THE MULTIFACETED IMPLICATIONS OF LIGHT FOR PSYCHOLOGICAL WELL-BEING AND MOOD

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It is to them, et mes dernières trois neurones, that I dedicate this thesis.

Content of Dissertation and Contributions of Authors

This dissertation is comprised of 3 articles: (*study I*) "Assessing the Effects of Polychromatic Light Exposures on Mood in Healthy Adults: A Systematic Review on the Relative Contribution of α-opic Equivalent Daylight Illuminances", (*study II*) "Temporal dynamics of subjective sleep profiles predicting mood improvements during adjunctive light therapy combined with sleep rescheduling", and (*study III*) "Light Therapy Associated with Sleep, Circadian and Mood Improvements in People with Mood Disorders; A Randomized Control Trial".

Study I (Nixon, Robillard, Leveille, Douglass, Porteous, & Veitch in preparation) will soon be submitted to a peer-previewed journal. Ashley Nixon, Rebecca Robillard and Jennifer Veitch led the study design. The writer of the thesis (Ashley Nixon), the first author, also set up the logistics of the study, oversaw its implementation and the work of all research assistants involved, contributed to statistical analyses, and wrote the manuscript draft. Also included as co-authors are graduate students Chloe Leveille and Meggan Porteous who helped with data collection and processing. Alan Douglass helped with the development of the statistical analyses. Jennifer Veitch also obtained the funding supporting this work and created the Scientific Advisory Board for this study. All co-authors contributed to the interpretation of results and critically reviewed the manuscript.

Study II was published in the peer-reviewed *Journal of Affective Disorders Reports* (Nixon, Strike, Feilds, Glozier, Thatte, Hickie, De Koninck, & Robillard, 2021). Rebecca

Robillard, Ian B. Hickie and Nick Glozier led the study design. Ashley Nixon and Kristy-Lee Feilds contributed to data collection and oversaw daily trial management at distinct sites. Ashley Nixon took the lead in processing and analyzing the data and wrote the first draft of the manuscript. Melanie K. Strike and Smita Thatte contributed to recruitment, assessments, and clinical management of the trial. Rebecca Robillard, Nick Glozier, Ian Hickie, Joseph De Koninck and Smitha Thatte were involved in securing funding and resources for this work. All co-authors contributed to the interpretation of results and critically reviewed the manuscript.

Study III (Nixon, Strike, Leveille, Douglass, Audet, Foti, Higginson, Lee, De Koninck, & Robillard in preparation) will soon be submitted to a peer-reviewed journal. Ashley Nixon, Rebecca Robillard, Marie-Claude Audet and Joseph De Koninck led the study design. Ashley Nixon contributed to data collection, oversaw daily trial management, and wrote the first draft of the manuscript. Together with Chloe Leveille and Michael-Christopher Foti, she processed and analyzed the data. Melanie Strike, Alan Douglass, and Elliott Kyung Lee were involved in clinical assessments and the clinical management of the trial. Marie-Claude Audet oversaw the hormonal data analyses. Caitlin Higginson processed the polysomnography data. All co-authors contributed to the interpretation of results and critically reviewed the manuscript.

Abstract

Light not only allows us to see but is also fundamental to our health and well-being. Several parameters of light exposure, such as wavelengths, intensity, and timing of exposure, all play an important role on its effects on psychophysiological functions. The way in which studies have previously quantified light (based on intensity), has been found to be inadequate since it does not consider the spectrum of light which influences non-visual effects. Among these non-visual effects, light has been found to have antidepressant effects, however, these effects remain inconsistent for non-seasonal depression and their underlying mechanisms remain elusive.

The three research studies in this thesis investigated the effects of light on mood. The first study focused on the direct pathway between light and mood, aiming to predict mood outcomes based on the amount of intrinsically photosensitive retinal ganglion cells (ipRGC) stimulation from polychromatic light in healthy individuals. The second and third studies focused on the indirect pathways, exploring predictors and underlying mechanisms of mood improvements by means of sleep and circadian re-alignment in the context of non-seasonal depression. These studies explored the antidepressant mechanisms of monochromatic light therapy and predictive models of mood improvement.

The results from *study I* (systematic review) suggest that ipRGCs may not be as involved in the mood improvement associated with polychromatic light. Drawing strong conclusions from these results are, however, cautioned. Mood metrics used across the studies were inconsistent and the light sources were not designed to maximally stimulate ipRGCs.

The results from *study II* (open-label trial) support the notion that light therapy does have antidepressant effects in people with non-seasonal depression. The underlying mechanisms for

these antidepressant effects may involve improvements in sleep initiation and daytime functioning. Individuals with difficulties with fallings asleep and waking-up may be those that respond most prominently to light therapy.

The results from *study III* (randomized controlled trial) indicate that depression symptoms improved slightly more in the active light therapy condition as opposed to a placebo condition. Although this effect was modest across the overall group, there were considerable inter-individual variations in treatment response. The degree of improvement in mood was associated with improvement in pre-sleep thoughts and the circadian rhythmicity of skin temperature. Short REM latency and worst global subjective sleep were predictive of greater response to light therapy.

Overall, further research is required to disentangle the involvement of the different photoreceptors in the mood response to polychromatic light in healthy individuals. Monochromatic light therapy for non-seasonal depression yields overall modest antidepressant effects. Clinical applications of light therapy may benefit from further research investigating differential effects in sub-groups of depression and underlying mechanisms in larger studies.

SECTION 1

INTRODUCTION & LITERATURE REVIEW

1.1 Mood Disorders and Their Associated Burden

Various types of mood disorders have been delineated and characterized to better describe the various types of pathological mood disruptions. Among these are Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Persistent Depressive Disorder (PDD). In the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V), MDD is described as a condition where there is a clear-cut change in an individual's cognition, affect, and neurovegetative functions which lasts a minimum of 2 weeks. This is also often accompanied by sleep disturbances (such as insomnia, hypersomnia, initial insomnia). BD, now separated from depressive disorders in a distinct section in the DSM-V, has a cyclical presentation of manic and depressive episodes which are notably accompanied by marked changes in sleep. Specifically, manic/hypomanic episodes are typically associated with a critical reduction in sleep and the depression episode with daily hypersomnia or insomnia. Finally, PDD is characterized as a lower level depressive mood on more days than not for at least two years (American Psychiatric Association, 2013).

Mood disorders have increasingly been a topic of concern with their augmented presence in our society. One study collecting Canadian data from 2002 to 2007 found an increase from year to year in the cumulative incidence of major depressive episodes (2002/03 (2.9%), 2004/05 (5.7%), 2006/07 (7.2%); Wang et al., 2010). They further suggest that the higher prevalence among young individuals would make this demographic group one to focus on while developing prevention efforts. More recent data from Statistics Canada (collected via the Canadian Community Health Survey; CCHS) echoes this increase in diagnosed mood disorders (such as MDD, BD, or PDD) from 2017 to 2018 (12-17years old: 4.5% to 4.6%; 18-34years old: 8.9% to 10.1%; 35-49years old: 9.1% to 9.7%; 50-64years old: 9.9% to 10.3%; Statistics Canada, 2019).

It thus appears that a more important increase over time occurs in young adults. Outside of Canada, prevalence rates follow a similar trend. One study done in the United States from 2005 to 2015 found a significant increase in depression prevalence (even when adjusting for demographic factors), and this increase was especially rapid in younger individuals (Weinberger et al., 2018).

With the alarming increase in the prevalence of mood disorders, also comes an increase in associated burden. This includes diminished quality of life, cognitive impairments, psychosocial problems, work disability, risk of suicide, cardio- and cerebrovascular problems, and societal/economic burdens. All of these factors also play a critical role in the higher mortality risk faced by individual with mood disorders (Fajutrao et al., 2009; Lépine & Briley, 2011; Nixon et al., 2017). In fact, in 2013, depression was observed to be the second leading cause of disability worldwide (Vos et al., 2015). The French GAZEL cohort study found that workers on sick-leave due to a psychiatric disorder such as mood disorders were at an increased risk of mortality due to suicide, cardiovascular disease, and smoke-related cancer as compared to workers without psychiatric sick-leave (Melchior et al., 2010). In the USA, on average, 27 days of work are lost per year per individual with depression, which was estimated to be a loss of $36.6billion per year (Kessler et al., 2006). Furthermore, depression has been found to have a bidirectional relationship with marital disruptions, specifically, people with marital disruptions (e.g., divorce or separated) tend to develop depression and those with depression tend to experience martial disruptions (Bulloch et al., 2009). Overall, this emphasizes how depression has far reaching impacts beyond the individual suffering from depression. In addition, a wide array of factors also affects the course of illness and clinical outcomes of an individual with depression. Notably, those who remitted from depression but were faced with psychosocial and

persistent sleep impairments thereafter were found to be more likely to experience a relapse into depression (Giles et al., 1987; Rush et al., 1986; Solomon et al., 2004; Steiger & Holsboer, 1997). Overall, individuals with mood disorders are faced with significant burden that affect various aspects of their lives, which in turn also has widespread impacts on a family, social and economic front. This reality highlights the urgent need to prevent and treat mood disorders.

Sleep and circadian abnormalities have been proposed to have a significant pull on the onset, maintenance, and relapse of mood disorders. These sleep disturbances have been suggested to be driven, in part, by underlying circadian abnormalities. Key circadian abnormalities that have been consistently found in past research on mood disorders include disturbances of the sleep-wake cycle, body temperature, and hormones (such as melatonin and cortisol). The present thesis will expand on these circadian abnormalities by first defining what circadian rhythms are and how they interact with sleep in a healthy state (section 2), followed by an in depth look at the circadian abnormalities commonly observed in people with mood disorders (section 3). This will be followed by a look at the potential of circadian rhythms as a treatment target for mood disorders (section 4), trailed by the therapeutic potential of light for the management of mood disorders (section 5).

1.2 Circadian Rhythms and Sleep

1.2.1 Circadian rhythms and the clocks defined

Numerous aspects of our physiology are carefully timed and synchronized to both internal and external events. Franz Halberg (1959) coined the term circadian rhythms, signifying “about a day”, which refers to the approximate 24hr cycles, or oscillations, followed by several physiological and behavioral functions such as the sleep-wake cycle, body temperature, brain

activity, hormone production, and cell regeneration (Aschoff, 1979; Halberg, 1969; Pittendrigh, 1993; Rietveld, 1996). This biological 24hr periodicity likely evolved from the 24hr periodicity of our planet's axal rotation enabling organisms to adapt to the light-dark cycle of their environment (Husse et al., 2015).

An interesting quality of circadian clocks is that they maintain some rhythmicity even when isolated from external cues for extended periods of time, and this, even at the cellular level (Husse et al., 2015; Kleitman, 1963; Yoo et al., 2004). However, if left isolated from external cues for long periods of time, a free-running pattern begins to appear in the sleep-wake cycle due to the approximate nature of the 24hr period of the circadian clocks (Kleitman, 1963). In other words, the daily resetting of the body clocks by external cues such as the sun, a process known as entrainment, is key in maintaining circadian periodicity very close to 24.0hr so that the circadian system stays synchronised with the external light-dark cycle. These external cues are also known as Zeitgebers (external elements that help synchronize our "world within" with our "outer world") and include, but are not limited to social cues, food intake, exercise, and the light-dark cycle (Wirz-Justice, 2007). Among these, light (and darkness) has been deemed as the strongest Zeitgeber (Li et al., 2006).

The suprachiasmatic nucleus (SCN) was established as the location of the primary mammalian circadian pacemaker ("master" biological clock) in 1972 (Moore & Eichler, 1972; Stephan & Zucker, 1972). Specifically, the SCN is a bilaterally paired hypothalamic nucleus near the midline and third ventricle and resting above the optic chiasm (Weaver, 1998). It is often considered at the top of the circadian hierarchy whereby the SCN sends signals to the peripheral clocks to keep them in sync (Husse et al., 2015). This was demonstrated by various studies where lesions to the SCN in rats brought about rhythmicity problems in corticosterone levels,

drinking, and physical activity among other problems (Moore & Eichler, 1972; Stephan & Zucker, 1972). In other words, this master clock allows mammals to optimally sync behavioural and physiologic rhythms (such as their sleep-wake cycle, their hormone fluctuations, and body temperature rhythms) with their external world (Mohawk et al., 2012).

Photonic input from the eye travels through non-visual pathways (mediated in part by the melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs)) and project to various parts of the brain, including the SCN (Berson et al., 2002). Specifically, the M1 ipRGC type (1 among 5 ipRGC types) projects to the SCN via the retinohypothalamic tract (RHT; Hannibal et al., 2004). This is thought to be one of the physiological mechanisms via which light influences a range of non-visual functions, including circadian rhythms.

A multitude of peripheral circadian oscillators (or peripheral body clocks) also contribute to the regulation of our daily rhythms. These peripheral oscillators can be found in virtually every cell, tissue, and organ of our body (Dibner et al., 2010). From the SCN, hormonal and neuronal information is sent to these local clocks which influences circadian behaviour and physiology (Dibner et al., 2010). It is the properly timed interplay between these various clocks that allow the maintenance of a healthy state. In certain cases, external factors, such as food intake restriction (Damiola et al., 2000; Stokkan et al., 2001) and light (Fonken & Nelson, 2014) can cause peripheral clocks to become uncoupled with the SCN which creates circadian disruptions. These disruptions have been theorized and explored as one of the variables contributing to various health problems such as dysplasia, obesity, diabetes, cardiovascular disease, cancer, sleep disorders, and mood disorders (Angelousi et al., 2018; Antunes et al., 2010; Logan & McClung, 2019; Momma et al., 2017; Pan et al., 2011; Polo et al., 2017; Robillard et al., 2013; Surridge-David et al., 1987; Vilches et al., 2014; Voiculescu et al., 2016;

Xiong et al., 2018; Zhao et al., 2018; Zhou et al., 2018). The circadian misalignment across various circadian rhythms found in mood disorders will be expanded upon in section 3.

1.2.2 Sleep and circadian rhythms in healthy individuals

Sleep-wake regulation

The Two-Process Model has been proposed to explain the regulation of sleep and wake states (Borbély, 1982). It involves dynamic interactions between the circadian signal sent by the master clock (Process C) and the homeostatic drive linked to the accumulation of sleep pressure during wake and its dissipation during sleep (Process S). During the day sleep pressure progressively increases while the master clock compensates to keep us awake. During the evening, sleep pressure is high, and the master clock signal weakens leading to increased sleepiness. At night, sleep pressure decreases, and the master clock signal continues to decrease which enables us to stay asleep. In the morning, sleep pressure dissipates and the master clock signal increases which wakes us up. It is the interplay of these two processes that modulate sleep propensity and define when we fall asleep and wake-up. Core body temperature, melatonin, or cortisol are often used as a marker for Process C and Slow Wave Activity (SWA) for Process S.

Sleep architecture

Sleep can be divided into 2 types: rapid eye movement (REM) and non-REM (NREM) sleep. NREM is further divided into 3 stages (NREM1 to NREM3) and is characterized by specific electroencephalogram (EEG) signals such as spindles (NREM2), k-complexes (NREM2), and slow waves (NREM3). REM sleep is known for its variable speed brain waves (Alpha, Theta, sawtooth waves), rapid eye movements and muscle paralysis. There is also a higher likelihood of dreaming in this sleep stage which is associated with more vivid and/or

bizarre dreams as compared to dreaming in other stages of sleep (Payne & Nadel, 2004). Sleep typically progresses through the different NREM and REM stages and cycles every 90 minutes. A higher proportion of NREM sleep is usually seen early in the sleep period and gradually transitions to a higher proportion of REM by the end of the sleep period. Sleep architecture varies considerably from birth to old age (Kryger et al., 2014). For instance, from preteen to adolescence, slow wave sleep (NREM3) decreases by 40% and continues to do so with advancing age (Keenan et al., 2013).

Chronotypes

The characterizing of individual time preference to go to sleep, wake-up, and undertake cognitive and physical activities, also known as a chronotype, is often used as a proxy of circadian phase. From the classical view of chronotypes, circadian preference is assessed with questionnaires such as the MEQ (Horne & Östberg, 1976). Chronotypes can be seen along a continuous spectrum spanning from "morningness" to "eveningness", or from a categorical perspective ranging from morning types (M-Type; morning larks) who prefer doing activities and going to sleep at earlier times, all the way to evening types (E-Type; night owls) who prefer later schedules (Natale & Cicogna, 2002). Somewhere in the middle are intermediate types (I-Type), which is where the majority of individuals have been found to score (Urbán et al., 2011).

Endogenous circadian markers

Melatonin (N-acetyl-5-methoxytryptamine) is a soporific hormone facilitating sleep initiation and maintenance (Brown, 1994). Tryptophan is synthesized into melatonin through various steps, which involves serotonin and norepinephrine input to the pineal gland (Cardinali & Pévet, 1998; Simonneaux & Ribelayga, 2003). The pineal gland is considered a neuroendocrine transducer; photopic information is received at the retina and transferred to the

pineal gland via the SCN. In a dark environment, norepinephrine is released, which activates β-adrenergic receptors and mediates the induction of pineal serotonin N-acetyltransferase and increases melatonin concentrations, whereas a bright environment will withhold the release of norepinephrine, thus keeping melatonin levels low (Brzezinski, 1997; Klein & Weller, 1972). Light not only has the ability to supress melatonin, but it can also shift the secretion rhythm of melatonin (Lewy et al., 1980; Shanahan et al., 1997). Melatonin release has been found to be closely harmonized with one's habitual sleep-wake cycle, where it increases prior to one's habitual bedtime and decreases near habitual waketime (see Figure 1; Benloucif et al., 2005). A circadian phase marker known as dim light melatonin onset (DLMO) is widely used to characterize the circadian phase of the melatonin rhythm and can be determined from urine, plasma, or saliva (Benloucif et al., 2005). DLMO is characterized as the point in time where concentrations of melatonin reach a certain threshold. On average this occurs between 19:30 and 22:00 in adults (Pandi-Perumal et al., 2007). Due to the circadian phase delay naturally occurring during adolescence, DLMO tends to progressively shift later with age within this developmental phase (Crowley et al., 2014). Desynchronization of melatonin's rhythm (due to e.g. jet lag, shift work, daylight savings time) has been associated with sleep disturbances and daytime functioning problems (Burch et al., 2005; Drake & Wright, 2010; Harrison, 2013).

The rhythms of the hormone cortisol, like other circadian rhythms, is highly driven by the SCN (Moore & Eichler, 1972) but is also strongly modulated by the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is involved in the regulation of glucocorticoid production by stimulating forward and feedback inhibition loops between the hippocampus, hypothalamus, pituitary, and adrenal cortex (Keller et al., 2017; Nicolson, 2008). The cortisol awakening response (CAR) is thought to be reflective of HPA axis function and is characterized by a peak

cortisol secretion 30 to 45 min post awakening and a return to baseline by 60minutes after awakening (Pruessner et al., 1997; Wilhelm et al., 2007; Wüst et al., 2000). Cortisol has alerting effects and has been found to be elevated in the evening in some individuals with sleep initiation difficulties such as insomnia (Rodenbeck et al., 2002). From a 24hr perspective, cortisol levels have been characterized as low in the evening, gradually increasing over the night, reaching the acrophase (or peak) in the morning, and gradually decreasing during the day (see Figure 1; Czeisler & Klerman, 1999; Desir et al., 1980; Van Cauter et al., 1994). Individuals with an E-type chronotype have shown lower salivary cortisol for the first hours following sleep offset compared to M-types, which was not explained by a difference in total sleep time nor time of awakening (Kudielka et al., 2006). With its near 24-hour rhythm, cortisol can be used as a phase marker of the circadian clock (Desir et al., 1980; Van Cauter & Refetoff, 1985).

Body temperature can be divided as skin (distal (feet and hands); proximal (thigh, forehead, infraclavicular region)) and core body temperature (CBT). Distal skin temperature tends to increase during the evening and decrease in the morning, whereas CBT follows the inverse pattern. Specifically, it decreases in the evening about 60 minutes before sleep, reaching a minimum between 1-3hours before wake-up time and increasing afterwards (see Figure 1; Krauchi & Wirz-Justice, 1994; Murphy & Campbell, 1997). This drop in CBT in the evening is important for sleep initiation, and the continued low temperature levels are important for sleep maintenance (Okamoto-Mizuno & Mizuno, 2012).

Various factors can have masking effects on circadian markers such as melatonin, cortisol, and CBT. These factors include bright light, food intake, movement, posture, and ambient temperature (Brandenberger et al., 1982; Brandenberger & Follenius, 1975; Duffy & Dijk, 2002; Jung et al., 2010; Rietveld et al., 1993). Constant or semi-constant routines are

implemented in the aim of reducing the effect of these masking factors and more accurately assess circadian parameters (Duffy & Dijk, 2002; Rietveld et al., 1993).

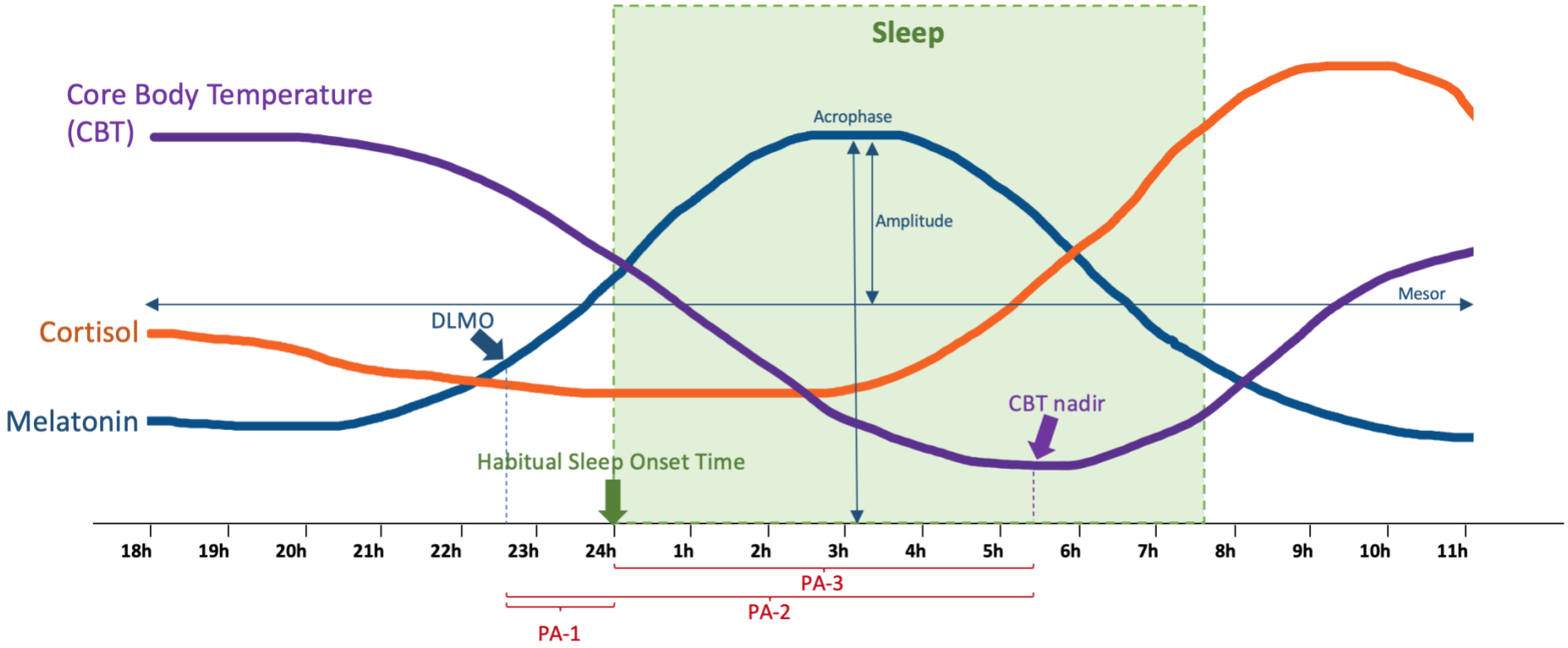

Figure 1. **Sleep and Circadian Rhythms in Healthy Individuals**. Variations in circadian rhythms across clock time in relation to the sleep episode (in green). The phase angles between DLMO and Habitual Sleep Onset Time (PA-1), DLMO and CBT nadir (PA-2) and Habitual Sleep Onset Time and CBT nadir (PA-3) are depicted in red. The main circadian parameters (acrophase, amplitude and mesor) are shown for the melatonin rhythm as an example. DLMO; Dim Light Melatonin Onset.

While many circadian rhythms are co-occurring, they are also influencing one another in significant ways (Germain & Kupfer, 2008). For instance, the increase in cortisol during the day and melatonin during the evening have been found to have a role in the entrainment of peripheral oscillators (Balsalobre et al., 2000; Pevet & Challet, 2011). Melatonin has also been found to be inversely coupled with core body temperature, and 40% of its amplitude can be accounted for by the hypothermic properties of melatonin (Cagnacci, 1992). Circadian fluctuations in subjective alertness, cognitive performance, and short-term memory have also been linked to CBT, where the nadir of CBT is associated with lower performance. This suggest that these cognitive outcomes may be controlled by the same pacemaker as endogenous rhythms such as body temperature (Johnson et al., 1992). Research also suggests that the position and duration of the sleep period relative to the endogenous circadian phase has a relationship with mood (Taub & Berger, 1973). In fact, the temporal organization of these rhythms is important for several aspects of mental health (Baron & Reid, 2014). Experimentally induced alterations in the temporal relationship between the light–dark cycle and circadian rhythms can induce mood impairments (Boivin et al., 1997; Surridge-David et al., 1987). Consequently, it has thus been suggested that circadian rhythms disruption may play a role in the pathophysiology of mood disorders (Germain & Kupfer, 2008; Wirz-Justice, 2006).

Chronotypes: its relation with endogenous circadian markers and developmental changes

In relation to chronotypes, it has been found that M-types have a higher daytime oral temperature with an earlier acrophase and lower post acrophase compared to E-types, whereas the I-types (intermediate-type) body temperature profile was somewhere in between M-Types and E-Types (Horne & Östberg, 1976). These robust body temperature rhythms are a result of changes in heat production and heat loss, with heat production being phase advanced by 1.2

hours in relation to heat loss (Aschoff & Heise, 1972). The average CBT in healthy individuals is roughly 37°C with ± 1°C (Aschoff, 1983). CBT_{nadir}, which is the time if the minimum of the fitted sinusoidal curve of the CBT rhythms, is often used as the circadian phase marker for body temperature.

Chronotypes are highly correlated with endogenous circadian phase markers such as core body temperature minimum (CBT_{min}) and dim light melatonin onset (DLMO) (Andrade et al., 1992; Baehr et al., 2000; Bailey & Heitkemper, 2001; Duffy et al., 2001). Variations in chronotypes are largely influenced by genetic factors (Hur, 2007; Hur et al., 1998).

Across the lifespan, there is a general tendency for children to be M-types, delaying towards more eveningness during adolescence and young adulthood (peak eveningness at approximately age 20 (Roenneberg et al., 2007)), and then receding back towards more morningness with in older adulthood (Caci et al., 2005; Carrier et al., 1997; Paine et al., 2006; Randler et al., 2009; Wickersham, 2006). On average, individuals over the age of 60 reach an early chronotype that is even earlier than during childhood (Roenneberg et al., 2007). There are also indications of differential age-related changes in males and females, where women attain their maximum eveningness by the age of 19.5 (Roenneberg et al., 2004) and males by the age of 21. Males remain with a later chronotype for the majority of adulthood, with this difference dissipating by the age of 50 (around menopause; Adan & Natale, 2002; Hollandera et al., 2001). Overall, variations in chronotype linked with age and sex (associated with puberty and menopause) suggests that endocrine factors may play a key role in age-dependent changes in chronotype across the lifespan (Carskadon et al., 1993; Gau & Soong, 2003).

Sleep-wake cycles are regulated based on the interaction between the circadian and sleep homeostasis processes, and external cues notably processed by photoreceptors. The sleep-wake

cycle feeds back onto these processes (Dijk & Lockley, 2002) and is closely tied to an individual's chronotype. Age-related changes also occur where younger individuals have a later sleep-wake cycle as compared to older individuals (Yoon et al., 2003). Sleep and wakefulness can start occurring at altered times and/or become out of phase with internal circadian rhythms should the factors previously mentioned become distorted (Dijk & Lockley, 2002). The phase of the sleep-wake cycle is typically defined using the time of sleep onset and offset, or sleep midpoint, which corresponds to the clock time equidistant to sleep onset and offset.

1.3 The Circadian and Sleep Profile of Mood Disorders: What we Know so Far

As an extension to the Two-Process Model (Borbély, 1982) described above in healthy individuals, Borbély also proposed the S-Deficiency Model which describes Process S as not rising enough during wake in people with depression (Borbely, 1987; Wirz-Justice, 2006). Specifically, this deficiency in the Process S would cause a reduced homeostatic pressure which would result in sleep disturbances such as increased sleep onset latency, shorter total sleep time, less SWS, and a reduced REM latency (David J Kupfer et al., 1984; Staner et al., 2003). However, seeing as sleep deprivation may diminish the phase-shifting ability of light by means of reducing the signal reaching the SCN, the body clock may be influenced by sleep homeostatic pressure. Thus, a continuous interaction between the Process C and Process S is likely (Borbély et al., 2016). Moreover, the reduced SWS as a result from early awakenings, could provide the opportunity for REM sleep to present itself in the early portion of the night (Borbély et al., 2016). Within the S-Deficiency Model, this early REM onset latency could be understood more so as the result of a disrupted homeostatic process rather than an endogenous phase advance.

However, in addition to alterations in the homeostatic process, clear circadian abnormalities, including phase shifting, have been tied to mood disorder in other lines of works.

