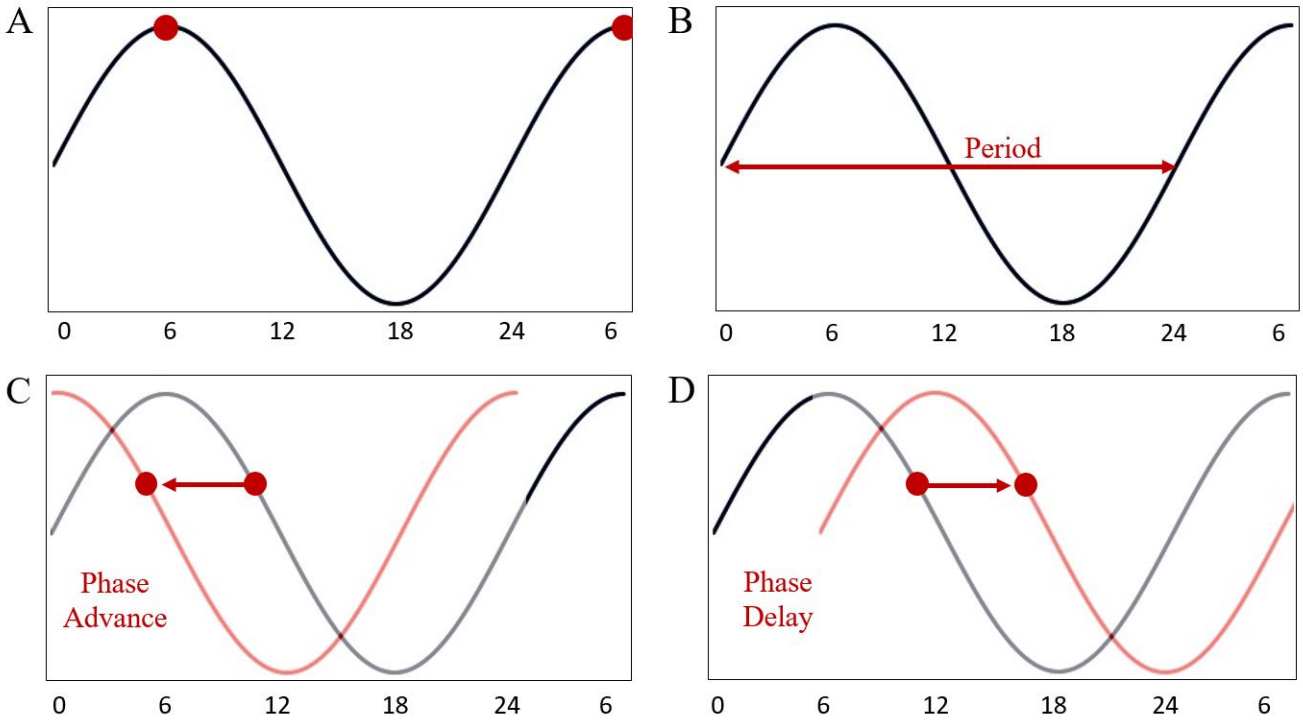

Figure 1. Circadian variables

(A) Circadian phase refers to the time at which a specific point on the oscillation. occurs In this example, the reference point is the peak of the oscillation (i.e. red dots). In both the first and second cycle, the peak occurs at roughly 6 hours and therefore the two cycles have the same phase. (B) Period refers to the duration that it takes to complete one full cycle. In this example, it takes 24 hours for one full cycle (C) represents a phase advance or when a reference point on an oscillation occurs at an earlier time (i.e. red line) than on a previous day (i.e. black line). Similarly, (D) represents a phase delay or when a reference point on an oscillation occurs at a later time than it had previously.

Circadian phase shifts are important for synchronizing our internal rhythms to the day length. The length of a single circadian cycle, or period (Figure 1B) is slightly greater than 24-hours in humans (Czeisler et al., 1999; Burgess et al., 2008; Carskadon et al., 1999), such that each rhythm must advance daily to synchronize, or entrain, to the day length. Entrainment is primarily due to environmental light exposure (Czeisler & Wright 1999). The timing of light

exposure predicts the magnitude and direction of circadian phase shifts. The phase response curve (Figure 2) details these predictions and indicates that light in the morning advances circadian phase, whereas evening light delays circadian phase (Revell et al., 2012; St. Hilaire et al., 2012; Honma et al, 1987; Minors et al., 1991; Khalsa et al., 2003; Rüger et al., 2013). Thus, light is the primary entraining cue and the timing of its exposure can predict circadian phase.

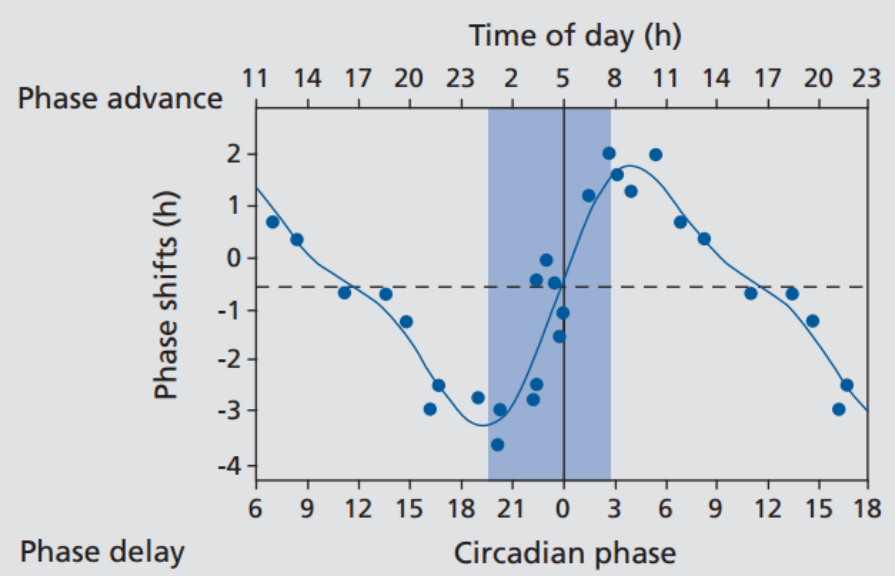

Figure 2. The phase response curve

This figure illustrates the phase response curve for a 6.7-hour pulse of bright white light. The positive values indicate a phase advance while the negative values indicate a phase delay. The dotted horizontal line indicates an anticipated phase delay of approximately 30 min that occurs in between phase assessments when measured under a constant routine protocol. This figure was reprinted from "Light and chronobiology: implications for health and disease" by M. Munch and V. Bromundt, 2012, *Dialogues in Clinical Neuroscience, 14*, p. 449. Copyright 2012 by LLS SAS. Reprinted for the purposes of a proposal committee meeting.

Given the role of light in circadian entrainment, the widespread use of artificial lighting likely impacts circadian phase (Bedrosian & Nelson 2013). Artificial lighting can lead to a decoupling between the timing of our internal circadian rhythms and the natural light-dark cycle, called external desynchrony (Figure 3A). Under artificial lighting conditions, light exposure extends further into the evening (de la Inglesia et al., 2015; Cinzano et al., 2001; Stothard et al., 2017; Wright et al., 2013) and is less intense during the morning and afternoon (Scheuermaier et al., 2010; Figueiro & Rea, 2016; Wright et al., 2013; Stothard et al., 2017). In line with the phase response curve, individuals under artificial lighting receive less morning light and a greater evening light delays circadian phase and leads to greater external desynchrony (Wright et al., 2013; Stothard et al., 2017).

Artificial light exposure can also alter the synchronization between two endogenous rhythms, known as internal desynchrony (Figure 3B). Internal desynchrony occurs when the phase angle, or interval, between two rhythms is either lengthened or shortened (Figure 3B). For example, artificial lighting can lead to internal desynchrony between melatonin and sleep-wake rhythms. Under these conditions, melatonin offset occurs after wake, which likely leads to greater sleepiness upon awakening (Wright et al., 2013). Of interest, external and internal desynchrony are associated with seasonal and non-seasonal depression, as detailed below. Thus, it is plausible that self-selected lighting conditions can exacerbate external and internal desynchrony and increase an individual's susceptibility to developing depression.

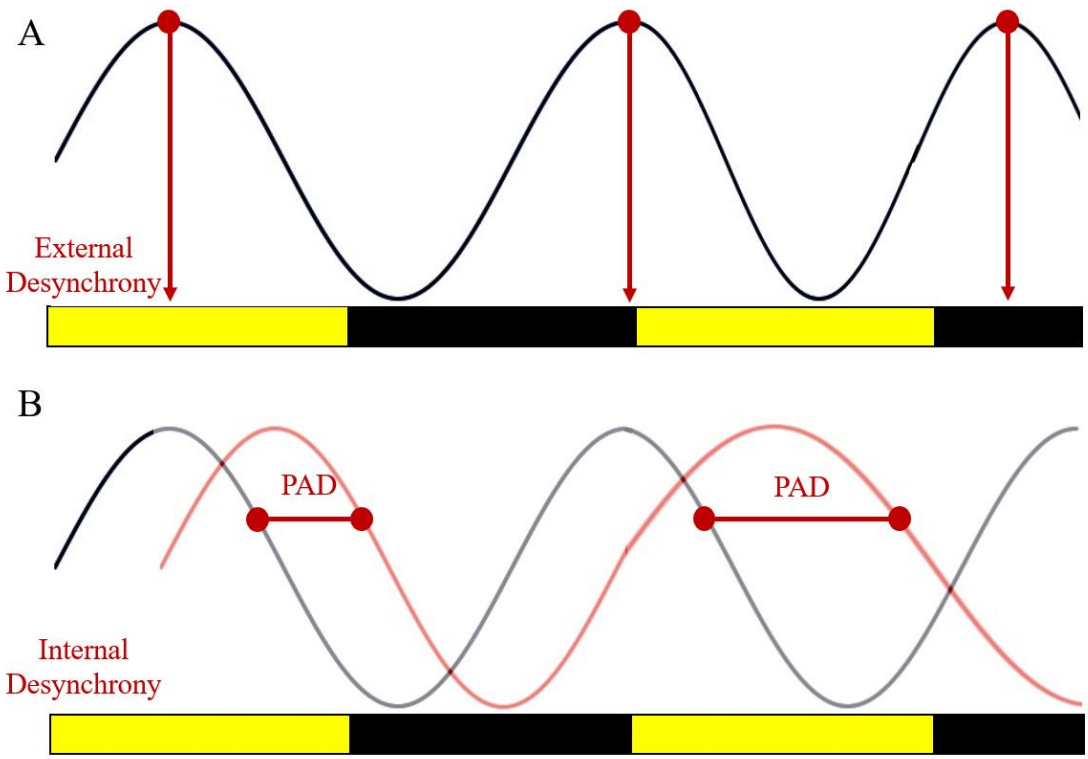

Figure 3. Internal and external desynchrony

The yellow and black lines represent as 12:12 light and dark cycle. (A) Depicts internal desynchrony that occurs between two rhythms. During the first cycle, the two oscillations that are synchronized and exhibit an optimal phase angle difference (phase angle). However, on the second cycle, phase angle between rhythms becomes lengthened and the rhythms become desynchronized. (B) Represents external desynchrony occurring between a specific oscillation and the external light-dark cycle. Across cycles, the same point in the oscillation (i.e., the peak) occurs at different times in the external light-dark cycle.

1.4 EXTERNAL DESYNCHRONY IN NON-SEASONAL DEPRESSION

It is well established that evening chronotype, which is indicative of a delayed circadian phase, is associated with depression. For example, numerous studies show that evening

preference is associated with increased depressive symptoms (Drennan et al., 1991; Chelminski et al., 1999; Hirata et al., 2007; Abe et al., 2011; Kim et al., 2010; Hasler et al., 2010a). Individuals who prefer the evening are more likely to report depressive symptoms (Hidalgo et al., 2009) and individuals with major depressive disorder have stronger evening preferences relative to non-depressed controls (Drennan et al., 1991; Chelminski et al., 1999). Even within individuals diagnosed with depression, those with greater eveningness have more severe symptoms (Gaspar-Barba et al., 2008). The literature consistently supports an association between evening chronotype and depression.

By contrast, evidence of a delayed phase in depression using objective measures of circadian phase have led to mixed findings. When evaluating the timing of sleep-wake rhythms, studies consistently support a delayed sleep onset in depression (Hasler et al., 2010b; Robillard et al., 2014). However, when circadian phase is measured by melatonin onset or core body temperature minimum, the evidence is less clear as to whether that individuals with depression are phase-delayed relative to controls (Hasler et al., 2010a; Hasler et al., 2010b). Daimon and colleagues (1992) found that only a subset of individuals with depression (23%) had delayed core body temperature rhythms relative to controls (Diamon et al., 1992). Furthermore, the timing of melatonin onset does not differ between young adults with clinical and subclinical depression, indicating that changes in phase do not alter as a function of depression severity (Naismith et al., 2012). Therefore, the timing of sleep, but not melatonin onset or core body temperature minimum, may be useful in differentiating individuals with depression from non-depressed controls.

Although the timing between melatonin onset and core body temperature do not clearly identify individuals with depression, circadian disruption could lead to greater symptoms in at

risk populations. Emens and colleagues (2009) reported that a delay in melatonin onset is associated with greater symptom severity in depressed women. However, this finding has failed to replicate in more recent studies that included men and women (Carpenter et al., 2017; Robillard et al., 2017), perhaps due to gender differences (Swanson et al., 2017). Circadian phase disruptions are also associated with an increased risk for developing depression. Of interest are individuals with delayed sleep phase disorder (DSPD) that, as the name suggests, have consistent delays in their sleep-wake cycle relative to societal norms. Nearly 60% of individuals with DSPD exhibit a delay in their melatonin onset, whereas the rest exhibit normal melatonin rhythms (Murray et al., 2017). Murray and colleagues (2017) demonstrate that among participants with DSPD, those with delayed melatonin onset reported greater depressive symptoms than those with normal melatonin rhythms. Thus, a delayed circadian phase may contribute to greater depressive symptomatology in an already susceptible sample.

Taken together, the findings indicate that individuals with depression exhibit a delayed phase in sleep timing but not in melatonin and core body temperature rhythms. However, a delayed phase leads to increased risk for depression. Seemingly small changes in circadian phase can lead to more drastic differences in the phase angle between two rhythms and cause internal desynchrony. Internal desynchrony is also implicated in depression.

1.5 INTERNAL DESYNCHRONY IN NON-SEASONAL DEPRESSION

The internal coincidence hypothesis by Wehr and colleagues (1979) first suggested internal desynchrony in depression. The authors suggest that endogenous rhythms are phase-

advanced (i.e., longer phase angle) relative to sleep in depression. Furthermore, advancing sleep onset, such that it is realigned with internal rhythms, reduces depressive symptoms (Wehr et al., 1979). Similarly, a recent study reports that depression severity is correlated with a shorter phase angle between melatonin onset and midsleep (i.e., greater internal desynchrony) in depressed women (Emens et al., 2009b).

More recent evidence suggests heterogeneity in the direction of internal desynchrony, such that both longer and shorter phase angles between melatonin and sleep characterize non-seasonal depression. More specifically, some studies find sex differences in the association between depression severity and phase angle between melatonin onset and midsleep. In women, a shorter phase angle (i.e., phase delay) associates with greater depressive symptoms (Emens et al., 2009b; Swanson et al., 2017). By contrast, a longer phase angle between melatonin onset and midsleep (i.e., phase advance) associates with more depressive symptoms in men (Swanson et al., 2017). A second study compares the phase angle of melatonin and sleep rhythms between adolescents at early and late stages of a major depressive episode. The findings indicate that the phase angle between melatonin and sleep rhythms shorten as depression progresses (Naismith et al., 2012). A shorter phase angle between melatonin onset and sleep is more commonly reported in depression, but the literature lacks longitudinal evidence to determine whether changes in the phase angle precede depression onset. In addition, samples that include both men and women may report null findings due to gender differences in the association between phase angle and depressive symptoms. It therefore remains unclear whether the phase angle alters as a function of symptom progression within an individual.

Despite evidence supporting an association between internal desynchrony and depression severity, the phase angle between sleep and melatonin rhythms does not distinguish between

individuals with and without depression (Hasler et al., 2010; Emens et al., 2009; Lewy et al., 2006). Although the phase angle between melatonin onset and habitual sleep onset shortens as a function of depression severity (Naismith et al., 2012), the measured phase angles are similar to those reported in healthy individuals (Burgess et al., 2003; Emens et al., 2009a). Furthermore, the phase angle between melatonin onset and sleep onset is not associated with depression severity (Carpenter et al., 2017). Therefore, it seems likely that internal desynchrony, along with environmental and/or biological vulnerabilities, contribute to individual differences in the risk of developing depression. Furthermore, sex differences might increase null findings in samples that are not powered to stratify analyses by gender. Thus, individuals with depression exhibit similar phase angles between melatonin and sleep to controls, but whether a shorter or longer phase angle is predictive of depressive symptoms may be gender specific.