1.3.1 Sleep architecture in mood disorders

Mood disorders are often accompanied by altered sleep architecture, with as many as 90% of individuals with depression reporting difficulties with falling asleep, staying asleep and early morning awakenings (Almeida & Pfaff, 2005; Tsuno et al., 2005). Meta-analyses of studies in adolescents and young adults with depression found an increase in self-reported subjective sleep disturbances, longer sleep onset latency (SOL), poorer sleep efficiency, disrupted sleep continuity, and lighter sleep as compared to controls (defined as having more NREM 1 sleep; Baglioni et al., 2017; Lovato & Gradisar, 2014). Studies in adults with affective disorders also found decreased sleep efficiency, total sleep time (TST) slow-wave sleep (SWS), rapid eye movement (REM) latency, and an increase in REM sleep and density as compared to controls (Benca, Obermeyer, et al., 1992; Pillai et al., 2011). Overall, there are some indications that sleep abnormalities associated with depression change with age (Armitage, 2007).

1.3.2 Endogenous circadian rhythms in mood disorders

Altered melatonin levels and temporal dynamics have been repeatedly described in individuals with mood disorders. However, limited research has been done in adolescents and young adults. Of the current research in that age group and in non-clinical samples, melatonin onset has been found to be delayed (Carpenter et al., 2017; Melo et al., 2017), with this delay being more pronounced in individuals with bipolar as opposed to unipolar depression (Robillard, Naismith, Rogers, Scott, et al., 2013). Keeping in mind that depression is a heterogenous

condition with various sub-types, subgroups of people with mood disorders may have different profiles of melatonin rhythms (Robillard, Carpenter, Rogers, et al., 2018). Specifically, there was a cluster of individuals with a more conventional circadian timing and another with a delayed timing. The DLMO of the delayed cluster was 3.7hrs later compared to the conventional timing cluster (Robillard et al., 2018). Increased depressive symptoms severity has also been found to linked to lower evening melatonin levels and delayed DLMO (Robillard et al., 2018; Sundberg et al., 2016).

Cortisol abnormalities in depression are typically tied back to HPA axis hyperactivity (Linkowski et al., 1985; Steckler et al., 1999) and those with elevated HPA activity have been found to be less responsive to psychotherapy (Fischer et al., 2017). The CAR in adolescents with depression was found to be increased compared to controls (Ulrike et al., 2013) and was also found to be a significant predictor of subsequent development of MDD (Adam et al., 2010). Conversely, other studies in older individuals with depression have reported a blunted CAR (Rhebergen et al., 2015; Stetler & Miller, 2005). The phase of cortisol rhythms in individuals with depression has been reported to be advanced with an earlier secretion acrophase (Dietzel et al., 1986; Goetze & Tölle, 1987; Koenigsberg et al., 2004; Linkowski et al., 1985), reduced circadian amplitude (Posener et al., 2000), and a more variable secretion pattern (Peeters et al., 2004). That being said, other studies have also reported no difference in cortisol parameters between mood disorders and controls (Oren et al., 1996; Thalén et al., 1997). In brief, evidence suggests that cortisol rhythms and HPA axis activity may be dysregulated in individuals with depression, but further work is required.

Body temperature rhythms in the context of depression have also been reported as altered compared to healthy controls. Specifically, depression has been associated with a blunted 24hr

temperature amplitude (Avery et al., 1982; Daimon et al., 1992; Souêtre et al., 1989), higher nocturnal temperature (Avery et al., 1982; Duncan, 1996; Souêtre et al., 1989), and mesor (Daimon et al., 1992) in both skin and CBT measurements. An earlier CBT nadir has also been reported (Dietzel et al., 1986), and commonly normalizes with clinical improvements in depressive symptoms (Avery et al., 1982).

1.3.3 Chronotypes in mood disorders

High rates of E-type chronotype have repeatedly been reported in people with mood disorders (Au & Reece, 2017; Melo et al., 2017) and have even been associated with depressive symptom severity, even in healthy individuals (Hidalgo et al., 2009). This has been further supported by a study which studied adolescents and young adults with primary mood disorders compared to healthy controls (Fares et al., 2015). A higher proportion of E-types was found in those with mood disorders compared to controls and was associated with increased symptom severity and psychological distress. A later chronotype has also been associated with several other outcomes such as diurnal mood variations where worst mood occurred in the morning (Antypa et al., 2016) and impaired emotional regulation (Horne & Norbury, 2018).

Few studies (Hasler et al., 2011; Robillard, Carpenter, Rogers, et al., 2018) have looked at biological rhythms simultaneously across multiple physiological systems in people with mood disorders, which has left many circadian rhythms studied in isolation. Considering that circadian rhythms are in complex multisystemic interactions with one another, and that multiple rhythms have been reported to be disrupted in individuals with depression, circadian rhythms are likely involved in the pathophysiology of depression and offer a therapeutic target avenue.

1.3.4 Interactions among circadian rhythms in mood disorders

Considering that a greater circadian misalignment is associated with more severe depression symptoms (Emens et al., 2009; Wehr et al., 1979) and that circadian rhythms are dynamic interacting processes, it is not only important to look at these rhythms individually, but also from a holistic point of view in order to properly understand the dysregulation of this complex system. This can notably be approached by assessing circadian phase angles, which is defined as the time difference between two circadian phase markers and is reflective of internal circadian alignment. Studies using this approach have found that a greater phase angle between sleep midpoint and CBT_{min}, and between DLMO and CBT_{min} are associated with more severe depressive symptoms (Hasler et al., 2010). Moreover, a larger phase angle between cortisol acrophase and DLMO were associated with MDD (Buckley & Schatzberg, 2010). Another study found subgroups with differing profiles of circadian alignments among those with affective disorders; there was a group with an inverted phase angle between evening melatonin release and habitual sleep time where DLMO occurred after habitual sleep time, and this was associated with more severe depression. Similarly, the same group had a longer phase angle between CBT_{min} with the midpoint of sleep (Robillard et al., 2018). In summary, circadian misalignment between endogenous rhythms and the sleep-wake cycle may be key markers for depression.

1.3.5 Sleep-wake cycles in mood disorders

Objective actigraphy studies assessing the sleep-wake cycle have reported poor sleep efficiency, longer sleep duration, a more variable sleep schedule, poorer sleep consolidation, and blunted circadian amplitude in youth with mood disorders (Carpenter et al., 2017; Glod et al., 1997; Robillard et al., 2014, 2015). Delayed sleep onset and offset times have also continuously

been associated with low mood (Robillard et al., 2018; Surridge-David et al., 1987) and depression, especially during adolescence and young adulthood when this delay is naturally occurring (Roenneberg et al., 2007). This association is even more pronounced in the context of bipolar disorder (Robillard, Naismith, Rogers, Ip, et al., 2013). Early studies suggested that depression may be associated with an advanced phase (Beck-Friis et al., 1985; Gwirtsman et al., 1989; Nair et al., 1984; Pflug et al., 1976), however subsequent studies pointed to an associated phase delay (Hasler et al., 2010; Kitamura et al., 2010). Considering the age-related changes in sleep-wake timing and considering that older studies were commonly done in older individuals who are typically prone to a phase advance, this inconsistency in the direction of phase shifts may be age-related. Regardless of the variations in direction of the phase shift (delay/advanced), and other sleep-wake abnormalities, these studies suggest a certain level of underlying circadian system vulnerability which may, in part, be driven by a dysregulation of endogenous rhythms.

Considering that different physiological rhythms resynchronize at different rates during phase-advance or delay (Moore-Ede et al., 1982), it is possible that certain rhythms get lost in constant resynchronization due to the constant phase changes shaped by today's societal demands and fast paced environment. Various social commitments, daylight saving time, quick travel to different time zones, and shift work, to name a few, may all contribute to this chronic internal chaos which may contribute to certain health problems, such as mood disorders. In the context of adolescences, circadian phase is pulled back and forth due to the interplay of imposed early school start times and a developmental biological phase-delay. This age group may thus be at a higher risk for circadian disruption and the potential associated mood disorders and hospitalization for suicide (Logan & McClung, 2019; Nixon et al., 2021).

1.4 Circadian Rhythms, a Therapeutic Target for Mood Disorders

The current predominant theory for the etiology of seasonal affective disorder (SAD) is the phase-shifting hypothesis, where low mood occurs due to the misalignments between circadian rhythms and habitual sleep-wake time (Lewy et al., 2022). Normalization of sleep and circadian rhythms in the context of other types of mood disorders would also appear to be a promising avenue of treatment for low mood. This should be done before undertaking other more cognitive approaches to treating depression or simultaneously (Forest et al., 2005). Such abnormalities have been found to be implicated in the pathogenies of mood disorders (Baumann et al., 2004; Carskadon et al., 2004; Klerman, 2005; Moon et al., 2016; Srinivasan et al., 2006) and there are indications that the restoration of these abnormalities may contribute to the remission of mood disorders and relapse-prevention (Gorwood, 2010; Wehr et al., 1979). Among others, melatonin agonists (Kennedy & Emsley, 2006; Robillard et al., 2018), interpersonal and social rhythm therapy (Crowe et al., 2020) have been successful at restoring sleep and circadian abnormalities and increasing mood. In sum, therapeutic tools targeting phase advancing the circadian system may be key in alleviating mood disorders and may represent a less invasive option for young individuals who are still in a developmental stage.

One of the other ways of manipulating circadian rhythms is with the use of properly timed bright light exposure, also known as light therapy (Even et al., 2008; Perera et al., 2016). This notably occurs via the suppression and phase shifting of melatonin by the master biological clock in the SCN following light input conveyed by photoreceptors (Lewy et al., 1988). The effects of light on the circadian system are influenced by three main factors: intensity, spectrum, and timing. Intensity levels as low as 1.5 melanopic lux have been reported to supress melatonin, with 305 melanopic lux being the saturation threshold (Prayag et al., 2019). Shorter wavelength

light (light in the blue-green part of the spectrum; 447 – 484nm) has been consistently found to be the most effective when it comes to circadian manipulation (Brainard, Hanifin, Rollag, et al., 2001; Cajochen et al., 2005; Gooley et al., 2010; Lockley et al., 2003, 2006; Revell et al., 2005, 2006; Zaidi et al., 2007). Finally, timing of the light exposure also plays a crucial role. Light exposure prior to the CBT_{min} is associated with a phase delay, exposure at the CBT_{min} will result in no phase shifting, and exposure after the CBT_{min} will create a phase advance (Khalsa et al., 2003).

In the context of mood disorders and considering the phase delay occurring during adolescence and young adulthood, where melatonin rhythms are shifted (Robillard et al., 2015), being exposed to bright light, especially in the blue-green spectrum, in the morning could help re-align the delayed phased in this target population. Traditionally light therapy has been delivered via a light box which requires the user to constantly face the light source. The recent development of portable light therapy glasses offers a more efficient and constant delivery of light.

Due to the close interactions between the circadian rhythms of different physiological systems, phase shifting the melatonin rhythm can lead to a cascade of changes in other rhythms and this combined effect may contribute to the antidepressant effects of light therapy. As an example, one study found a phase advance of about 1hr in core body temperature following morning light therapy (Burgess et al., 2004). Moreover, not only does light have melatonin supressing, chronobiotic (circadian phase shifting), and antidepressant effects, but it also acts on different non-visual pathways to increase cognitive functions such as alertness (Cajochen et al., 2005) and memory (Bersani et al., 2008; Yoshiike et al., 2019). Improved cognition has been found to be linked to improved functional disability in people with mood disorders (Lee et al.,

2015), which may suggest that one of the ways via which light may improve mood could be by improving cognition. In sum, restoring sleep and/or circadian rhythms has beneficial effects on mood, and light may be one of the means of achieving this with collateral effects on various physiological systems and cognition. This could be considered as an indirect pathway underlying some of the antidepressant effects of light.

1.5 Current Evidence about the Effects of Light for Mood

With the consideration that we evolved with light, and that today's western society and other parts of the world are spending more time indoors with less exposure to the rich benefits of natural light, it is logical to make the bridge between this type of environment, disrupted circadian rhythms, and low mood (Harb et al., 2015).

Light therapy has been established as first-line treatment for SAD (Campbell et al., 2017), but this is not the case for non-seasonal depression. Despite reviews indicating equal or better effect sizes as compared to antidepressant drugs (Al-Karawi & Jubair, 2016; Even et al., 2008; Golden et al., 2005; Penders et al., 2016; Perera et al., 2016), and as opposed to the numerous studies indicating the efficacy of light therapy for SAD (Glickman et al., 2006; Golden et al., 2005; Rosenthal et al., 1984), results from studies using light therapy for non-seasonal depression remain inconsistent. Certain studies done with individuals with mood disorders indicate significant improvements in mood with light therapy (Beauchemin & Hays, 1997; Kripke et al., 1992; Martiny, 2004; Wirz-Justice et al., 2011), while others do not (Dauphinais et al., 2012; Mackert et al., 1991; Yerevanian et al., 1986). In the general population, light has also been found to have benefits on mood and cognition (Cajochen, 2007; Duffy & Czeisler, 2009).

Numerous suggestions have been postulated to explain these inconsistencies. Among others, it has been proposed that this might result from the considerable heterogeneity across people with depression (Perera et al., 2016). In other words, the variety of depression sub-types (Beijers et al., 2019) and the considerable variability in sleep and circadian profiles may influence treatment response to light therapy. For instance, 40% of individuals with depression had a delayed circadian profile which was also associated with abnormal circadian organization and more severe mood symptoms when compared to those who presented with a more conventional circadian profile (Monteleone & Maj, 2008; Robillard et al., 2018). If the antidepressant effects of light therapy are in fact partly driven by sleep and circadian restoration, those with a disrupted circadian rhythm may be a key subgroup to target. Importantly, previous light therapy trials did not take into account these subtypes of sleep and circadian profiles linked with mood disorders which may have obscured significant changes in subgroups of individuals.

Another possible contributing factor to the inconsistent results of previous light therapy trials is the questionable placebos that have been used. Previous studies have used various placebo conditions such as exposure to dim light, dim red light, dim yellow light, and a deactivated negative ion generator to name a few (Benedetti et al., 2003; Fritzsche et al., 2001; Neumeister et al., 1996; Yamada et al., 1995). However, a study looking at melatonin suppression via light has warranted caution in interpreting such studies since even lower levels of light are sufficient to supress melatonin levels (Prayag et al., 2019). The rational for using red light as a placebo is that blue-green light is the strongest wavelength to influence circadian rhythms (Cajochen et al., 2005). That being said, there are indications that infrared light, which is even further away from blue on the light spectrum, could be equally effective as bright white light in increase mood (Meesters et al., 1999). Additionally, although a negative ion generator

can be deactivated, it does not represent a comparable placebo condition for light therapy. This therefore creates a great need for better adapted placebo conditions to fully disentangle the antidepressant effects of light therapy.

Another limitation of past studies pertains to potential differences in light characteristics. With the discovery of ipRGCs (Freedman et al., 1999; Lucas et al., 1999) and their involvement in the light effects on human non-visual physiology and behaviour (Abbott et al., 2018; Rupp et al., 2019), it became apparent that the previous methods of reporting light in photometric light measures using V_λ spectral weighting function (i.e. photopic lux) were insufficient for predicting the non-image-forming effects of a given light source. This was driven by the assumption that non-imagine-forming photoreceptors may have a different spectral sensitivity as compared to the other photoreceptors and that the peak circadian, behavioural, and physiological sensitivity of the visual spectrum (447-484nm) was different than the peak predicted with V_λ (555nm). Lucas et al. (2014) proposed that effective irradiance (W/cm^2) for each photoreceptive input (short-/ medium-/ long-wavelength cones, ipRGCs, and rods) should also be reported in order to increase comparability and replicability of studies. The International Commission on Illumination published an international standard for metrology of light exposure in 2018 (CIE, 2018), which indicates that α-opic Equivalent Daylight Illuminance (EDI) should be reported for each of the 5 photoreceptors. The different peak sensitivity for each photoreceptor type can be seen in Figure 2. This shift in methods underlines not only the need to translate past studies so they can be properly compared, but also another possible explanation for the lack of consistency in past research on light therapy.

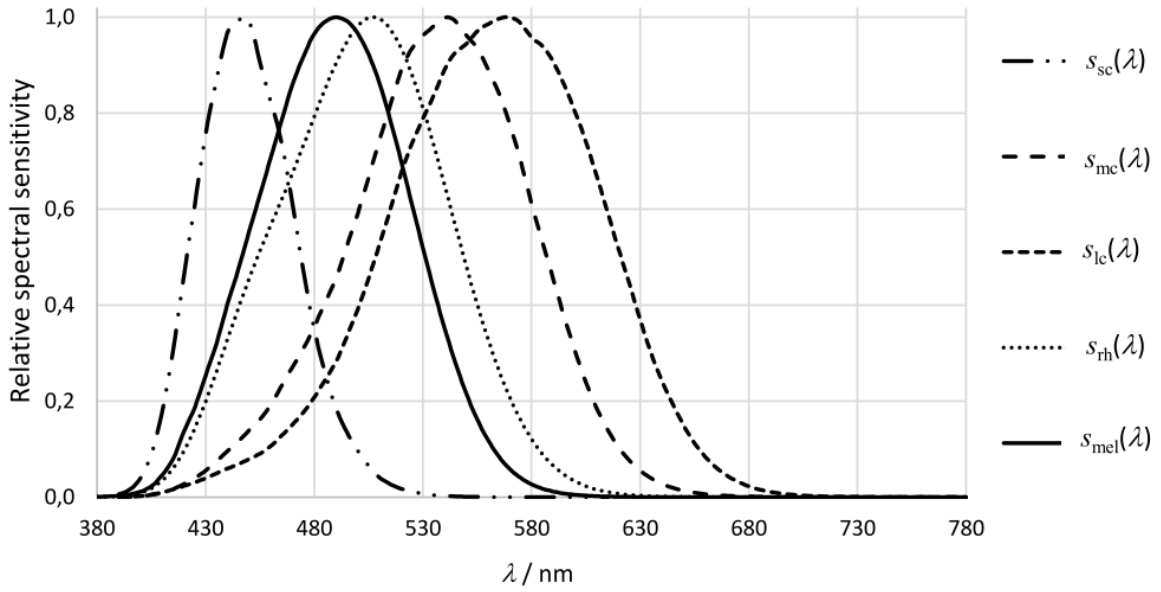

Figure 2. The α-opic action spectra for the five photoreceptors (CIE, 2018). Small cone; $s_{sc}(\lambda)$, medium cone; $s_{mc}(\lambda)$, long cone; $s_{lc}(\lambda)$, rhodopic; $s_{rh}(\lambda)$ and melanopic; $s_{mel}(\lambda)$, plotted against wavelength, λ.

1.6 Other Benefits of Light

Along with its mood enhancing effects and its fundamental benefit of allowing us to see, light has an influence on many aspects of life such as cognition (Vandewalle et al., 2009) and well-being (Fernandez et al., 2018; Ospri et al., 2017; Legates et al., 2012). Some of these effects are thought to stem mainly from the non-visual pathways from the eye to the brain, which could be considered the direct pathway. The ipRGCs, which are the main non-visual photoreceptors linked to the melanopsin system, also receive synaptic impulses from neighboring visual photoreceptors (S-, M-, L-cones and rods) which contribute to non-image-forming functions (Belenky et al., 2003; Dacey et al., 2005; Jusuf et al., 2007; Schmidt & Kofuji, 2010; Wong et al., 2007). Peak sensitiviy for these five photoreceptors are: S-cone (V_λ max = 440 nm) ipRGC

(V_λ max = 482 nm), rod (V_λ max = 507 nm), M-cone (V_λ max = 543 nm) and L-cone (V_λ max = 566 nm; Feigl & Zele, 2014). Functions related to mood, learning, sleep and circadian rhythms were significantly altered in studies where ipRGCs were ablated, suggesting that the melanopsin system plays a central role in these functions (Güler et al., 2008; Legates et al., 2012, 2014). However, while many studies focused on the melanopsin system, the five photoreceptor systems are closely interacting and their relative contribution for the effects of light on well-being in healthy individuals remains poorly understood.

1.7 Objectives

The present thesis aims to explore the direct and indirect pathways underlying the effects of light on mood, as well as to gain some insights on for whom bright light exposure can have positive effects on mood. Firstly, how specific light parameters stimulating distinct types of photoreceptors may predict mood in healthy individuals will be explored (*Study I*). Secondly, the time course of mood improvements with light therapy will be examined (*Study II*). Thirdly, it will be determined whether the antidepressant effects of light therapy in young people with non-seasonal mood disorders can be predicted by their initial sleep and circadian profile and whether these antidepressant effects are modulated by parallel changes in sleep and circadian rhythms (*Studies II & III*). A new placebo condition will be tested to assess the efficacy of light therapy. Finally, biomarkers of treatment response and more accessible putative predictors of the antidepressant effects of light therapy that could potentially be used in clinical settings will be assessed (*Study III*). These hypotheses and predictions are further detailed as follows for each study:

Assessing the Effects of Polychromatic Light Exposures on Mood in Healthy Adults: A Systematic Review on the Relative Contribution of α-opic Equivalent Daylight Illuminances (*Study I*)

1. **Hypothesis**: Different light exposure parameters can predict mood in healthy individuals.
   Prediction: Melanopic EDI will be more strongly associated with positive mood compared to other α-opic EDIs.

Temporal Dynamics of Subjective Sleep Profiles Predicting Mood Improvements during Adjunctive Light Therapy Combined with Sleep Rescheduling (*Study II*)

1. **Hypothesis**: Combing light therapy and a phase advance of the sleep-wake cycle should improve mood.
   Prediction: Depression symptoms will be reduced after four weeks of light therapy combined with a phase advance of the sleep-wake cycle.
2. **Hypothesis**: The relationship between changes in mood, sleep, and daytime functioning along the course of light therapy combined with a phase advance of the sleep-wake cycle will vary across the early (after two weeks) and later (after four weeks) intervention phases.
   Prediction: The reduction in depression symptoms in the first two weeks of light therapy combined with a phase advance of the sleep-wake cycle will be associated with improvements in sleep initiation and quality, whereas the reduction in depression symptoms in the last two weeks will be associated with improvements in sleep offset and daytime functioning.
3. **Hypothesis**: Subjective sleep-related metrics can predict mood improvement following light therapy combined with a phase advance of the sleep-wake cycle.
   Prediction: Individuals with greater difficulties getting to sleep and waking up prior to the intervention will show the greatest reduction in depression symptoms following light therapy combined with a phase advance of the sleep-wake cycle.

The Synergy of Mood Improvements, Adjunctive Light Therapy and A Novel Light Placebo; **A Randomized Control Trial (*Study III*)**

1. **Hypothesis**: Light therapy will be more efficacious than a placebo condition to alleviate depressive symptoms severity.

   Prediction: There will be a greater decrease from pre- to post-intervention in depression symptom severity in the active light therapy condition as compared to the placebo condition.

2. **Hypothesis**: Potential mechanisms of action and predictors of the antidepressant response to light can be characterized by in-depth sleep and circadian assessment.

   Prediction:

   Across the intervention, mood improvements (reduced score on the QIDS-A17-C) will parallel:

   a) Circadian Model: phase advance of the acrophase and increase in circadian rhythmicity (R^2) for rest-activity and peripheral body temperature cycles.
   b) Sleep Model: improved scores for GCTI, LSEQ – GTS, and higher sleep efficiency derived from actigraphy.

   Those with the highest decrease in depressive symptoms (reduced score on the QIDS-A17-C) following light therapy will be those with:

   a) Circadian Model: more delayed and desynchronized circadian rhythms (later DLMO, later CBT_{nadir}, shorter REM latency).
   b) Sleep Model: more sleep disturbances (shorter TST, lower sleep efficiency derived from actigraphy).

3. **Hypothesis**: More accessible predictors of the antidepressant response to light can be characterized by self-reported and ambulatory sleep and circadian measures.

   Prediction: Those with the highest decrease in depressive symptoms (QIDS-A17-C) in response to light therapy will be individuals with:

   a) **Circadian Model:** delayed and weaker circadian rhythms (later acrophase and lower circadian rhythmicity (R^2) for the rest-activity and peripheral body temperature cycles).
   b) **Sleep Model:** worse sleep disturbances (poor scores on the GCTI, LSEQ-GTS, and PSQI).

SECTION 2

STUDIES (I-III)

Study I

Assessing the Effects of Polychromatic Light Exposures on Mood in Healthy Adults: A Systematic Review on the Relative Contribution of α-opic Equivalent Daylight Illuminances

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Abstract

Objective/Introduction: This is a systematic review of studies that assessed the effects of polychromatic (white) ambient light on mood in healthy adults. It was hypothesized that higher melanopic EDI would be associated with better mood.

Methods: A total of 2,994 publications were identified and 14 met inclusion criteria. Spectral power distribution, illuminance, mood measures, and methods were documented. Using the CIE S026 toolbox, α-opic equivalent daylight illuminances (EDI) were calculated for each of the five photoreceptors characterizing the light exposures in each study. Regression models were applied to determine how α-opic EDI, duration, and timing relate to mood.

Results: The results showed that none of the five α-opic values were significantly associated with mood (all estimates < 0.044, $p > 0.490$). A longer duration of light exposure (all estimates < 0.154, $p < 0.018$) and timing of light exposure in the morning (all estimates < 0.233, $p < 0.001$) were associated with better mood, but these effects did not persist after adjusting for the data being nested within studies. Qualitative observations indicated that mood outcomes were comparable across light conditions with distinct a-opic EDI profiles, and that none of the studies included had a peak for melanopic EDI greater than the other α-opic EDI values.

Conclusions: The hypothesized association between melanopic EDI and mood could not be supported due to the restricted range of α-opic EDI profiles calculated *a-posteriori* from published studies. There is a need for studies contrasting selected light parameters to identify which subtypes of photoreceptors are maximally involved in the effects of light on mood.

Keywords: polychromatic light, mood, light exposure, ipRGC, α-opic equivalent daylight illuminance

2.1.1 Introduction

In addition to stimulating visual perception, light influences many non-visual physiological and psychological processes, including cognition, sleep, and mood (Cajochen, 2007; Duffy & Czeisler, 2009; Golden et al., 2005). Light intensity, spectrum, duration, and timing are all thought to play a role in these non-visual effects (Prayag et al., 2019). Over recent years, researchers have revealed the prominent involvement of intrinsically photosensitive retinal ganglion cells (ipRGCs) in regulating circadian rhythms, melatonin secretion, and other biological processes. ipRGCs express melanopsin, a photopigment making them photosensitive. They also receive synaptic input from other retinal photoreceptors (S-, M-, L-cones and rods) and contribute to diverse physiological and behavioral functions (Belenky et al., 2003; Brown et al., 2021; Dacey et al., 2005; Jusuf et al., 2007; Schmidt & Kofuji, 2010; Wong et al., 2007). Direct pathways linking ipRGCs and various brain regions involved in emotional processing have also been found: in both animal: (Fernandez et al., 2018; Hattar et al., 2006; Huang et al., 2019; Legates et al., 2014) and human (Vandewalle et al., 2010; Weil et al., 2022) studies. While many studies focused on the melanopsin system, all photoreceptor systems closely interact and their relative contribution to the effects of light on mood in healthy humans remains poorly understood. Furthermore, because indoor lighting is typically polychromatic (i.e., white appearing and inclusive of many wavelengths), there is a need to move beyond monochromatic light comparisons, which are often used in studies that examine fundamental processes.

Specifying light exposures

To synthesize the evidence gathered to date on the effects of polychromatic light on mood, the light specifications from past studies need to be converted to a standard scale to decipher the relative contribution of the different photoreceptors. It has become apparent that

reporting light in photopic illuminance was, based on the classical photoreceptors' peak sensitivity at 555 nm, inadequate for predicting the effects of a given light source on ipRGC-influenced functions since melanopsin has a peak sensitivity at 483 nm. In order to improve comparability and replicability of studies, it was proposed that effective irradiance of a light source should be calculated for each photoreceptor type (Lucas et al., 2014). The units initially proposed were, however, not consistent with the Système International (SI) of weights and measures (CIE, 2015), which would have complicated future scientific progress.

In 2018, the International Commission on Illumination published an international standard for the metrology of light exposures, known as CIE S026:2018 (CIE, 2018). The CIE system defines physical quantities based on action spectra for the five known photoreceptor types, the quantities being given the adjectives S-cone-opic, M-cone-opic, L-cone-opic, rhodopic (rod sensitivity), and melanopic (melanopsin based light sensitivity of ipRGCs). Collectively these are known as α-opic quantities. CIE S026: 2018 provides definitions that are SI-compliant, which ensures measurement traceability. Using spectral irradiance data for a given light exposure and these action spectra, one can calculate the five α-opic irradiances that characterize that light exposure. One can relate these α-opic irradiances to the equivalent exposure of the CIE standard daylight illuminant (D65), and express the value as an illuminance, known as the α-opic Equivalent Daylight Illuminance (EDI), in lux. Converging past results on a common scale using the CIE S026:2018 metrology system may enable more accurate conclusions and recommendations to be drawn about the properties of polychromatic light that may support better mood.

Objectives/ Hypotheses

This systematic review integrates existing data relating to the effects of polychromatic light exposure on mood in healthy human adults based on the contribution of the different photoreceptors as estimated by α-opic EDI. Considering previous findings (e.g., Legates et al., 2012; Vandewalle et al., 2010) higher melanopic EDI was predicted to be the α-opic measure most strongly associated with positive mood.

2.1.2 Methods

Data Sources

This report is part of a broader systematic review addressing the optimal light characteristics for mood, cognition, and physiological responses (other themes will be addressed in subsequent reports). The publication search was conducted in the databases PubMed, Web of Science, Scopus, PsycINFO, and in the journals *Lighting Research & Technology, LEUKOS – Journal of Illuminating Engineering Society*, and conference proceedings on January 15th, 2020. Grey literature (conferences and other unpublished reports) was searched in APA PsycExtra on September 30th, 2020. The pre-defined search strategy used for each database can be found in the supplemental material (S1. Search Strategy). Only studies published in English or French between 1990 and 2020 were considered. The review protocol was registered in PROSPERO (CRD42020149818). Although we had initially planned to do a quality and risk of bias assessment inspired by the Cochrane 'Risk of bias' assessment tool (Higgins et al., 2011) for randomized controlled trials and the Risk of Bias Criteria for Effective Practice and Organization of Care (EPOC) Reviews, such approaches turned out to be not optimally adapted for the studies

included in the current review (e.g., particular challenges regarding blinding due to the nature of the interventions). Hence, we opted to focus on summarizing core methodological information relevant for light research as was done in a previous Cochrane review (Pachito et al., 2018). Nevertheless, all studies included in the final dataset were reviewed by the authors and deemed to be of sufficient methodological quality to be included in the current study.

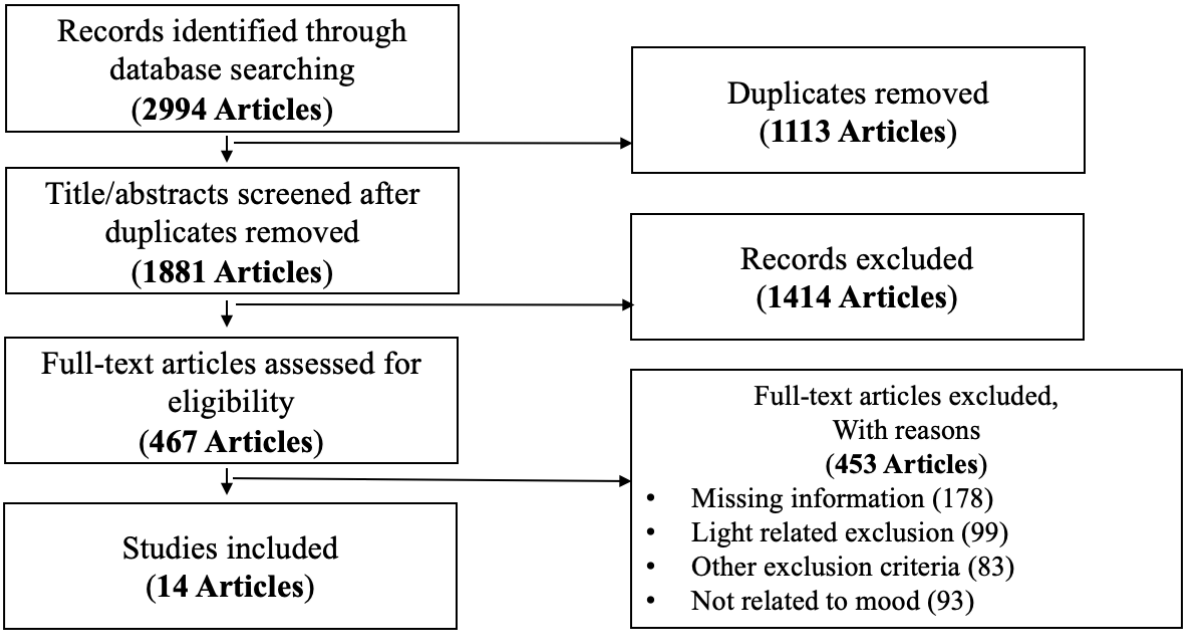
Study Selection

The collective search for mood, cognition, and physiological responses returned 2,994 potentially relevant publications, from which 1,113 duplicates were removed. Only studies conducted with healthy human adults (≥ 18 years old) were included. Studies focused on people with mental or physical health conditions were excluded from this review, but studies in individuals with myopia, hyperopia, or astigmatism were included. To be included, studies were required to provide sufficient light characteristics based on vertical light measurements to quantify α-opic equivalent daylight illuminance (α-opic EDI) values using the CIE toolbox (see Data Processing section for details) or the light source needed to be reported in S 026 or CIE TN 003 quantities. Studies reporting only α-opic equivalent daylight luminance (EDL) were excluded because this metric is not directly comparable with EDI values. Studies were excluded if they were based on non-ocular light perception (eyes closed), were limited to light conditions that varied across the study (e.g., dynamic lighting), involved light exposure during sleep, used only monochromatic light, or only provided outcome data following a night of total sleep deprivation. Studies on shift work (real or simulated) were excluded because in such studies many extraneous variables, in addition to light exposure, can affect mood. If the full article was not available or no new empirical data was provided (e.g., previously published data or a

review), the publication was also excluded. In the last step, all studies with outcomes related to mood were selected to be included in the current report. For the purpose of this review, mood is considered to reflect affect, hedonic tone, and/or happiness-sadness.

The screening of the dataset was done in multiple steps (see Figure 3). First, the above criteria were applied for screening the titles and abstracts (1,881 publications for mood, cognition, and physiological responses) which was completed twice by two research assistants using the Covidence software (Melbourne, Australia). This resulted in 467 publications being retained. These publications were then subject to a full-text evaluation using the criteria previously mentioned and again done twice by two research assistants. The resulting dataset, containing 111 publications, was then revised by the Scientific Advisory Board to ensure no key publications were missed. The final dataset for this report includes 14 publications with mood outcomes and for which light exposures could be calculated. Quality checks were completed by a different individual from the research team after each step. The authors of selected articles were contacted to collect more information if all criteria were met but the article was lacking certain details.

Figure 3. PRISMA Flow Diagram



Note: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021).

Data Processing

Light exposure and outcome extraction

Following data extraction, light information for the publications that did not report light characteristics as EDI values based on the CIE S026:2018 metrology system were converted (toolbox available at https://doi.org/10.25039/S026.2018.TB; CIE, 2018) and scaled to the photopic illuminance reported in the study. Several articles provided spectral data in 1 nm bands. For other publications that reported spectrum information as a spectral power distribution (SPD) figure, these figures were digitized to extract numerical values for each 5 nm band (WebPlotDigitizer, Version 4.4, California, USA). Visual inspection and manual adjustments were implemented to reduce error in all digitized data extraction.

Correa et al. (2016) reported the Lucas et al. (2014) "melanopic illuminances". We converted this value into the CIE S026 melanopic EDI using a conversion factor (Schlangen & Price, 2021). No conversion factor exists for other α-opic EDIs; therefore, only melanopic irradiance was analyzed for this study. Viola et al. (2008) reported that the light exposures included a combination of daylight and electric light, but there was sufficient information available to estimate melanopic EDI for the conditions.

Subjective mood outcomes included measures such as the Positive and Negative Affect Schedule (PANAS; Watson & Clark, 1988) or other Likert scales, visual analogue scales, and check lists pertaining to mood. Means and standard deviations or standard errors were transcribed from each article; outcomes reported in figures were also digitized to extract central tendencies and variance indices. Only scales with higher scores reflecting better mood were included. Raw scores were converted to standardized scores using the following formula:

$$\text{Standardized Mood} = \frac{(\text{Mean in a given light condition} - \text{Minimum possible score})}{(\text{Maximum possible score} - \text{Minimum possible score})}$$

When mood measures were collected at multiple time points within a single light condition, the time point showing the strongest mood effect, the largest sample size, or the longest elapsed time between light onset and the mood measure was selected (in that order).

Additional study details, such as light exposure duration and time of day of light exposure, were also aggregated into the database. These were considered as possible factors influencing light effects.

Statistical Analyses

Standard meta-analytic approaches were not appropriate for this review because the lighting conditions used in the reviewed studies varied considerably and the main focus of the

current review was the contribution of the five α-opic EDIs on mood outcomes rather than global effect sizes.

Multiple linear regression using the maximum likelihood estimates approach was applied to determine how standardized mood outcomes (dependent variable) were associated with each of the α-opic EDIs (continuous in lux), while adjusting for duration (continuous in minutes) and time of light exposure (categorical: morning (7:00 to 11:59), afternoon (12:00 to 16:59), night (17:00 to 6:59), or uncontrolled times). Distinct regressions were fit for each α-opic EDI because of the small sample size and multicollinearity (within any one light condition, the five α-opic EDI values are inherently correlated). The α-opic EDIs and duration of exposure were $\log_{10}$-transformed to improve normality. Additional exploratory analyses with interaction terms between α-opic EDIs, time and duration of exposure were also conducted (see supplemental table S3). Interaction terms did not yield any significant effects and therefore, this report focuses on the simpler regression without interaction terms.

A second set of analyses was conducted to account for the fact that these data stem from light exposure conditions overlapping across multiple studies integrated in a meta-analysis. Linear mixed-effects regressions were conducted using the same design as the multiple regression described above with the addition of the study identifier as a random-effect parameter.

All regressions were performed using the “lm” function or the “lme4” package (Bates, 2020) of the R software, version 4.1 (R Core Team, 2021). The Akaike Information Criterion (AIC) was used to compare the multiple linear regression to the linear mixed-effects regression, with lower AIC values indicating a better balance between goodness-of-fit and parsimony of the regression model (Akaike, 1987).

Similar to approaches used in previous reviews on light (Souman et al., 2018), data was separated by light characteristics and visually presented to highlight patterns in light profiles.

2.1.3 Results

Study characteristics

Table 1 summarizes the characteristics of the included studies. Overall, these studies included a total of approximately 475 participants (339 female; 57 % female) exposed to a total of 52 light conditions following a crossover (n = 31 light conditions), cross-sectional (n = 12 light conditions), or mixed (n = 9 light conditions) design. None of these studies used pharmacological pupil dilation. Two publications were based on field studies, seven on simulated office environments, and five on laboratory studies. Eight studies had a controlled lighting period to adapt the eyes prior to the experimental light conditions. Other methodological characteristics of the included studies are reported in Table 1.

Table 1

Methodological details for each light condition across all studies.

Reference	Study Design*	n	Age (X ±SD)	Sex (%F)	Control for previous light history	Time of exposure	Time of exposure Notes/ Details	Duration (minutes)	Light Sources	Photopic Illuminance (lx)	EDI (s-cone/ m-cone/ l-cone/ rhodopic/ melanopic)	Mood measure
Smolders et al. 2014	Crossover ‡‡	28 28	23.0 (4.1) 23.0 (4.1)	57.1 57.1	~36 min	AM, PM, Night	AM: 9:00, 10:20,11:45 PM: 13:15, 14:45,16:15	22.5	Ceiling and wall florescence tubes ¶	200 1000	137.6/ 176.0/ 200.1/ 141.1/ 127.0 703.4/ 875.7/ 1002.4/ 701.3/ 631.7	Positive affect (happy) 5-point Likert Scale §
Veitch et al. 2012	Cross sectional‡	20 22	Unspecified Unspecified	51.2 51.2	Uncontrolled	AM	8:45 - 11:45	****160	A matrix of 7 LEDs	~500 ~500	88.1/ 179.7/ 239.2/ 115.3/ 91.3 266.7/ 229.6/ 236.9/ 227.7/ 235.8	Mood Scores-Pleasantness (Affect Grid)
Correa et al. 2016	Crossover †	15 15	19.9 (3.2) 19.9 (3.2)	68.2 68.2	<12 min	Night	22:00	65	A matrix of 16 LEDs	< 3 3550	n/a/ n/a/ n/a/ n/a/ 1.4 n/a/ n/a/ n/a/ n/a/ 1635.6	Mood 9-point Likert Scale §
Huiberts et al. 2017	Cross sectional‡	18 21 18 21 17 17 17 17	21.7 (2.0) 20.8 (2.2) 21.7 (2.0) 20.8 (2.2) 20.7 (2.1) 20.5 (2.4) 20.7 (2.1) 20.5 (2.4)	61.1 81.0 61.1 81.0 64.7 47.1 64.7 47.1	~36 min	AM PM AM PM AM PM AM PM	9:00 - 10:30 15:45 - 17:15 9:00 - 10:30 15:45 - 17:15 9:00 - 10:30 15:45 - 17:15 9:00 - 10:30 15:45 - 17:15	52	Recessed ceiling luminaires with three florescent tubes (54W)	165 165 1700 1700 165 165 1700 1700	143.3/ 153.8/ 164.4/ 136.4/ 128.5 143.3/ 153.8/ 164.4/ 136.4/ 128.5 1211.1/ 1527.5/ 1693.0/ 1255.3/ 1138.4 1211.1/ 1527.5/ 1693.0/ 1255.3/ 1138.4 143.3/ 153.8/ 164.4/ 136.4/ 128.5 143.3/ 153.8/ 164.4/ 136.4/ 128.5 1211.1/ 1527.5/ 1693.0/ 1255.3/ 1138.4 1211.1/ 1527.5/ 1693.0/ 1255.3/ 1138.4	Happy 5-point Likert Scale (Single item mood question) §
Iskra-Golec et al. 2012	Crossover †	30 30 30 30 30 30	28.3 (2.8) 28.3 (2.8) 28.3 (2.8) 28.3 (2.8) 28.3 (2.8) 28.3 (2.8)	100.0 100.0 100.0 100.0 100.0 100.0	Uncontrolled	AM AM PM AM AM PM	7:15 7:14 - 11:45 7:15 - 14:15 7:15 7:14 - 11:45 7:15 - 14:15	15 285 435 15 285 435	120 ceiling luminaires each containing 4 fluorescent tubes ¶	500 500 500 500 500 500	261.4/ 437.7/ 495.4/ 329.7/ 285.0 261.4/ 437.7/ 495.4/ 329.7/ 285.0 261.4/ 437.7/ 495.4/ 329.7/ 285.0 856.3/ 530.0/ 495.1/ 564.4/ 585.1 856.3/ 530.0/ 495.1/ 564.4/ 585.1 856.3/ 530.0/ 495.1/ 564.4/ 585.1	Hedonic tone Mood (UWIST Mood Adjective Check List)
Knaier et al. 2018	Cross sectional‡	13 13	26.0 (6.7) 25.0 (6.7)	61.5 53.8	Uncontrolled	AM	8:00	25	Two fluorescent lights	4400 230	4250.3/ 4268.4/ 4302.7/ 3801.5/ 3576.4 222.2/ 223.1/ 224.9/ 198.7/ 186.9	Multidimensional Mood State Questionnaire

												(MDMQ) – good/bad mood scale
Huiberts et al. 2015	Crossover †‡	32	Unspecified	56.3	15 min	AM	9:00 - 11:45	37.5	Recessed ceiling luminaires with three florescent tubes (54W)	200	137.7/ 176.9/ 200.6/ 144.9/ 132.2	Happy 5-point Likert Scale (Single item mood question) §
		32	Unspecified	56.3						1000	652.3/ 874.5/ 1000.3/ 691.2/ 616.8	
		32	Unspecified	43.8		PM	12:15 - 16:45			200	137.7/ 176.9/ 200.6/ 144.9/ 132.2	
		32	Unspecified	43.8						1000	652.3/ 874.5/ 1000.3/ 691.2/ 616.8	
Veitch 1997	Cross sectional‡	26	35.7 (8.2)	50.0	Unspecified length	AM, PM	Unspecified	****90	Recessed fluorescent troffers with 40W lamps	680	168.5/ 252.0/ 288.0/ 179.8/ 159.5	Pleasure (Russell and Mehrabian Three Factor Mood Scale)
		26	35.7 (8.2)	50.0						680	218.8/ 273.2/ 287.5/ 240.3/ 226.6	
Leichtfried et al. 2015	Crossover †‡	33	33.0 (7.2)	51.5	100 min	AM	7:40 - 8:10	30	Fluorescent lamps	5000	4903.9/ 4856.4/ 4905.3/ 4363.0/ 4171.2	Subjective mood (VAS) §
		33	33.0 (7.2)	51.5						400	224.1/ 347.7/ 395.2/ 251.0/ 213.9	
Chellappa et al. 2011	Crossover †	16	24.3 (2.1)	0.0	210 min	Night	21:30 - 23:30	30	2 fluorescent and 1 incandescent light	40	10.5/ 31.7/ 40.7/ 21.6/ 18.3	Subjective well-being (VAS) §
		16	24.3 (2.1)	0.0				70		40	10.5/ 31.7/ 40.7/ 21.6/ 18.3	
		16	24.3 (2.1)	0.0				110		40	10.5/ 31.7/ 40.7/ 21.6/ 18.3	
		16	24.3 (2.1)	0.0				30		40	37.9/ 39.2/ 38.9/ 35.0/ 32.8	
		16	24.3 (2.1)	0.0				70		40	37.9/ 39.2/ 38.9/ 35.0/ 32.8	
		16	24.3 (2.1)	0.0				110		40	37.9/ 39.2/ 38.9/ 35.0/ 32.8	
		16	24.3 (2.1)	0.0				30		40	7.0/ 29.9/ 40.5/ 16.1/ 11.1	
		16	24.3 (2.1)	0.0				70		40	7.0/ 29.9/ 40.5/ 16.1/ 11.1	
		16	24.3 (2.1)	0.0				110		40	7.0/ 29.9/ 40.5/ 16.1/ 11.1	
Borragan et al. 2017	Crossover †‡	17	23.7 (3.6)	41.2	Uncontrolled	PM	15:00 - 17:00	20	Wearable glasses-like device	< 200	0.0/ 36.2/ 248.0/ 2.3/ 0.3	Affect (VAS)
		17	23.7 (3.6)	41.2						2000	2343.4/ 1910.8/ 2027.4/ 1807.6/ 1897.0	
		17	23.7 (3.6)	41.2						< 200	0.0/ 36.2/ 248.0/ 2.3/ 0.3	Positive Affect (PANAS)
		17	23.7 (3.6)	41.2						2000	2343.4/ 1910.8/ 2027.4/ 1807.6/ 1897.0	
Smolders et al. 2012	Mixed**†	41	22.0 (4.0)	46.3	30 min	AM, PM	Condensed from am (9:00 or 11:00) and pm (1:00 or 3:00) groups	37.5	Ceiling and wall surface-mounted luminaires each containing six fluorescent tubes (28W)	200	127.6/ 176.0/ 199.6/ 138.8/ 124.3	Positive affect (happy) 4-point Likert Scale §
		42	22.0 (4.0)	53.1						1000	638.2/ 880.0/ 997.9/ 694.1./ 621.7	
Viola et al. 2008	Crossover †	94	36.4 (10.2)	47.9	Uncontrolled	AM, PM	8:30 - 16:45	495	2 fluorescent tubes	310.35	269.3/ 178.3/ 167.4/ 192.7/ 200.2	Positive mood (PANAS)
		94	36.4 (10.2)	47.9						421.07	119.4/ 153.1/ 167.3/ 127.5/ 117.9	
Ru et al. 2019		28	20.2 (1.6)	67.9	5 min		10:00 - 17:00	22		100	37.2/ 81.6/ 100.8/ 55.4/ 47.0	

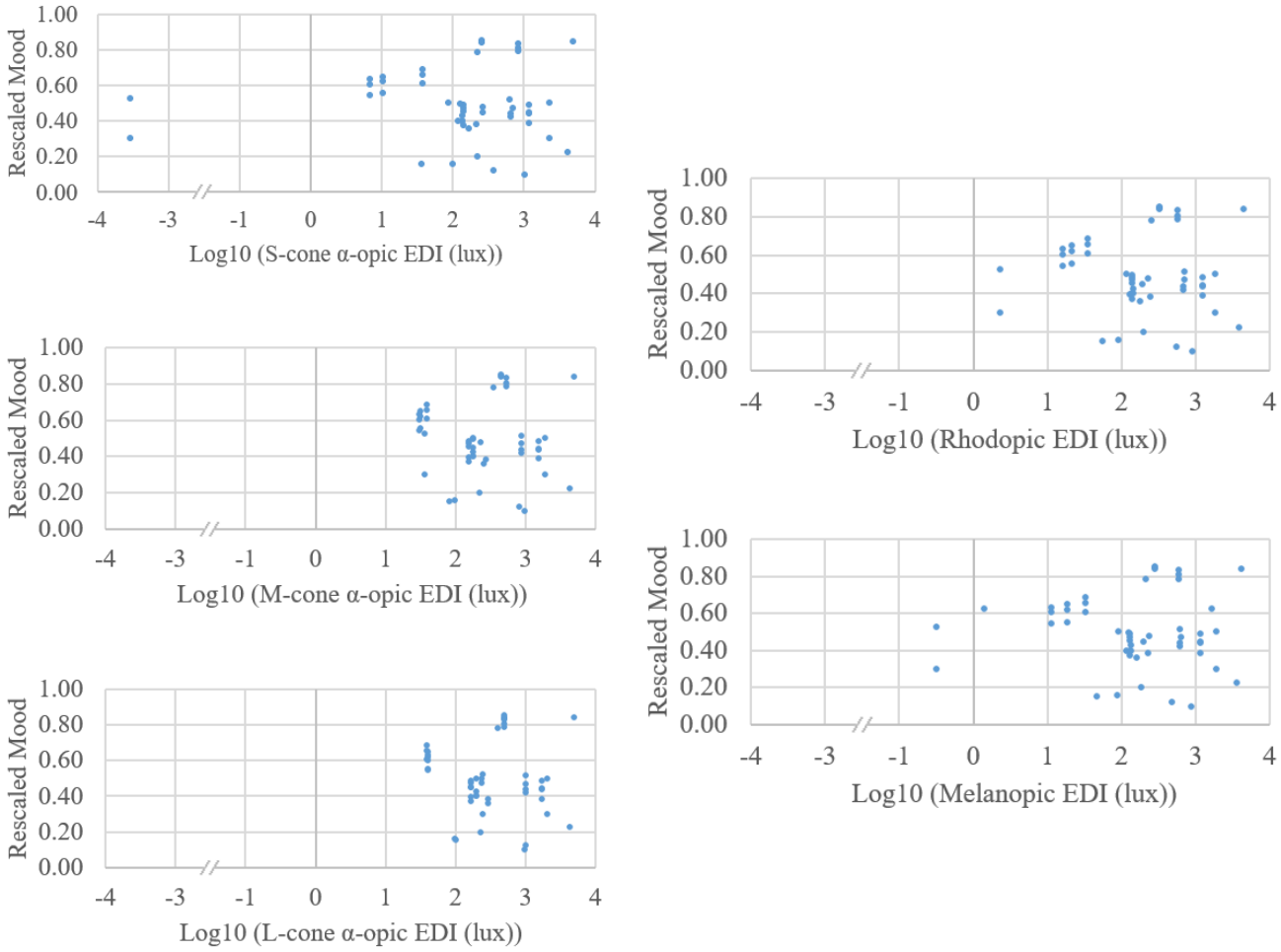
Mixed*** †‡	28	20.2 (1.6)	67.9	AM, PM, Night	6 ceiling mounted luminaires with 3 LED tubes and 3 mounted luminaires with 2 LED tubes	1000	373.0/ 816.1/ 1007.9/ 553.6/ 470.2	Mood Appraisals (PANAS)
	29	20.2 (1.6)	65.5			100	102.4/ 98.1/ 98.4/ 91.0/ 87.8	
	29	20.2 (1.6)	65.5			1000	1024.5/ 980.8/ 984.2/ 909.9/ 877.6	

Note: Time of exposure categorized into AM (6:00-11:59), PM (afternoon; 12:00-16:59), Night (17:00-6:59), standard deviation (SD), light emitting diodes (LED), Positive and Negative Affect Schedule (PANAS), Visual Analogue Scale (VAS), University of Wales Institute of Science and Technology (UWIST), Equivalent daylight illuminance (EDI). *Study design relevant to light conditions included in this review, **Mixed design in which all participants were exposed to all light conditions in a crossover manner, but where most participants were allocated to either a morning or an afternoon session cross-sectionally. ***Mixed design in which participants were exposed to different illuminance levels in a crossover manner but were allocated to either a high or low Correlated Color Temperature. **** Not a multiday light exposure study design. †Counterbalanced order of light exposure. ‡Randomized groups. ††Randomly assigned to counterbalanced order. All light measurements taken at eye level or converted to vertical (Veitch et al 1991, 2012 & Viola et al 2008). F: females. § Custom-made mood measures. ¶ Spectral data was provided in 1nm bands.

Relative contribution of α-opic EDIs

Figure 4 shows plots of standardized mood metrics as a function of the five α-opic EDIs. A sub-division of these plots by duration (< 30 minutes, 30 to 60 minutes, and > 60 minutes; minimum = 15 minutes, maximum = 495 minutes) can be found in the supplemental material (S2).

Figure 4. Standardized mood metrics as a function of each α-opic EDI



Note: Results did not differ when the two studies with low EDI values were removed, therefore the two studies were kept in the analyses.

Based on multiple linear regression, higher mood ratings were significantly associated with longer light exposure (all estimates < 0.154, $p < 0.018$) and with morning light exposure compared to uncontrolled timing of light exposure (all estimates < 0.233, $p < 0.001$) for all α-opic EDIs (see Table 2). None of the α-opic EDIs were significantly associated with mood outcomes (all estimates < 0.044, $p > 0.490$).

Table 3 reports statistics from the linear mixed-effect regression in which the study identifier was added as a random effect. Significant random effects of study identifiers (all $F > 12.6$, $p < 0.001$) were found for each α-opic EDIs regression. The time (all estimates <|0.153|, $p > 0.128$) and duration of exposure (all estimates <|0.020|, $p > 0.484$) effects did not survive this adjustment for the study identifiers. None of the α-opic EDIs were found to be significantly associated with mood outcomes (all estimates <0.004, $p > 0.849$).

The AIC was significantly lower in the linear mixed-effect models (all AIC < -95.2 compared to the multiple linear regression models (all AIC > -33.4; Chi-squared > 67.3, $p < 0.0001$), suggesting that the linear mixed-effect regression models had a better balance between goodness-of-fit and parsimony than the multiple linear regression models.

Table 2. Multiple linear regression models assessing the relationship between α-opic EDIs and mood

	S-cone-opic			M-cone- opic			L-cone- opic			Rhodopic			Melanopic		
	Est.	**SE**	***p***	**Est.**	**SE**	***p***	**Est.**	**SE**	***p***	**Est.**	**SE**	***p***	**Est.**	**SE**	***p***
Time (vs morning)															
Uncontrolled	-0.22	0.065	0.001	-0.23	0.065	0.001	-0.23	0.064	0.001	-0.23	0.064	0.001	-0.23	0.062	0.001
Afternoon	-0.09	0.063	0.163	-0.09	0.063	0.190	-0.08	0.066	0.215	-0.08	0.064	0.208	-0.08	0.063	0.193
Night	0.09	0.099	0.383	0.08	0.094	0.393	0.05	0.075	0.524	0.07	0.086	0.440	0.06	0.074	0.454
Duration	0.15	0.059	0.012	0.15	0.058	0.013	0.14	0.058	0.018	0.15	0.057	0.015	0.14	0.056	0.014
α-opic EDI	0.04	0.062	0.490	0.04	0.053	0.499	0.01	0.019	0.720	0.02	0.040	0.571	0.01	0.030	0.645

Note: Estimates (Est.; calculated for fixed effects per one unit of log_{10}-transformed values for continuous variables, and relative to morning for time of exposure (categorical: morning (6:00 to 11:59), afternoon (Noon to 16:59), night (17:00 to 6:59), or uncontrolled times), Standard Error (SE), and p values.

Table 3. Linear mixed-effect models assessing the relationship between α-opic EDIs and mood

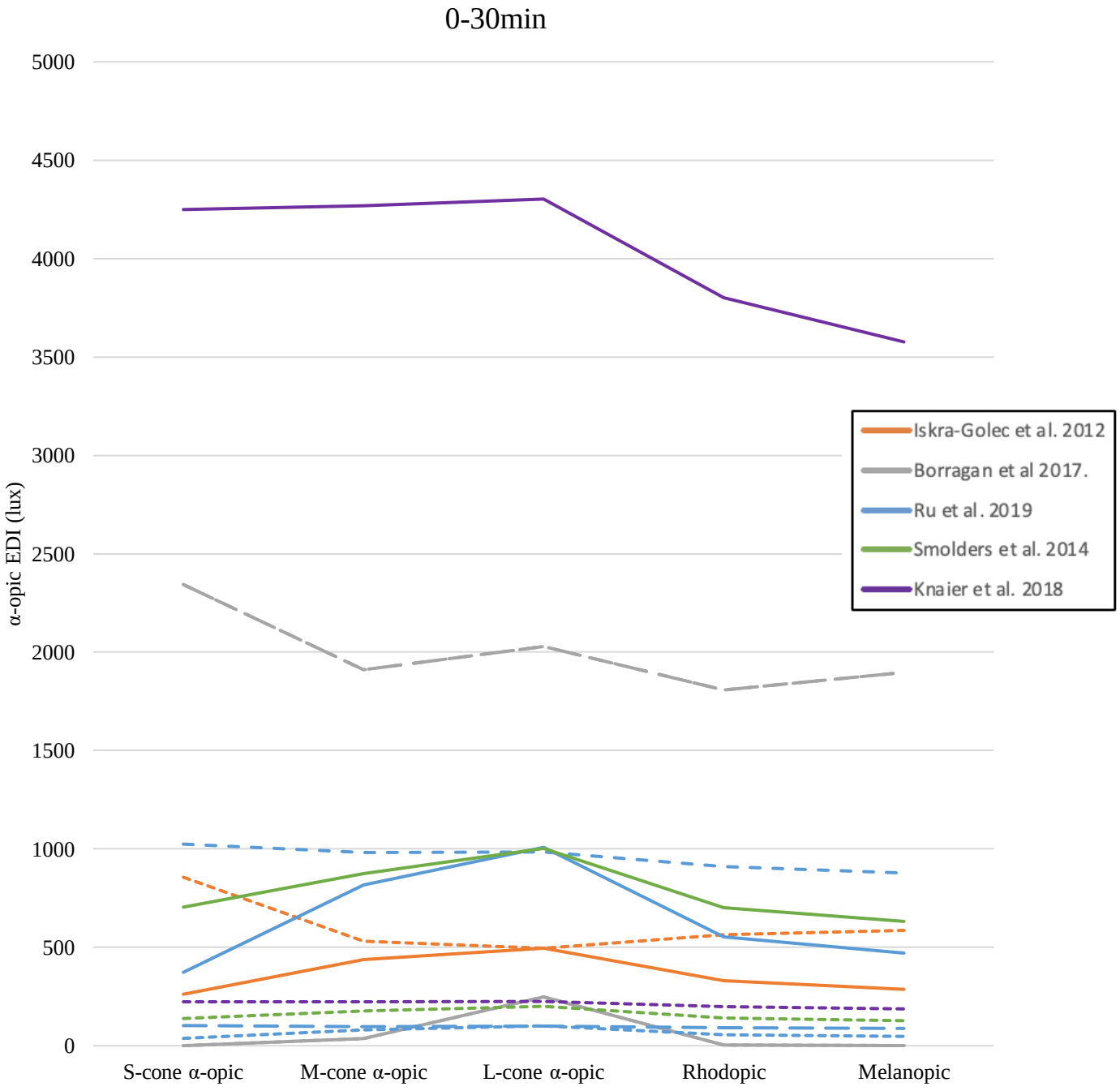
	L-cone-opic			M-cone-opic			S-cone-opic			Rhodopic			Melanopic		
	Est./F	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**
Study Identifier	13.25	0.172	<0.001	13.24	0.172	<0.001	13.24	0.172	<0.001	13.24	0.172	<0.001	12.62	0.165	<0.001
Time (vs morning)															
Uncontrolled	-0.15	0.103	0.146	-0.15	0.103	0.144	-0.15	0.103	0.143	-0.15	0.103	0.143	-0.15	0.099	0.128
Afternoon	-0.03	0.024	0.185	-0.03	0.024	0.185	-0.03	0.024	0.186	-0.03	0.024	0.186	-0.03	0.023	0.177
Night	0.10	0.186	0.606	0.10	0.186	0.608	0.09	0.185	0.617	0.10	0.185	0.611	0.10	0.135	0.474
Duration	-0.02	0.028	0.486	-0.02	0.028	0.486	-0.02	0.028	0.484	-0.02	0.028	0.485	-0.02	0.027	0.487
α-opic EDI	0.00	0.019	0.849	0.00	0.016	0.856	0.00	0.006	0.958	0.00	0.013	0.874	0.00	0.009	0.903

Note: F values for Study Identifier and Estimates for all other parameters (Est.; calculated for fixed effects per one unit of log_{10}-transformed values for continuous variables, and relative to morning for time of exposure (categorical: morning (6:00 to 11:59), afternoon (Noon to 16:59), night (17:00 to 6:59), or uncontrolled times), Standard Deviation (SD) for Study Identifier and Standard Error (SE) for all other parameters, and p values.