1.6 THE PHASE SHIFT HYPOTHESIS OF SAD

Similar to non-seasonal depression, circadian rhythm disruption is also relevant for SAD. Lewy and colleagues (1983; 1985b; 1988) hypothesize that circadian rhythms are delayed compared to the external environment in SAD. However, studies investigating the phase shift hypothesis report mixed results. In support of the phase shift hypothesis, early studies find a delayed phase in SAD relative to non-depressed controls in both melatonin onset (Lewy et al., 1987; Sack et al., 1990; Lewy et al., 1998) and core body temperature (Wirz-Justice et al., 1995). However, data from other laboratories fail to replicate a delayed circadian phase in either melatonin onset (Checkley et al., 1993; Thompson et al., 1997; Dahl et al., 1993; Wehr et al. 2001), or core body temperature minimum (Rosenthal et al., 1990; Eastman et al., 1993;

Schwartz et al., 1997; Levendosky et al., 1991). Importantly, the majority of the studies cited have small sample sizes (N = 6 - 22 per group), making it difficult to detect small to moderate effect sizes. Notably, the study recruiting the most participants (N =100) detected a moderate delay in melatonin onset in SAD relative to controls (Lewy et al., 1998; d = 0.42). Some studies include currently depressed participants with both unipolar and bipolar SAD (Lewy et al., 1988; Checkley et al., 1993; Sack et al., 1990), while other studies select specifically for unipolar SAD (Thompson et al., 1997). Therefore, diagnostic heterogeneity and small samples make it difficult to conclude a delayed phase in SAD.

The phase shift hypothesis was revised to emphasize internal desynchrony (Lewy et al., 1987; Lewy et al., 1985) and suggests that the phase angle between melatonin onset and midsleep can be longer or shorter than that of non-depressed individuals. The phase angle of melatonin onset and mid-sleep is approximately 6 ± 1 hours in non-depressed controls (Burgess et al., 2003; Emens et al., 2009a). Individuals with SAD exhibit a phase angle both longer and shorter than 6 hours, suggesting heterogeneity within the disorder (Lewy et al., 2006; Figure 4). Phase angles both longer and shorter than 6 hours are associated with greater depression severity in SAD (Lewy et al., 2006; 2007). After a treatment intervention, participants that resynchronize to a phase angle of 6 hours report reduced depression severity (Lewy et al., 2006). As both phase advances (i.e., phase angle greater than 6 hours) and phase delays (i.e., phase angle less than 6 hours) are present in SAD, assessment of circadian phase could aid in tailoring treatments to resynchronize endogenous rhythms to an optimal phase angle.

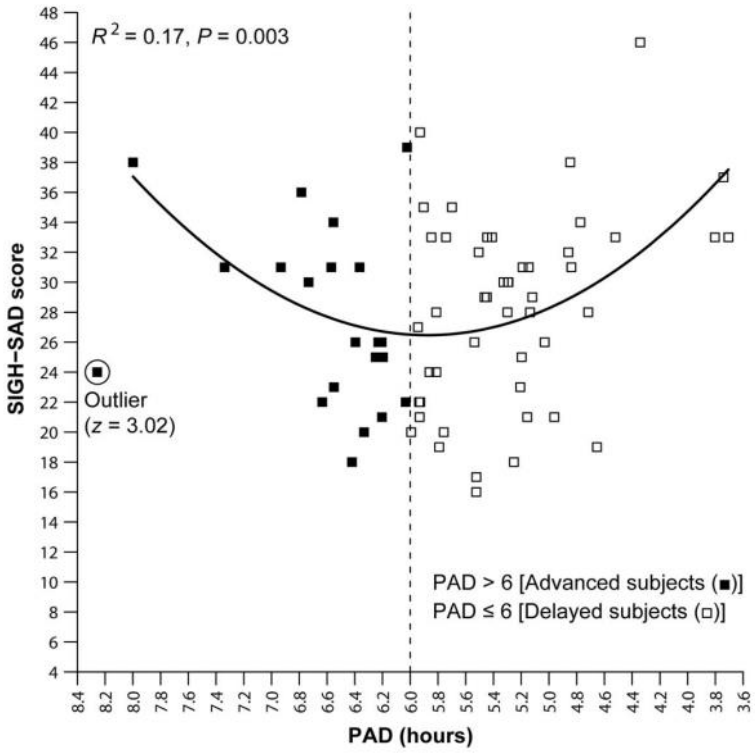

Figure 4. Relationship between depression and phase angle of melatonin and sleep onset

Greater depression severity (SIGHSAD) was associated with a greater deviation from a phase angle of 6 hours. This figure was reprinted from "The circadian basis of winter depression.: by A.J. Lewy, B. J. Lefler, J.S. Emens, and Bauer V.K., 2006, *Proceedings of the National Academy of Sciences, 103(10),* p.7414-7419.

1.7 LIGHT THERAPY FOR THE TREATMENT OF SAD

As mentioned earlier, light is the strongest entraining cue and is therefore used to treat the proposed circadian misalignment in SAD. Rosenthal and colleagues (1984) provided initial evidence supporting light therapy as an effective treatment for SAD. Results from a meta-analysis suggest that light therapy is beneficial for SAD with an overall effect size similar to that of antidepressant medications (d = 0.84; Golden et al., 2005) with fewer side effects (reviewed in Terman & Terman 2005). The current guidelines for light therapy are 7,000-10,000 lux of white light for 30-60 minutes immediately following wake (Terman & Terman 2005).

Given that the majority of individuals with SAD exhibit a delayed phase (Lewy et al., 1987; Avery et al., 1997; Terman et al., 2001), advancing circadian rhythms should lead to symptom improvement. In line with this assumption, morning light therapy, which advances circadian phase, is more effective than evening light therapy (Terman et al., 1989; Lewy et al., 1987; Lewy 1998; Avery et al., 1990). In participants who received morning light therapy, a more advanced phase is associated with reduced symptom severity post-treatment (Terman et al., 2001). Since there is a small percentage of individuals with SAD that are phase-advanced, Lewy and colleagues (2006) stratify treatment outcome by whether the participant receives light therapy at the correct time. For example, SAD participants with a pre-treatment advanced phase are expected to benefit from evening light therapy while the opposite is true of a phase-delayed participant. The results suggest that receiving light therapy at the appropriate time of the day to correct for pre-treatment phase shifts lead to a greater reduction in depressive symptoms relative to placebo (Lewy et al., 2006). Individuals that received inappropriately timed light therapy experienced no greater symptom reduction than those in the placebo group, while those who received correctly timed light therapy had a significant improvement in symptoms (Lewy et al.,

2006). Therefore, phase shifting in response to light therapy is correlated with its degree of efficacy.

Although correcting phase shifts is the proposed mechanism of light therapy, some studies fail to find correlations between the magnitude of phase shift and antidepressant response after light treatment (Wirz-Justice et al., 1993; Murray et al., 2005). Importantly, one of the studies that fail to find an association use self-reported measures of circadian preference rather than objective measures of circadian phase (Murray et al., 2005). The second study that failed to replicate this finding compared evening and morning concentrations of the melatonin metabolite, 6-sulfatoxymelatonin (aMT6s). Individuals with higher aMT6s in the morning relative to the evening are classified as phase-delayed; however, individuals with SAD secrete greater concentrations of melatonin in the morning compared to non-depressed controls (Wehr et al., 2001), making it likely that SAD participants are misclassified as phase-delayed despite changes in circadian phase post-treatment (Wirz-Justice et al., 1993). Although the evidence is mixed, studies utilizing objective measures of circadian phase generally support the phase shift hypothesis (Lewy et al., 1989; Terman et al., 2001).

In short, the majority of individuals with SAD exhibit a delayed phase, rather than an advance (Lewy et al., 1987; Avery et al., 1997; Terman et al., 2001). Advancing circadian rhythms in SAD with morning light therapy leads to clinical improvement. As light phase shifts the clock, SAD etiology may be due, in part, to altered patterns of environmental light exposure in the winter. It is therefore hypothesized that reduced morning light and/or increased evening light in the winter leads to a delayed phase and make an individual more susceptible to SAD.

1.8 BIOLOGICAL VULNERABILITIES IN SAD

While the present study focuses on the role of environmental light exposure, both biological and environmental vulnerabilities likely contribute to the role of light in SAD etiology. Therefore, biological evidence supporting the role of light exposure in SAD is reviewed below. As everyone living in non-equatorial latitudes experience reduced photoperiod in the winter, it seems plausible that individuals with reduced responsivity to light are susceptible to developing SAD. The evidence largely indicates that individuals with SAD have reduced retinal sensitivity.

Retinal sensitivity is measured by various protocols, each providing information on different types of photoreceptors. Electroretinography (ERG) measures the overall electrical activity within the retina in response to light. Studies using ERG report reduced retinal sensitivity in the winter in individuals with SAD (Hébert et al., 2004) and S-SAD (Hébert et al., 2002) compared to individuals without depression. In addition to reporting overall retinal sensitivity, ERG also differentiates rod- and cone-mediated electrical signals. Studies that investigate photoreceptor specific responses report that individuals with SAD exhibit reduced sensitivity in both rods (Hébert et al., 2004; Lavoie et al., 2009) and cones (Lavoie et al., 2009) in the winter. One study fails to replicate these findings, but reported their sample size as a plausible limitation (n = 10 per group; Gagné et al., 2011). Overall, it appears that retinal sensitivity is reduced in SAD during the winter when measured by ERG.

In addition to ERG, melatonin suppression is used as an indirect measure of light responsivity. Since light exposure acutely inhibits nighttime melatonin secretion (Lewy et al., 1980) and greater sensitivity to light exposure leads to a reduction in melatonin secretion. Importantly, melatonin suppression is optimally sensitive to short wavelengths of light (Thapan

et al., 2001), suggesting that this mechanism is mediated by ipRGCs. The majority of findings indicate that individuals with SAD are hypersensitive to melatonin suppression by light in winter (Nathan et al., 1999; Thompson et al., 1990; McIntyre et al., 1990) and demonstrate subsensitivity in the summer compared to controls (Thompson et al., 1990). However, one study fails to find differences in melatonin suppression between SAD and non-depressed controls (Murphy et al., 1993). Importantly, the study reporting null findings exposed participants to light at a later in the evening (Murphy et al., 1993), indicating that the timing of light exposure influences its ability to suppress melatonin. Taken together, the majority of evidence suggests that individuals with SAD have heightened responsivity to the effects of light exposure on melatonin suppression in the winter.

A third measure of retinal sensitivity is the pupil light reflex in which the pupil constricts in response to a light stimulus. The pupil light reflex directly assesses the magnitude of ipRGC-specific responses to light (Lucas et al., 2001; Lucas et al., 2003; Park et al., 2011; Gamlin et al., 2007). Cones are mainly responsible for the initiation and maintenance of pupil constriction during the light presentation; however, after light offset, the pupil remains constricted for an extended period of time. This long-term constriction is referred to as the post-illumination pupil response (PIPR; Gamlin et al., 2007) and is mediated by ipRGCs. Thus, the PIPR measures ipRGC responsivity to light, such that a greater PIPR (i.e., greater sustained pupil constriction) corresponds to greater ipRGC responsivity to a light stimulus (Berson et al., 2002; Ruby et al., 2002; Hattar et al., 2003; Barnard et al., 2006). Individuals with SAD have reduced ipRGC responsivity (i.e., reduced PIPR) in the winter compared to non-depressed controls (Roecklein et al., 2013; Berman et al., 2018). Assuming that the PIPR is indicative of the magnitude of ipRGC input to the central pacemaker (i.e., SCN), then reduced input to the SCN via reduced ipRGC

responsivity may result in diminished entrainment of circadian rhythms by light in SAD. Taken together, the data suggest that even if SAD patients and controls receive similar light input in the winter, individuals with SAD may respond more weakly to that light exposure (Figure 5).

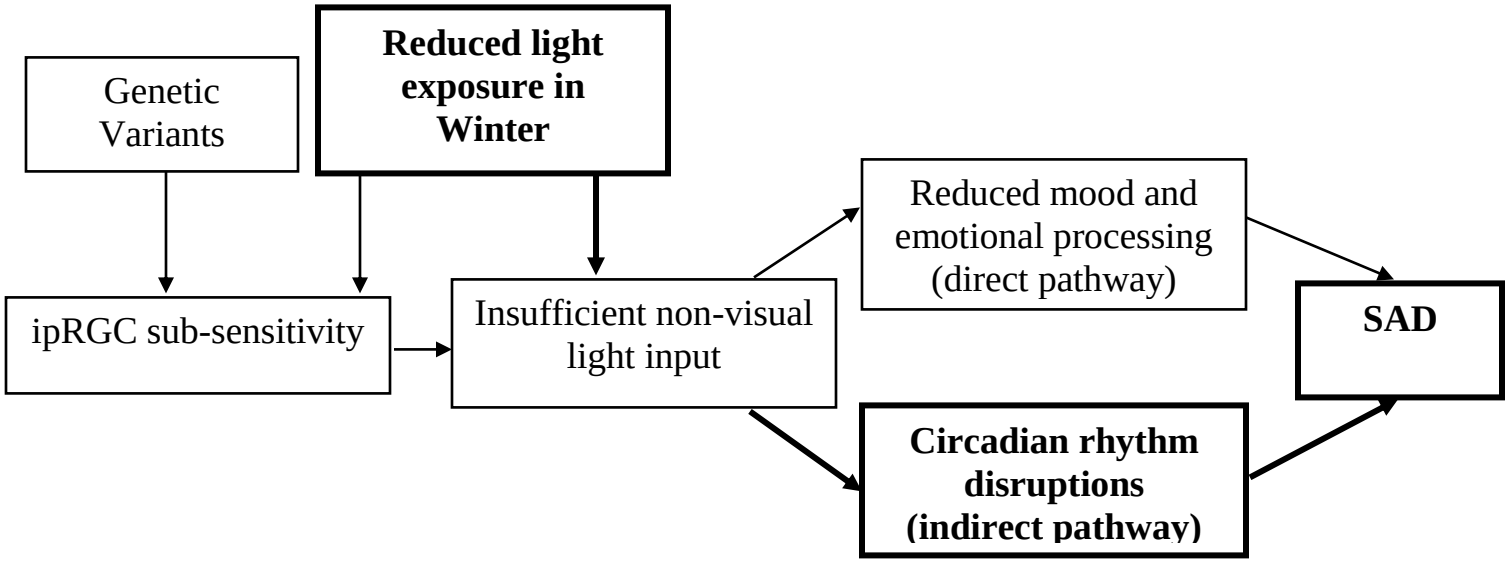

Figure 5. The melanopsin sub-sensitivity model

The melanopsin sub-sensitivity model. In this model, both genetic and environmental factors contribute to reduced ipRGC sensitivity and ultimately reduced light input. Less photic input can lead to depressive symptoms by both the direct and indirect pathways, as discussed earlier. In bold are the portions of the model that are tested in the current study.

1.9 LIGHT EXPOSURE IN SAD

In individuals with retinal subsensitivity, exposure to different patterns of light may further exacerbate the risk for SAD. Several studies investigate light exposure in SAD patients and controls and fail to find differences, likely due to methodological limitations. One of these studies uses self-report measures of outdoor activity as a proxy for outdoor light exposure (Graw

et al., 1999). They find that women with SAD and non-depressed controls do not differ in their outdoor activity during the winter, suggesting that there are no self-imposed increases in exposure to outdoor lighting during the season of risk (Graw et al., 1999). Outdoor lighting can exceed 10,000 lux of white light (Wright et al., 2013), which is an intensity greater than necessary to shift (i.e., delay or advance) circadian phase (Khalsa et al., 2003). The lack of group differences suggest that outdoor light exposure may not be the only variable relevant for the development of SAD. However, this study relies on self-report and does not differentiate between exposure at different times of day, such that discrete group differences in environmental light exposure at times relevant for the circadian clock might be overlooked.

Another study by Oren et al. (1994) measures light exposure objectively using a watch equipped with a light sensor to test for differences in light exposure between SAD participants and controls. The authors report that individuals with SAD are not exposed to less light compared to controls when assessed across all seasons. However, this study calculates the average light exposure between groups across the entire year by combining data from SAD participants during a depressive episode and periods of remission. As patients with SAD only report depression in the winter, it is possible that they are only receiving abnormal light exposure when symptomatic, such that differences in light exposure would be more apparent in winter (Oren et al., 1994).

Guillemette and colleagues (1998) investigate the effects of light exposure on individual differences in seasonality. The authors show that individuals high in seasonality are exposed to equivalent amounts of light as their less-seasonal counterparts (Guillemette et al., 1998). However, this study compares healthy controls with individuals who are high in seasonality, but not clinically depressed. Therefore, it is expected that this sample would show less robust

differences compared to controls than is expected for a clinically depressed SAD sample. Additionally, given the small sample size (N = 19), this study is likely underpowered to detect group differences in light exposure.