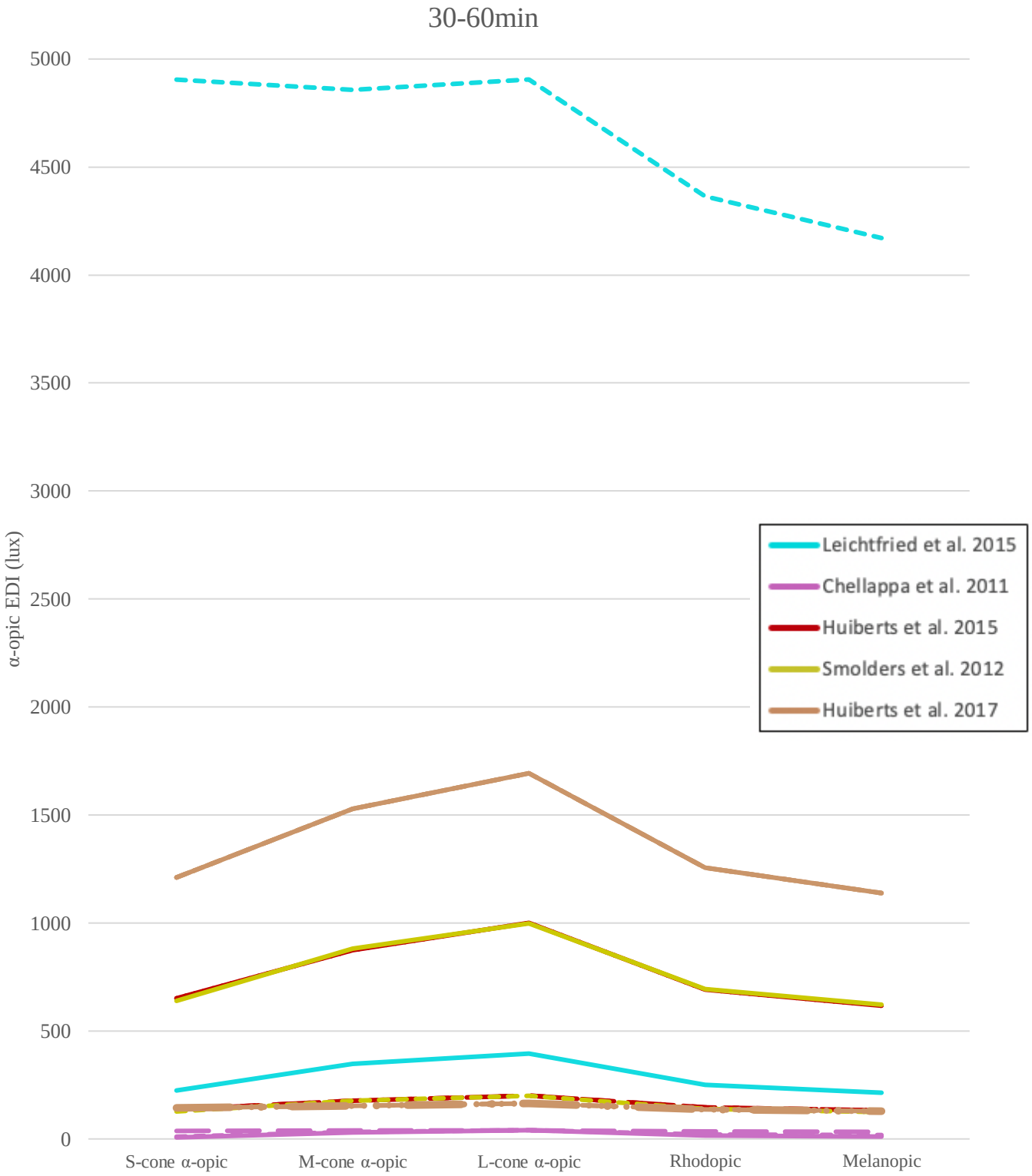
Mood outcomes across distinct α-opic EDI profiles

Figure 5 depicts α-opic EDI values for each light condition in each study included in this review separated by exposure duration (< 30minutes, 30-60 minutes, and > 60 minutes). Overall, α-opic EDIs ranged from 0 to 4,905 lux and different EDI profiles emerged where certain photoreceptors had higher EDI values depending on the light source spectrum. Specifically, in two of the light conditions the S-, M-, and L-cone-opic EDIs were higher than the rhodopic and melanopic EDIs (Knaier et al., 2018; Leichtfried et al., 2015). Five light conditions had higher S-cone-opic EDIs relative to all other EDIs (Borragán et al., 2017; Iskra-Golec et al., 2012; Ru et al., 2019; A. U. Viola et al., 2008), 11 had higher L-Cone-opic EDIs (Borragán et al., 2017; Huiberts et al., 2015, 2017; Ru et al., 2019; K. C. H. J. Smolders et al., 2012; K. Smolders & de Kort, 2014) and none had a peak for the M-Cone-opic, rhodopic, or melanopic EDIs (including those studies that had targeted ipRGC stimulation).

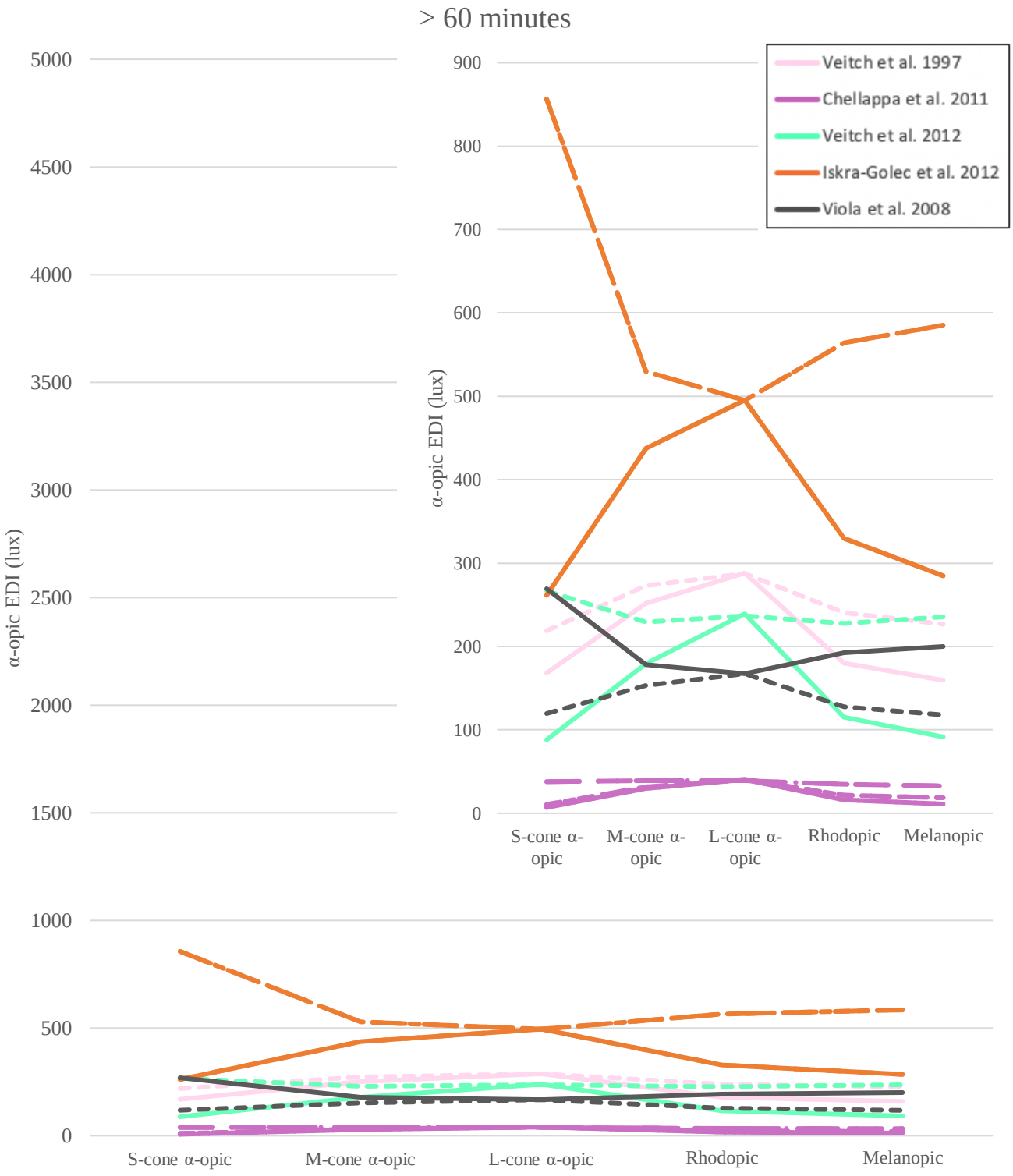
Figure 5.



Note: Studies are grouped by color and the conditions differentiated by type of line (e.g., dotted, dashes), Equivalent Daylight Illuminance (EDI).



Note: Studies are grouped by color and the conditions differentiated by type of line (e.g., dotted, dashes), Equivalent Daylight Illuminance (EDI).



Note: Studies are grouped by color and the conditions differentiated by type of line (e.g., dotted, dashes), Equivalent Daylight Illuminance (EDI).

Table 4 reports standardized mood outcomes averaged across these different EDI profiles. Although the small number of light conditions included in each EDI profile precluded statistical analyses by EDI profile, mood outcomes were observed to be highly comparable across the different EDI profiles. A figure depicting the EDI profiles of light conditions with a peak in the short wavelength section of the spectrum can be found in the supplemental material (S4). As can be seen, these studies did not have higher melanopic EDI values as compared to the other photoreceptors. A figure of all SPDs with a peak in the short-wavelength range and their associated EDI profile can also be found in the supplemental material (S5).

Table 4. Mood metrics across the different relative α-opic profiles

	n of conditions	Mean	SD	Min	Max
S-cone higher	5	0.65	0.24	0.30	0.83
L-cone higher	11	0.41	0.11	0.12	0.53
SML-cone higher	2	0.53	0.44	0.23	0.84
Similar EDI across α-opic	31	0.50	0.19	0.10	0.86

Note: Correa et al 2016 was not included in profile analyses because only melanopic EDI could be retrieved.

Synthesis of individual study findings

Nine studies out of the 14 included in this review did not report any significant effect of light intensity or spectral composition on mood (Borragán et al., 2017; Correa et al., 2016; Huiberts et al., 2015, 2017; Iskra-Golec et al., 2012; Knaier et al., 2018; K. C. H. J. Smolders et al., 2016; Veitch, 1997). Of the five studies reporting a significant effect, all observed that better mood was associated with higher illuminance light conditions (Chellappa et al., 2011; Leichtfried et al., 2015; Mason et al., 2022; Ru et al., 2019; K. Smolders & de Kort, 2014; A. U. Viola et al., 2008) and/or higher correlated color temperature (CCT) (Chellappa et al., 2011;

Leichtfried et al., 2015; A. U. Viola et al., 2008), except for one study reporting an association with lower CCT (Ru et al., 2019). Most of the studies with short light exposures had the highest α-opic EDI values (see Figure 5).

2.1.4 Discussion

Results from this systematic review could not reveal any significant effects of α-opic EDI values on mood outcomes. Accordingly, the inspection of individual study results revealed that a large proportion of the studies included in this review did not report any significant effect of light intensity or spectrum on mood outcomes. These observations could not support the proposed hypothesis that the effects of polychromatic light on mood would rely more heavily on melanopic photoreceptors. Better mood was associated with morning light exposure and longer durations of exposure, as would be expected based on previous studies (e.g., Smolders et al., 2012, 2013). This suggests a potential dose-response curve more dependent on the timing and duration of light exposure than on a-opic differences in EDI values in the ranges of polychromatic light covered in the current review. However, these effects of timing and duration were no longer significant in the more complex models adjusting for the data being nested within studies. Conclusions regarding the lack of association with melanopic EDI are limited, notably because of the restricted range of EDI profiles that have been tested so far in published polychromatic studies. This highlights the need for further studies to assess interactions between EDI, duration, and timing of exposure more directly.

Associations between mood and α-opic EDIs

Current findings depart from those of previous controlled studies focused on narrowband (close to monochromatic) light on mood (e.g., Vandewalle et al., 2010). Our systematic review could not confirm that variations in light intensity and spectrum within polychromatic white light have short term effect on mood in healthy individuals. Some of the previous research has shown that short-wavelength light, daytime light with higher melanopic EDI, and general lighting with a higher CCT can improve mood and well-being (Borisuit et al., 2015; Mills et al., 2007; Münch et al., 2020; A. U. Viola et al., 2008; Xiao et al., 2021). In the current review, after rescaling light on comparable units to estimate its effects on individual photoreceptors, there was no clear evidence that the intensity of light exposure predicted mood and no evidence that stimulation of any one photoreceptor was more influential on mood than others. One reason for this might be the small differences between the α-opic EDIs for any one light condition within studies (seen in the overall relatively flat profiles, presented in groups by exposure duration, in Figure 5).

Through visual inspection of light data from individual studies, we sought to identify profiles of peaks across α-opic EDIs. This aimed to determine whether the different light sources in this combined dataset could differentiate exposures to the different photoreceptors (particularly the ipRGCs) and to provide insight into which photoreceptors could be linked to mood outcomes. None of the polychromatic light conditions from the included studies had a higher peak in melanopic EDI compared to other α-opic EDIs. This prevented any insights on α-opic EDI profiles which may activate ipRGCs more strongly than other photoreceptors. Some studies did use conditions in which polychromatic light resulted in higher S-, M-, and/or L-cone-opic EDIs, but the mood outcomes were rather similar across these light conditions. There might have been a slightly higher mood rating on average in conditions with a higher peak in S-cone-

opic EDI (see supplemental material, S2), but this remains to be confirmed through larger datasets enabling statistical comparisons.

Overall, the current observations are limited by the α-opic EDI distribution of the specific polychromatic light used in the reviewed studies. Despite using light sources with an SPD peak in the short-wavelength range ("blue-enriched light"), many studies used light where these peaks were combined with peaks in longer-wavelength light (red light). This creates a light which may be deemed to be more visually natural, which was likely an important goal for these studies, but would not necessarily lead to a major peak in melanopic EDI relative to other α-opic EDIs. For instance, beyond the increase in ipRGC activations, this type of light could also lead to increased L-cone activation. It was expected that the EDI profiles of study conditions with a SPD peaking in the short wavelengths would have higher melanopic EDI. This was, however, not observed. Importantly, the light stimulus in many of these studies were not designed to preferentially activate the ipRGCs; many of these studies aimed to increase the short-wavelength components of polychromatic light which have long been tied to non-visual effects, but not to maximally activate ipRGCs specifically.

Mood, duration, timing of light exposure, and melanopic EDI

The primary goal of including duration and time of exposure in these analyses was to control for these factors because they are known to influence the effects of light on mood (Bedrosian & Nelson, 2017; Chang et al., 2012; Chellappa et al., 2011; Khalsa et al., 2003; Rüger et al., 2013; St Hilaire et al., 2012; G. Vandewalle et al., 2015). Specifically, it has been suggested that improvements in mood are likely to manifest over longer durations of bright light exposure or when repeated over several days (Partonen & Lönnqvist, 2000), although no dose-

response curve has been created yet, to our knowledge. A large longitudinal study also reported that individuals with more daytime spent outdoors have a reduced risk of lifetime depression (Burns et al., 2021). Furthermore, greater improvements in mood have been reported following light exposure in the morning compared to other times of the day (Bedrosian & Nelson, 2013, 2017; Leichtfried et al., 2015). It is also understood that high melanopic EDI during the day and low melanopic EDI light exposure during the night is supportive for alertness, circadian rhythms, and sleep (CIE, 2019), which can indirectly influence mood (Baron & Reid, 2014; DeWeerdt, 2022; Finan et al., 2015; Kahn-Greene et al., 2007). This being said, the evidence on an association between light, sleep/circadian rhythms, and mood in healthy individuals remains conflicted (Böhmer et al., 2021). In the current review, the effects of duration and time of exposure did not survive more complex models accounting for data being nested within studies. Considering that in the articles covered in the current review, the variations in light exposure durations and time of exposures were limited (n=16 morning, n=12 afternoon, n = 11 night, uncontrolled time = 12), no strong conclusion should be drawn about these parameters. However, it is unlikely that variations in time of exposure were significant confounders affecting the main α-opic results at the center of the current review's objectives since we observed no significant interaction between time of exposure and α-opic EDIs (see supplemental material table S3).

Study population

Mood is a complex phenomenon that can be influenced by many contextual factors which are bound to vary from one study to the other, such as other properties of the physical environment, social interactions, and a vast range of situational and personal factors. These

factors could not be measured or quantified in this review and are very likely to have created significant noise in the data.

One may also postulate that α-opic EDIs may be a stronger predictor of positive mood in the context of mood disorders than for general mood in mentally healthy individuals. Firstly, in the context of mood disorders, poorer mood creates a greater potential for mood improvement whereas, in mentally healthy people, general mood might plateau, leaving less room for potential improvements. Accordingly, one study (Smolders et al., 2012) included in the current review highlighted that their participants felt on average happy and without tension or sadness prior to light exposure, which left little room for improvement. Secondly, tools to measure general mood (often based on a single question) might not have enough sensitivity as compared to scales used to measure combinations of specific symptoms linked to mood disorders. Thirdly, individuals with mood disorders could respond differentially to light than healthy individuals. Indeed, there are indications that light may have a different effect in individuals with mood disorders compared to controls (Laurenzo et al., 2016). This notion is supported by previous observations of variations in the human peak sensitivity of melanopsin to short wavelength light (Bailes & Lucas, 2013), the contribution of ipRGCs to mood regulation processes in rodents (Legates et al., 2012, 2014), and the abnormal sensitivity of the circadian clock to light in the context of mood disorders (Ben Bullock et al., 2019; McGlashan et al., 2019; K. Roecklein et al., 2013). Furthermore, studies have shown that light (monochromatic and polychromatic) can elevate mood in the context of mood disorders (Geoffroy et al., 2019; Glickman et al., 2006; Meesters et al., 2016, 2018; Nixon et al., 2021) and fMRI studies also suggest that it can increase brain responses to emotional stimuli (Vandewalle et al., 2010).

Methodological refinement

Studies conducted prior to the publication of action spectra on melatonin suppression (Brainard, Hanifin, Greeson, et al., 2001; Thapan et al., 2001) and the identification of ipRGCs (Berson et al., 2002) necessarily could not be designed to target these photoreceptors, nor use current reporting standards for light as these had not yet been established. The literature landscape spreading over these different periods thus necessarily holds methodological inconsistencies and gaps. With the benefit of more knowledge, guidance documents have been developed to ensure that future investigations can be more readily compared (CIE, 2020; Spitschan et al., 2019). Authors are recommended to report α-opic EDIs (or at least illuminance and light source SPD) measured at the eye in the direction of gaze in addition to horizontal light measurements. The luminance distribution of the physical space also affects what the retina receives and by extension the ipRGC-influenced response to light (CIE, 2020; Glickman et al., 2003; Lasko et al., 1999; Rüger et al., 2005; Visser et al., 1999). Therefore, researchers also should describe, in detail, the physical space used in the study (e.g., surface reflectance, temporal light modulation characteristics, color fidelity, and intensity/spectrum measurements from different possible viewing perspectives, where applicable; see CIE, 2020).

Designing light source spectra to target specific photoreceptors is more complex than increasing the exposure to specific wavelengths (e.g., adding a spectral peak around 490 nm to target ipRGCs) because the results could differ in color appearance or color rendering, or could also stimulate other photoreceptors more than intended. Therefore, studies using metameric spectral tuning may be required to fully differentiate the relative influence of distinct α-opic profiles of polychromatic light on mood. Metameric lighting, which has matching light source color appearance with different SPDs, is a quickly growing field, with studies already exploring

its use on alertness and melatonin production (Allen et al., 2018; Souman et al., 2018). Using this method, a recent study employed a multi-channel LED system to find chromaticity areas in the CIE *xy* color space that are relevant for melanopic efficacy (Zandi et al., 2021). Keeping in mind that increased color fidelity can induce better mood (Cajochen et al., 2019), more studies investigating mood in combination with this lighting approach optimized for ipRGC activation are needed.

Limitations

The vast methodological inconsistencies across studies hinder firm conclusions. The variety of mood measures used across the studies also limit their comparability by reducing construct validity. Mood, a difficult construct to measure that may be conceptualized in different ways (Larsen & Diener, 1992), was integrated as a secondary measure in several of the studies in this review.

This review was limited by the light conditions used in published studies, which were not designed from the outset to cover distinct α-opic profiles and were confounded by other factors. For instance, most studies which had higher α-opic EDIs were also the ones where the duration of light exposure was the shortest which may have confounded results. Considering that in mice, there are direct effects of light on mood driven by a direct projection of ipRGCs to the perihabenular (PHb) and lateral habenula (LHb; Aranda & Schmidt, 2021; Fernandez et al., 2018; Legates et al., 2012). the involvement of ipRGCs in mood responses to light could possibly emerge more clearly from studies comparing well-controlled polychromatic light conditions that clearly differ in α-opic EDI.

In contrast to other reviews, which have included monochromatic light exposures (Brown, 2020; Siraji et al., 2022), this review focused on the effects of polychromatic light, which is more common in naturalistic living environments. This perhaps reduced the α-opic EDI differences between experimental conditions relative to the contrasts typically attained when comparing monochromatic light conditions. However, limited α-opic EDI differences increased the generalizability of the findings.

The lack of reported or controlled pre-exposure history also created an important limitation in the interpretation of results. Light exposure can change the sensitivity of ocular photoreception to subsequent exposures (Chang et al., 2011; Hebert et al., 2002; Jasser et al., 2006; Kozaki et al., 2015; te Kulve et al., 2019; Zeitzer et al., 2011). Without consistent information concerning prior light exposure, it was not possible to control for differences between studies on this variable. Most studies had a multiday exposure design which may have additional uncontrolled factors that could account for the resulting mood outcomes. Visual comfort and glare have been found to affect mood (Borisuit et al., 2015; Cajochen et al., 2019). Considering that many studies did not control or study these variables, they may have masked mood improvements.

Considering representativeness, although the samples were overall balanced for sex, many of the studies included participants from a limited age range, often young adults. There was also limited cultural variability, as most were performed in Europe or North America.

2.1.5 Conclusions

Overall, the results from this systematic review could not support the hypothesis that higher polychromatic light exposure intensity detected by any one of the five ocular photoreceptors described in CIE S026:2018 is associated with better mood. Although further work based on polychromatic light sources with EDI profiles specifically designed to enhance the relative stimulation of ipRGCs is required, the current findings could imply that the differential activation patterns of photoreceptor subtypes may have limited influence on the mood enhancing effects of polychromatic light over rather short-term light exposures and within the narrow range of EDI profiles that were included in the current review. The range of α-opic EDI profiles covered in this review may have been too limited to tease apart the effects of spectrum and intensity from the strong effects of light exposure duration and between-study differences in procedure and/or context. As such, more polychromatic light studies are warranted to systematically test specific combinations of α-opic EDI values optimally targeting each photoreceptor while controlling for exposure duration. Consistent use of the CIE metrology system to measurements of light exposures in all studies of physiological and behavioral outcomes will enable more accurate conclusions about the potential involvement of different photoreceptor systems in the effects of light in humans. Such information could enable revised guidance for interior lighting design and for daily light exposure patterns supportive of well-being, health, and performance.

Supplementary Material

S1. Search Strategy

Scopus

((TITLE (light OR wavelength OR illumin*) AND TITLE-ABS-KEY (cognit* OR alert* OR vigilance OR sleepiness OR attention OR memory OR psychomotor OR "reaction time" OR "response time" OR arous* OR productivity OR mood OR pupil* OR electroretinography OR well-being OR physiology OR circadian OR brain OR fmri OR eeg OR electroencephalography) AND TITLE-ABS-KEY (human OR adults OR participants OR men OR women OR male OR female OR subject) AND TITLE-ABS- KEY (poly* OR "white light" OR spectrum* OR "bright light" OR "light pulse" OR "Light flash" OR (light AND exposure)) AND NOT TITLE-ABS-KEY (membrane OR nano* OR dna OR tissue OR drosophila OR mice OR rat OR cat OR fish OR "shift work" OR shiftwork OR "seasonal affective disorder" OR neonatal OR infant OR children OR treat* OR disorder OR species OR jaundice OR psoriasis OR tumor OR tumour OR glaucoma OR cancer OR polymer* OR hamster OR chick* OR injury OR fly))) AND (LIMIT-TO (SRCTYPE , "j") OR LIMIT-TO (SRCTYPE , "p")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp")) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019) OR LIMIT-TO (PUBYEAR , 2018) OR LIMIT-TO (PUBYEAR , 2017) OR LIMIT-TO (PUBYEAR , 2016) OR LIMIT-TO (PUBYEAR , 2015) OR LIMIT-TO (PUBYEAR , 2014) OR LIMIT-TO (PUBYEAR , 2013) OR LIMIT-TO (PUBYEAR , 2012) OR LIMIT-TO (PUBYEAR , 2011) OR LIMIT-TO (PUBYEAR , 2010) OR LIMIT-TO (PUBYEAR , 2009) OR LIMIT-TO (PUBYEAR , 2008) OR LIMIT-TO (PUBYEAR , 2007) OR LIMIT-TO (PUBYEAR , 2006) OR LIMIT-TO (PUBYEAR , 2005) OR LIMIT-TO (PUBYEAR , 2004) OR LIMIT-TO (PUBYEAR , 2003) OR LIMIT-TO (PUBYEAR , 2002) OR LIMIT-TO (PUBYEAR , 2001) OR LIMIT-TO (PUBYEAR , 2000) OR LIMIT-TO (PUBYEAR , 1999) OR LIMIT-TO (PUBYEAR , 1998) OR LIMIT-TO (PUBYEAR , 1997) OR LIMIT-TO (PUBYEAR , 1996) OR LIMIT-TO (PUBYEAR , 1995) OR LIMIT-TO (PUBYEAR , 1994) OR LIMIT-TO (PUBYEAR , 1993) OR LIMIT-TO (PUBYEAR , 1992) OR LIMIT-TO (PUBYEAR , 1991) OR LIMIT-TO (PUBYEAR , 1990)) AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "French") OR EXCLUDE (LANGUAGE , "German") OR EXCLUDE (LANGUAGE , "Japanese") OR EXCLUDE (LANGUAGE , "Polish") OR EXCLUDE (LANGUAGE , "Portuguese") OR EXCLUDE (LANGUAGE , "Croatian") OR EXCLUDE (LANGUAGE , "Spanish") OR EXCLUDE (LANGUAGE , "Thai"))

PsycINFO/Embase

((light or wavelength or illumin*).ti. and ((cognit* or alert* or vigilance or sleepiness or attention or memory or psychomotor or "reaction time" or "response time" or arous* or productivity or mood or pupil* or electroretinography or well-being or physiology or circadian or brain or fmri or eeg or electroencephalography).ab. or (cognit* or alert* or vigilance or sleepiness or attention or memory or psychomotor or "reaction time" or "response time" or arous* or productivity or mood or pupil* or electroretinography or well-being or physiology or circadian or brain or fmri or eeg or electroencephalography).ti. or (cognit* or alert* or vigilance

or sleepiness or attention or memory or psychomotor or "reaction time" or "response time" or arous* or productivity or mood or pupil* or electroretinography or well-being or physiology or circadian or brain or fmri or eeg or electroencephalography).id.) and ((human or adults or participants or men or women or male or female or subject).ab. or (human or adults or participants or men or women or male or female or subject).ti. or (human or adults or participants or men or women or male or female or subject).id.) and ((poly* or "white light" or spectrum* or "bright light" or "light pulse" or "Light flash" or (light and exposure)).ab. or (poly* or "white light" or spectrum* or "bright light" or "light pulse" or "Light flash" or (light and exposure)).ti. or (poly* or "white light" or spectrum* or "bright light" or "light pulse" or "Light flash" or (light and exposure)).id.)) not ((membrane or nano* or dna or tissue or drosophila or mice or rat or cat or fish or "shift work" or shiftwork or "seasonal affective disorder" or neonatal or infant or children or treat* or disorder or species or jaundice or psoriasis or tumor or tumour or glaucoma or cancer or polymer* or hamster or chick* or injury or fly).ab. or (membrane or nano* or dna or tissue or drosophila or mice or rat or cat or fish or "shift work" or shiftwork or "seasonal affective disorder" or neonatal or infant or children or treat* or disorder or species or jaundice or psoriasis or tumor or tumour or glaucoma or cancer or polymer* or hamster or chick* or injury or fly).ti. or (membrane or nano* or dna or tissue or drosophila or mice or rat or cat or fish or "shift work" or shiftwork or "seasonal affective disorder" or neonatal or infant or children or treat* or disorder or species or jaundice or psoriasis or tumor or tumour or glaucoma or cancer or polymer* or hamster or chick* or injury or fly).id.) limit 1 to human
limit 2 to yr="1990 - 2020" limit 3 to (english or french)

Web of Science

TI=(light OR wavelength OR illumin*) AND TS=(cognit* OR alert* OR vigilance OR sleepiness OR attention OR memory OR psychomotor OR "reaction time" OR "response time" OR arous* OR productivity OR mood OR pupil* OR electroretinography OR well-being OR physiology OR circadian OR brain OR fmri OR eeg OR electroencephalography) AND TS=(human OR adults OR participants OR men OR women OR male OR female OR subject) AND TS=(poly* OR "white light" OR spectrum* OR "bright light" OR "light pulse" OR "Light flash" OR (light AND exposure)) NOT TS=(membrane OR nano* OR dna OR tissue OR drosophila OR mice OR rat OR cat OR fish OR "shift work" OR shiftwork OR "seasonal affective disorder" OR neonatal OR infant OR children OR treat* OR disorder OR species OR jaundice OR psoriasis OR tumor OR tumour OR glaucoma or cancer or polymer* or hamster or chick* or injury or fly)
Refined by: LANGUAGES: (ENGLISH OR FRENCH)
Timespan: 1990-2020. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.