Although the aforementioned studies all report null findings, methodological limitations preclude confident interpretation that individuals with SAD are not exposed to different levels of light at critical time points compared to non-depressed controls. Perhaps most notably, these studies fail to discriminate different (1) times of the day and (2) wavelengths of light that are particularly relevant for synchronizing circadian rhythms to the light-dark cycle. Morning and evening are critical times for light exposure, as light at these times has greater effects on the circadian phase than light presented at mid-day (Lewy et al., 1987; Revell et al., 2012; St. Hilaire et al., 2012; Ramkisoensing & Meijer 2015; Homna et al, 1987). Although Guillemette and colleagues (1998) investigate differences in light exposure at different times of the day in highly seasonal participants, the data are aggregated across the entire day into bins spanning four hours. As the effect of light exposure on circadian phase changes across the day (i.e., PRC), it is important to determine whether light exposure during shorter epochs is relevant in SAD.

1.10 RELEVANCE OF WAVELENGTH

In addition to timing, the wavelength of light differentially affects non-visual functions. Non-visual functions such as melatonin suppression (Thapan et al., 2001; Wright & Lack 2001; Lockley et al., 2003), phase shifting (Wright & Lack 2001; Lockley et al., 2003), and alertness (Cajochen et al., 2005; Lockley et al., 2006) are maximally sensitive to blue wavelengths. Indeed, the optimal wavelength sensitivity of the non-visual system is consistent with that of

ipRGC responsivity (Brainard et al., 2001; Thapan et al., 2001). However, monochromatic green (Wright & Lack 2001) and red (Hanifin et al., 2006) light are also capable of suppressing melatonin, indicating that other photoreceptors might be involved in circadian entrainment.

The non-visual functions of light are driven by ipRGCs, but both rods and cones can modulate ipRGC activity. Rodents with ablated ipRGCs are unable to entrain to light cues (Güler et al., 2008), suggesting that ipRGCs are necessary for the effects of light on entrainment. When ipRGCs remain intact but are no longer photosensitive, then the mice can entrain to light, but to a lesser degree than wild type mice (Panda et al., 2002; Ruby et al., 2002). ipRGCs are more responsive to their own photosensitivity than to rod or cone input (Schmidt & Kofuji 2010), which could explain why circadian input is less effective when ipRGCs do not have functional photopigment. Although non-visual effects of light are primarily driven by ipRGCs, it cannot be assumed that these effects are independent of rod and cone input.

Although blue wavelengths of light are optimal for phase shifting (Wright & Lack 2001; Lockley et al., 2003), the effect of wavelength on antidepressant response is less clear. Indeed, lower intensities of blue light can lead to the same degree of phase shifts as brighter white light (Warman et al., 2003). Similarly, preliminary evidence suggests 750 lux of blue-enriched light elicited the same antidepressant effects as 10,000 lux of white light (Meesters et al. 2011), in SAD participants; although other studies fail to detect differences in either treatment outcome (Gordijn et al., 2012; Anderson et al., 2009), or phase shifting (Smith et al, 2009) by wavelength. A more recent study shows that blue spectrum light can lead to similar rates of remission as light without blue wavelengths (Anderson et al., 2016). However, the study does not include a no-treatment group, making it difficult to know whether or not the intervention was effective. Taken together, these findings demonstrate that in the absence of blue light, other wavelengths that

stimulate rods and cones can provide antidepressant effects. Thus, the current project investigates the role of both blue and full-spectrum white light exposure in SAD.

1.11 HYPOTHESES AND STUDY AIMS

In summary, the current study investigates whether circadian phase mediates the association between environmental blue light exposure and depressive symptomatology in the winter in SAD. Both reduced morning light and enhanced evening light are associated with a delayed circadian delay (Figure 6, pathway a). Since ipRGCs are necessary for photoentrainment and are optimally responsive to blue wavelengths of light, the primary analyses focus on blue light exposure. It is hypothesized that individuals with SAD are phase-delayed relative to controls (Figure 6, pathway b). The current project proposes that reduced blue light in the morning and/or greater evening blue light are associated with greater depressive symptoms (Figure 6, pathway c). Lastly, it is hypothesized that a delayed circadian phase mediates the association between reduced morning and/or increased evening blue light exposure and greater depressive symptoms. (Figure 6, pathway c′).

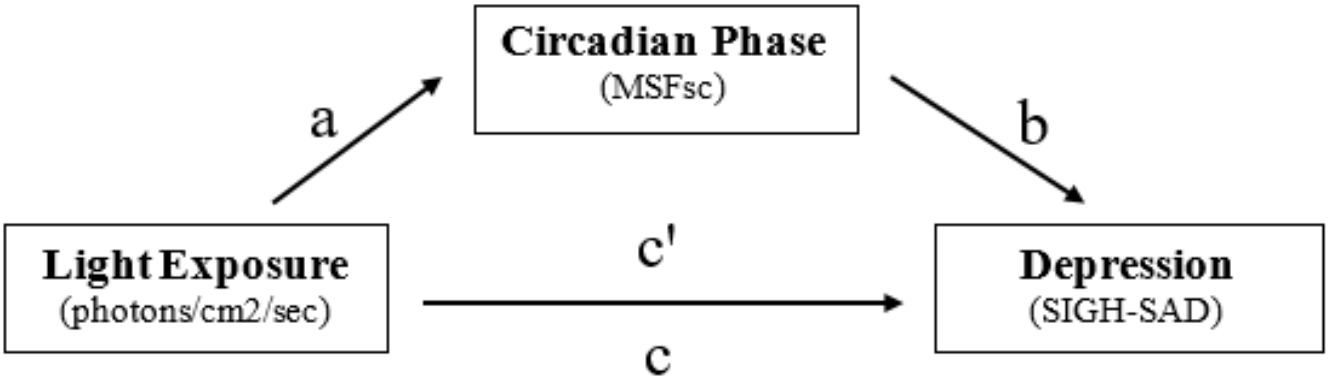

Figure 6. The theoretical model

The association between light exposure and depression severity is mediated by circadian phase. The current study will test the association between (a) light exposure and chronotype; (b) chronotype and depression severity; (c) light exposure and depression severity; and (c') chronotype as a mediator in the association between light exposure and depression severity. Both morning light and evening light will be assessed using separate analyses.

2.0 RESEARCH DESIGN AND METHODS

The current study is a cross-sectional design with individuals recruited during consecutive winters (Dec 21st – March 21st; years 2013-2017). Eligible participants were given a battery of self-report questionnaires to complete in the laboratory. Prior to leaving the initial visit, an actigraphy watch was given to each participant to wear for a minimum of four days. The participants then returned to the laboratory for a Friday evening visit to assess circadian phase.

2.1 PARTICIPANTS

Ninety-one participants (SAD n = 32; S-SAD n = 11; control n = 48) were recruited in the winter as part of a larger study investigating the seasonality of mood. The Institutional Review Board at the University of Pittsburgh approved all procedures and informed consent was obtained prior to experimental procedures. Individuals were excluded if they reported a history of bipolar disorder or psychosis. Current shift work, post-traumatic stress disorder, anorexia, and substance use disorder other than mild alcohol use disorder were also criteria for exclusion. Participants were also excluded if they reported a primary sleep-wake disorder diagnosis with secondary mood symptoms. Participants were free from eye disorders, color blindness, and fasting blood-glucose concentrations at or above the pre-diabetic range (> 110 mg/dL; Rydén et

al., 2007), as each might affect the ability of light to stimulate retinal cells (Tarongoy et al., 2009; Smith & Smith 1983). Criteria for group membership can be found in Table 1.

Table 1. Criteria for establishing group membership

	Group Membership		
	Control	S-SAD	SAD
SCID	No past or current major depressive episode	No past or current major depressive episode	Meets criteria for recurrent major depressive disorder with seasonal pattern specifier
MSPAQ (GSS)	GSS < 7 *or* GSS 8-9 but reports 'no problems'	GSS ≥ 10 *or* GSS > 8 and reports at least 'mild severity'	GSS ≥ 10, reports at least 'moderate severity,' and feels worst in Jan and/or Feb
SIGH-SAD / BDI	BDI < 10	SIGHSAD below criteria specified for SAD	SIGHSAD sores: Total ≥ 20 Typical symptoms ≥ 10 Atypical symptoms ≥ 5

Note. SCID = Structured Clinical Interview for DSM-IV (First et al., 2015); MSPAQ = Modified Seasonal Pattern Assessment Questionnaire; GSS = Global Seasonality Score from the modified Seasonal Pattern Assessment Questionnaire; SIGH-SAD = The Structured Interview Guide for the Hamilton Depression Rating Scale, SAD Version (Terman et al., 1990; Kasper et al., 1989).

2.2 MEASUREMENTS

2.2.1 Light exposure

Participants wore an Actiwatch Spectrum (Philips Respironics Inc., Bend, OR) equipped with a photodiode to detect blue (400-500 nm), green (500-600 nm), and red (600-700 nm) wavelengths of light. The actiwatch was set to an activity threshold of 40 counts, and activity level less than or equal to 40 counts for 20 consecutive epochs were considered sleep onset. These thresholds were previously validated and are highly correlated with polysomnography measurements of sleep (Ancoli-Israel et al., 2003; Baandrup & Jennum 2015). Light levels were recorded in 30-second epochs and actigraphy data was manually cleaned by an individual blind to group membership according to laboratory guidelines. See Appendix A for study-specific guidelines established for cleaning actiwatch output.

2.2.2 Seasonality

The Modified Seasonal Pattern Assessment Questionnaire (M-SPAQ) is a questionnaire used to assess self-reported seasonality (Lam, 1998; Rosenthal et al., 1984). The MSPAQ was used to aid diagnosis and group membership selection (see Table 1). The Global Seasonality Score (GSS) is a subset of 6 questions on the M-SPAQ that asks participants to rate the degree to which sleep duration, mood, appetite, social activity, weight and energy levels change across seasons. Each item is scored from 0 – 4, with 0 representing ‘no change’ and 4 representing ‘extremely marked change.’ The M-SPAQ has high internal consistency (Cronbach’s alpha = 0.80; Young et al., 2003) and test-retest reliability (r = 0.76; Young et al., 2003).

2.2.3 Depressive symptoms

The Structured Interview Guide for the Hamilton Depression Rating Scale, SAD Version (SIGH-SAD; Williams et al., 1992) was used to assess depression symptomatology. The SIGH-SAD uses the original nine questions from the Hamilton Rating Scale for Depression (HAM-D) with an additional eight questions to assess atypical symptoms that are common in SAD (Tam et al., 1997). The SIGH-SAD has high test-retest reliability (r = 0.82; Williams, 1988) and high internal consistency (Cronbach's alpha = 0.78-0.90; Rohan et al., 2003). The SIGH-SAD was used both as inclusion criteria for study eligibility and group membership (Table 1), and used in regression analyses as a measure of depressive symptoms.

2.2.4 Phase of entrainment

The Munich Chronotype Questionnaire (MCTQ; Roenneberg et al., 2003) is a self-report questionnaire that assesses sleep and wake times on both work days and free days. In addition, participants are asked about the amount of time spent outdoors, stimulant consumption, and work schedules. Individual questions from the MCTQ are used to calculate the timing of midsleep after correcting for sleep debt that accumulates during work days (MSFsc; detailed in Appendix B). The MSFsc was used to estimate circadian phase as it is currently synchronized to the environment (*i.e.,* circadian phase of entrainment). Other chronotype questionnaires assess circadian preference, while the MSFsc estimates circadian phase of entrainment by self-reported habitual sleep-wake times. In line with its emphasis on circadian phase above preference, objective measurements of circadian phase are more strongly associated with MSFsc than alternative chronotype questionnaires (Table 2; Kitamura et al., 2014; Kantermann et al., 2015).

Table 2. Comparing various studies that report the correlation between MSFsc and DLMO

Study	Sample characteristics	*r*	*p* - value
Kitamura et al., 2014	37 Japanese adults	0.54	0.002
Kantermann et al., 2015	36 non-depressed controls 24 with delayed sleep phase disorder	0.68	< 0.001
Current study	33 non-depressed controls, 8 S-SAD and 17 SAD participants	0.29	0.01
	SAD/S-SAD only	-0.08	0.69
	Non-depressed controls only	0.51	0.002

2.2.5 Circadian phase

DLMO was used as a marker for circadian phase in a subset (n = 58) of the sample. During DLMO, participants arrived in the laboratory five hours prior to their habitual bedtime and left 2 hours after their habitual bedtime. During this time, participants were kept in a dim-light environment (< 25 lux) and salivary melatonin was collected every 30 minutes. DLMO was defined as the time when salivary melatonin crosses the threshold of 3pg/mL (Benloucif et al., 2008). This threshold was selected due to high inter-rater reliability (r = 0.98) and it was more similar to visually-assessed DLMO, compared to setting individual DLMO thresholds relative to the participants' baseline levels of melatonin concentration (Voultsios et al., 1997).

2.2.6 Sleep variables

Sleep disturbances are a common symptom of depression and individuals with SAD often report hypersomnia. Therefore, sleep variables such as average sleep duration, wake time, and

midsleep were extracted from actigraphy data to investigate group differences in sleep variables (See appendix B for the R script used to calculate sleep variables). Any group differences in sleep variables will be included as covariates since differences in sleep timing or duration might account for differences in light exposure between groups.

2.3 PRELIMINARY ANALYSES OF DATA

The current analyses do not separate work day and free day light exposure. Although individuals exhibit work day and free day differences in light exposure (Crowley et al., 2015), information about work schedules on the days of actiwatch recordings were not collected prior to 2016, resulting in 43.3% (n = 39) of participants with missing work day information. As work days and free days could not be accurately evaluated, the analyses were not separated as such. Light exposure was analyzed only during periods of wakefulness when the eyes are open as blue light minimally penetrates the eyelid (Ando & Kripke 1996; Cole et al., 2002; Robinson et al., 1991; Bierman et al., 2011; Figueiro et al., 2013). In analyses using the MSFsc to measure circadian phase of entrainment, all available light data was used to calculate light variables. In contrast, light data was limited to the six days prior to circadian phase assessment in analyses using DLMO. Each day that is further from DLMO assessment is less likely to contribute to circadian phase. However, by including participants with light data within six days prior to DLMO, we were able to increase power without reducing the correlation between light and DLMO. Light exposure was quantified in four separate ways: (1) hourly light exposure by time since wake, (2) hourly light exposure by clock time (i.e., zeitgeber time), (3) timing of light exposure above a particular threshold, and (4) duration of light exposure above threshold.

Although previous reports looked at hourly light exposure since melatonin onset (Emens et al., 2009; Goulet et al., 2007), the current study measures hourly light exposure by time since wake. The light exposure was aggregated based on the wake time on each separate day of actigraphy recording, whereas melatonin onset was only collected on a single day for a subset of participants. As melatonin onset shifts between workday and non-workdays (Stothard et al., 2017), using melatonin onset as a reference might inaccurately represent the timing of light exposure on days further from melatonin assessment. These four different ways to quantify light exposure provide different information on duration, intensity, and timing of light exposure that might be relevant for circadian phase of entrainment and depressive symptoms. Results and analyses of hourly light data by time since wake and clock time can be found in Appendix C.

2.3.1 Timing and duration of light above threshold

As noted above, the intensity of light is relevant for circadian entrainment. Therefore, the third measurement of light was assessed by determining the mean light exposure above threshold (MLiT; Reid et al., 2014), or the time at which light above a particular threshold is centered. Figure 7 illustrates the MLiT for a single participant. Calculating the standard deviation of MLiT (SD MLiT) is equivalent to the duration of light exposure above a particular threshold (Figure 7). Therefore, these analyses provide information on both the timing (MLiT) and duration (SD MLiT) of light exposure above threshold that might be relevant for circadian phase of entrainment, and subsequent depressive symptomatology. One-tailed Pearson's correlations were calculated between various thresholds of MLiT and MSFsc. One-tailed correlations were used as a positive relationship was expected between MLiT and MSFsc, such that a later timing of light exposure later in the day should be associated with a delayed circadian phase of entrainment. As

such, any threshold of MLiT that yielded negative correlations with MSFsc were not considered for further analysis. The threshold with the highest correlations between MLiT and MSFsc were used for subsequent analyses as blue light exposure must predict MSFsc in order to test for the full mediation analyses (Baron & Kenny, 1986).

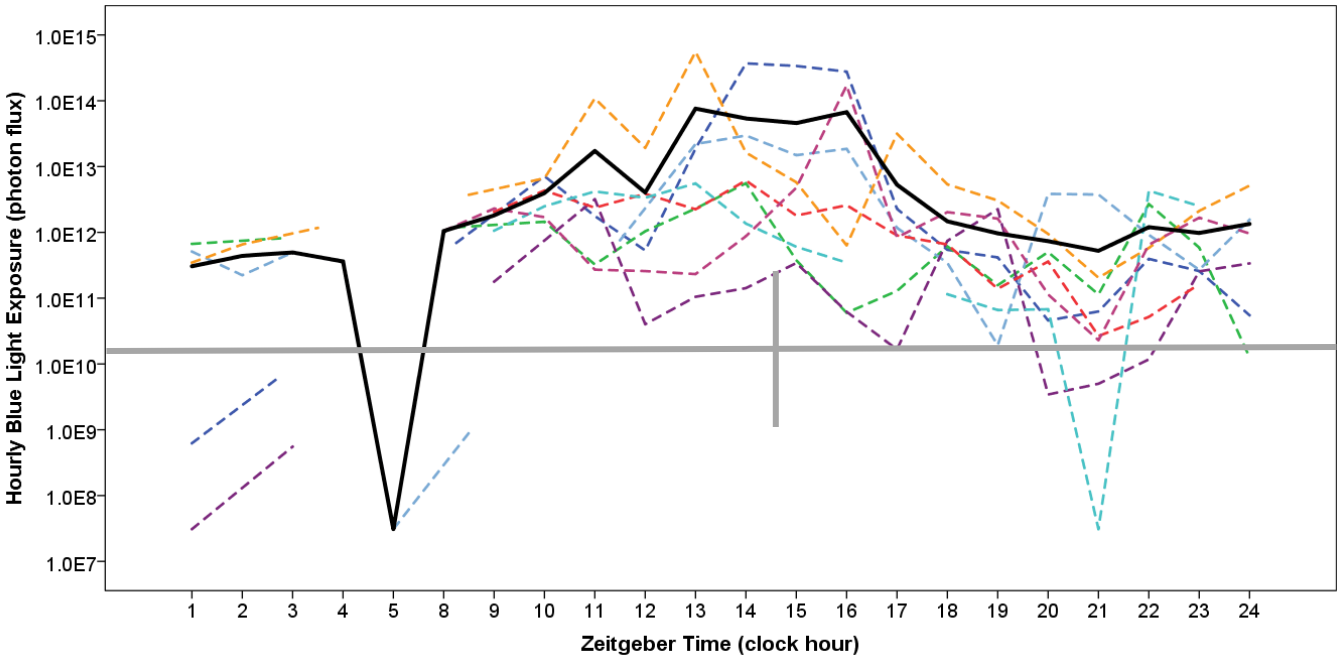

Figure 7. MLiT and SD MLiT for a single SAD participant

The dotted lines are the hourly light exposure for each individual day and the solid black line represents the average hourly light exposure across days. The horizontal gray line demonstrates the threshold of 1.0×10^{11}. The intensity of light is averaged across all days of actigraphy. All number of epochs above threshold is summated and divided by the total number of epochs per day to determine the mean timing of light above the threshold (the vertical gray line). The MLiT for this participant occurs at 14:37 (*SD* = 5:50).

2.4 PRIMARY ANALYSES

Ordinary least squares regression was used to assess each pathway of the proposed mediation model. All statistical analyses were calculated in SPSS 24 (SPSS, Inc., Chicago, IL) and mediation analyses were computed by the PROCESS macro (Version 2.16.3; Hayes, 2013). The current sample size is underpowered to detect a statistical significance using the Sobel test (Sobel, 1982); therefore, bootstrapping was performed to determine statistically significant mediation. Bootstrapping was used (n = 5,000) to compute confidence intervals for the indirect effects of light exposure on depressive symptoms (Shrout & Bolger, 2002). Confidence intervals of indirect effects that did not contain zero indicate statistical significance.

2.4.1 Covariates

Age and sex were used as covariates. Age was considered a covariate due to age-dependent differences in social contributions to light exposure (Walch et al., 2016) and since older adults are more likely to be morning types relative to younger adults (Roenneberg et al., 2003; Park et al., 2002; Duffy & Czeisler 2002; Dijk et al., 2000; Carskadon et al., 1999; Roenneberg et al., 2004). Sex was considered as a covariate since SAD is more prevalent in women than men (Lucht & Kasper, 1999). Antidepressant use was originally considered as a covariate, however only 7.8% (n = 7) of the sample was currently on antidepressant medication. Antidepressant use was not a significant predictor in any of the models and was therefore not included in the final analyses. Sleep variables and photoperiod on day of assessment were considered as covariates if there were significant group differences.

2.5 ANCILLARY AIMS

2.5.1 DLMO

DLMO is the gold-standard, objective measurement of circadian phase (Lewy et al., 1995; Lewy et al., 1999; Pandi-Perumal et al., 2007); however, only a subset of our sample (N = 58) had complete DLMO data. Ancillary analyses investigated the role of DLMO, rather than MSFsc, as a mediator between light exposure and depression symptomatology.

2.5.2 White light exposure

The primary analyses focus on blue wavelengths of light as ipRGCs are optimally sensitive to short wavelength light (Tu et al., 2005; Berson et al., 2002) and ipRGCs have direct projections to the SCN (Hattar et al., 2006; Hattar et al., 2002). However, other wavelengths of light can still affect the circadian system via rod and cone input to ipRGCs (Schmidt & Kofuji 2010). Therefore, full spectrum white light was also analyzed to determine whether the hypothesized effects were specific to blue light or a general response to light exposure.

3.0 RESULTS

3.1 PARTICIPANTS

In the total sample, one S-SAD participant was excluded as an outlier for having hourly light levels that were consistently greater than three standard deviations above the mean, as this individual may have had a malfunctioning photodiode. This participant was excluded from all analyzes including demographic and descriptive statistic variables. The final sample (N = 90) had a mean age of 38.8 years (SD = 13.5) and SAD/S-SAD participants (M = 41.6, SD = 13.3) had a higher average age than controls (M = 36.3; SD = 13.4), but this was not a statistically significant difference ($F(1, 88) = 3.6$, $p = 0.06$; Table 3). The total sample was 81.1% (n = 73) women and the SAD/S-SAD group had more women than the control group ($\chi^2(1, N = 90) = 4.9$, $p = 0.03$; Table 3). The sample included 78.9% Caucasian (n = 71), 12.2% African American (n = 11), 7.8% Asian (n = 7), and 1.1% biracial (n = 1) participants. There were no statistically significant differences in racial representation between groups ($\chi^2 (1, N = 90) = 7.0$, $p = 0.07$; Table 3). There were also no group differences in photoperiod on day of intake ($F(1, 88) = 2.17$, $p = 0.14$).

Table 3. Demographic and descriptive statistics of entire sample by group

	Diagnostic Group	
Variable	Control (n = 47)	S-SAD/SAD (n = 43)
Age	36.3 (13.4)	41.6 (13.3)
Sex		
Woman	34 (72.3%) *	39 (90.7%)
Race		
Caucasian	33 (70.2%)	38 (88.4%)
African American	8 (17.0%)	3 (7.0%)
Asian	6 (12.7%)	1 (2.3%)
Biracial	-	1 (2.3%)
GSS	2.7 (2.4) ***	14.3 (3.8)
SIGH-SAD		
Typical scale	2.0 (2.4) ***	14.2 (6.8)
Atypical scale	1.4 (1.9) ***	11.5 (6.8)
Total scores	3.4 (3.8) ***	25.7 (11.1)
Circadian Variables		
MSFsc	3:24 (0:52)	3:35 (0:39)
Sleep Variables		
Wake time	8:27 (2:12)	8:06 (1:13)
Sleep duration	7:00 (1:39)	7:11 (0:54)
Midsleep	4:57 (1:47)	4:30 (1:12)
Light Exposure		
Blue Light ($1x10^{11}$)	13:54 (5:37)	14:08 (5:23)
White Light (5 lux)	13:53 (5:26*)	14:06 (4:56)
Photoperiod	10:22 (2:50)	9:16 (4:11)

Note. GSS = Global Seasonality Score from the modified Seasonal Pattern Assessment Questionnaire; SIGH-SAD = The Structured Interview Guide for the Hamilton Depression Rating Scale, SAD Version; MSFsc = Midsleep on free days corrected for sleep deprivation accumulated during the work week. Light exposure variables are displayed in terms as such: MLiT (SD MLiT). MSFsc, Sleep variables, MLiT, SD MLiT, and photoperiod are presented in the format of hours: minutes based on time of day. Significance is annotated if there is a significant difference between SAD/S-SAD and controls, such that (*) represents $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$. All comparisons are made between SAD/S-SAD and control participants using either a one-way ANOVA or X^2.

3.2 DEPRESSIVE SYMPTOMS

Control participants endorsed few depressive symptoms on the SIGH-SAD (M = 3.4, SD = 3.8) and reported low seasonality on the MSPAQ (M = 2.7, SD = 2.4; Table 3). As expected, individuals with S-SAD endorsed less seasonality ($F(1, 41) = 7.5$, $p < 0.01$) and fewer depressive symptoms than individuals with SAD ($F(1, 41) = 24.4$, $p < 0.001$; Table 3).

3.3 SLEEP AND CIRCADIAN VARIABLES

On average, the participants woke around 8:17 am (SD = 1h:47m), slept for a mean total of 7 hours and 5 minutes (SD = 1h:20m), and reached midsleep on average at 4:44 am (SD = 1h:32m). There were no differences in wake time ($F(1, 88)= 0.9$, p =0.34), sleep duration ($F(1, 88)= 0.4$, p =0.52), or midsleep ($F(1, 88)= 2.0$, p =0.16) between the control and the combined SAD/S-SAD group (Table 3). When taking into consideration sleep debt that was accrued throughout the work week, the average self-reported midsleep (i.e., MSFsc) occurred at 3:29 am (SD = 0h:46m). There was no difference in MSFsc between control and SAD/S-SAD groups ($F(1, 88) = 1.4$; p = 0.2; Table 3). MSFsc and actigraphy-measured midsleep were moderately correlated (2-tailed, $r = 0.54$, $p < 0.001$).

3.4 LIGHT EXPOSURE VARIABLES

In order to determine a relevant threshold for MLiT analyses, one-tailed Pearson correlations assessed the relationship between various thresholds and MSFsc (Figure 8). MLiT was most strongly correlated with MSFsc (r = 0.19, p = 0.04; Figure 8A) when using a threshold of 1 x 10^{11} photons/cm^2/sec. The SD MLiT at a threshold of 1 x 10^{11} photons/cm^2/sec was also correlated with MSFsc (r = 0.27, p = 0.005; Figure 8B). Light at this intensity is equivalent to levels of natural sunlight during sunrise (Wright et al., 2013; Stothard et al., 2017). Therefore, the primary analyses will include MLiT and SD MLiT with a threshold of 1 x 10^{11} photons/cm^2/sec as a measurement of blue light exposure. There were no group differences in either the timing (F(1, 88) = 1.98, p = 0.16), or duration (F(1, 88) = 1.50, p = 0.23) of light exposure at this threshold.

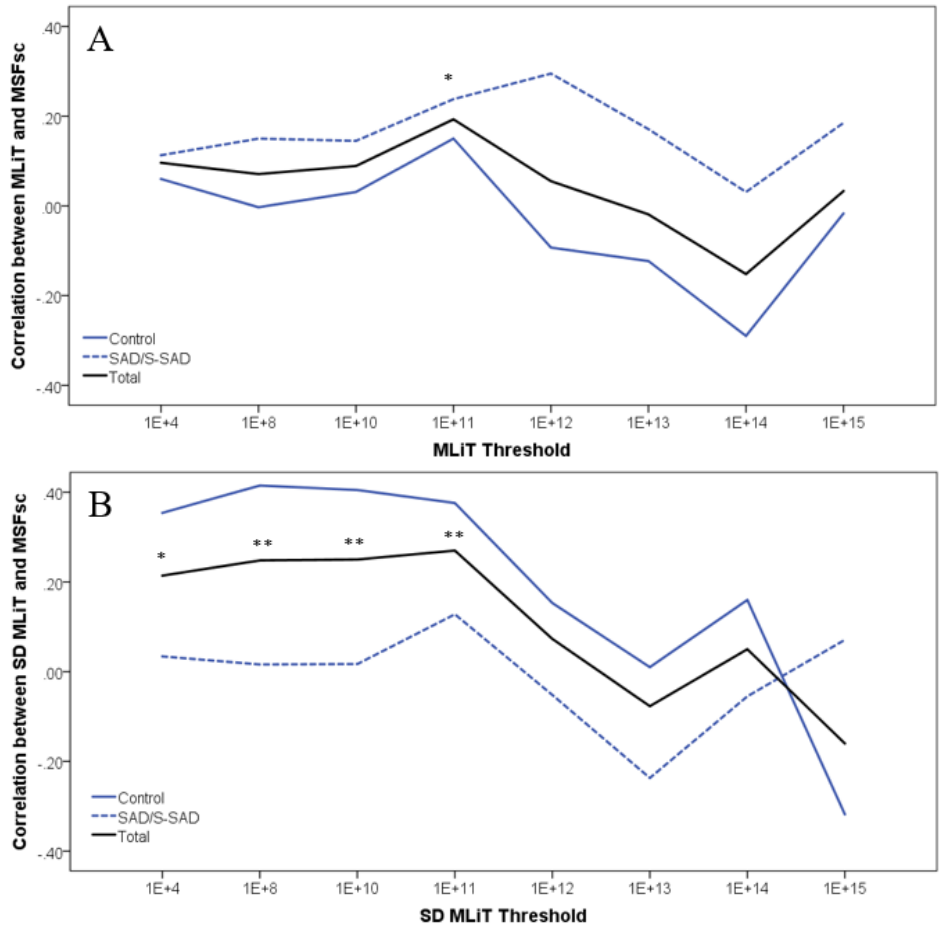

Figure 8. Correlations between thresholds of blue light and circadian phase

Correlations between the timing (A) and duration (B) of blue light exposure and circadian phase of entrainment at various thresholds. The strongest correlation occurred at a threshold of 1 x 10^{11} based on MLiT correlations with MSFsc in total sample. (*) represents statistically significant one-tailed Pearson's correlations with $p < 0.05$ between variables in the total sample. (**) represents statistical significance less of $p < 0.01$.

3.5 PRIMARY AIMS

The first aim hypothesized that a longer duration of blue light later in the day is associated with greater depression symptomatology. Neither the timing (MLiT; $\beta = 0.03$, $t(89) =$

0.23, p = 0.82), nor the duration of blue light exposure (SD MLiT; β = 0.02, t(89) = 0.15, p = 0.88) predicted depressive symptoms (Table 4). The second aim hypothesized that a longer duration of blue light later in the day is associated with a delayed circadian phase of entrainment. As predicted, both later exposure to blue light (MLiT; β = 0.30, t(89) = 3.05, p = 0.003) and longer duration of blue light (SD MLiT; β = 0.29, t(89) = 2.81, p = 0.006) was associated with a delayed circadian phase of entrainment (Table 5). The third aim hypothesized that a later circadian phase of entrainment is associated with greater depressive symptomatology. However, circadian phase of entrainment did not predict depressive symptoms (β = 0.13, t(89) = 1.08, p = 0.28; Table 6). As circadian phase of entrainment did not significantly predict depressive symptoms, mediation analyses were precluded.

Table 4. Model of blue light timing and duration predicting depressive symptoms

Predicting SIGH-SAD								
	Full sample				Subsample			
Variable	*B*	*SE B*	β	*p*	*B*	*SE B*	β	*p*
Age	0.08	0.12	0.08	0.46	0.18	0.13	0.27	0.045
Sex	-5.0	4.29	-0.14	0.25	-2.13	4.76	-0.17	0.24
MLiT	0.008	0.03	0.03	0.82	0.01	0.02	0.05	0.73
SD MLiT	0.005	0.03	0.02	0.88	0.003	0.03	-0.06	0.69
R^2			0.03	0.61			0.06	0.11

Note. *B* is the Unstandardized regression coefficient, and β is the standardized regression coefficient.