Lighting Research and Technology

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men] OR [All women] OR [All male] OR [All female] OR [All subject]] AND [[All poly*] OR [All "white light"] OR [All spectrum*] OR [All "bright light"] OR [All "light pulse"] OR [All "light flash"] OR [[All light] AND [All exposure]]] AND NOT [[[All membrane] OR [All nano*] OR [All dna] OR [All tissue] OR [All drosophila] OR [All mice] OR [All rat] OR [All cat] OR [All fish] OR [All "shift work"] OR [All shiftwork] OR [All "seasonal affective disorder"] OR [All neonatal] OR [All infant] OR [All children] OR [All treat*] OR [All disorder] OR [All species] OR [All jaundice] OR [All psoriasis] OR [All tumor] OR [All tumour] OR [All glaucoma] OR [All cancer] OR [All polymer*] OR [All hamster] OR [All chick*] OR [All injury]] AND [All or fly]] within Lighting Research & Technology Since 1990

LEUKOS/ Journal of the Illuminating Engineering Society

[[Publication Title: light] OR [Publication Title: wavelength] OR [Publication Title: illumin*] OR [Publication Title: pupil*]] AND [[All: cognit*] OR [All: alert*] OR [All: vigilance] OR [All: sleepiness] OR [All: attention] OR [All: memory] OR [All: psychomotor] OR [All: "reaction time"] OR [All: "response time"] OR [All: arous*] OR [All: productivity] OR [All: mood] OR [All: pupil*] OR [All: electroretinography] OR [All: well-being] OR [All: physiology] OR [All: circadian] OR [All: brain] OR [All: fmri] OR [All: eeg] OR [All: electroencephalography]] AND [[All: human] OR [All: adults] OR [All: participants] OR [All: men] OR [All: women] OR [All: male] OR [All: female] OR [All: subject]] AND [[All: poly*] OR [All: "white light"] OR [All: spectrum*] OR [All: "bright light"] OR [All: "light pulse"] OR [All: "light flash"] OR [[All: light] AND [All: exposure]]] AND NOT [[All: membrane] OR [All: nano*] OR [All: dna] OR [All: tissue] OR [All: drosophila] OR [All: mice] OR [All: rat] OR [All: cat] OR [All: fish] OR [All: "shift work"] OR [All: shiftwork] OR [All: "seasonal affective disorder"] OR [All: neonatal] OR [All: infant] OR [All: children] OR [All: treat*] OR [All: disorder] OR [All: species] OR [All: jaundice] OR [All: psoriasis] OR [All: tumor] OR [All: tumour] OR [All: glaucoma] OR [All: cancer] OR [All: polymer*] OR [All: hamster] OR [All: chick*] OR [All: injury] OR [All: fly]] AND [in Journal: LEUKOS] AND [Publication Date: (01/01/1990 TO 31/12/2020)]

PubMed

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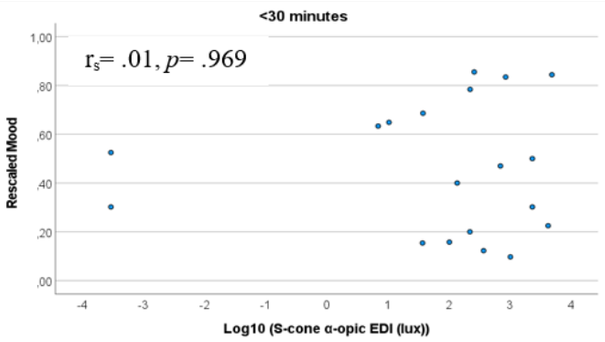
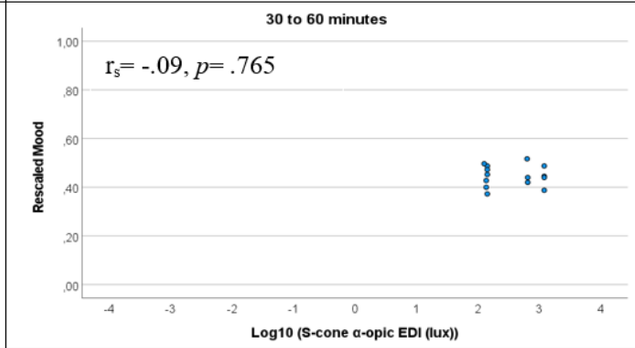
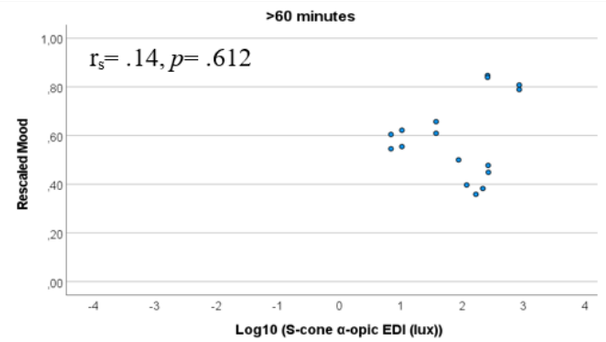
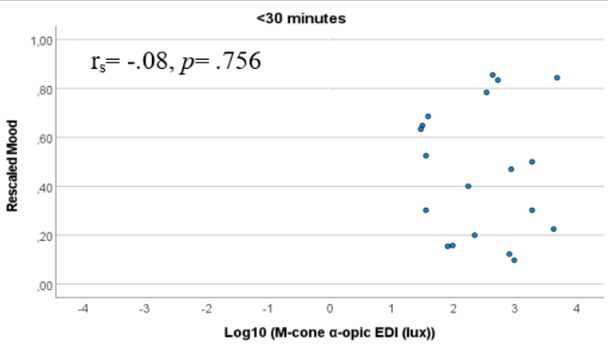
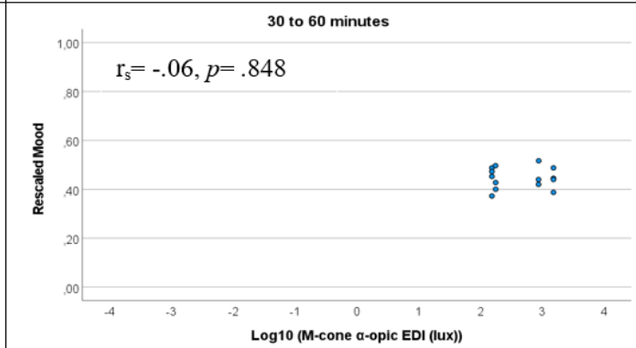
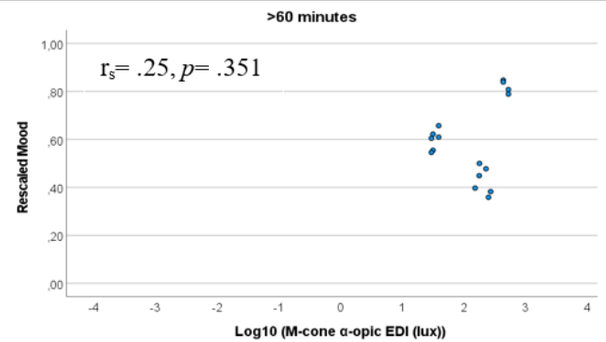
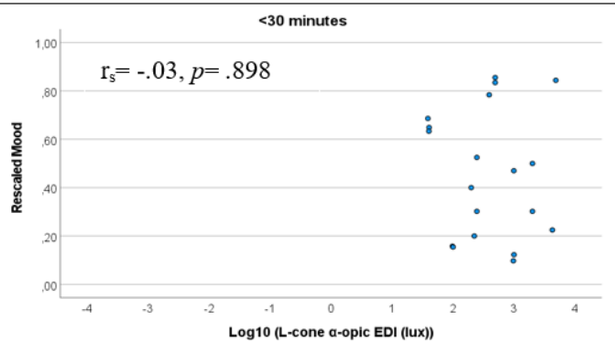
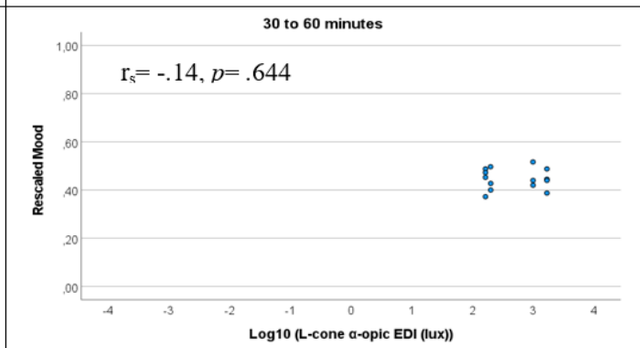
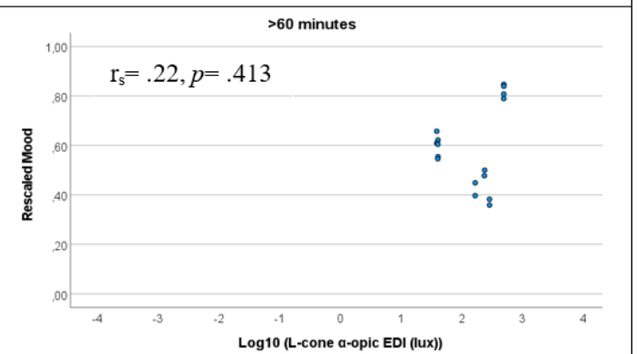
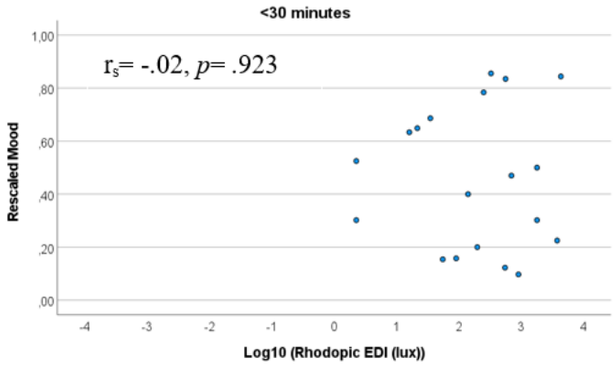
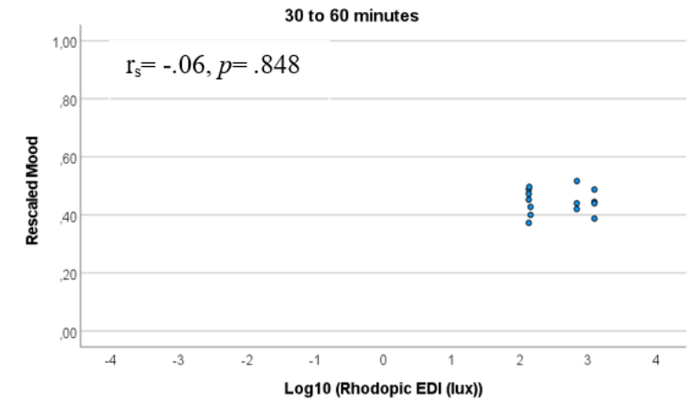
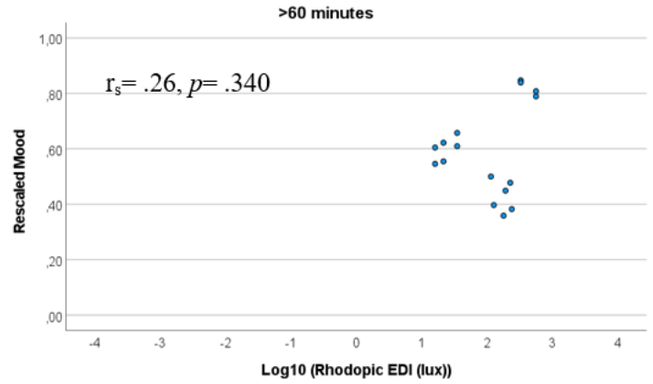
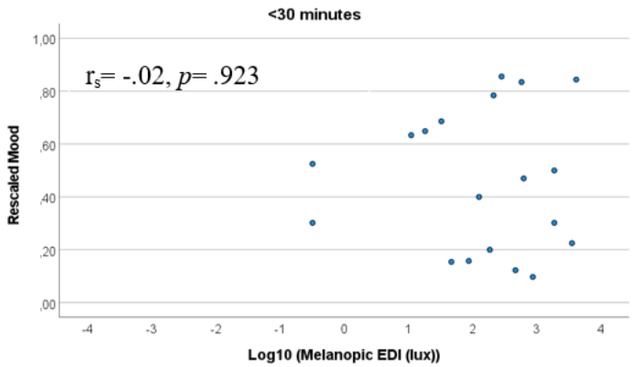
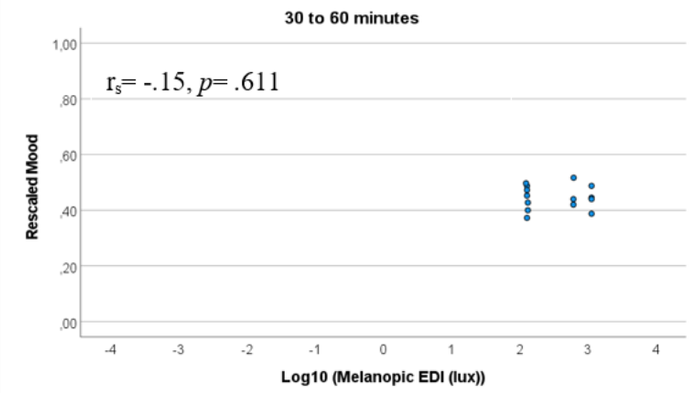
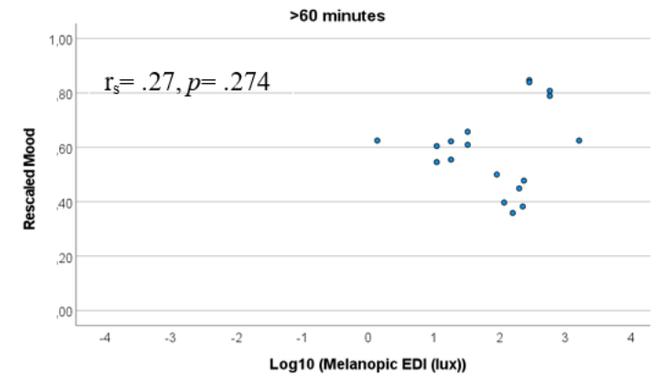
Add filters – Human, 1990-2020, English, French

S2. Standardized mood metrics as a function of the five α-opic EDIs divided by duration

	< 30 min	**30 – 60 min**	**> 60 min**
S-cone-opic			
M-cone-opic			
L-cone-opic			

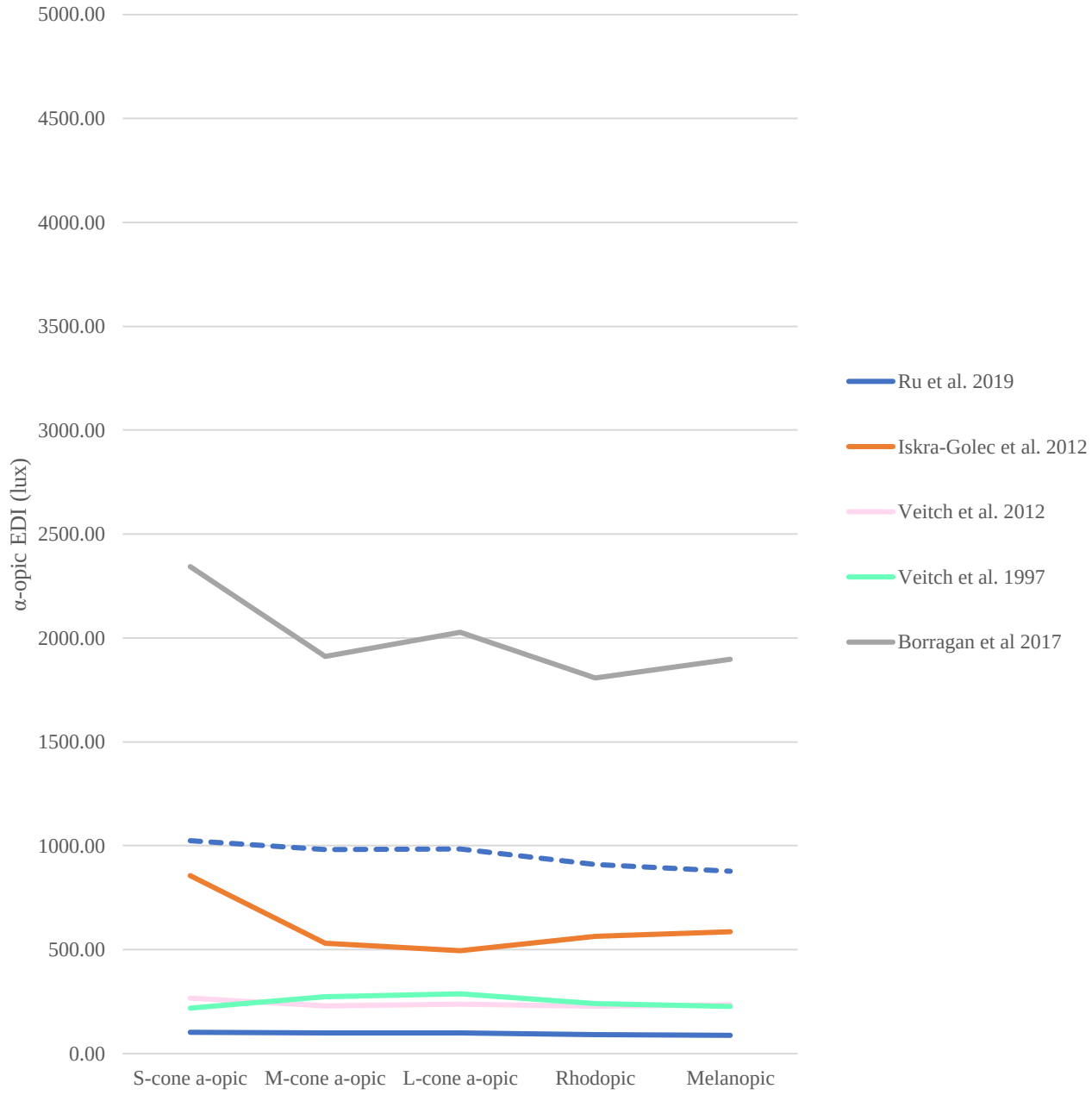
rhodopic			
melanopic			

S3. Interaction terms between α-opic EDIs, time and duration of exposure

	L-cone-opic			M-cone-opic			S-cone-opic			Rhodopic			Melanopic		
	Est./F	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**	**Est./F**	**SE/SD**	**p**
Study Identifier	14.30	0.168	<0.001	13.89	0.169	<0.001	14.09	0.170	<0.001	14.06	0.170	<0.001	13.02	0.163	<0.001
Time (vs morning)															
Uncontrolled	-0.14	0.173	0.415	-0.19	0.165	0.265	-0.18	0.148	0.229	-0.19	0.156	0.242	-0.19	0.149	0.221
Afternoon	-0.06	0.085	0.468	-0.06	0.082	0.443	-0.06	0.071	0.385	-0.07	0.077	0.385	-0.06	0.073	0.396
Night	0.39	0.296	0.198	0.15	0.258	0.568	0.08	0.196	0.705	0.07	0.214	0.734	0.13	0.147	0.371
Duration	0.05	0.308	0.867	-0.22	0.218	0.318	-0.16	0.082	0.062	-0.24	0.127	0.067	-0.16	0.089	0.075
α-opic EDI	0.03	0.178	0.864	-0.12	0.123	0.332	-0.08	0.047	0.100	-0.13	0.073	0.089	-0.09	0.055	0.115
α-opic EDI*length of exposure*Uncontrolled	-0.02	0.132	0.866	0.09	0.093	0.341	0.06	0.039	0.129	0.10	0.058	0.104	0.07	0.045	0.141
α-opic EDI*length of exposure*Morning	-0.02	0.114	0.871	0.08	0.081	0.323	0.05	0.031	0.094	0.09	0.049	0.080	0.06	0.036	0.102
α-opic EDI*length of exposure*Afternoon	-0.01	0.115	0.904	0.09	0.084	0.311	0.06	0.035	0.101	0.09	0.053	0.083	0.07	0.040	0.110
α-opic EDI*length of exposure*Night	-0.12	0.196	0.530	0.07	0.144	0.641	0.07	0.041	0.087	0.11	0.081	0.199	0.05	0.033	0.134

Note: F values for Study Identifier and Estimates for all other parameters (Est.; calculated for fixed effects per one unit of $\log_{10}$-transformed values for continuous variables, and relative to morning for time of exposure (categorical: morning (6:00 to 11:59), afternoon (Noon to 16:59), night (17:00 to 6:59), or uncontrolled times), Standard Deviation (SD) for Study Identifier and Standard Error (SE) for all other parameters, and p values.

S4. EDI Profiles of study conditions with a peak in short-wavelength region of the spectrum

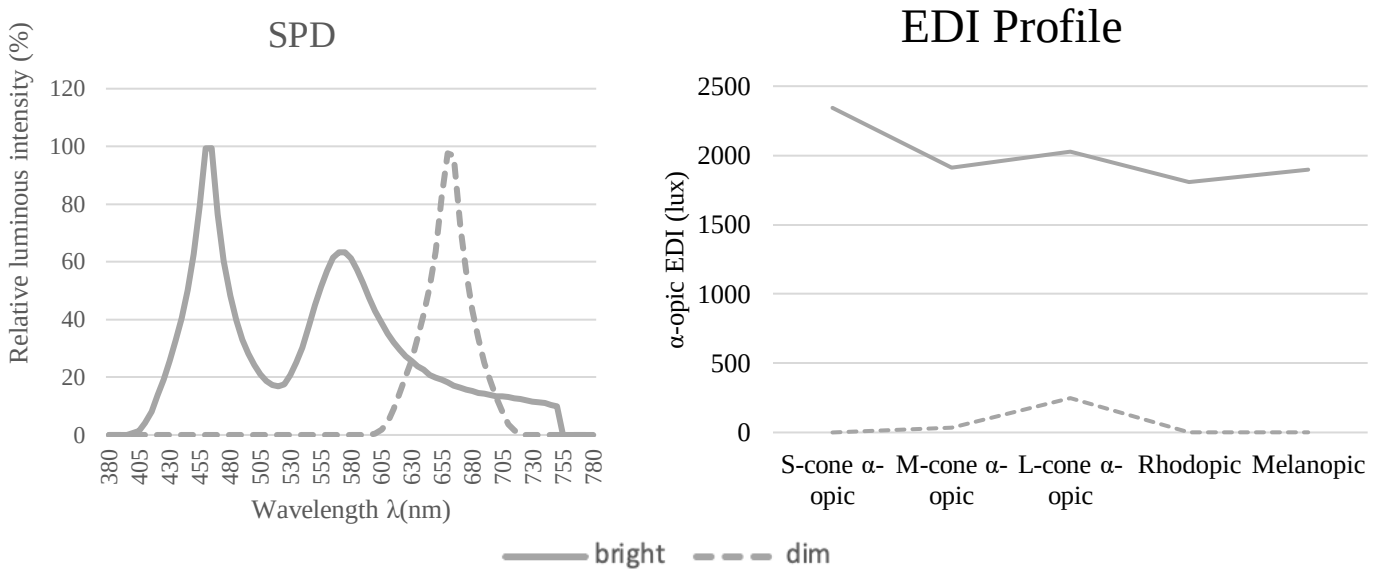


Note: Equivalent daylight illuminance (EDI) profile of study conditions with a peak in the short wavelength section of the spectral power distribution (SPD). Viola et al. 2008 and Correa et al. 2016 are not included since there EDIs were not extract from an SPD.