Table 5. Models of blue light timing and duration predicting circadian phase

	Predicting MSFsc				Predicting DLMO			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	-0.02	0.1	-0.40	< 0.001	-0.001	0.02	-0.01	0.93
Sex	-0.08	0.20	-0.04	0.71	0.49	0.63	0.12	0.45
MLiT	0.005	0.002	0.30	0.003	-0.003	0.002	0.27	0.053
SD MLiT	0.004	0.001	0.29	0.006	-0.001	0.004	0.44	0.002
R^2			0.30	< 0.001			0.22	0.01

Note. B is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

Table 6. Models of circadian phase predicting depressive symptoms

	MSFsc Predicting SIGH-SAD				DLMO Predicting SIGH-SAD			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	.13	0.12	0.12	0.30	0.25	0.12	0.25	0.05
Sex	-4.76	3.72	-0.14	0.20	-6.18	4.83	-0.16	0.21
Circadian phase	2.26	2.08	0.13	0.28	-2.01	1.13	-0.23	0.08
R^2			0.04	0.32			0.17	0.02

Note. B is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

3.6 ANCILLARY AIMS

3.6.1 DLMO

Participants. Out of the original sample, fifty-eight participants had detectable DLMO and were therefore used for ancillary analyses. This subsample had a mean age of 37.8 (*SD* = 13.4), and controls (*M* = 33.9, *SD* = 12.4) were significantly younger than the SAD/S-SAD group (*M* = 43.0, *SD* = 13.2; $F(1, 56) = 7.2$, $p = 0.009$; Table 7). There were no group differences in racial representation between groups ($\chi^2(1, N = 58) = 7.7$, $p = 0.052$) and the DLMO subsample was 79.3% Caucasian, 8.6% African American, 10.3% Asian, and 1.7% biracial (Table 7). There were no group differences in self-reported circadian phase of entrainment ($F(1, 56) = 0.08$, $p = 0.78$), or objectively measured circadian phase ($F(1, 56) = 1.6$, $p = 0.21$). There were no group differences in wake onset ($F(1, 56) = 2.0$, $p = 0.06$), or sleep duration ($F(1, 56) = 0.42$, $p = 0.52$). Individuals with SAD had a significantly earlier midsleep time compared to controls ($F(1, 56) = 3.6$, $p = 0.048$; Table 7). There were no group differences in photoperiod on day of circadian assessment ($F(1, 56) = 0.19$, $p = 0.67$; Table 7).

Timing and duration of light above threshold. Neither the timing ($\beta = 0.05$, $t(57) = 0.35$, $p = 0.73$) nor duration ($\beta = -0.06$, $t(57) = -0.40$, $p = 0.69$) of light exposure at this threshold predicted depressive symptomatology (Table 4). By contrast, the duration ($\beta = 0.44$, $t(57) = 3.27$, $p = 0.002$), but not timing ($\beta = 0.27$, $t(57) = 1.98$, $p = 0.05$) of light exposure above a threshold of 1×10^{11} photons/cm^2/sec predicted circadian phase (Table 5). In addition, melatonin onset did not significantly predict depressive symptomatology ($\beta = -0.23$, $t(57) = -1.79$, $p = 0.08$; Table 6).

Table 7. Demographic and descriptive statistics by group in subsample with DLMO

Variable	Diagnostic Group	
	Control (n = 33)	S-SAD/SAD (n = 25)
Age	33.9 (12.4) **	43.0 (13.2)
Sex		
Woman	26 (78.8%)	24 (96.0%)
Race		
Caucasian	23 (69.7%)	23 (92.0%)
African American	5 (15.2%)	-
Asian	5 (15.2%)	1 (4.0%)
Biracial	-	1 (4.0%)
GSS	2.7 (2.4) ***	14.3 (3.8)
SIGH-SAD		
Typical scale	2.0 (2.5) ***	13.2 (6.7)
Atypical scale	1.3 (1.7) ***	11.9 (6.7)
Total scores	3.3 (3.6) ***	25.1 (11.0)
Circadian Variables		
MSFsc	3:28 (0:48)	3:30 (0:36)
DLMO	21:30 (1:36)	21:00 (1:26)
Sleep Variables		
Wake time	7:28 (2:07)	6:50 (0:48)
Sleep duration	7:17 (1:48)	7:33 (1:02)
Midsleep	3:50* (1:53)	3:04 (0:46)
Photoperiod	11:05 (0:43)	10:59 (0:48)
Light Exposure		
Blue Light ($1x10^{11}$)	13:55 (5:35)	14:14 (5:27)
White Light (5 lux)	13:56 (5:29)	14:07 (5:03)

Note. GSS = Global Seasonality Score from the modified Seasonal Pattern Assessment Questionnaire; SIGH-SAD = The Structured Interview Guide for the Hamilton Depression Rating Scale, SAD Version; MSFsc = Midsleep on free days corrected for sleep deprivation accumulated during the work week; phase angle = Phase angle difference between dim light melatonin onset and midsleep. Light exposure variables are displayed in terms as such: MLiT (SD MLiT). MSFsc, sleep variables, MLiT, SD MLiT, and photoperiod are presented in the format of hours: minutes based on time of day. Significance is annotated if there is a significant difference between SAD/S-SAD and controls, such that (*) represents $p < 0.05$, (**) $p < 0.01$, and (***) $p < 0.001$. All comparisons are made between SAD/S-SAD and control participants using either a one-way ANOVA or X^2.

3.6.2 White light exposure

Timing and duration of light above threshold. One-tailed Pearson correlations were calculated for MLiT and MSFsc at various thresholds (Figure 9). MLiT was most strongly correlated with MSFsc (r = 0.20, p = 0.03; Figure 9A) when using a threshold of 5 lux of white light (7 x 10^{12} photons/cm^2/sec; Lucas et al., 2014). The SD MLiT was also correlated with MSFsc (r = 0.20, p = 0.03; Figure 9B) at a threshold of 5 lux. Individuals with SAD were exposed to a shorter duration of white light (F(1, 88) = 5.95, p = 0.02) compared to controls, but the timing of white light exposure was similar between groups (F(1, 88) = 1.20, p = 0.28). Neither the timing (β = 0.07, t(89) = 0.60, p = 0.55) nor duration (β = -0.08, t(89) = -0.64, p = 0.53; Table 8) of white light exposure above 5 lux predicted depression symptomatology. White light later in the day was associated with a delayed circadian phase of entrainment (MLiT; β = 0.22, t(88) = 2.29, p = 0.03), whereas there was no association with the duration of white light exposure (SD MLiT; β = 0.17, t(88) = 1.58, p = 0.12; Table 9). However, the opposite emerged for melatonin onset, such that the duration (β = 0.44, t(57) = 3.16, p = 0.003), but not timing (β = 0.16, t(88) = 1.20, p = 0.24) of white light exposure predicted circadian phase (Table 9). A summary of all results from regression analyses can be found in Table 13.

Table 8. Model of white light timing and duration predicting depressive symptoms

	Predicting SIGH-SAD			
Variable	*B*	*SE B*	*β*	*p*
Age	0.07	0.11	0.07	0.52
Sex	-3.48	4.16	-0.10	0.41
MLiT	0.02	0.03	0.07	0.55
SD MLiT	-0.02	0.03	-0.08	0.53
R^2			0.04	0.48

Note. *B* is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

Table 9. Model of white light timing and duration predicting circadian phase

	Predicting MSFsc				Predicting DLMO			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	-0.02	0.01	-0.40	< 0.001	< 0.001	0.01	0.01	0.99
Sex	-0.05	0.21	-0.02	0.82	0.37	0.59	0.08	0.53
MLiT	0.003	0.001	0.22	0.03	0.005	0.01	0.16	0.24
SD MLiT	0.002	0.001	0.17	0.12	0.013	0.01	0.44	0.003
R^2			0.25	< 0.001			0.20	0.02

Note. *B* is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

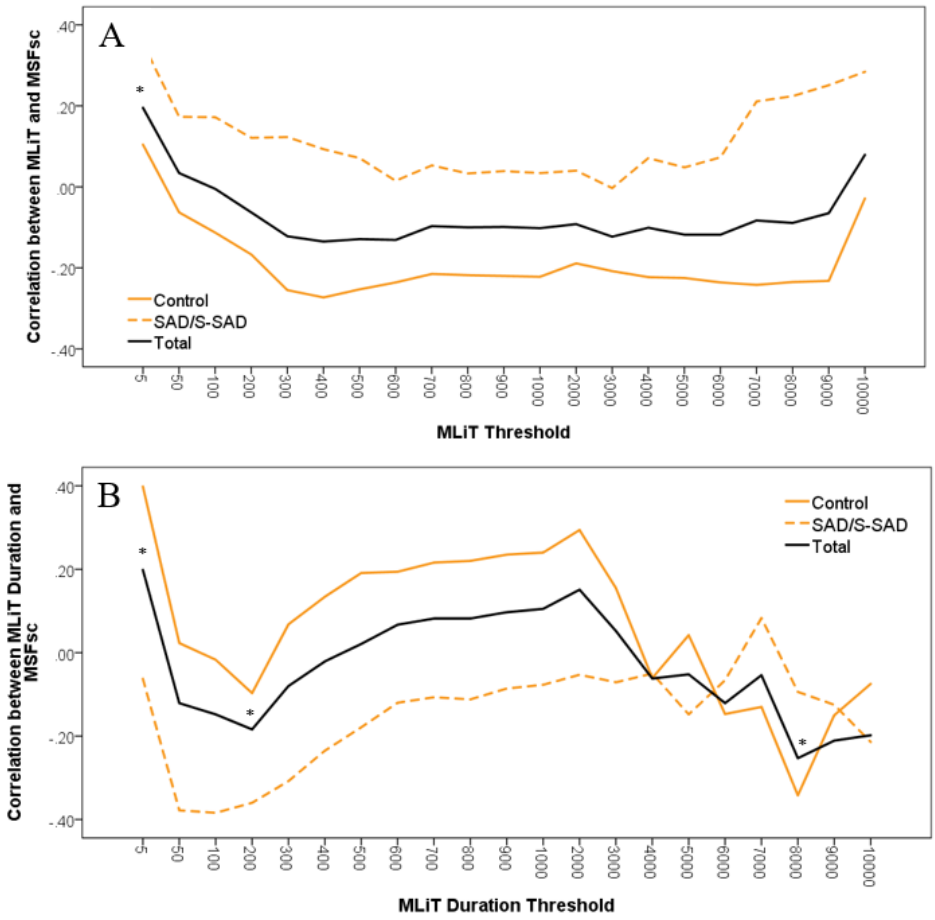

Figure 9. Correlations between thresholds of blue light and circadian phase

Correlations between the timing (A) and duration (B) of white light exposure and circadian phase of entrainment at various thresholds of light exposure. The strongest correlation occurred at a threshold of 5 lux based on MLiT correlations with MSFsc in total sample. (*) represents statistically significant one-tailed Pearson's correlations with $p < 0.05$ between variables in the total sample.

3.7 POST HOC ANALYSES

3.7.1 Women-only sample

The above analyses indicate that the duration of blue light exposure does not significantly predict DLMO in the subsample, despite a medium effect size (d = 0.48; Table 10). It was then predicted that heterogeneity within the sample might be reducing the overall association between blue light exposure and DLMO, perhaps due to previously noted gender differences in circadian phase (Emens eet al., 2009b; Swanson et al., 2017). Thus, analyses for MLiT and SD MLiT of blue light exposure were re-analyzed excluding men (N = 50; control n = 26; SAD/S-SAD n = 24). In concordance with other analyses, age was used as a covariate for all analyses using the women-only subsample.

Table 10. Model of blue light timing and duration predicting depressive symptoms in women

	Predicting SIGH-SAD			
Variable	*B*	*SE B*	*β*	*p*
Age	-0.02	0.001	-0.37	0.001
MLiT	0.01	0.002	0.34	0.002
SD MLiT	0.003	0.002	0.18	0.09
R^2			0.26	< 0.001

Note. *B* is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

Similar to the entire sample findings, neither the timing (β = 0.01, t(49) = 0.05, p = 0.96) nor duration (β = -0.05, t(49) = -0.31, p = 0.76) of blue light exposure predicted depressive symptoms (Table 10). Interestingly, a shorter duration of blue light exposure was associated with an earlier circadian phase (β = 0.42, t(49) = 3.06, p = 0.004), whereas the timing of blue light was not associated with phase (β = 0.23, t(49) = 1.72, p = 0.09; Table 11). In addition, an earlier

circadian phase was associated with greater depressive symptoms (β = -0.29, $t(57)$ = -2.20, p = 0.04; Table 12). Thus the standardized indirect effect is (.42)(-0.29) = -0.12. To test whether the indirect effect was statistically significant, bootstrapping was used (n = 5,000) to calculate the unstandardized effect size, while controlling for age. Bootstrapping analyses indicate that circadian phase significantly mediates the relationship between the duration of blue light exposure and depressive symptoms among women alone (B = -0.04; SE = 0.02; 95% CI = -0.09 – -0.005). Specifically, shorter durations of blue light exposure centered in the afternoon are associated with advanced circadian phase and greater depressive symptoms.

Table 11. Model of blue light timing and duration predicting circadian phase in women

	Predicting MSFsc				Predicting DLMO			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	-0.02	0.01	-0.40	< 0.001	-0.01	0.01	-0.08	0.56
MLiT	0.003	0.001	0.22	0.03	0.01	0.01	0.23	0.09
SD MLiT	0.002	0.001	0.17	0.12	0.02	0.01	0.42	0.004
R^2			0.25	< 0.001			0.19	0.02

Note. B is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

Table 12. Models of circadian phase predicting depressive symptoms in women

	MSFsc Predicting SIGH-SAD				DLMO Predicting SIGH-SAD			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	0.07	0.13	0.07	0.570	0.24	0.14	0.23	0.09
Circadian phase	2.57	2.26	0.15	0.26	-2.76	1.29	-0.29	0.04
R^2			0.02	0.52			0.14	0.03

Note. B is the Unstandardized regression coefficient, and *β* is the standardized regression coefficient.

Table 13. Summary of findings including effect sizes and p-values

	Regression models				
	Full sample			DLMO subsample	
	Light predicting SIGH-SAD	Light predicting MSFsc	MSFsc predicting SIGH-SAD	Light predicting DLMO	DLMO predicting SIGH-SAD
			Blue light exposure		
MLiT	β = 0.03 p = 0.82 d = 0.06	β = 0.30 p = 0.003 d = 0.63	β = 0.13 p = 0.28 d = 0.26	β = 0.27 p = 0.053 d = 0.57	β = -0.23 p = 0.08 d = 0.48
SD MLiT	β = 0.02 p = 0.88 d = 0.04	β = 0.29 p = 0.006 d = 0.61		β = 0.44 p = 0.002 d = 1.00	
	White light exposure				
Clock Time	β = 0.08 p = 0.46 d = 0.16	β = -0.22 p = 0.03 d = 0.45		β = -0.22 p = 0.11 d = 0.46	
MLiT	β = 0.07 p = 0.55 d = 0.14	β = 0.22 p = 0.03 d = 0.45		β = 0.16 p = 0.24 d = 0.33	
SD MLiT	β = -0.08 p = 0.53 d = 0.16	β = 0.17 p = 0.12 d = 0.35		β = 0.44 p = 0.003 d = 1.00	
	Woman-only results: blue light exposure				
MLiT	β = 0.01 p = 0.96 d = 0.01	β = 0.34 p = 0.002 d = 0.72	β = 0.15 p = 0.26 d = 0.30	β = 0.23 p = 0.09 d = 0.49	β = -0.29 p = 0.04 d = 0.61
SD MLiT	β = -0.05 p = 0.76 d = 0.10	β = 0.18 p = 0.09 d = 0.37		β = 0.42 p = 0.004 d = 0.94	

Note. Bolded portions of the table are statistically significant. MLiT and SD MLiT analyses for blue light were performed above a threshold of 1 x 10^{11} photons/cm^2/sec and 5 lux for white light.

4.0 DISCUSSION

The current study investigates whether circadian phase mediates the relationship between light exposure and depressive symptoms in individuals with SAD, S-SAD, and non-depressed controls. The results demonstrate that a longer duration of light exposure is associated with a delayed circadian phase, but that neither light exposure nor circadian phase are associated with depressive symptoms in the full sample. However, when women are analyzed separately, a shorter duration of blue light exposure centered in the afternoon is associated with greater depressive symptoms, and this association is mediated by a relatively advanced circadian phase.

Neither self-reported or objectively-assessed markers of circadian phase were associated with depressive symptoms in the full sample. This is inconsistent with numerous studies that find an association between evening preference and reports of greater depressive symptoms (Drennan et al., 1991; Chelminski et al., 1999; Hirata et al., 2007; Abe et al., 2011; Kim et al., 2010; Hasler et al., 2010a; Hidalgo et al., 2009). Our results fail to replicate these findings, likely due to the low correlation between self-reported midsleep and DLMO in participants with SAD and S-SAD (Table 2). Notably, there was no association between DLMO and depressive symptoms in the current sample. This finding is in line with more recent studies of non-seasonal depression that do not find an association between objective markers of circadian phase and depressive symptoms (Carpenter et al., 2017; Robillard et al., 2017). Gender differences could possibly explain the lack of association between objective markers of phase and depressive symptoms.

For example, if men and women exhibited phase shifts in opposite directions, then the results would appear to be null.

Indeed, when women are analyzed separately, an earlier circadian phase was associated with greater depressive symptoms in our sample. Swanson and colleagues (2017) also noted gender differences when measuring melatonin onset in men and women with non-seasonal depression at baseline and after a sleep intervention. The results indicate that depression ratings and melatonin onset were not correlated in women either at baseline or following the intervention. However, contrary to our findings, their data indicate that women who delayed after the intervention (n = 3) report higher depressive symptoms than those who advance as a consequence of the intervention (n = 4). Based on these findings, the authors report that a delayed phase is associated with greater depression in women; however, the data should be considered preliminary due to its small sample size (N = 15 women; Swanson et al., 2017).

Although our data also suggest a gender difference, the current results indicate that an advanced circadian phase, rather than a delay, is associated with depressive symptoms in women with SAD. The majority of studies in SAD and non-seasonal depression demonstrate just the opposite, such that depression is associated with greater evening preference (Drennan et al., 1991; Chelminski et al., 1999), delayed sleep timing (Hasler et al., 2010b; Robillard et al., 2014), and delayed circadian phase (Emens et al., 2009; Swanson et al., 2012). Although less common, other samples have also reported an advanced phase in depressed women. For example, Parry and colleagues (2008) demonstrated that women with a personal or family history of depression were phase-advanced during pregnancy relative to individuals without a family history. Furthermore, an advanced phase is associated with greater atypical depressive symptoms in perimenopausal women with subclinical depression (Meliska et al., 2011). As women typically

show advanced melatonin onset relative to men (Mongrain et al., 2004; Cain et al., 2010), it is possible that further advances in melatonin onset can lead to greater internal desynchrony and exacerbate depressive symptoms in women. However, further research is necessary in this area to confirm these speculations.

The current findings suggest that a shorter duration of blue light exposure, centered in the afternoon, is associated with an advanced phase in women with SAD. These results are contrary to previous reports indicating that individuals with an earlier circadian phase had a greater duration of bright white light exposure (Goulet et al., 2007). Importantly, Goulet and colleagues (2007) use a threshold of 1,000 lux, which is well above the threshold used in the current study. Therefore, it is plausible that phase-advanced individuals receive more high-intensity light, particularly in the morning, but less overall light exposure compared to their delayed counterparts.

Despite our seemingly low thresholds for blue (0.7 lux; 1 x 10^{11} photons/cm^2/sec) and white light (5 lux; 7 x 10^{12} photons/cm^2/sec; Lucas et al., 2014), previous research suggests that light at this intensity affects the circadian system. For example, a light stimulus as low as 1 x 10^{11} photons/cm^2/sec can elicit a pupillary response in a blind individual without functional rods and cones (Gooley et al., 2012). Thresholds as low as 4 x 10^5 and 1 x 10^{10} photons/cm^2/sec can lead to increased retinal firing rates and pupillary constriction, respectively, in mutant mice lacking rods and cones (Lucas et al., 2003; Do et al., 2009). Chang and colleagues (2015) found a 1.5-hour phase delay after using an electronic tablet that emitted approximately 2.5 x 10^{11} photons/cm^2/sec for five consecutive nights. Taken together, these studies demonstrate that low intensity light, as reported here, is capable of activating ipRGCs and can alter circadian phase.

4.1 LIMITATIONS

The current study is the first to investigate the role of blue light in SAD using wrist actigraphy with hourly epochs, but failed to find significant correlations between light and depressive symptoms. The first limitation is that the depression ratings were collected prior to light recordings. It is likely that light exposure *prior* to depression ratings would better predict symptoms. As a second limitation, the current study is cross-sectional and fails to investigate whether circadian phase changes as a function of season. If circadian phase is causally related to depressive symptoms, then it is expected that circadian phase shifts would precede symptom relapse in winter. Therefore, longitudinal data are necessary to investigate whether seasonal phase shifts precede symptoms onset. A third limitation is that data from SAD and S-SAD participants were aggregated to improve statistical power, however, removing the individuals with S-SAD did not change the obtained results (data not shown). A fourth limitation is that the main study findings uses a self-report questionnaire to estimate circadian phase of entrainment (MSFsc) that was weakly correlated with DLMO in our sample relative to other reports (Table 2). The correlation between MSFsc and DLMO was negligible in SAD/S-SAD participants, such that MSFsc was not an accurate measurement of circadian phase in this group. The final limitation is that a wrist photodiode was used to record light data, although light exposure measured at the wrist less accurately depicts light hitting the retina than when measured at eye level (Figueiro et al., 2013) and could be obscured by clothing in winter.

4.2 FUTURE DIRECTIONS

The current study provides preliminary evidence that an advanced phase mediates the relationship between reduced blue light exposure centered in the afternoon and greater depressive symptoms in women with SAD. Few studies investigate whether gender moderates the relationship between circadian phase and depressive symptoms in either seasonal or non-seasonal depression. Exploring the link between gender and direction of phase shift might explain why melatonin onset is not always correlated with depressive symptoms. In addition, it is possible that the magnitude, rather than the direction, of the phase shift is more relevant for the development of depression. Thus, future studies will recruit more men with an aim to understand whether gender moderates the relationship between phase and depressive symptoms in SAD and non-seasonal depression. In addition, longitudinal studies are needed to confirm whether individuals with SAD experience a phase shift in the winter during a depressive episode relative to the summer when they have remitted, and whether the magnitude of the phase shift is associated with depressive symptoms. By understanding the nuanced relationship between circadian phase and depression, chronotherapies can be tailored to individual patients.

APPENDIX A: ACTIWATCH CLEANING PROTOCOL

A.1 CLEANING THE DATA

We ultimately want to trust the algorithm that is generated by the Actiwatch software, but sometimes the algorithm is not quite accurate. We just want to check for these inconsistencies and correct them.

A.1.1 Off-wrist

The Actiwatch spectrum software should do this manually, but we still need to check that any prolonged period of time with an activity count of 0 should be considered ‘off-wrist.’ During sleep, there will be both periods of 0 activity and low amounts of activity. These periods are not to be excluded.

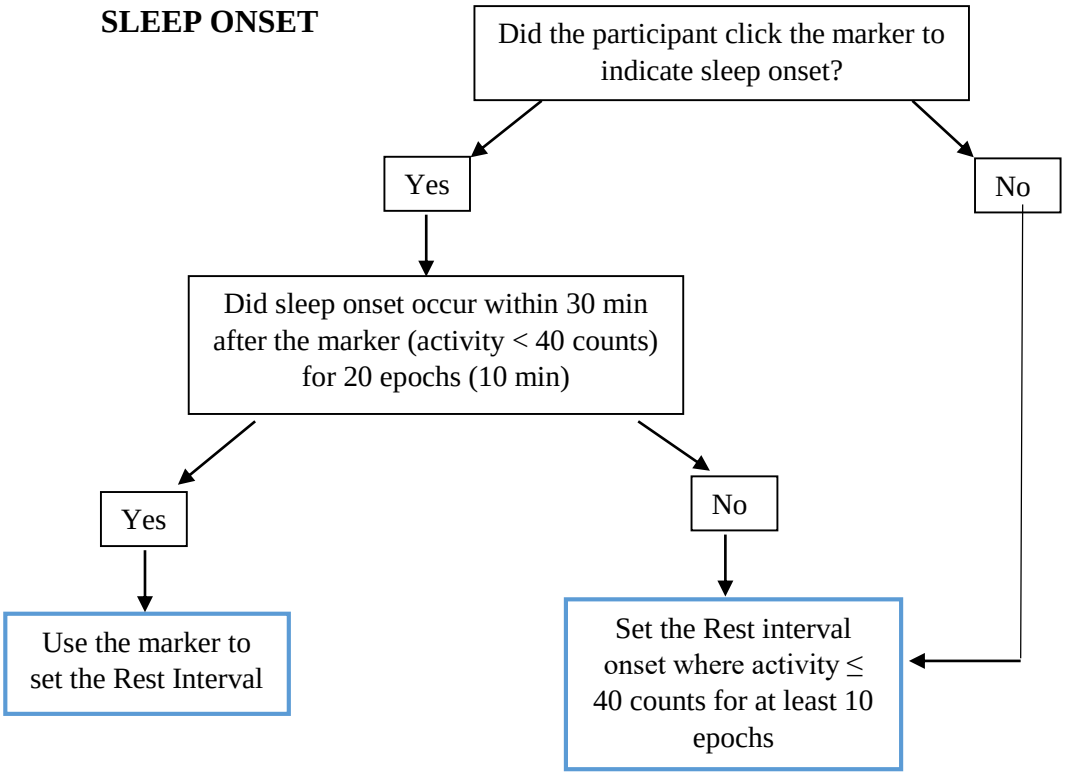

Figure 10. Flow chart to determine sleep onset

A.1.2 Sleep onset

To determine when a participant went to bed, we want to double check (1) did they click the marker, (2) does the marker seem accurate, and (3) when is the activity level below 40 counts?

Did the participant use the marker? Does it seem accurate? The rule of thumb is that if the marker was pressed within 30 minutes of sleep onset, then use the marker to define the beginning of a rest interval. The end of the rest interval will be defined by an increase in activity following sleep. The end of the sleep interval will be defined as the last instance where the activity level was below 40 counts.

If the participant did clock the marker, but it is not within 30 minutes of sleep. Do not use the marker to define the rest interval. Instead, first check where the algorithm marked the start of the sleep interval. If this seems accurate, then leave it. If the algorithm did not correctly identify a period with an activity of below 40 counts to be the start of the sleep interval and the last activity count of below 40 to be the end of the sleep interval.

To determine if the algorithm seems 'accurate.' It may be helpful to look at both light and activity data to make this decision. If the light levels suddenly drop off followed by a drop in activity, then it seems likely that the participant turned off the lights and went to bed.

A.1.3 WASO and sleep offset

To determine when the participant woke up, we need to consider (1) did the participant press the marker, (2) does the marker seem accurate, (3) is there a spike in activity and/or light levels, (4) does the participant go back to bed after activity, if so, (5) when does this occur, and (6) how long does this activity persist for? (See below for flow chart).

In the cases where there is a large bout of activity during the major rest interval. In this case, it is very likely that the sleep algorithm identifies only one half of the major sleep interval. If there is 2 hours or less of activity in-between the two sleep intervals *and* the second sleep interval occurs within 9 hours of the first sleep onset, then the two sleep intervals should be combined and set as the major rest interval. The activity in-between them will be considered WASO.

A.1.4 Bad watches

In order to test whether or not the actigraphy watches are functioning correctly, the following guidelines were used:

(1) If any wavelength of light (i.e., red, blue, or green) does not fall below 1 photon/cm^2/sec.

(2) If activity counts do not fall below 20 counts at any point during the recording.

If any of the two criteria are met, then a 'watchtopsy' must be performed. To do this, the watch will be placed on a table in complete darkness (we can use the PIPR room for that). Keep the watch in there for 30 minutes and then collect and look at the data. You must go into the setting under Options -> Auto Intervals -> uncheck 'Convert off-wrist time to Excluded Intervals.' You can zoom in on the data and see whether any color range of light exceeds 1 photon/cm^2/sec or if the activity counts exceed 20 counts while lying still. If so, the watch need to be returned to Philips, Respironics ASAP for repairs.

APPENDIX B: MSFsc CALCULATION

$$\mathrm{MSF} - \left(\frac{\mathrm{SD_f} - \left(\frac{\mathrm{SD_f}\ (N_f) + \mathrm{SD_w}\ (N_w)}{7} \right)}{2} \right)$$

MSF = midpoint of sleep on free days

SD_{nw} = sleep duration on free days

N_{nw} = number of free days per week

SD_w = sleep duration on work days

N_w = number of work days per week

Sleep debt accrued during the week is estimated by calculating the average sleep duration during the week, including both free days and work days. The estimated sleep debt is then subtracted from sleep duration during free days. The resulting sleep duration accounting for sleep debt is divided in half to provide the estimated midsleep (MSFsc).

APPENDIX C: HOURLY LIGHT EXPOSURE BY CIRCADIAN AND CLOCK TIME ANALYSES OF LIGHT DATA

Exploratory analyses were used to identify group differences in the timing, intensity, and duration of light exposure. This approach was used to define specific morning and evening hours when light exposure might be relevant for circadian phase and subsequent depressive symptomatology. Individuals were separated into controls and a combined SAD and S-SAD group according to the inclusion criteria. SAD and S-SAD participants were grouped together due to low recruitment in the S-SAD group (N = 12). Light data were first smoothed by computing rolling averages of 10 minute windows for each day. Each epoch was then averaged across all days of actigraphy for each participant. Then, 120 consecutive epochs (i.e.,1 hour) was averaged for each hour of wakefulness. Hourly average light exposure was calculated in relation to both clock time (i.e., zeitgeber time) and time since wake. Group differences in hourly light exposure were analyzed by repeated measures ANOVA with heterogeneous compound symmetry to account for higher correlations between light exposure occurring at similar times of the day relative to light at more distal times. Hourly bins of light exposure that yielded significant group differences were then used to assess study aims. (R scripts for all computed variables can be found in Appendix D).

A.2 PRIMARY AIMS

A.2.1 Clock time

A one-way ANOVA with heterogeneous compound symmetry[1] failed to detect a main effect of group ($F(1, 18.5) = .12$, $p = 0.73$) or group*time interaction ($F(23, 23.4) = 1.5$, $p = 0.16$) for blue light exposure by clock time. There was significant main effect of time, reflecting that blue light exposure increased during the morning, peaked in the afternoon and then declined during the evening ($F(23, 23.1) = 124.4$, $p < 0.001$; Figure C1A).

A.2.2 Time since wake

Similarly, there was no main effect of group ($F(1, 446.3)= 0.12$, $p = 0.73$) or group*time interaction ($F(23, 244.8) = 0.98$, $p = 0.50$) for blue light exposure by time since wake. There was again a main effect of time, such that blue light varied by hours since wake, peaking nearly six hours after wake time ($F(23, 245.2) = 89.12$, $p < 0.001$; Figure C1B).

[1] This statistical method allowed for correlations in light exposure to differ by time. This model accounts for the fact that light at one time will have stronger correlations with light occurring at similar times relative to more distal time points. The within-group degrees of freedom are a decimal given the assumed sphericity in repeated measures ANOVA.

A.3 ANCILLARY AIMS - DLMO

A.3.1 Clock time

A one-way ANOVA with heterogeneous compound symmetry failed to detect a main effect of group ($F(1, 77.3) = 0.47$, $p = 0.50$) or group*time interaction ($F(23, 80.1) = 0.89$, $p = 0.61$) on blue light exposure. There was a significant main effect of time, such that blue light exposure altered across the day ($F(23, 79.6) = 77.2$, $p < 0.001$; Figure C2A). As there were no significant group differences in blue light exposure by clock time, mediation analyses were precluded.

A.3.2 Time since wake

Similarly, there was no main effect of group ($F(1, 70.1) = 1.11$, $p = 0.30$) or group*time interaction ($F(20, 70.1) = 0.95$, $p = 0.53$) on blue light exposure from time since wake. There was a main effect of time, such that blue light varied by time since wake, and peaked nearly 5 hours after wake ($F(23, 78.8) = 58.3$, $p < 0.001$; Figure C2B). Again, due to a lack of significant group differences in blue light exposure by time since wake, no further analyses were conducted.

A.4 ANCILLARY AIMS – WHITE LIGHT EXPOSURE

A.4.1 Clock time

A one-way ANOVA with heterogeneous compound symmetry failed to detect a main effect of group ($F(1, 31.8) = 1.63$, $p = 0.21$) on white light exposure. There was both a significant main effect of time ($F(23, 51.02) = 115.5$, $p < 0.001$) and group*time interaction ($F(23, 51.54) = 2.11$, $p = 0.013$; Figure C3A). Post-hoc analyses concluded that there were significant group differences at hours 2:00-3:00 am ($t(22.5) = 3.72$, $p = 0.001$), 6:00-7:00 am ($t(164.7) = -2.31$, $p = 0.02$), and 10:00-11:00 am ($t(161.8) = -2.43$, $p = 0.02$). Given the low sample sizes at 2:00-3:00 am ($n = 30$) and 6:00-7:00 am ($n = 58$), only white light exposure from 10:00-11:00 am ($N = 90$) was used for further analyses. Average morning light exposure (10:00-11:00 am) did not predict depression symptomatology ($\beta = 0.08$, $t(89) = 0.75$, $p = 0.46$; Table C1). Greater white light exposure in the morning (10:00-11:00 am) predicted earlier circadian phase of entrainment ($\beta = -0.22$, $t(88) = -2.20$, $p = 0.03$; Table C2). However, greater morning white light exposure did not predict objective measures of circadian phase in the DLMO subsample of participants ($\beta = -0.22$, $t(58) = -1.65$, $p = 0.11$; Table C2).

A.4.2 Time since wake

There was no main effect of group ($F(1, 426.1) = 0.22$, $p = 0.64$) or group*time interaction ($F(23, 227.9) = 0.77$, $p = 0.76$) on white light exposure by time since wake. There was again a main effect of time, such that white light varied by time since wake ($F(23, 228.2) = 87.25$, $p < 0.001$; Figure C3B).