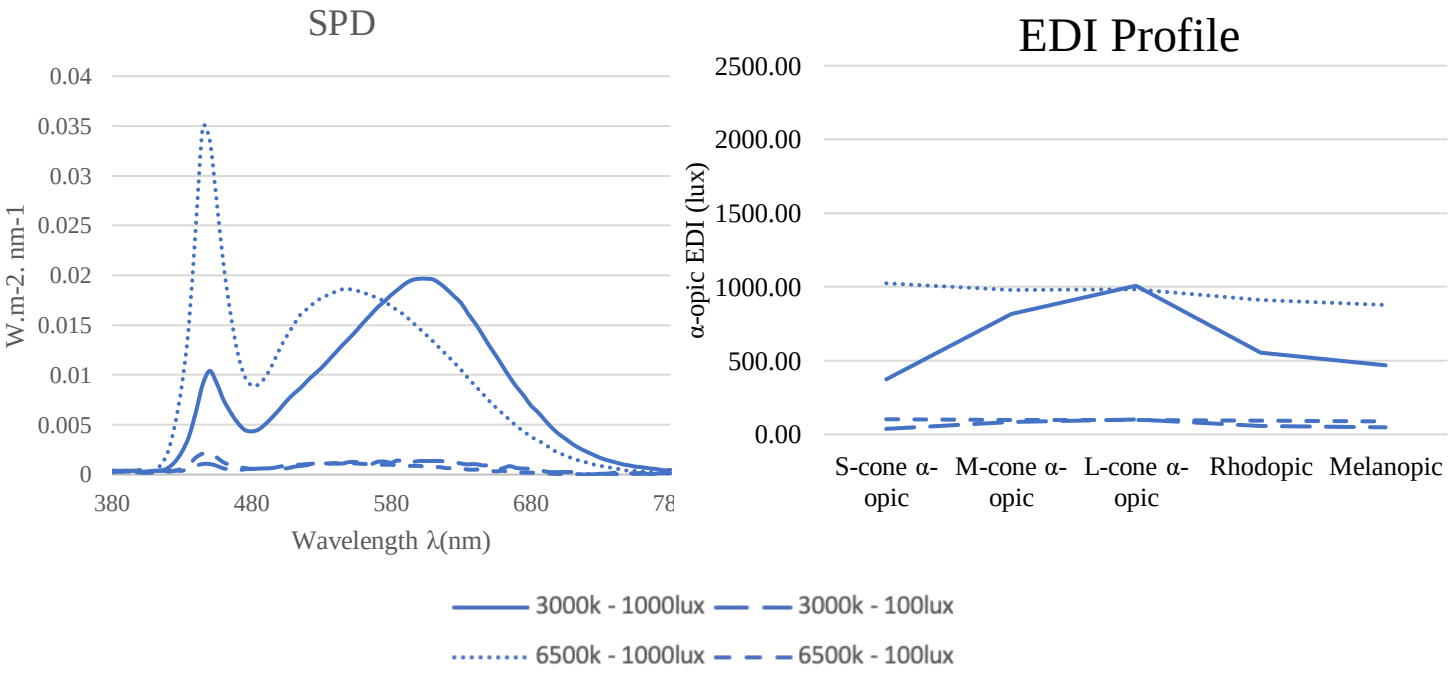
S5. Spectral power distribution for studies with an SPD with at least one peak in short wavelength light and EDI profiles

< 30 minutes

Borragan et al. 2017

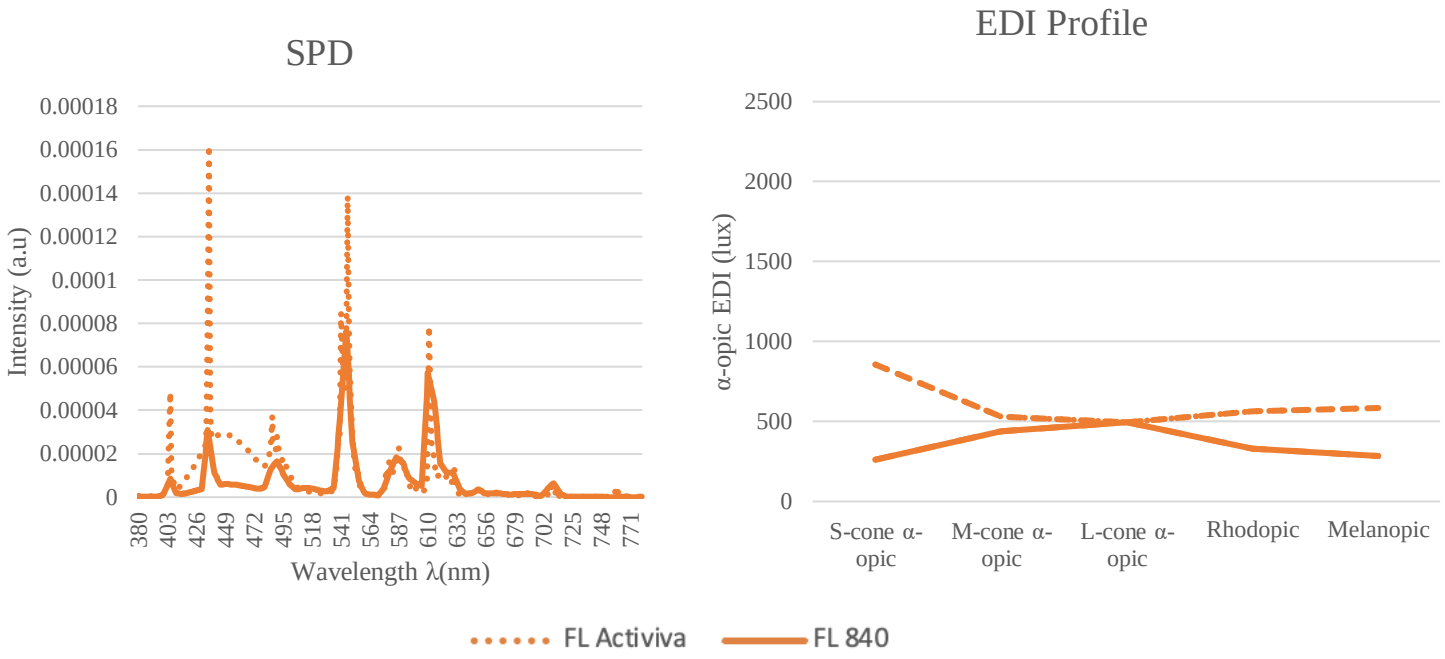


Ru et al. 2019



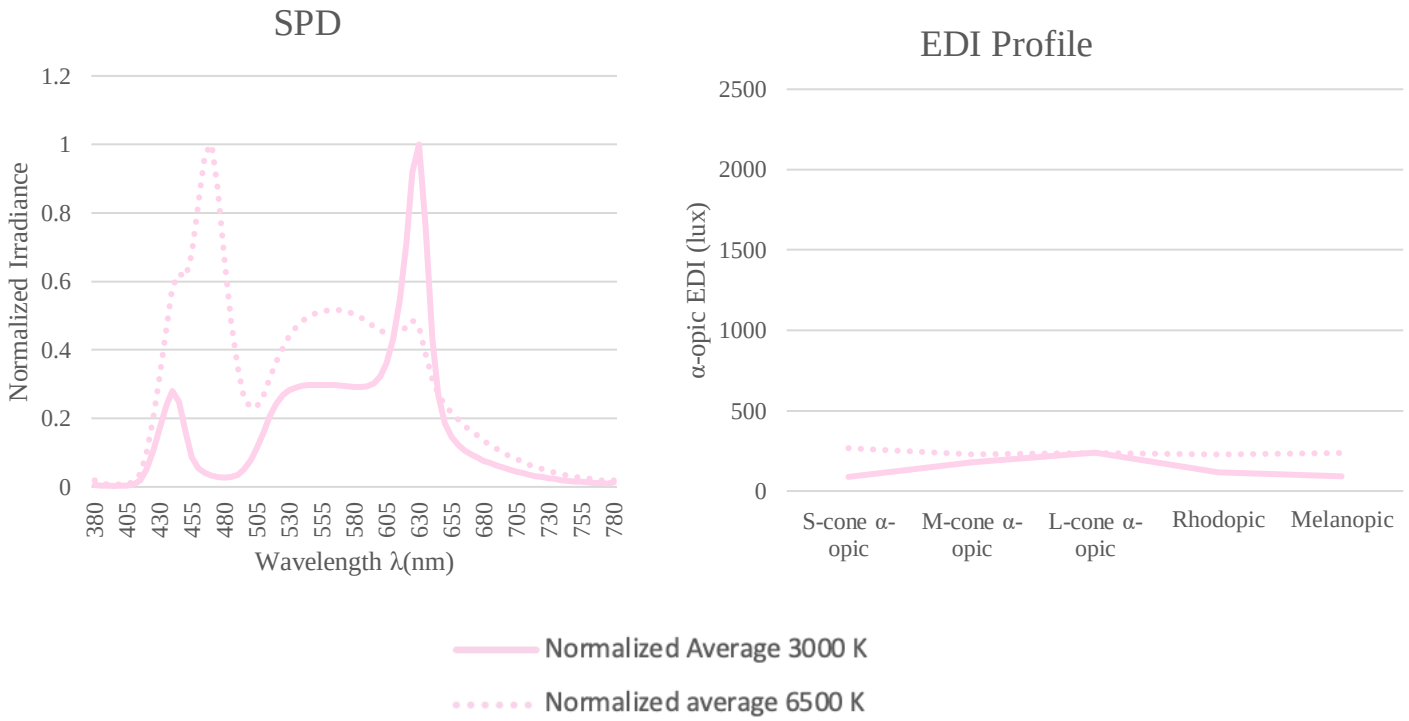
< 30 minutes & > 60 minutes

Iskra-Golec et al. 2012

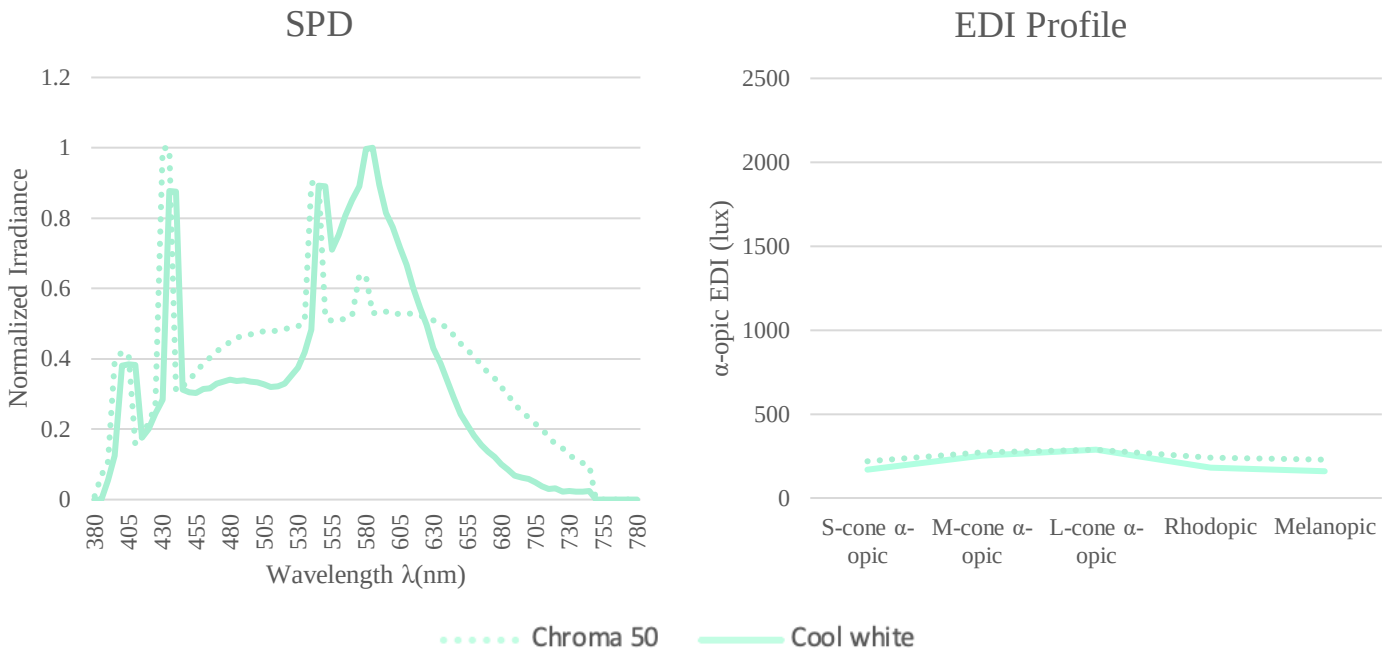


> 60 minutes

Veitch et al. 2012



Veitch et al. 1997



Note: Viola et al. 2008 and Correa et al. 2016 are not included because their EDIs were not extracted from an SPD.

Study II

Temporal dynamics of subjective sleep profiles predicting mood improvements during adjunctive light therapy combined with sleep rescheduling

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Abstract

Background: Light therapy yields inconsistent results in people with non-seasonal depression, which may in part be due to heterogeneous responses and the temporal dynamics of changes in sleep, daytime functioning, and mood. This study assessed the timeline of the antidepressant effects of light therapy and sleep rescheduling relative to changes in sleep and daytime sleep-related factors and sought to identify predictors of treatment response in young people with depression.

Methods: Twenty-four individuals with depression (mean ± SD: 21.2 ± 1.0 years old; 17% male) underwent adjunctive morning light therapy with a wake-up phase advance over four weeks. They completed the Beck Depression Inventory-II (BDI-II) and Leeds Sleep Evaluation Questionnaire.

Results: On average, BDI-II scores decreased significantly after four weeks of intervention ($F(2,32) = 3.5$, $p = .044$, $\eta p^2 = 0.18$). After two weeks, improvements in the ease of getting to sleep and sleep quality were significantly associated with BDI-II improvements ($F(2,21) = 6.3$, $p = .007$). From two to four weeks, improvements in daytime sleep-related factors were significantly associated with BDI-II improvements ($F(2,12) = 6.0$, $p = .015$). More sleep-related difficulties prior to the intervention tended to predict BDI-II improvements across the four weeks of light therapy ($F(2,14) = 3.7$, $p = .053$).*Limitations:* Open-label design and small sample size.

Limitations: Open-label design and small sample size.

Conclusions Sleep-enhancement emerging in the early phase of light therapy and sleep rescheduling may subsequently alleviate sleep-related daytime dysfunctions, which may in turn

further improve mood. Controlled trials are required to confirm whether the antidepressant effects of light may be linked to the attenuation of sleep-related difficulties, and whether sleep difficulties may be useful predictors of the antidepressant response to light therapy.

Highlights

- Sleep-enhancement following light therapy may contribute to rapid mood improvements.
- Subsequent alleviation of sleep-related daytime dysfunction may further improve mood.
- Self-reported sleep variables may predict antidepressant response to light therapy.

Keywords: Light therapy; Depression; Sleep

2.2.1 Introduction

Light therapy has long been used to restore sleep and circadian rhythms (Terman et al., 1995). Its efficacy for mood improvement in the context of seasonal affective disorder is also well established (Lam & Levitt, 1999), but findings remain somewhat inconsistent for people with non-seasonal depression (Tuunainen et al., 2009). This discrepancy may notably be influenced by the considerable heterogeneity in depression phenotypes.

For instance, various profiles of sleep have been observed in people with depression; some show conventional sleep and circadian patterns, while others have various degrees of sleep initiation/maintenance difficulties and/or circadian phase shifts (Gillin et al., 1979; Robillard et al., 2018). The degree of sleep and circadian disturbances has been found to be associated with more severe depression (Kerkhofs et al., 1988; Robillard et al., 2018), and sleep problems are thought to contribute to the maintenance of depression (Dolsen et al., 2014). It has thus been proposed that actively restoring sleep and circadian rhythms may enhance mood (e.g. Hickie et al., 2013).

The response to antidepressant medications relative to placebo has been reported to emerge after two weeks (Quitkin et al., 1984), but little is known about the time course of the antidepressant effects of light therapy. A study on seasonal affective disorder reported greater reductions in depressive symptoms following four weeks of light therapy (Bauer et al., 1994). Considering the fairly rapid sleep-enhancing and chronotropic effects of appropriately timed light exposure (Lack et al., 2007), improvement in the ease to fall asleep, driven by sleep and circadian restoration, may have rapid direct effects on mood. Since high fatigue levels are also associated with more severe depression (Tylee et al., 1999), sleep improvements following light therapy could also have subsequent indirect effects on mood by facilitating waking-up, feeling

more refreshed upon awakening, and increasing daytime functioning. The profile of sleep difficulties and daytime consequences of poor sleep may thus be some of the factors modulating the antidepressant response to light therapy. This may be especially relevant during youth, a period marked by delayed circadian rhythms and sleep initiation difficulties, two factors which may interact with the sleep disturbances linked to depression.

This open-label study aimed to evaluate the time course of mood improvements during adjunctive light therapy combined with a phase advance of wake-up time and to determine how it relates to sleep and sleep-related daytime outcomes in young people with depression. It was hypothesized that improvements in depressive symptoms during light therapy would be associated with sleep improvements occurring early in the course of the intervention and with subsequent improvements in sleep-related daytime functioning.

2.2.2 Methods

Participants

Young individuals with a diagnosis of a depressive syndrome were recruited from specialised mental health facilities in Ottawa (Canada) and Sydney (Australia) across multiple seasons. All participants met the following entry criteria: between 15 and 30 years of age; current diagnosis of a depressive syndrome (e.g. major depression, dysthymia) confirmed by their healthcare provider; at least mild depressive symptoms on the self-rated version of the Quick Inventory of Depressive Symptomatology [QIDS-SR$_{16}$ or QIDS-A$_{17}$-SR; Score $\geq$6 (Rush et al., 2003); and had a first episode of depression before the age of 25 years.

Exclusion criteria were: any self-reported sleep disorders (except insomnia or circadian disorders); medical conditions that could explain the current depression, contribute to sleep

difficulties or pose risks for bright light exposure; psychiatric comorbidities (except anxiety); significant substance dependence; using medications increasing risks of photoallergic reactions; recent shift-work or transmeridian travel. None of the participants started medications that may affect sleep, circadian rhythms, or alertness within the month preceding study entry.

This study was approved by institutional research ethics boards. All participants provided written informed consent and assent was obtained from legal guardians of those under 16 years of age.

Procedures

Participants received a brief educational session about the biological clock and light. They were lent a pair of light-emitting glasses (RE- TIMER, *Re*-Time Pty Ltd, Australia; blue-green 500 nm dominant wavelength; 506 Lux lm/m^2; α-opic equivalent daylight (D65) illuminance values can be found in Table S6 and a photograph of the glasses in Figure S8) to use at home every day for four weeks as an adjunct to standard clinical care. They were instructed to wear the light-emitting glasses for 45 to 60 min upon awakening, starting at their habitual wake up time, and to progressively shift light exposure earlier by 15 min every day until the end of the intervention or until they reached 7.30am.

Measurements

The Beck Depression Inventory-II (BDI-II) and Leeds Sleep Evaluation (LSEQ) questionnaires were administered at baseline (prior to the intervention start), after two weeks (early phase), and after four weeks (late phase) of intervention.

The BDI-II (Beck et al., 1961) is a 21-item questionnaire with good sensitivity and specificity, an internal consistency of 0.9, and a re-test reliability ranging between 0.73 to 0.96 (Wang & Gorenstein, 2013). Occurrences of minimal clinically important differences (MCID) on

the BDI-II from pre- to post-intervention were determined for each participant based on a previously established threshold (i.e. 17.5%; Button et al., 2015).

The LSEQ counts 10 analogue scale items creating four subscales: *getting to sleep (GTS), quality of sleep (QOS), awake following sleep (AFS),* and *behavior following wakefulness (BFW)* (Parrott & Hindmarch, 1980). Internal consistency has been found to range from α=0.78 to 0.92 (Tarrasch et al., 2003).

Statistics

Statistical analyses were conducted with the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk, USA). Repeated measures ANOVAs were used to assess changes in depressive symptoms across the intervention period.

Multivariate linear regressions were used to evaluate associations between relative changes in mood (BDI-II re-calculated without sleep items to avoid circularity) and: i) relative changes in sleep indices (GTS and QOS) in the early intervention phase, and ii) relative changes in indices of sleep-related daytime functioning (BFW and AFS) in the later phase. A multivariate linear regression was also run to determine if the initial profile of the ease of falling asleep and waking up in the morning (GTS and AFS) predicted changes in mood across the four weeks of intervention. Univariate regressions were used for exploratory analyses.

The LSEQ data for two participants was missing for the last two weeks of the study. These participants were excluded from analyses involving the LSEQ at this time point.

2.2.3 Results

Thirty-one participants were recruited, and of those, 24 completed at least 2 weeks of the intervention and were thus included in the analyses (see descriptive characteristics in table 5).

Seven participants were lost to follow-up after four weeks. Treatment adherence is outlined in Figure S9 of the supplemental material. Depression severity at study enrollment ranged from mild to very severe (QIDS scores between 7 and 25). There was no significant correlation between the main outcome variables and age or hours of illumination documented at each individual's geographic location on the date at which they started the intervention. There was no significant effect of sex or psychotherapy status on the main outcome variables (all $p>.050$).

Table 5. Sample characteristics

	N=24
	Mean (SD)
Age (years)	21.2 (1.0)
QIDS score	13.1 (1.0)
	N (%)
Sex (males)	4 (17)
Comorbid anxiety disorder	13 (54)
Regular Alcohol Use	5 (23)
Regular Cannabis Use	3 (14)
Taking any type of psychotropic medication	14 (58)
Antidepressants	13 (54)
Atypical-Antipsychotics	1 (4)
Anticonvulsant	1 (4)
Benzodiazepine	1 (4)
Psychostimulant	2 (8)
Engaged in psychotherapy	15 (63)
Engaged in psychotherapy and taking psychotropic medication	12 (50)

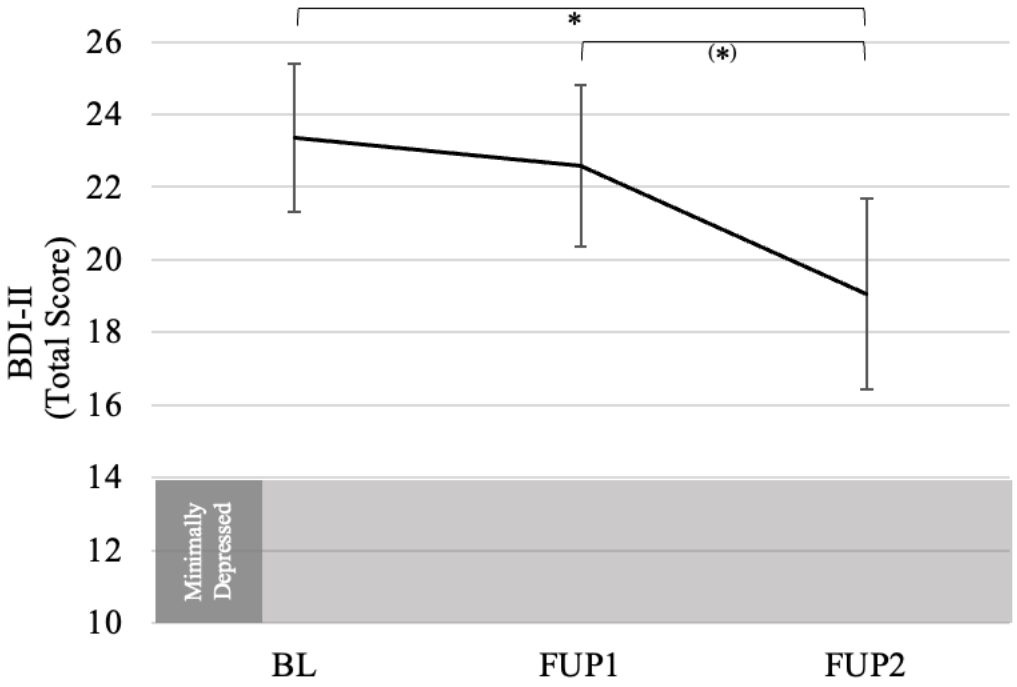
Note: Regular alcohol and cannabis use refers to using weekly or more frequently.

Overall changes in depressive symptoms

There was a main effect of time for total BDI-II scores across the intervention period ($F(2,32)=3.5$, $p=.044$, $\eta p^2=0.18$; Fig. 6). No significant overall change was observed during the early phase, but there was a trend for a decrease during the late phase ($t(16)=2.0$, $p=.063$) and a significant decrease across the entire intervention period ($t(16)=2.5$, $p=.023$). A minimal clinically important difference on the BDI-II was observed after the intervention in 59% of

participants (n = 10/17). The average reduction in BDI-II scores over the intervention period was 21.1% (SD = 41.0%).

Fig. 6. Changes in Depression Symptoms Across Four Weeks of Intervention



Note: Changes in the Beck Depression Inventory-II (BDI-II) scores across the three study time points (BL (baseline): before intervention start (mean ± SD: 23.4 ± 8.4), FUP1: after 2 weeks of intervention (mean ± SD: 22.6 ± 9.1), FUP2: after 4 weeks of intervention (mean ± SD: 19.1 ± 10.9)). A score lower than 14 on the BDI-II indicates minimal depressive symptoms. Error bars represent standard errors of the mean. *: p<.050, $^{(*)}$: p <0.065.

Associations between changes in depressive symptoms and sleep-related outcomes

The global multivariate regression for depressive symptoms changes in the early (F(2,21)=6.3, p=.007, Adjusted R^2=0.37) and late (F(2,12)=6.0, p=.015, Adjusted R^2=0.42) intervention phases were significant (see Table S7 in supplementary material for regression coefficients). Over the first two weeks of the intervention, improvements on the BDI-II were independently associated with improvements on the GTS (β=0.51, p=.009), but not the QOS (β=0.23, p=.207) subscale. Over the third and fourth weeks, improvements on the BDI-II were

independently associated with improvements on the BFW (β=0.74, p=.011), but not the AFS (β=−0.06, p=.817) subscale. Similar results were found in univariate regression.

Baseline sleep profile and changes in depressive symptoms across the intervention

A trend was found for the global multivariate regression predicting overall depressive symptoms changes along the intervention based on initial sleep profiles (F(2,14)=3.7, p=.053, R^2=0.25). None of the predictors had a significant independent contribution to this model. Univariate regression showed that depressive symptom changes were associated with worse initial sleep and sleep-related daytime functioning as measured by the GTS (Adjusted R^2=0.28, β=−0.53, p=.028) and AFS (Adjusted R^2=0.29, β=−0.54, p=.025) subscales, respectively.

2.2.4 Discussion

The present findings suggest that depressive symptoms attenuate with considerable inter-individual variability along the course of four weeks of light therapy and sleep rescheduling. This is associated with rapid improvements in sleep and subsequent alleviation of sleep-related daytime dysfunctions. Treatment response was found to vary based on the magnitude of sleep improvements across the intervention, supporting the idea that sleep restoration may represent one of the mechanisms underlying the mood enhancing effects of bright light exposure.

As opposed to the more rapid antidepressant response reported in other studies (e.g. Kripke et al., 1992), we observed an overall significant reduction in depressive symptoms only after four weeks of light therapy and sleep rescheduling. One of the potential factors that may contribute to this difference is the apparatus used to deliver the light therapy, which differed

notably in terms of the intensity and spectral composition of light. Also, in addition to being younger than in most previous trials, participants in the current study were outpatients. Inpatients are more likely to be in an acute illness phase that may allow for a more rapid treatment response.

Our findings suggest that the ability to fall asleep, most likely resulting from circadian entrainment, facilitated by the phase advancing properties of light (Lack et al., 2007) and the progressive advance of wake-up time, may start improving fairly rapidly after the start of light therapy combined with sleep rescheduling. This could possibly contribute to changes in mood in the early intervention phase. Subsequent mood improvements in the later intervention phase were associated with enhanced quality of wake following sleep. In sum, light therapy and sleep rescheduling may have firstly facilitated sleep initiation, most likely via circadian entrainment, which may be accompanied by rapid positive effects on mood, and secondly these improvements in sleep may have in turn led to an attenuation of the daytime consequences of sleep disruptions, with additional mood benefits. This echoes previous observations in youths with depression showing that sleep problems are associated with poorer daytime functioning and low mood (Wolfson & Carskadon, 1998).

Herein, individuals who initially had worse difficulties falling asleep and more trouble awakening in the morning tended to have more pronounced mood improvements following morning light therapy and sleep rescheduling. The fact that the combination of these two factors tended to be predictive of the antidepressant response and that these factors were significant predictors at the univariate level but were not independently predictive at the multivariate level could suggest that they may be strongly connected in their relation to individual mood sensitivity to light and sleep interventions. In line with the notion that restoring sleep and circadian rhythms

may contribute to depression remission (e.g. Hickie et al., 2013), this suggests that light therapy combined with sleep rescheduling may be a relevant therapeutic tool, especially in this identifiable subgroup of people with depression.

This study is limited by its open-label design and adjunctive nature precluding inferences of causality, small sample size, age range spanning across multiple developmental phases, and imperfect adherence. Also, it was not possible to differentiate the effects of light therapy from that of sleep rescheduling. To further disentangle the relative contribution of circadian entrainment from other possible pathways via which light could influence mood, future studies could notably compare a regularly timed daily light therapy schedule to irregular light therapy schedules. Larger placebo-controlled trials with objective measures are required to delineate the role of sleep restoration, circadian entrainment, and sleep-related daytime outcomes in the antidepressant effects of light. Although subjective measures have their limitations, the fact that scores on simple questionnaires could possibly predict treatment response suggests that further work should be done to assess whether such accessible tools may be used to orient the planning of sleep-related interventions in clinical settings.

Overall, the current findings reinforce the hypothesis that some of the underlying antidepressant mechanisms of light therapy concurrent with a progressive advance of wake-up time in youths with depression may possibly be linked to the restoration of sleep, circadian rhythms, and related daytime outcomes. Subjective sleep characteristics could conceivably predict treatment response and may thus represent a useful and accessible tool to orient treatment decisions.

Supplementary Material

Temporal Dynamics of Subjective Sleep Profiles Predicting Mood Improvements During Adjunctive Light Therapy Combined with Sleep-Rescheduling

S6. α-opic Equivalent Daylight (D65) Illuminances for the Light Emitting Glasses

Photoreceptor	**Photopigment**	**α-opic EDI**
Short-wavelength cones (S)	S-cone photopsin (cyanolabe)	262.80
Medium-wavelength cones (M)	M-cone photopsin (chlorolabe)	947.25
Long-wavelength cones (L)	L-cone photopsin (erythrolabe)	617.68
Rods	Rhodopsin	1303.91
ipRGCs	Melanopsin	1318.12

Photoreceptor weighted α-opic equivalent daylight (D65) illuminance (α-opic EDI) values (in lux) as per international standard CIE 026/E:2018. (CIE, S. (2018). 026/E: 2018. *CIE system for metrology of optical radiation for ipRGC-influenced responses to light. Vienna: Commission Internationale de l'éclairage*. Toolbox available at https://doi.org/10.25039/S026.2018.TB) ipRGCs: Intrinsically photosensitive retinal ganglion cells.

S7. Summary of multiple regression models

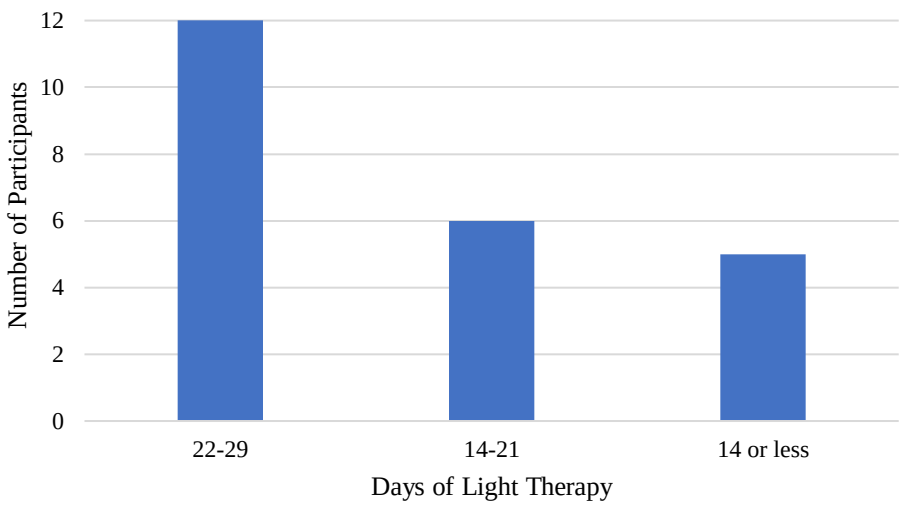
	Univariate Models						Multivariate Models					
	Coefficients		Full Model				Coefficients		Full Model			
	β	***p***	***F***	***df***	***p***	**Adj. R^2**	***β***	***p***	***F***	***df***	***p***	**Adj. R^2**
Early Relative Improvements on the BDI-II												
Overall model									6.3	2,21	0.007	0.37
Δ GTS	0.57	0.004	10.5	1,22	0.004	0.32	0.51	0.009				
Δ QOS	0.35	0.090	3.1	1,22	0.090	0.13	0.23	0.207				
Later Relative Improvements on the BDI-II												
Overall model									6.0	2,12	0.015	0.42
Δ AFS	0.36	0.193	1.9	1,13	0.193	0.13	-0.06	0.817				
Δ BFW	0.71	0.003	13.0	1,13	0.003	0.50	0.74	0.011				
Overall Relative Improvements on the BDI-II												
Overall model									3.7	2,14	0.053	0.25
BL-GTS	-0.53	0.028	5.9	1,15	0.028	0.28	-0.30	0.318				
BL-AFS	-0.54	0.025	6.2	1,15	0.025	0.29	-0.34	0.271				

Δ: Relative change scores calculated as the difference between two adjacent time points divided by the score at the initial time point: A) BDI-II (recalculated without the sleep items) and GCTI= [(Baseline – Follow-up 1)/ Baseline * 100] for the early intervention phase and [(Follow-up 1 – Follow-up 2)/ Follow-up 1 * 100] for the late intervention phase); B) LSEQ and FOSQ (higher scores reflect better positive outcomes) = [(Follow-up 1 - Baseline)/ Baseline * 100] for the early intervention phase and [(Follow-up 2 – Follow-up 1)/ Follow-up 1 * 100] for the late intervention phase.

S8. Light Projection from the Light Emitting Glasses

Reproduced with permission from Re-Timer Pty Ltd.

S9. Treatment Adherence



Reported number of days using light therapy glasses in the morning for 30 to 60 minutes across the four weeks intervention. Adherence data was missing for one participant. During the four weeks (28 days) of intervention, 12 participants (50% of the total sample) reported using the light therapy glasses in the morning for 30 to 60 minutes between 22 and 29 days, 6 participants (25%) reported using them between 14 and 21 days, and 5 participants (21%) reported using them on less than 14 days.

Study III

Light Therapy Associated with Sleep, Circadian and Mood Improvements in People with Mood Disorders; A Randomized Control Trial

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Abstract

Background: The different sub-types of depression and the various ways in which light can affect mood have clouded our understanding of the efficacy of light therapy for depression. This study explores whether the effects of light therapy are superior to that of a placebo while identifying potential sleep and circadian mechanism of action and treatment predictors.

Methods: Twenty-seven individuals in a major depressive episode (mean ± SD: 24 ± 5.6; 11% male) underwent two weeks of active green (500nm) light exposure and two weeks of a placebo condition in a cross-over design with a two-week washout period in-between. Before the intervention, they completed a semi-constant routine protocol and were instructed to use the light therapy glasses for 30 minutes to one-hour after their habitual sleep offset thereafter. Self-reported- and clinician-rated questionnaires on sleep and mood were done before and after each intervention arm. Actigraphy and skin temperature were collected continuously across the study.

Results: At the end of the study, more than 50% of participant where either unsure or believed that they had been allocated to an active infrared condition as opposed to a placebo infrared condition. There was a significant main effect of time on depression symptoms (reduction in symptoms from pre- to post-intervention; $F(1,22) = 12.6$, $p = .002$, $\eta p^2 = .36$), but no significant effect of Condition (active vs placebo). There was a trend for a Time*Condition interaction ($F(1,22) = 4.2$, $p = .053$, $\eta p^2 = .16$) in which improvements in depression symptoms were slightly greater in the active compared to the placebo condition. The degree of improvements in intrusive pre-sleep thoughts ($\beta = .52$, $p = .035$) and skin temperature rhythmicity ($\beta = -1.07$, $p = .032$) during the intervention were significantly correlated with improvements in mood. Short

REM latency (β = -.45, p = .047) and worst global subjective sleep (β = .53, p = .045) prior to the intervention was associated with improved mood. Overall, responders had higher minima, lower amplitude, and lower mesor of skin temperature compared to non-responders ($p < .05$).

Limitations: Small sample size and potential confounding effect of partial sleep deprivation.

Conclusions: Light therapy was found to yield mild antidepressant effects in people with depression, but these effects were variable from one individual to the next. Findings suggested that attenuation of pre-sleep cognition and the restoration of skin temperature rhythmicity may be involved in the mechanisms underlying the antidepressant effects of light therapy. Short REM latency and poor sleep may be possible predictors of treatment response. Larger studies are needed to disentangle the heterogeneous response to light therapy in people with non-seasonal depression.

Keywords: Light Therapy, Depression, Sleep

2.3.1 Introduction

The effects of light on various behavioural and physiological processes have been studied (Duffy & Czeisler, 2009; Lockley et al., 2006; Xiao et al., 2021). It is well established that light can have mood enhancing effects, and many mechanisms by which this may occur have been proposed, notably through direct and indirect pathways. Direct pathways involve the impacts of light on parts of the brain involved in emotion regulation, such as the amygdala (Legates et al., 2014). Through indirect pathways, which is the focus of the current study, light could improve mood by re-aligning disrupted circadian rhythms and/or restoring sleep (Germain & Kupfer, 2008; Vogel et al., 1980, 1990).

Sleep and circadian disruptions are thought to be involved in the pathogenesis of mood disorders. This is notably supported by experimental studies which demonstrated that delaying sleep onset causes a reduction in mood in healthy subjects (Surridge-David et al., 1987). It has long been proposed that the restoration of circadian rhythms can contribute to depression remission and relapse-prevention (Germain & Kupfer, 2008; Gorwood, 2010; Hickie et al., 2013; Monteleone et al., 2011; Wirz-Justice, 2009). Considering that light is the strongest synchroniser to entrain endogenous circadian rhythms to the 24-hour cycle, it is a strong chronotherapeutic tool.

The circadian phase delay, characteristic of the adolescent developmental period, is exacerbated in young people with emerging affective disorders (Robillard et al., 2013; Robillard et al., 2013). Abnormally flat circadian amplitude and disturbed timing of melatonin and body temperature rhythms have been observed in adults with depression (Mendlewicz et al., 1979; Nair et al., 1984). For instance, some studies observed a phase-advance of the evening rise in melatonin secretion (dim light melatonin onset; DLMO; Rubin et al., 1992) or of the nocturnal

melatonin peak (Beck-Friis et al., 1985; Nair et al., 1984), while others reported a delay in DLMO (Beck-Friis et al., 1985; Hasler et al., 2010), nocturnal melatonin peak (Crasson et al., 2004; Rubin et al., 1992), or morning melatonin offset (Tuunainen et al., 2002). These abnormalities in circadian rhythms are likely to worsen sleep disturbances commonly associated with depression. Although most of these studies integrated individuals from large age ranges (e.g., 23–67 years), a phase delay may be more frequent in adolescents and young adults with mood disorders (Robillard et al., 2013). Considering that the chronobiotic effects of bright light exposure are strongly influenced by the time of the day, with sleep and circadian rhythms being shifted earlier by morning light and later by evening light, exposing these groups of individuals to light in the morning may help advance their circadian rhythms to an earlier time, improve their sleep, and increase mood.

The efficacy of light therapy for mood improvement is well established in people with seasonal affective disorder (Rosenthal et al., 1988; Thalén et al., 1995). In the context of non-seasonal depression, while mild to moderate antidepressant effects have been reported following light therapy, the quality of the evidence remains low, and no clear factors have been found to properly explain the heterogeneity in treatment responses (Tao et al., 2020). Major depressive disorder is an illness with a wide range of possible presentations and aetiologies, which are likely to strongly influence the response to bright light exposure. For instance, if the antidepressant effects of light therapy are modulated by circadian and sleep functions, people with mood disorders who have a delayed rest-activity cycle or more severe sleep difficulties may have a better response to morning light therapy than those with more conventional circadian and sleep profiles. There is thus a need to investigate biomarkers to identify the best candidates for light therapy, and to better understand mechanisms of treatment response.

Another important methodological challenge in the design of studies assessing the effects of light therapy resides in the difficulty to create a valid placebo condition. Previous studies have used various placebos such as dim light, dim red light, dim yellow light, and normal room light (under 300lux) (Deltito et al., 1991; Fritzsche et al., 2001; Giedke & Bloching, 1989; Sit et al., 2018; Wirz-Justice et al., 1986). This being said, a study looking at melatonin suppression via light has warranted caution in interpreting such studies since even low levels of light are sufficient to supress melatonin levels (Prayag et al., 2019). More robust methods to create placebo conditions are required to fully disentangle the antidepressant effects of light therapy. One published article proposed that infrared light has positive impacts on mood and circadian rhythms in seasonal depression (Meesters et al., 1999). Furthermore, studies using animal models of depression suggested that infrared radiation has potential antidepressant effects (Tanaka et al., 2011; Tsai et al., 2007). Since infrared light is non-detectable to the human eye, these studies opened the door to create a credible rationale for a placebo condition in which participants could be led to believe that they are being exposed to active but non-visible light.

The aims of this study are to establish whether antidepressant effects of light therapy are superior to that of a placebo condition (Objective 1), to determine predictors of treatment response and potential mechanisms of action nested within sleep and circadian physiology (Objective 2), and to identify accessible screening tools that may predict treatment response (Objective 3). It is hypothesised that:

Objective 1 – There will be a greater decrease from pre- to post-intervention in depression symptom severity in the active light therapy condition as compared to the placebo condition.

Objective 2 – Improvement on circadian and sleep variables across the intervention will parallel mood improvements. Individuals with more desynchronized circadian rhythms and sleep disturbances at baseline will be those with the highest decrease in depression symptoms following light therapy.

Objective 3 –A combination of more accessible self-report and ambulatory measures will predict treatment response to light therapy.

2.3.2 Methods

Participants

Young individuals with unipolar mood disorders were recruited from the Royal Ottawa Mental Health Centre (ROMHC) through posters, clinician referrals, and waitlists. All participants met the following entry criteria which was assessed by a clinician or clinical student: between 13 and 35 years of age, at least mild depression symptoms on the self-rated version of the Quick Inventory of Depressive Symptomatology (QIDS-A_{17}-SR; Score $\geq$6, ;Rush et al., 2003), and met criteria for a major depression episode as defined by the M.I.N.I. International Neuropsychiatric Interview 7.0.2 for DSM-5 (American Psychiatric Association, 2013).

Participants were excluded if they had any evidence of: a sleep disorder (except for insomnia and circadian disorders); medical conditions that could explain the current depression (e.g., chronic pain, cancer), contribute to the sleep-wake difficulties, or pose risks associated with bright light exposure; a formal diagnosis of seasonal affective disorder, psychotic disorder, PTSD and/or rapid-cycling bipolar disorder; being currently in a euthymic, manic, or mixed episode (based on psychiatric assessment); significant alcohol or other substance dependence; medications that increased the risk of photoallergic reactions and/or taking hypnotics,

benzodiazepines, or neuroleptics; shift-work involving overnight shifts or recent travel to a different time zone. None of the participants started medications that could affect sleep, circadian rhythms, and/or alertness within the month preceding study start.

Written informed consent was provided by all participants and assent was sought from parents or legal guardians if participants were under the age of 16 years. The study was approved by the Research Ethic Board of the Institute of Mental Health Research (REB #2015007).

Procedures

A. Baseline Assessment

Ambulatory Sleep and Circadian Monitoring

Skin temperature, wrist actigraphy, and a sleep log were used to monitor changes in skin temperature and the rest-activity cycle throughout the study (i.e., starting 7-days before the first intervention arm and ending with the last intervention arm).

In-laboratory Sleep and Circadian Assessment

Participants attended the laboratory 5 hours prior to their habitual sleep time to undergo a semi-constant routine protocol under controlled light exposure (i.e., below 10 lux), posture (i.e., semi-recumbent in a comfortable chair), movement and food intake to derive circadian metrics before and after polysomnography. The timing of all measurements was based on the individual's mean actigraphic sleep schedule over the week prior to intervention.

Throughout the constant routine, participants wore an actigraphy device which measured movement and light exposure. Core body temperature (CBT) was also measured using an ingestible capsule-size sensor. Participants were allowed to eat light snacks served at room

temperature during that period, but they were not to drink coffee, tea, or other caffeinated products. Participants also completed their baseline questionnaires during this time.

Starting 4.5 hours before their habitual sleep time, participants were asked to remain seated and awake in a controlled light environment. Eleven saliva samples were collected every 30-minutes until 1-hour past habitual sleep time, which created a 1-hour phase shift of bedtime. After the last saliva sample, participants were invited to sleep until their habitual wake up time. During this period, their sleep was recorded with polysomnography. Morning saliva samples were collected upon awakening and 10, 20, 30, 40, 60 minutes after waking up. Saliva samples were centrifuged and frozen for subsequent analysis of melatonin concentration.

B. Intervention

Following baseline assessment, all participants underwent two intervention arms in a cross-over design following a randomized counterbalanced order: two weeks of active light therapy with green light and two weeks of placebo intervention. During both treatment arms, participants completed a sleep, mood, and light exposure log to track changes and monitor adherence to the treatment schedule. Prior to starting the first arm, participants watched a 10-minute educational video on the effects of light, and specifically infrared light, on the biological clock and mood with the aim to maximise treatment expectancies uniformly across participants and intervention arms.

In both the active and placebo condition, all participants were lent a pair of light emitting glasses (RE-TIMER, Re-Time Pty Ltd, Australia; blue-green 500 nm dominant wavelength; 506 Lux lm/m^2; α-opic equivalent daylight (D65) illuminance values can be found in Table S10 and a photograph of the glasses in Figure S11) to use at home every day for two weeks. They were

instructed to wear the light glasses for 45 to 60 minutes starting 5 to 20 minutes following their individual habitual wake up time as determined by actigraphy at baseline. However, in the placebo condition, they were deceptively told that these glasses emit infrared light, which is invisible to the human eye. These placebo glasses did not emit any light (when pressing the 'on' button, participants activated the same visual indicator as in the active condition informing them that the glasses are "turned on", but the light output was deactivated).

The active and placebo interventions were separated by a two-week wash-out period (i.e., without using the glasses). Half of the participants started with the placebo condition and the other half started with the active condition. Randomization to the two condition orders was stratified by sex and age (13-18 years old, 19 to 25 years old, and 25 to 35 years old) and was conducted by a research assistant not involved in any other aspect of this project. Across both arms and the entire study, all participants remained engaged in their ongoing treatment.

C. Deception

Considering the aim of creating a credible placebo condition while keeping the deception level as low as possible, participants were told (both verbally and via the study information statement) that they would undergo both an active and a placebo intervention but based on a slightly different protocol than the one that effectively took place.

Participants were misled to believe that this study investigated the effects of light therapy based on green light and infrared light exposure as compared to two different placebo conditions: using "placebo green" or "placebo infrared" glasses designed to look exactly the same as the real green or infrared glasses when they are turned on, but in which the most active components of the light was deactivated so that they were no longer effective. Half of the participants were told

that the green light was the active condition, and the infrared light was the placebo condition, while the other half of the participants were told that the infrared light was the active condition, and the green light was the placebo. Participants were told that they would be randomly allocated to one of the following four groups:

a) starting with active infrared light followed by ‘placebo green light’,

b) starting with ‘placebo green light’ followed by active infrared light,

c) starting with active green light followed by ‘placebo infrared light’,

d) starting with ‘placebo infrared light’ followed by active green light.

However, all participants were only allocated to either group c) or d). See Figure 7 for details.

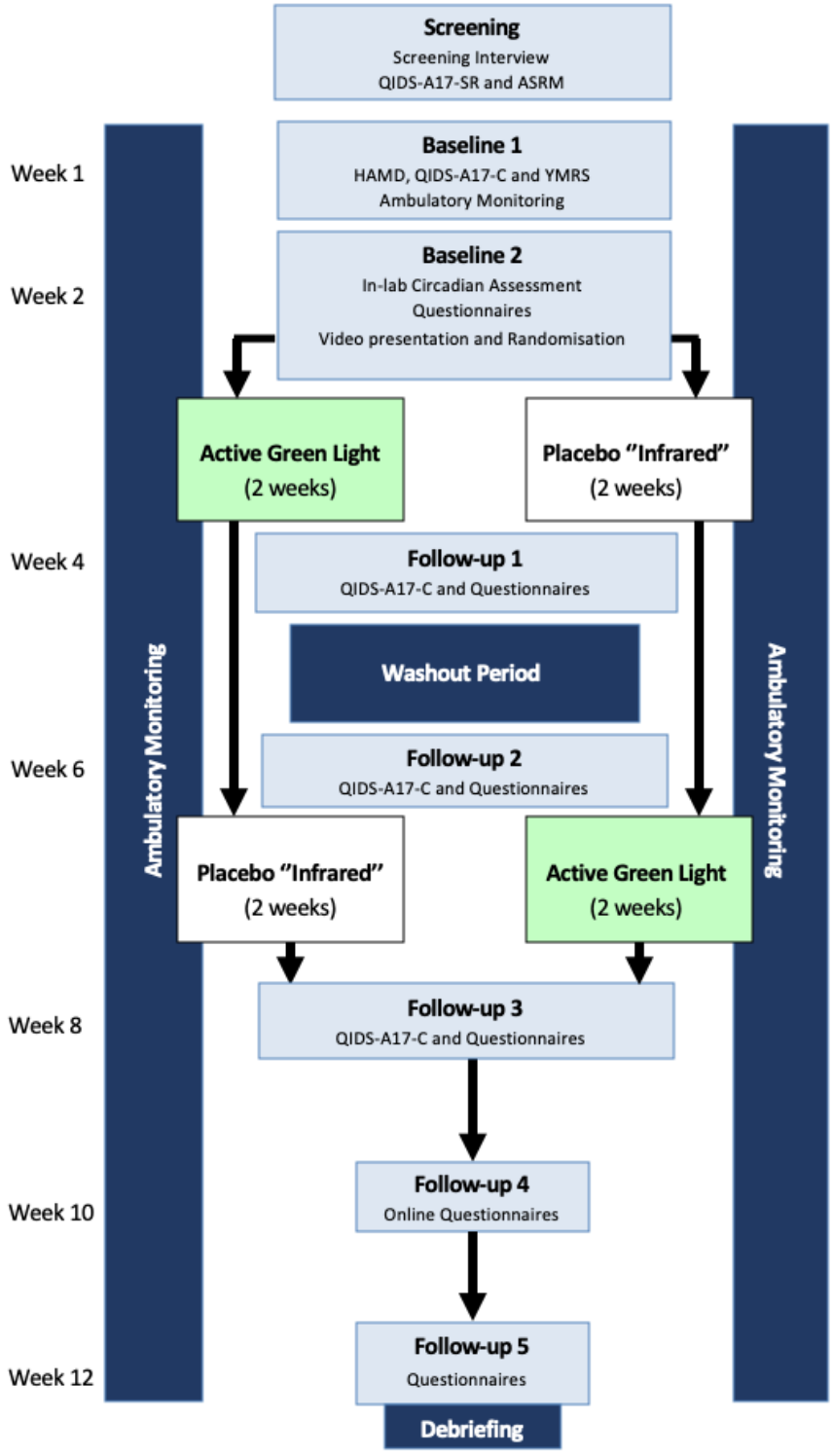


Figure 7. Crossover design protocol

D. Follow-up assessments

Immediately before and after each intervention arm, participants visited the research site to undergo a psychological assessment and fill out some questionnaires (see table 6). After each intervention arm, participants underwent monitoring of possible side effects. Following the completion of the second arm, participants underwent a debriefing session.

E. Assessment of the effectiveness of the placebo condition and debriefing

To try to estimate the level of credibility of the placebo condition, questionnaires were administered to assess treatment expectations before each intervention arm (at BL and FUP2), and treatment satisfaction after each intervention arm (at FUP1 and FUP3). Questionnaires about nocebo/placebo effects were also administered at the end of the second condition.

Measurements/ Materials

Questionnaires/Assessments

The following assessment scales and questionnaires were administered at the time points highlighted in table 6.

Table 6. Assessment scales and questionnaires at each study time points

	BL (W1-2)	FUP1 (W4)	FUP2 (W6)	FUP3 (W8)
Assessment Scales				
Modules A, C and AY of the M.I.N.I.	X			
QIDS-A17-C	X	X	X	X
Questionnaires				

GCTI	X			
LSEQ	X	X	X	X
MEQ	X	X	X	X
FOSQ	X			
FSS	X			
PSQI	X			

BL: Baseline, FUP: Follow-up, W: Week. Quick Inventory of Depressive Symptomatology clinician based (QIDS-A17-C), The Glasgow Content of Thoughts Inventory (GCTI), Leeds Sleep Evaluation Questionnaire (LSEQ), Horne-Ostberg questionnaire (MEQ), Functional Outcomes of Sleep Questionnaire (FOSQ), Fatigue Severity Scale (FSS), Pittsburgh Sleep Quality Index (PSQI).

Modules A, C and AY of the M.I.N.I.

The M.I.N.I. International Neuropsychiatric Interview 7.0.2 for DSM-5 (D Sheehan, 2016) is a standard structured clinician-based assessment tool commonly used in clinical trials to confirm psychiatric diagnoses. It uses a decision-tree structure to assess the diagnostic criteria for mental disorders based on DSM-5 criteria. Its general content has been validated with a Cohen's kappa of 0.84, sensitivity of 0.96, and specificity of 0.88 for major depressive disorder (Sheehan et al., 1998). Modules A (major depressive episodes), C (manic and hypomanic episodes), and AY (persistent depressive disorder) were used to confirm current diagnoses at study enrollment.

Quick Inventory of Depressive Symptomatology (QIDS-A17-C)

This version of the QIDS has been designed to account for some of the atypical symptoms of depression more commonly found during youth. Focussing on the past week, it contains 17 items for which respondents are asked to rate the severity of symptoms such as sleep disturbances (either reductions or increases in sleep), sadness, irritability, appetite, and weight

changes (either reductions or increases), and restlessness. Internal consistency for the QIDS-A17-C was found to be high (a = .84; Haley, 2009).

The Glasgow Content of Thoughts Inventory (GCTI)

The 25-item GCTI (Shahid et al., 2011) was used to assess the content, character, and intrusiveness of cognitions occurring prior to sleep initiation in the prior week. The GCTI was found to have an internal consistency of .87 and a test re-test reliability of .88 (Harvey & Espie, 2004).

Leeds Sleep Evaluation Questionnaire (LSEQ)

The LSEQ is a 10-item analogue scale with four subscales: *getting to sleep (GTS), quality of sleep (QOS), awake following sleep (AFS),* and *behavior following wakefulness (BFW)* (Parrott and Hindmarch 1980). Internal consistency has been reported to range from $\alpha = 0.78$ to 0.92 (Tarrasch et al., 2003).

Horne-Ostberg Morningness Eveningness Questionnaire (MEQ)

The Horne-Ostberg morningness-eveningness Questionnaire (J. A. Horne & Östberg, 1976) is a 19-item questionnaire evaluating the time at which one feels most alert, and prefers to go to sleep, wake-up and conduct different types of activities. It generates a total score ranging between 16 and 86, with higher scores reflecting stronger ‘morningness’. MEQ scores between 86 and 70 are considered to reflect ‘definite/extreme morning’ chronotype, 69-59 to reflect ’moderate morning’ chronotype, 58-42 to reflect ‘intermediate’ chronotype, 41-31 to reflect ‘moderate evening’ chronotype, and 30-16 to reflect ‘definite/extreme evening’ chronotype. All

items were found to be homogenous and with a high internal consistency of .82 (C. S. Smith et al., 1989).

Functional Outcomes of Sleep Questionnaire (FOSQ)

This questionnaire has 30 items assessing the impacts of sleepiness or tiredness on behaviors pertaining to physical, mental, and social daily activities. For each item, respondents are asked to rate the severity of these impacts using the following scale: 0 = I don't do this activity for other reasons, 1 = Yes, extreme, 2 = Yes, moderate, 3 = Yes, a little, 4 = No. Five subscales are generated when scoring including: Activity Level, Vigilance, General Productivity, Social Outcome, and Intimacy and Sexual Relationships. The internal reliability of these subscales has been found to be $\alpha = 0.86$ to 0.91 and the total score to be $\alpha = 0.95$. Test-retest reliability has been found to range from $r = 0.80$ to 0.90 for the subscales and $r = 0.90$ for the total score (Weaver et al., 1997).

Fatigue Severity Scale (FSS)

Compared to other fatigue scales, this brief questionnaire has been reported to generate a more comprehensive measure of fatigue-related severity, symptomatology, and functional disability. It is based on the past week and includes 9 items for which various aspects of fatigue are rated from 1 ('strongly disagree') to 7 ('strongly agree') and a 10^{th} item rating general fatigue on a scale ranging from 0 ('worst') to 10 ('normal'; Krupp et al., 1989). Internal consistency has been reported as $\alpha = 0.929$ and test-retest correlation as $r = 0.916$ (Chung & Song, 2001).

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a 24-item questionnaire based on the last two weeks, with a seven-component score ranging from 0 – 21 points, was initially developed to assess sleep disturbances related to mood disorders and is currently one of the most widely used sleep questionnaires for various clinical populations, notably insomniacs. A global score higher than 5 is indicative of significant sleep disturbances. Research has shown that the PSQI has a high degree of internal consistency (Cronbach's $\alpha = 0{\cdot}83$), sensitivity (89·6%), and specificity (86·5%) in distinguishing good and poor sleepers. It was also found to have high test-retest reliability ($r = 0{\cdot}85$, $p < 0{\cdot}00$; Buysse et al., 1989).

Ambulatory Measures

Actigraphy

Micro Motionlogger watches were used for actigraphy monitoring (Ambulatory Monitoring Inc., Ardsley, NY, USA; AMI). This Actigraph model allowed for simultaneous data collection of activity, ambient light, and off-wrist detection over several days. The watch was set to 1-minute epochs to maximise battery life. Data was manually scored, and off-wrist periods were removed. Action-W Version 2.7.3045 software (AW2.7; Ambulatory Monitoring Inc., Ardsley, USA) was used to generate sleep parameter estimates such as Total Sleep Time (TST; the total amount of minutes spent asleep), Sleep Efficiency (SE; the percentage of time spent sleeping during a given sleep period), and Sleep Onset/Offset (the time of falling asleep and waking up). A custom MATLAB script for extended cosinor models was used to calculate parameters such as the acrophase (the time at which the fitted curve reaches its peak), circadian

rhythmicity (a goodness of fit measure between the data and the fitted curve), and amplitude (difference between the peak and through of the fitted curve; Marler et al., 2006).

Peripheral Body Temperature

Thermochron iButtons (iButtonLink, LLC, Whitewater, USA) were used to monitor peripheral body temperature. The iButton was placed on the non-dominant side of the abdomen, near the navel. A numerical method was implemented to preprocess the skin temperature recordings. Most of the artifacts were mainly due to sensor displacement or disconnection. Large segments containing aberrant temperature were manually removed, then an algorithm was implemented to correct short, abrupt temperature drops and transients. This algorithm is based on the "LOESS smoother" and computes the trend from a locally weighted regression that smooths local transients in the recordings (Cleveland et al., 1990). The fluctuations with amplitude larger than the mean of the negative fluctuations were considered as missing data, whereas positive fluctuations larger than 3 degrees Celsius were identified as artifacts and marked as missing data. These missing temperatures were then estimated with a local interpolation. The final signal was then obtained with a moving local averaging smoother (11-point window) over the entire recording (Fronczek, 2008). Data was then submitted to an extended cosinor model to derive the acrophase and circadian rhythmicity index (Marler et al., 2006).

Sleep Log

A custom sleep log was created with 3 sections (to complete when waking up, during the day, and before going to sleep). It contained questions relating to sleep, mood, and social activities. It also asked participants to log treatment details such as time and duration of treatment. The sleep log was utilized consistently across the 12 weeks of the study (de Alcantara

Borba et al., 2020) and was used as a validation tool for scoring actigraphy and to confirm treatment adherence.

In-Lab Measures

Saliva Collection

Saliva was collected using Salivettes® (Starstedt AG & Co., Nümbrecht, Germany) to measure cortisol and melatonin concentrations. Samples were centrifuged for 10minutes and frozen in -20°C before being transferred and stored into a -80°C freezer. Samples were assayed in duplicate using ELISA (Novolytix, Switzerland). The mean detection threshold was 0.20±0.05 pg/mL and the coefficients of variability were <10 and <15 for Intra- and Inter-assay %CV respectively. DLMO was defined as the time when melatonin concentration reached a threshold of 3pg/mL and remained above this threshold for the next three samples. Evening and morning melatonin levels were characterised using the area under the curve computed with the trapezoid method in the samples collected within 60 minutes of each individual bedtime and in the 40 minutes following awakening in the morning.

Core Body Temperature (VitalSense Pill)

The Philips VitalSense ® (Mini Mitter Co., Inc., Bend, OR, USA) temperature capsule was used to collect core body temperature. The capsule passes through the gastrointestinal tract and collects and transmits body temperature 4 times per minute for a period of 12-48hours. The device was found to be as accurate as a rectal probe monitor and was better accepted by participants (McKenzie & Osgood, 2004). To extract the Nadir value from the previous temperature signal, a 3rd-degree polynomial fit was applied from which the minimum temperature value and its

corresponding time were analytically computed to obtain the Nadir parameters. To evaluate the goodness of fit, the statistical R^2 parameter was computed. This parameter is defined by the given function, $R^2 = 1- (RSS/TSS)$, where *RRS* corresponds to the sum of squares of residual and *TSS* corresponds to the total sum of squares of the data. This parameter is between 0 and 1. Better the fit is, closer to 1 is the parameter value.