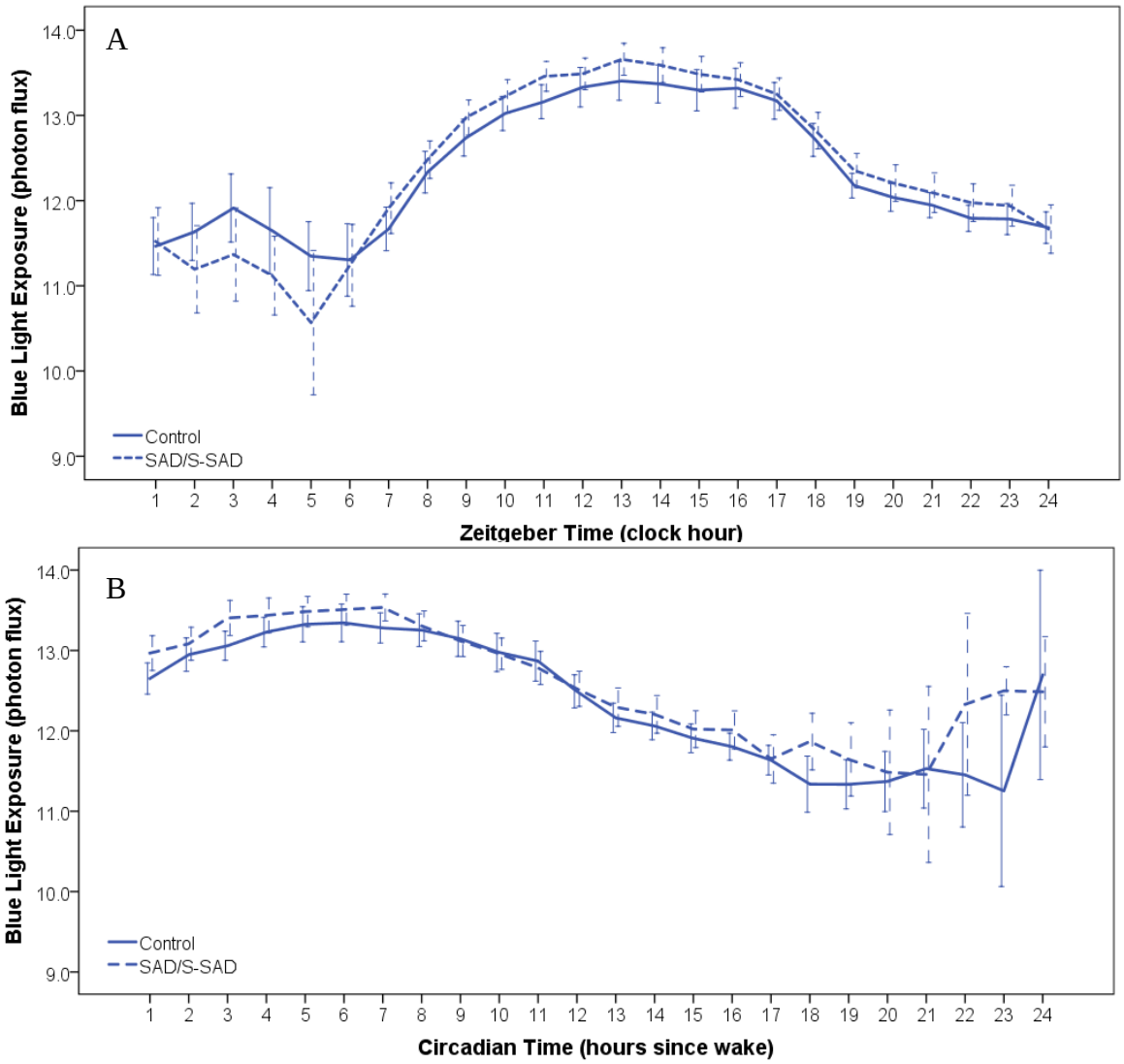

Figure 11. Group hourly blue light exposure by (A) clock time and (B) time since wake

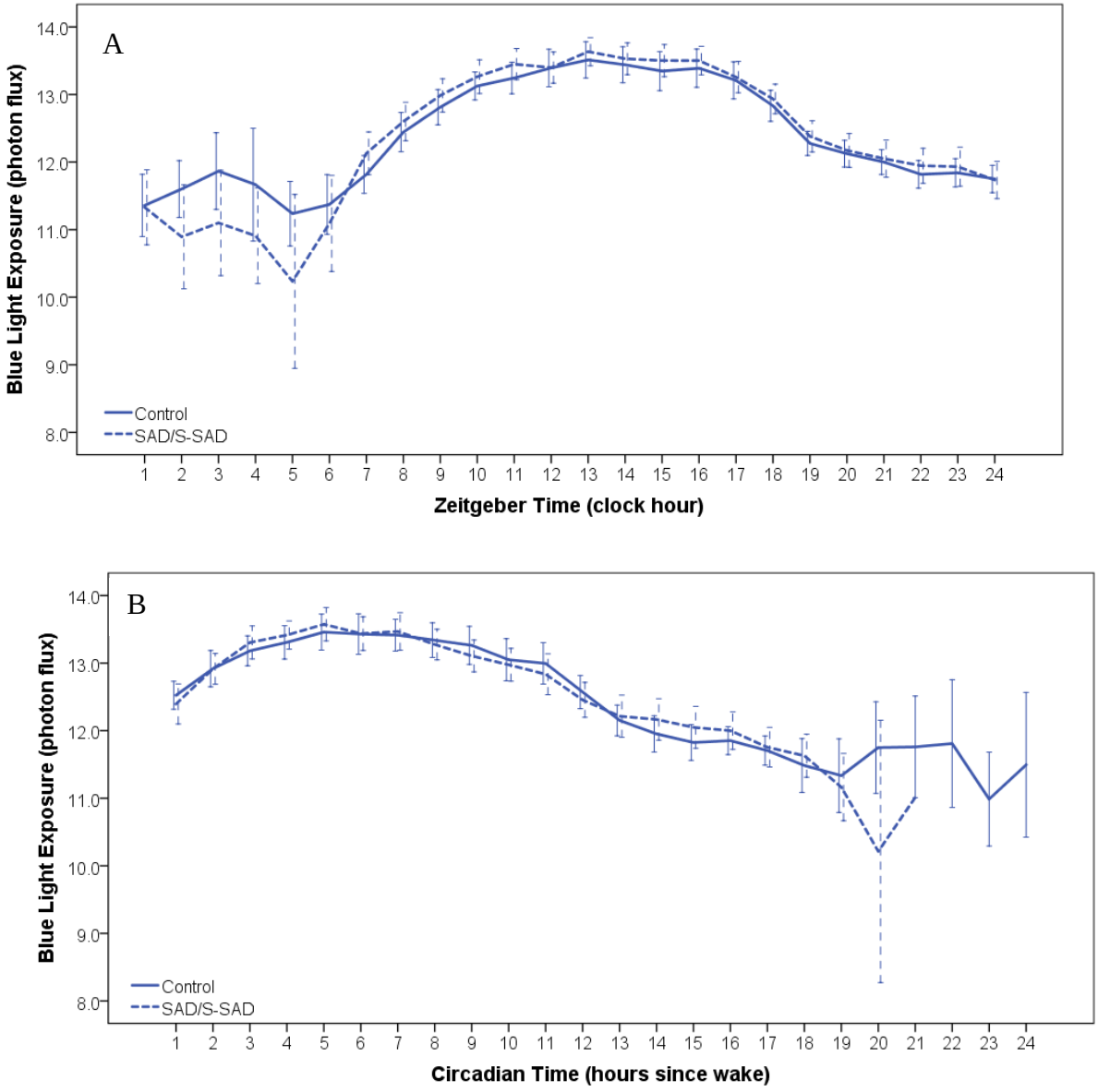

Figure 12. Group hourly blue light exposure by (A) clock time and (B) time since wake for a subsample of participants with DLMO

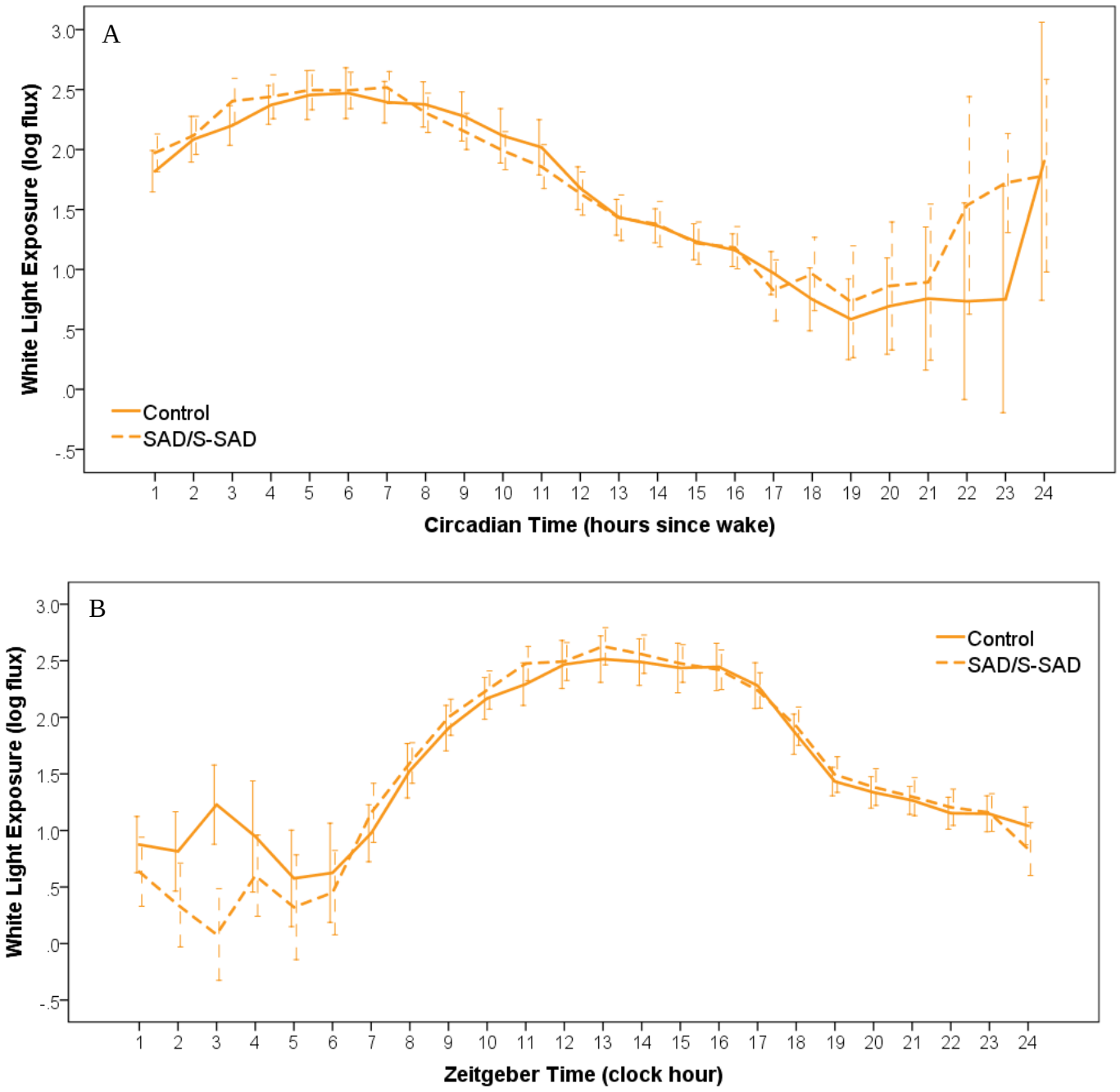

Figure 13. Hourly white light exposure by (A) clock time and (B) time since wake

Table 14. Model of white light exposure from 10:00 – 11:00am predicting depressive symptoms

	Predicting SIGH-SAD			
Variable	*B*	*SE B*	*β*	*p*
Age	0.08	0.11	0.08	0.44
Sex	-4.42	3.84	-0.13	0.25
White light	1.91	2.57	0.08	0.46
R^2			0.04	0.36

Table 15. Models of white light exposure from 10:00 – 11:00am predicting circadian phase

	Predicting MSFsc				Predicting DLMO			
Variable	*B*	*SE B*	*β*	*p*	*B*	*SE B*	*β*	*p*
Age	-0.03	0.01	-0.43	< 0.001	-0.01	0.02	-0.09	0.51
Sex	-0.12	0.20	-0.06	0.55	0.56	0.58	0.13	0.34
White light	-0.28	0.13	-0.22	0.03	0.56	0.34	-0.22	0.11
R^2			0.23	< 0.001			0.09	0.18

APPENDIX D: R SCRIPTS USED TO CALCULATE LIGHT DATA AND SLEEP VARIABLES

A.4.3 All days since DLMO – calculating hourly light exposure since wake

```
library(dplyr)
library(zoo)
library(readr)
library(tidyr)

ref <- read_csv("~/Desktop/Caitlin/DataFiles/Covariates_csv.csv")
SleepVariables <- read_csv("~/Desktop/Caitlin/DataFiles/SleepVariables.csv")
setwd("~/Desktop/Caitlin/ActigraphyData/EpochbyEpoch/MSFsc_AllDaysSinceDLMO/ExcludingNaps")
output <- data.frame()
files <- list.files()

for (file in files) {

    d <- read.csv(file)
    d <- d[d$Interval.Status != "EXCLUDED",]

    isNA <- is.na(d$White.Light)
    d$White.Light[isNA] <- 0
    isNA <- is.na(d$Blue.Light)
    d$Blue.Light[isNA] <- 0
    isNA <- is.na(d$Green.Light)
    d$Green.Light[isNA] <- 0
    isNA <- is.na(d$Red.Light)
    d$Red.Light[isNA] <- 0

    d$ID <- file
    d$ID <- as.numeric(gsub(".csv", "", d$ID))
    ref$ID <- as.numeric(ref$ID)

    d$Interval.Status <- gsub("REST-S", "1", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("REST", "0", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("ACTIVE", "0", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("EXCLUDED", "0", d$Interval.Status, fixed = TRUE)

    d$count <- NA
    d$count <- ifelse(d$Interval.Status == 0, 1, 0)
```

```
      for(i in 2:nrow (d)) {
       d$count[i] <- ifelse(d$Interval.Status[i] == 0, d$count[i-1] + 1, 0)
        }

    d <- d[d$Interval.Status != "1",]
    by_c <- dplyr::group_by(d, count)
     WeeklyLight <- summarise(by_c, mean_white = mean(White.Light),
                         mean_blue = mean(Blue.Light), mean_green = mean(Green.Light),
                         mean_red = mean(Red.Light))

    output_white <-list()
        for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_white[[i+1]] <- mean(WeeklyLight$mean_white[WeeklyLight$count < end & WeeklyLight$count >=
start])
          }
     output_blue <-list()
        for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_blue[[i+1]] <- mean(WeeklyLight$mean_blue[WeeklyLight$count < end & WeeklyLight$count >=
start])
         }
          output_green <-list()
     for (i in 0:23) {
       start <- i * 120
       end <- start + 120
       output_green[[i+1]] <- mean(WeeklyLight$mean_green[WeeklyLight$count < end & WeeklyLight$count >=
start])
     }
     output_red <-list()
     for (i in 0:23) {
       start <- i * 120
       end <- start + 120
       output_red[[i+1]] <- mean(WeeklyLight$mean_red[WeeklyLight$count < end & WeeklyLight$count >= start])
     }

    WeeklyLight <- data.frame(white_light=unlist(output_white), blue_light=unlist(output_blue),
                          green_light=unlist(output_green), red_light=unlist(output_red))
    WeeklyLightT <- as.data.frame(t(WeeklyLight), row.names = NULL)
    WeeklyLightT <- cbind(light_color = c("white", "blue", "green", "red"),
                  WeeklyLightT)
    WeeklyLightT <- cbind(ID = d$ID[1], WeeklyLightT)
     output <- rbind(output, WeeklyLightT)
     }
colnames(output)[3:26] <- paste0("hour_", 1:24)

isNA <- is.na(output)
output[isNA] <- ""
SleepVariables$ID <- as.numeric(SleepVariables$ID)
output$ID <- as.numeric(output$ID)
ref$ID <- as.numeric(ref$ID)

output <- dplyr::left_join(output, ref, by = "ID")
```

```
output <- dplyr::left_join(output, SleepVariables, by = "ID")

write.table(output, file = "CT_AllDays_allWavelengths_wide.csv", sep = ",", col.names = NA)

d <- output
d$ID <- factor(d$ID)
d <- tidyr::gather(d, hour, light, hour_1:hour_24)
d$hour <- gsub("hour_", "", d$hour)

write.table(d, file = "CT_AllDays_allWavelengths_long.csv", sep = ",", col.names = NA)
```

A.4.4 All days since DLMO – calculating hourly light exposure by clock time

```
library(dplyr)
library(readr)
library(tidyr)

Covariates <- read_excel("~/Desktop/Caitlin_MS/Covariates.xlsx")
ref <- read_csv("~/Desktop/Caitlin/DataFiles/Covariates_csv.csv")
setwd("~/Desktop/Caitlin/ActigraphyData/EpochbyEpoch/MSFsc_AllDaysSinceDLMO/IncludingNaps")

output <- data.frame()
files <- list.files()

for (file in files) {

  d <- read.csv(file)
  d <- d[d$Interval.Status != "REST-S",]
  d <- d[d$Interval.Status != "EXCLUDED",]

  isNA <- is.na(d$White.Light)
            d$White.Light[isNA] <- 0
  isNA <- is.na(d$Blue.Light)
             d$Blue.Light[isNA] <- 0
  isNA <- is.na(d$Green.Light)
             d$Green.Light[isNA] <- 0
  isNA <- is.na(d$Red.Light)
             d$Red.Light[isNA] <- 0
  d$ID <- file
  d$ID <- as.numeric(gsub(".csv", "", d$ID))
  as.numeric(ref$ID)

  d <- dplyr::left_join(d, ref, by = "ID")

  d <- data.frame(ID = d$ID, Epoch = d$Epoch, Date = d$Date, Time = d$Time,
                  White_light = d$White.Light,  Blue_light = d$Blue.Light,
                  Green_light = d$Green.Light, Red_light = d$Red.Light,
                  DLMO_date = d$DLMO_date)

  d$Date <- strptime(as.character(d$Date), "%m/%d/%Y")
```

```
 d$DLMO_date <- strptime(as.character(d$DLMO_date), "%m/%d/%Y")
 d$DaysFromDLMO <- difftime(d$DLMO_date, d$Date, units= "days")
 d$DLMO_date <- as.Date(d$DLMO_date)
 d$Date <- as.Date(d$Date)

 EpochMin <- d$Epoch%%2880
 LightbyEpoch <- data.frame(Epoch = d$Epoch, R = EpochMin, WhiteLight = d$White_light,
                    BlueLight = d$Blue_light, GreenLight = d$Green_light,
                    RedLight = d$Red_light)
 by_R <- group_by(LightbyEpoch, R)
 weeklyLight <- summarise(by_R, mean_white_light = mean(WhiteLight),
                   mean_blue_light = mean(BlueLight), mean_green_light = mean(GreenLight),
                   mean_red_light = mean(RedLight))

 output_white <- list()
  for (i in 0:23) {
  start <- i * 120
  end <- start + 120
  output_white[[i+1]] <- mean(weeklyLight$mean_white_light[weeklyLight$R < end & weeklyLight$R >= start])
 }
 output_blue <-list()
 for (i in 0:23) {
  start <- i * 120
  end <- start + 120
  output_blue[[i+1]] <- mean(weeklyLight$mean_blue_light[weeklyLight$R < end & weeklyLight$R >= start])
 }
  output_green <-list()
 for (i in 0:23) {
  start <- i * 120
  end <- start + 120
  output_green[[i+1]] <- mean(weeklyLight$mean_green_light[weeklyLight$R < end & weeklyLight$R >= start])
 }
  output_red <-list()
 for (i in 0:23) {
  start <- i * 120
  end <- start + 120
  output_red[[i+1]] <- mean(weeklyLight$mean_red_light[weeklyLight$R < end & weeklyLight$R >= start])
 }
 WeeklyLight <- data.frame(white_light=unlist(output_white), blue_light=unlist(output_blue),
                    green_light=unlist(output_green), red_light=unlist(output_red))

 WeeklyLightT <- as.data.frame(t(WeeklyLight), row.names = NULL)

 WeeklyLightT <- cbind(light_color = c("white", "blue", "green", "red"),
                  WeeklyLightT)
 WeeklyLightT <- cbind(ID = d$ID[1], WeeklyLightT)

 output <- rbind(output, WeeklyLightT)
}
colnames(output)[3:26] <- paste0("hour_", 1:24)

isNA <- is.na(output)
output[isNA] <- ""

SleepVariables <- read_csv("~/Desktop/Caitlin/DataFiles/SleepVariables.csv")
SleepVariables$ID <- as.numeric(SleepVariables$ID)
```

```
output$ID <- as.numeric(output$ID)
ref$ID <- as.numeric(ref$ID)

output <- dplyr::left_join(output, ref, by = "ID")
output <- dplyr::left_join(output, SleepVariables, by = "ID")

write.table(output, file = "ZT_AllDays_allWavelengths_wide.csv", sep = ",", col.names = NA)
d <- output
d$ID <- factor(d$ID)
d <- tidyr::gather(d, hour, light, hour_1:hour_24)
d$hour <- gsub("hour_", "", d$hour)
write.table(d, file = "ZT_AllDays_allWavelengths_long.csv", sep = ",", col.names = NA)
```

A.4.5 Six days since DLMO – calculating hourly light exposure since wake

```
library(dplyr)
library(zoo)
library(readr)

Covariates <- read_excel("~/Desktop/Caitlin_MS/Covariates.xlsx")
ref <- read_csv("C:/Users/cmd142/Desktop/Lab/Projects/Light_SAD/MS_Thesis/DataFiles/Covariates_csv.csv")
SleepVariables <- read_csv("C:/Users/cmd142/Desktop/Lab/Projects/Light_SAD/MS_Thesis/DataFiles/
        SleepVariables_6DaysSinceDLMO.csv")
setwd("C:/Users/cmd142/Desktop/Lab/Projects/Light_SAD/MS_Thesis/ActigraphyData/EpochbyEpoch/
        6DaysSinceDLMO/ExcludingNaps")

output <- data.frame()
files <- list.files()

for (file in files) {

    d <- read.csv(file)
    d <- d[d$Interval.Status != "EXCLUDED",]

    isNA <- is.na(d$Blue.Light)
        d$Blue.Light[isNA] <- 0
    isNA <- is.na(d$White.Light)
         d$White.Light[isNA] <- 0
    isNA <- is.na(d$Green.Light)
        d$Green.Light[isNA] <- 0
    isNA <- is.na(d$Red.Light)
        d$Red.Light[isNA] <- 0

    d$ID <- file
    d$ID <- as.numeric(gsub(".csv", "", d$ID))

    d2 <- dplyr::left_join(d, ref, by = "ID")
    d <- data.frame(ID = d2$ID, Epoch = d2$Epoch, Date = d2$Date, Time = d2$Time,
                Blue_light = d2$Blue.Light, White_light = d2$White.Light,
                Green_light = d2$Green.Light, Red_light = d2$Red.Light,
```

```
                DLMO_date = d2$DLMO_date, Interval.Status = d$Interval.Status)
    d$Date <- strptime(as.character(d$Date), "%m/%d/%Y")
    d$DLMO_date <- strptime(as.character(d$DLMO_date), "%m/%d/%Y")
    d$DaysFromDLMO <- difftime(d$DLMO_date, d$Date, units= "days")
    d$DLMO_date <- as.Date(d$DLMO_date)
    d$Date <- as.Date(d$Date)
    d$Interval.Status <- gsub("REST-S", "1", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("REST", "0", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("ACTIVE", "0", d$Interval.Status, fixed = TRUE)
    d$Interval.Status <- gsub("EXCLUDED", "0", d$Interval.Status, fixed = TRUE)
    d$count <- NA
    d$count <- ifelse(d$Interval.Status == 0, 1, 0)

     for(i in 2:nrow (d)) {
      d$count[i] <- ifelse(d$Interval.Status[i] == 0, d$count[i-1] + 1, 0)
       }

   d <- d[d$Interval.Status != "1",]
   by_c <- dplyr::group_by(d, count)
   WeeklyLight <- summarise(by_c, mean_white = mean(White_light),
                       mean_blue = mean(Blue_light), mean_green = mean(Green_light),
                       mean_red = mean(Red_light))
   output_white <-list()
       for (i in 0:23) {
       start <- i * 120
       end <- start + 120
       output_white[[i+1]] <- mean(WeeklyLight$mean_white[WeeklyLight$count < end & WeeklyLight$count >=
start])
        }
   output_blue <-list()
       for (i in 0:23) {
       start <- i * 120
       end <- start + 120
       output_blue[[i+1]] <- mean(WeeklyLight$mean_blue[WeeklyLight$count < end & WeeklyLight$count >=
start])
        }
  output_green <-list()
      for (i in 0:23) {
      start <- i * 120
      end <- start + 120
      output_green[[i+1]] <- mean(WeeklyLight$mean_green[WeeklyLight$count < end & WeeklyLight$count >=
start])
    }
 output_red <-list()
    for (i in 0:23) {
      start <- i * 120
      end <- start + 120
      output_red[[i+1]] <- mean(WeeklyLight$mean_red[WeeklyLight$count < end & WeeklyLight$count >= start])
    }

    WeeklyLight <- data.frame(white_light=unlist(output_white), blue_light=unlist(output_blue),
                        green_list=unlist(output_green), green_list=unlist(output_red))
    WeeklyLightT <- as.data.frame(t(WeeklyLight), row.names = NULL)
    WeeklyLightT$CumDays <- 6
    WeeklyLightT <- cbind(light_color = c("white", "blue", "green", "red"),
                WeeklyLightT)
```

```
    WeeklyLightT <- cbind(ID = d$ID[1], WeeklyLightT)
    output <- rbind(output, WeeklyLightT)
    }
colnames(output)[3:26] <- paste0("hour_", 1:24)
isNA <- is.na(output)
output[isNA] <- ""
SleepVariables$ID <- as.numeric(SleepVariables$ID)
output$ID <- as.numeric(output$ID)
ref$ID <- as.numeric(ref$ID)
output <- dplyr::left_join(output, ref, by = "ID")
output <- dplyr::left_join(output, SleepVariables, by = "ID")
write.table(output, file = "CT_AllDays_allWavelengths_wide.csv", sep = ",", col.names = NA)

d <- output
d$ID <- factor(d$ID)
d <- tidyr::gather(d, hour, light, hour_1:hour_24)
d$hour <- gsub("hour_", "", d$hour)
write.table(d, file = "CT_AllDays_allWavelengths_long.csv", sep = ",", col.names = NA)
```

A.4.6 Six days since DLMO – calculating hourly light exposure by clock time

```
library(dplyr)
library(readr)
library(tidyr)

Covariates <- read_excel("~/Desktop/Caitlin_MS/Covariates.xlsx")
ref <- read_csv("~/Desktop/Caitlin/DataFiles/Covariates_csv.csv")
setwd("~/Desktop/Caitlin/ActigraphyData/EpochbyEpoch/6DaysSinceDLMO/IncludingNaps")

output <- data.frame()
files <- list.files()
for (file in files) {
      d <- read.csv(file)
      d <- d[d$Interval.Status != "REST-S",]
      d <- d[d$Interval.Status != "EXCLUDED",]

      isNA <- is.na(d$White.Light)
           d$White.Light[isNA] <- 0
      isNA <- is.na(d$Blue.Light)
            d$Blue.Light[isNA] <- 0
      isNA <- is.na(d$Green.Light)
           d$Green.Light[isNA] <- 0
      isNA <- is.na(d$Red.Light)
           d$Red.Light[isNA] <- 0
      d$ID <- file
      d$ID <- as.numeric(gsub(".csv", "", d$ID))

      d2 <- dplyr::left_join(d, ref, by = "ID")
      d <- data.frame(ID = d2$ID, Epoch = d2$Epoch, Date = d2$Date, Time = d2$Time,
                  White_light = d2$White.Light,  Blue_light = d2$Blue.Light,
```

```
                Green_light = d2$Green.Light, Red_light = d2$Red.Light,
                DLMO_date = d2$DLMO_date)
      d$Date <- strptime(as.character(d$Date), "%m/%d/%Y")
      d$DLMO_date <- strptime(as.character(d$DLMO_date), "%m/%d/%Y")

      d$DaysFromDLMO <- difftime(d$DLMO_date, d$Date, units= "days")

      d$DLMO_date <- as.Date(d$DLMO_date)
      d$Date <- as.Date(d$Date)

  d<- dplyr::filter(d, d$DaysFromDLMO <= 6)

      EpochMin <- d$Epoch %% 2880
      LightbyEpoch <- data.frame(Epoch = d$Epoch, R = EpochMin, WhiteLight = d$White_light,
                          BlueLight = d$Blue_light, GreenLight = d$Green_light,
                          RedLight = d$Red_light)
      by_R <- group_by(LightbyEpoch, R)
      weeklyLight <- summarise(by_R, mean_white_light = mean(WhiteLight),
                        mean_blue_light = mean(BlueLight), mean_green_light = mean(GreenLight),
                        mean_red_light = mean(RedLight))
      output_white <- list()
      for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_white[[i+1]] <- mean(weeklyLight$mean_white_light[weeklyLight$R < end & weeklyLight$R >=
start])
        }
      output_blue <-list()
      for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_blue[[i+1]] <- mean(weeklyLight$mean_blue_light[weeklyLight$R < end & weeklyLight$R >= start])
        }
      output_green <-list()
      for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_green[[i+1]] <- mean(weeklyLight$mean_green_light[weeklyLight$R < end & weeklyLight$R >=
start])
      }
      output_red <-list()
        for (i in 0:23) {
        start <- i * 120
        end <- start + 120
        output_red[[i+1]] <- mean(weeklyLight$mean_red_light[weeklyLight$R < end & weeklyLight$R >= start])
      }
      WeeklyLight <- data.frame(white_light=unlist(output_white), blue_light=unlist(output_blue),
                          green_light=unlist(output_green), red_light=unlist(output_red))
      WeeklyLightT <- as.data.frame(t(WeeklyLight), row.names = NULL)
      WeeklyLightT$CumDays <- 6
      WeeklyLightT <- cbind(light_color = c("white", "blue", "green", "red"),
                WeeklyLightT)
      WeeklyLightT <- cbind(ID = d$ID[1], WeeklyLightT)
      output <- rbind(output, WeeklyLightT)
      }
colnames(output)[3:26] <- paste0("hour_", 1:24)
```

```
isNA <- is.na(output)
output[isNA] <- ""

SleepVariables <- read_csv("~/Desktop/Caitlin/DataFiles/SleepVariables_6DaysSinceDLMO.csv")
SleepVariables$ID <- as.numeric(SleepVariables$ID)
output$ID <- as.numeric(output$ID)
ref$ID <- as.numeric(ref$ID)
output <- dplyr::left_join(output, ref, by = "ID")
output <- dplyr::left_join(output, SleepVariables, by = "ID")
write.table(output, file = "ZT_6DaysSinceDLMO_allWavelengths_wide.csv", sep = ",", col.names = NA)

d <- output
d$ID <- factor(d$ID)
d <- gather(d, hour, light, hour_1:hour_24)
d$hour <- gsub("hour_", "", d$hour)
write.table(d, file = "ZT_6DaysSinceDLMO_allWavelengths_long.csv", sep = ",", col.names = NA)
```

A.4.7 Calculating sleep variables

```
setwd("C:/Users/cmd142/Desktop/Lab/Projects/Light_SAD/MS_Thesis/ActigraphyData/EpochbyEpoch/
excluding_naps")

library(readr)
library(zoo)

output <- data.frame()

files <- list.files()

for (file in files) {
  d <- read.csv(file)
  d <- d[d$Interval.Status != "EXCLUDED",]

  d$ID <- file
  d$ID <- gsub("_.*", "", d$ID)

  d$Interval.Status <- gsub("REST-S", "1", d$Interval.Status, fixed = TRUE)
  d$Interval.Status <- gsub("REST", "0", d$Interval.Status, fixed = TRUE)
  d$Interval.Status <- gsub("ACTIVE", "0", d$Interval.Status, fixed = TRUE)
  d$Interval.Status <- gsub("EXCLUDED", "0", d$Interval.Status, fixed = TRUE)

  d$count <- NA
  d$count <- ifelse(d$Interval.Status == 0, 1, 0)

  for(i in 2:nrow (d)) {
    d$count[i] <- ifelse(d$Interval.Status[i] == 0, d$count[i-1] + 1, 0)
```

```
  }

   wake <- dplyr::filter(d, count==1)
   wake$R <- wake$Epoch %% 2880
   avg_wake <- (mean(wake$R))*0.5

  NDays  <- nrow(wake)
  SleepDur <- ((sum(d$Interval.Status == 1)/2)*(1/(NDays)))
  midptMin <- SleepDur/2
  MidptTime <- avg_wake - midptMin

WakeTime <- data.frame(ID = wake$ID[1], AvgWakeTime = avg_wake, AvgSleepDur = SleepDur,
SleepMidPt = MidptTime)

   output <- rbind(output, WakeTime)
}

write.table(output, file = "SleepVariables.csv", sep = ",", col.names = NA)
```

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