Polysomnography

Level 1 Polysomnography (PSG) was acquired with two systems. Some participants underwent PSG at a sampling rate of 500 Hz using the Embla N7000 system and RemLogic software (Natus Medical Incorporated, San Carlos, CA, USA). Loose electrodes were placed according to the 10-20 system with: 13 scalp electroencephalogram (EEG) channels (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, O1, O2, A1, and A2), ground and reference channels, right and left electrooculograms (EOG), and 2 chin electromyograms (EMG). Respiration was monitored with 2 respiratory effort belts. Other participants underwent PSG at a sampling rate of 500 Hz using a 128-channel EEG cap (Braincap, Brain Products Gmbh, Germany) connected to four MR-compatible 32-channel amplifiers (Brainamp, Brain Products Gmbh, Germany). The montage also included a ground, and 2 EOG leads. The FCz channel was used as the active EEG reference. Skin resistance was reduced to below 5 KOhm for EEG channels and below 10 KOhm for other channels. Signals were acquired with BrainVision Recorder software (Brain Products Gmbh, Germany). A registered sleep technologist performed sleep stage scoring in accordance with the American Academy of Sleep Medicine guidelines (Berry et al., 2016). Total sleep time and sleep efficiency (ratio of total sleep time to the time spent in bed) were computed.

Statistics

Statistical analyses were conducted with the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 23.0. Armonk NJ, USA). Descriptive analyses were done to capture rates of adherence, treatment expectation, as well as pre-intervention sample characteristics, mental health, and sleep profiles.

For the main analyses, all data was curtailed to 1.5 SD to handle outlying values. Normality was then assessed with the Shapiro-Wilk test and log or square root transformations were used to improve normality when required. Analyses were done with an intention to treat framework and effect sizes were calculated for all analyses.

Objective 1. Effects of Light Therapy as Compared to a Placebo Condition

Minimal clinically important differences in depression symptoms were computed based on a 2-point reduction on the QIDS-A17-C (Hedayati et al., 2017; Walther et al., 2017). QIDS-A17-C scores were also submitted to a repeated measures analyses of covariance (ANCOVA) with two within-subject factors: Time (pre- versus post-intervention arm) and Condition (Placebo versus Active light therapy) while controlling for the intervention order (placebo first and active second versus active first and placebo second). Interactions were decomposed using paired t-tests.

Objective 2. Predictors of Treatment Response and Potential Mechanisms of Action

To investigate associations between changes in mood (i.e., QIDS-C-17 relative change score calculated from baseline to post-intervention) and circadian/sleep improvements along the course of the active intervention, two multiple regression models (adjusted for the intervention

order) were run on metrics amenable to field measurements, one focused on sleep and one focused on circadian rhythms. The sleep model was designed to assess the potential contribution of changes in factors reflecting sleep initiation and sleep maintenance problems (Predictors: changes in pre-sleep arousal (i.e., GCTI), changes in the ease of getting to sleep (LSEQ GTS), and changes in sleep efficiency (actigraphy)). The circadian model was designed to assess the potential contribution of changes in the timing and robustness of two circadian rhythms (Predictors: acrophase and circadian rhythmicity index (R2) of the rest-activity and peripheral body temperature rhythms).

To determine predictors of treatment response, multiple regression analyses will assess whether longitudinal improvements in depression (i.e., QIDS-A17-C relative change score calculated from baseline to post-intervention) in the active intervention arm can be predicted by baseline in-laboratory physiological measures (collected prior to any intervention). Due to the limited sample size, two models were run (adjusted for the intervention order): i) Sleep model (Predictors: total sleep time and sleep efficiency (both from polysomnography), and ii) Circadian timing model (predictors: time of DLMO, time of the nadir of core body temperature (CBT), and latency to REM Sleep).

Objective 3 (Identify accessible predictors of the antidepressant response to light therapy)

To determine whether treatment response can also be predicted by more accessible baseline measures, two multiple regression models (adjusted for the intervention order) were computed: i) Sleep model (Predictors: baseline scores for GCTI, LSEQ GTS and PSQI)), and ii) Circadian timing model (predictors: baseline acrophase and circadian rhythmicity index (R^2) from actigraphy and peripheral body temperature) to assess whether these more accessible

metrics are predictive of improvements in depression (i.e. QIDS-C-17 relative change score calculated from baseline to post-intervention arm) in the active intervention arm. A partial correlation (adjusted for the order of the intervention arms) was also conducted between pre-intervention HO scores and improvements in depression.

Exploratory analyses were conducted to compare more comprehensive baseline circadian profiles across the subgroup of participants who underwent an MCID to those who did not based on the following parameters: acrophase, amplitude, mesor and circadian rhythmicity index (R^2) of the rest-activity cycle and peripheral temperature rhythms.

2.3.3 Results

Sample Characteristics

Table 7 reports demographic and clinical characteristics. Overall, this sample ranged from 16 to 35 years of age and contained 89% females. The mean QIDS-A17-C score fell within the range for moderate depression. Most participants (78%) were using psychotropic medications (see details in table 7), and about half of the sample was undergoing psychotherapy at the time of study enrolment. All but one participant had a PSQI score suggestive of significant sleep disturbances, yet there was high inter-individual variability in actigraphic sleep estimates.

Table 7. Sample characteristics

	Count	%	Min	Max	Mean	SD
Demographic and clinical factors						
Age (years)			16.0	35.0	24.0	5.6
Sex (Females vs Males)	24	89%				
QIDS-A17-C			5.0	17.0	12.7	3.5
Comorbid anxiety disorder	15	60%				
Using psychotropic medication	21	78%				
Engaged in psychotherapy	14	52%				

Circadian preference						
Morning Type	2	10%				
Intermediate Type	13	65%				
Evening Type	5	25%				
MEQ Total Score			35.0	70.0	47.4	8.0
Actigraphic Sleep Estimates						
Rest Onset time (Clock time)			20:59	27:17	24:17	1:25
Rest Offset time (Clock time)			5:21	13:58	8:39	1:56
Sleep Efficiency (%)			50.1	98.8	88.2	10.9
Total Sleep time (hours			4.0	10.1	7.2	1.5
Sleep Factors						
GCTI			1.0	53.0	29.9	13.9
Pittsburgh Sleep Quality Index (PSQI)						
PSQI above threshold	26	96%				
PSQI Total Score			3.0	14.0	9.0	2.8
LSEQ Subscales						
Getting To Sleep			2.3	4.3	3.1	0.6
Quality Of Sleep			1.0	4.0	2.3	0.8
Ease of Awakening from Sleep			1.0	5.0	2.3	1.1
Behaviour Following Wakefulness			1.3	3.7	2.1	0.5
Diurnal impacts of sleep problems						
Functional Outcomes of Sleep Questionnaire (FOSQ)						
FOSQ Total Score			1.3	3.9	2.9	0.6
FOSQ subscales						
General Productivity			1.5	4.0	2.9	0.6
Social Outcome			1.0	4.0	2.8	0.8
Activity Level			1.3	3.8	2.5	0.7
Vigilance			1.4	4.0	3.1	0.6
Intimate Relationships and Sexual Activity			1.0	4.0	3.0	1.0
Fatigue Severity Scale (FSS)						
FSS above threshold	11	41%				
FSS Total Score			1.8	5.0	3.8	0.7

Quick Inventory of Depressive Symptomatology clinician based (QIDS-A17-C), The Glasgow Content of Thoughts Inventory (GCTI), Leeds Sleep Evaluation Questionnaire (LSEQ), Horne-Ostberg questionnaire (MEQ), Pittsburgh Sleep Quality Index (PSQI). Functional Outcomes of Sleep Questionnaire (FOSQ). Fatigue Severity Scale (FSS). MEQ data was missing for 7 participants.

Placebo perceptions and adherence to the intervention

At the end of the study, participants were asked which one of the intervention arms they thought were the active and placebo condition and less than 50% of participants believed the green light condition (active) was the active condition.

On average, the total number of sessions lasting over 30 minutes and within four hours of waking up was 10±3.6 in the active condition (ranging from 2 to 15 sessions) and 11.7+2.3 in the placebo condition (ranging from 7 to 16 sessions). In the active condition, 89% (24/27) participants completed at least 5 sessions of light therapy lasting over 30 minutes within the prescribed time window.

Effects of Light Therapy on Mood as Compared to a Placebo Condition

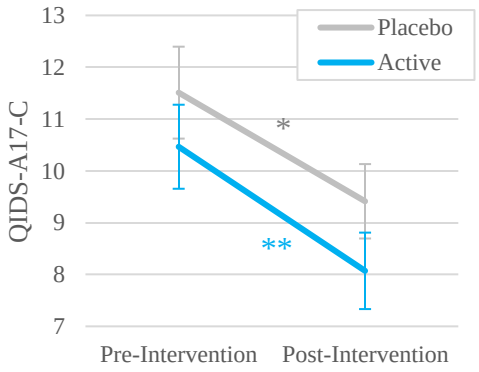
In the active condition, 74.1% (20/27) of participants underwent a minimal clinically important reduction in depression symptoms relative to baseline as assessed by the QIDS-A17-C. Depression symptoms severity as assessed by the QIDS-A17-C before and after the placebo and active condition are presented in table 8 and figure 8. The ANCOVA controlling for the intervention order revealed a significant main effect of Time, in which QIDS-A17-C scores decreased significantly from pre- to post-intervention ($F(1,22) = 12.6$, $p = .002$, $\eta p^2 = .36$). The main effect of Condition did not reach statistical significance ($F(1,22) = 0.1$, $p = .918$, $\eta p^2 < .01$). A non-significant trend was observed for the *Time*Condition* interaction ($F(1,22) = 4.2$, $p = .053$, $\eta p^2 = .16$). Specifically, QIDS-A17-C scores decreased significantly from pre- to post-intervention in both conditions, but this effect was slightly more pronounced in the active condition ($t(26) = 3.5$, $p = .002$, Cohen's $d = .67$) than in the placebo condition ($t(23) = 2.6$, $p = .015$, Cohen's $d = .53$).

Table 8. Effect of light therapy

	Pre-Intervention			Post-Intervention			Contrasts decomposition		
	n	Mean	*SD*	*n*	Mean	*SD*	*t(df)*	*p*	Cohen's *d*
Placebo	24	11.0	4.2	22	8.9	3.5	2.6(23)	.015	.53
Active	24	10.0	4.0	24	7.6	3.6	3.5(26)	.002	.67

Values represent scores for the QIDS-A17-C: Clinician-rated Quick Inventory of Depressive Symptomatology for Adolescents. Pre-intervention: before the intervention arm. Post-intervention: after the intervention arm.

Figure 8. Global changes in depression symptoms

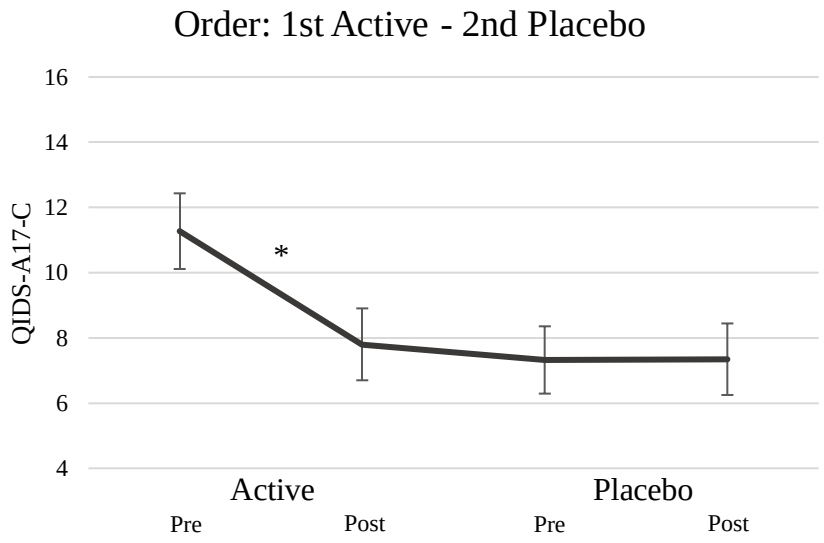


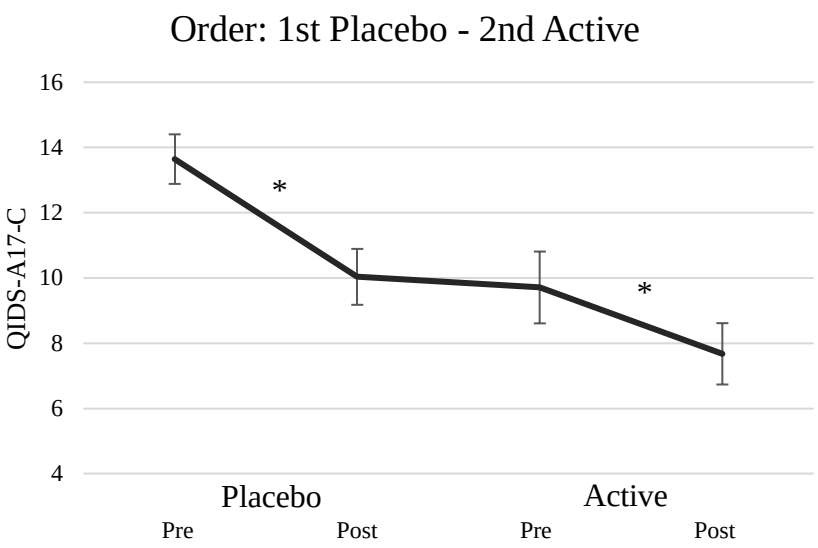
QIDS-A17-C: Clinician-rated Quick Inventory of Depressive Symptomatology for Adolescents. Pre-intervention: before the intervention arm. Post-intervention: after the intervention arm. Error bars indicate Standard Error of the Mean. *: p = .015, Cohen's d = .53 . **: p = .002, Cohen's d = .67

Since there was a trend for the *Time*Condition*Order* interaction term ($F(1,22) = 4.2$, $p = .053$, $\eta p^2 = .16$), secondary analyses were conducted to assess the influence of the intervention order on these effects. Figure 9 shows QIDS-A17-C scores before and after the placebo and active condition based on the order in which they occurred. In both order groups, there was a significant decrease in depression symptoms from pre-intervention to post-intervention in the first intervention arm (i.e. regardless of whether this was the placebo ($t(13) = 3.9$, $p = .002$, Cohen's $d = 1.0$) or active ($t(10) = 2.3$, $p = .041$, Cohen's $d = .70$) intervention). However, in the second intervention arm, the active condition decreased depression symptoms ($t(15) = 2.7$, $p = .018$, Cohen's $d = 0.67$), whereas there was no such effect in the placebo condition ($t(9) = -0.02$,

p = .985, Cohen's d < .01). Sensitivity analyses confirmed that these effects persisted if only including participants with at least 4 days of light therapy with the target timing and duration (supplemental material S12.). These effects also persisted when excluding the sleep items from the QIDS-A17-C total scores (supplemental material S12.). None of these effects survived adjustment for sex or age.

Figure 9. Changes in depression symptoms stratified by intervention order





QIDS-A17-C: Clinician-rated Quick Inventory of Depressive Symptomatology for Adolescents. Error bars indicate Standard Error of the Mean. Pre: before the intervention arm, Post: after the intervention arm. *p<.050

Potential Mechanisms of Action and Predictors of Treatment Response

Associations between mood and sleep improvements

Coefficients from the multiple linear regression models assessing how relative changes in depression symptoms during the active intervention relate to changes in sleep and circadian factors (adjusted for the order of the intervention arms) are presented in Table 9.

The model based on changes in sleep factors predicted 31% of the variance in depression symptoms improvements (adjusted R^2 = .12). Higher mood improvement (decrease in QIDS-A17-C from baseline to post-intervention) was significantly associated with higher improvement in pre-sleep cognitions (i.e., decrease in GCTI scores from baseline to post-intervention; β = .52, p = .035). Changes in mood were not significantly associated with changes in sleep efficiency (β =.04, p = .864) or in the ease to fall asleep as reflected by the LSEQ GTS subscale (β = -.14, p = .517).

The model based on changes in circadian factors predicted 74% of the variance in depression symptoms changes (adjusted R^2 = .41). Higher improvement in circadian rhythmicity of peripheral body temperature (i.e., an increase in the Cosinor model fit from baseline to post-intervention) was significantly associated with higher mood improvements (i.e., decrease in QIDS-A17-C from baseline to post-intervention; β = -1.07, p = .032). There was no significant association between changes in depression symptoms and the acrophase of peripheral body temperature (β = -.10, p = .342), nor in the acrophase (β = .08, p = .770) or circadian rhythmicity (β = .65, p = .112) of the activity-rest cycle.

Similar results were observed when excluding the sleep items from the QIDS-A17-C scores, except that a new significant association emerged between lower improvement in circadian rhythmicity of the activity-rest cycle (i.e., a decrease in the Cosinor model fit from baseline to post-intervention) and higher mood improvements (i.e., decrease in QIDS-A17-C from baseline to post-intervention; β = .75, p = .020).

Table 9. Associations between depression improvements following active light therapy and sleep and circadian changes.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*
Sleep Model						
Intervention Order	2.96	13.18	-25.14	31.06	0.05	0.825
GCTI total score (per 1 point)	0.30	0.30	0.30	0.30	0.52	0.035
LSEQ GTS (per 1 point)	-1.65	2.48	-6.94	3.64	-0.14	0.517
Sleep Efficiency (per 10%)	1.69	97.17	-190.23	223.99	0.04	0.864
Circadian Model						
Intervention Order	26.53	17.50	-22.06	75.12	0.45	0.204
Actigraphy						
Acrophase (per hour)	0.20	0.64	-1.58	1.98	0.08	0.770
Circadian Rhythmicity (R^2)	46.36	22.83	-17.04	109.75	0.65	0.112
Peripheral Temperature						
Acrophase (per hour)	-4.70	13.71	-42.77	33.38	-0.10	0.749
Circadian Rhythmicity (R^2)	-39.40	12.23	-73.36	-5.44	-1.07	0.032

DV: relative change in QIDS-A17-C from baseline to after active intervention arm. Sleep efficiency based on actigraphy. SE: Standard error of B, CI: Confidence interval, LL: lower limit, UL: upper limit, DLMO: dim light melatonin onset, CBT: core body temperature, REM: rapid eye movement sleep. The Glasgow Content of Thoughts Inventory (GCTI). Leeds Sleep Evaluation Questionnaire (LSEQ) – Getting To Sleep (GTS).

Objective sleep and circadian predictors of treatment response

Coefficients from the multiple linear regression models assessing whether initial sleep and circadian characteristics (measured at baseline, prior to the intervention start) were associated with relative changes in depression symptoms occurring during the active light therapy intervention (adjusted for the order of the intervention arms) are presented in Table 10.

The model based on baseline polysomnographic sleep characteristics predicted 17% of the variance in subsequent depression symptoms changes (adjusted R^2 = .047). Neither total sleep time (β = .37, p = .120), nor sleep efficiency (β =.30, p = .222) were significantly associated with changes in depression symptoms.

The model based on baseline endogenous circadian characteristics predicted 24% of the variance in depression symptoms changes occurring during the active light therapy intervention (adjusted R^2 = .076). Shorter latency to REM sleep was significantly associated with higher improvements in depression symptoms along the course of the active intervention (β = -.45, p = .047). This effect became a trend when the model was applied to QIDS-A17-C scores recalculated without the sleep items (β = -.42, p = .063; see further details in supplemental material S12.). No significant association was found for DLMO (β = .15, p = .534) or CBT nadir (β = -.03, p = .905).

Table 10. Associations between initial sleep and circadian profiles and depression changes following active light therapy.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*

Sleep Model						
Intervention Order	21.13	13.21	-6.42	48.68	0.36	0.125
Total Sleep Time (per min)	0.14	0.09	-0.04	0.33	0.37	0.120
Sleep Efficiency (per log 10%)	13.56	10.76	-8.87	36.00	0.30	0.222
Circadian Model						
Intervention Order	20.30	12.43	-5.72	46.33	0.35	0.119
DLMO (per log hour)	92.52	145.90	-212.86	397.89	0.15	0.534
CBTnadir (per log hour)	-12.62	103.92	-230.13	204.90	-0.03	0.905
REM Latency (per log min)	-28.32	13.34	-56.23	-0.40	-0.45	0.047

DV: relative change in QIDS-A17-C from baseline to after active intervention arm. Sleep metric based on actigraphy. SE: Standard error of B, CI: Confidence interval, LL: lower limit, UL: upper limit, DLMO: dim light melatonin onset, CBT: core body temperature, REM: rapid eye movement sleep.

Identify accessible predictors of the antidepressant response to light therapy

Coefficients from the multiple linear regression models assessing accessible sleep and circadian predictors of relative changes in depression symptoms during the active intervention (adjusted for the order of the intervention arms) are presented in Table 11.

The model based on sleep characteristics predicted 22% of the variance in depression symptoms changes (adjusted R^2 = .08). Worse global sleep quality as assessed by the PSQI at baseline was significantly associated with higher improvements in depression symptoms (β = .53, p = .045). This effect did not persist when excluding the sleep items of the QIDS-A17-C (β = .41, p = .122). Baseline pre-sleep cognitions (GCTI) and ease of getting to sleep (LSEQ GTS) were not significantly linked to changes in depression symptoms.

The model based on baseline circadian characteristics predicted 8% of the variance in depression symptoms changes (adjusted R^2 < .01). None of the circadian parameters assessed in the multiple regression model were found to be significant predictors of mood changes (β < .16, p > .638). There was no significant correlation between total MEQ scores and mood changes following the intervention (r = .06, p = .819).

Table 11. Associations between initial sleep and circadian profiles derived from accessible metrics and depression changes following active light therapy.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*
Sleep Model						
Intervention Order	5.55	12.27	-19.90	31.00	0.10	0.655
PSQI total score (per 1 point)	52.04	24.44	1.36	102.73	0.53	0.045
GCTI total score (per 1 point)	-0.31	0.50	-1.36	0.73	-0.15	0.543
LSEQ GTS (per 1 point)	9.71	12.08	-15.35	34.76	0.18	0.430
Circadian Model						
Intervention Order	11.72	16.77	-24.82	48.25	0.20	0.498
Actigraphy						
Acrophase (per hour)	-30.56	127.23	-307.77	246.64	-0.07	0.814
Circadian Rhythmicity (R^2)	149.56	1013.62	-2058.92	2358.05	0.06	0.885
Peripheral Temperature						
Acrophase (per hour)	5.90	18.59	-34.61	46.41	0.12	0.756
Circadian Rhythmicity (R^2)	202.44	418.96	-710.39	1115.26	0.16	0.638

DV: relative change in QIDS-A17-C from baseline to after active intervention arm. SE: Standard error of B, CI: Confidence interval, LL: lower limit, UL: upper limit. Pittsburgh Sleep Quality Index (PSQI. The Glasgow Content of Thoughts Inventory (GCTI). Leeds Sleep Evaluation Questionnaire (LSEQ) – Getting to Sleep (GTS).

Exploratory analyses: Characteristics of the responder subgroup

Table 12 contrasts the initial demographic, clinical, sleep and circadian profiles in individuals who responded to the active light therapy intervention compared to those who did not respond (based on the QIDS-A17-C MCID and adjusted for the intervention order). Responders initially had slightly but not significantly more severe depression symptoms than non-responders. The two groups did not differ significantly in terms of general demographic and clinical profiles. A non-significant trend suggested that responders had worse subjective sleep as reflected by higher PSQI total scores ($F = 3.85$, $p = .061$, $\eta p^2 = .14$). Compared to non-responders, responders had a significantly higher minima and lower amplitude and mesor of the circadian rhythm of skin temperature (all $p < .050$).

Table 12. Baseline characteristics of responders and non-responders

	Non-Responders				Responders						
	Mean	***SD***	**Count**	**%**	**Mean**	***SD***	**Count**	**%**	***F / Chi²[a]***	***p***	ηp^2 **Cramer'sV[b]**
Demographic and clinical profile											
Sex (Females vs Males)			7	100%			17	85%	1,18	0.277	0.21
Age (years)	26.00	5.66			23.35	5.56			0.77	0.388	0.03
QIDS-A17-C	11.43	4.08			13.10	3.24			0.25	0.619	0.01
Comorbid anxiety disorder			4	57%			11	61%	0.03	0.856	0.04
Using psychotropic medication			7	100%			14	70%	2.70	0.100	0.32
Engaged in psychotherapy			4	43%			9	55%	0.31	0.580	0.11
Age at onset of sleep problems (years)	16.64	7.33			15.43	6.27			0.31	0.582	0.01
Age at onset of mood problems (years)	11.50	4.09			13.15	4.90			1.69	0.206	0.07
Subjective sleep profile											
FSS	3.78	0.52			3.75	0.79			0.12	0.731	0.01
PSQI (*)	7.00	2.71			9.65	2.60			3.85	0.061	0.14
LSEQ - GTS	3.24	0.53			3.07	0.60			0.20	0.659	0.01
LSEQ - QOS	2.29	0.70			2.25	0.90			0.23	0.636	0.01
LSEQ - AFS	3.00	1.47			2.00	0.81			4.49	0.045	0.16
LSEQ - BFW	2.14	0.74			2.12	0.44			0.34	0.568	0.01
GCTI	26.00	13.49			31.25	14.13			0.25	0.623	0.01
Actigraphic sleep estimates											
Rest onset time (clock time)	0:17	1:04			0:20	1:28			0.03	0.863	<0.01
Rest offset time (clock time)	8:34	1:04			8:36	1:56			0.02	0.896	<0.01
Midpoint of the rest period	4:25	0:57			4:39	1:59			0.07	0.787	<0.01
Sleep Efficiency (%)	87.21	11.26			89.96	6.58			1.27	0.271	0.05
Total Sleep Time (hours)	6.77	1.22			7.37	1.25			1.75	0.198	0.07
Circadian Profile											
Chronotype - MEQ									3.30	0.192	0.41
Neither			3	50%			10	71%			
Morning			0	0%			2	14%			
Evening			3	50%			2	14%			

Endogenous circadian markers							
DLMO (clock time)	21:48	1:28	21:49	1:51	0.00	0.985	<0.01
MT AUC 60min pre-sleep (pg/mL*hour)	11.09	8.55	17.84	11.09	2.24	0.153	0.12
MT AUC 40min post sleep (pg/mL*hour)	1.78	1.00	2.43	1.45	0.92	0.349	0.04
CBT Nadir (clock time)	2:49	2:42	3:04	2:35	0.01	0.928	<0.01
CBT Minima (°C)	36.56	0.28	36.60	0.23	1.19	0.288	0.05
Circadian Phase Angles							
DLMO-SleepON (hours)	2.58	1.82	2.48	0.98	0.13	0.721	0.01
SleepMid-CBT (hours)	-1.61	2.91	-1.63	2.17	0.02	0.881	<0.01
DLMO-CBT (hours)	5.07	2.49	5.30	1.42	0.07	0.800	<0.01
Skin temperature rhythm							
Acrophase (clock time)	04:20	02:04	09:44	09:58	1.00	0.320	0.05
Minima (log °C)*	0.76	1.38	1.90	0.97	5.77	0.030	0.28
Amplitude (log °C)*	1.60	2.77	-0.70	1.93	5.23	0.037	0.26
Mesor (log °C)*	1.56	0.01	1.55	0.01	9.64	0.007	0.39
Circadian Rhythmicity Index (R^2)	0.25	0.15	0.26	0.17	0.05	0.828	<0.01
Activity rhythm							
Acrophase (clock time)	16:17	1:01	16:17	01:49	0.07	0.788	<0.01
Minima (log activity count)	0.47	0.40	0.43	0.34	0.13	0.719	0.01
Amplitude (log activity count)	1.76	0.51	1.77	0.34	0.09	0.764	<0.01
Mesor (log activity count)	1.35	0.15	1.32	0.19	0.16	0.698	0.01
Circadian Rhythmicity Index (R^2)	0.50	0.20	0.49	0.14	0.01	0.910	<0.01

Quick Inventory of Depressive Symptomatology clinician based (QIDS-A17-C), The Glasgow Content of Thoughts Inventory (GCTI), Leeds Sleep Evaluation Questionnaire (LSEQ), Horne-Ostberg questionnaire (MEQ), Pittsburgh Sleep Quality Index (PSQI). Fatigue Severity Scale (FSS). Dim Light Melatonin Onset (DLMO). Core Body Temperature (CBT). Rapid Eye Movement Sleep (REM). Melatonin Area Under the Curve (MT AUC). * $p < 0.05$, $^{(*)}$ non-significant trend.

2.3.4 Discussion

Summary of Results

Past results from light therapy studies in people with non-seasonal depression have been rather inconsistent (Mårtensson et al., 2015; Perera et al., 2016; Tuunainen et al., 2009). This may have been influenced by methodological limitations such as the difficulties with blinding inherent to light interventions and the considerable heterogeneity of this clinical group and their response to light intervention. To the best of our knowledge, this is the first cross-over randomized controlled trial of light therapy to use a placebo condition that does not involve dim or red light (both of which may induce some effects on mood (Meesters et al., 1999; Prayag et al., 2019). Despite the small sample size, mild effects of active light exposure were found to exceed placebo effects after taking in account the fact that our placebo condition was confounded with potential antidepressant effects of partial sleep deprivation. Our results also confirmed a considerable inter-individual variability in the antidepressant response to light and unveiled potential predictors and mechanisms of action which should be further investigated in larger samples.

Effects of Light Therapy as Compared to a Placebo Condition

Considering that most participants expected the infrared light condition to work and that less than half of the participants believed the green light was the active condition at the end of the study suggests that inducing deception about the inactive placebo condition being invisible because it involves infrared light is feasible. Results also suggest a strong placebo effect, with a significant decrease in depression symptoms during the inactive condition. However, active light exposure had an effect above and beyond this placebo effect. This was evidenced by the fact

that: i) the improvement in mood was slightly but significantly greater in the active compared to the placebo condition when they occurred as the first intervention arm, and ii) when the active condition occurred in the second intervention arm, it led to further mood improvement beyond the level already attained after the placebo condition.

The mood improvements seen during the first two weeks of the intervention, regardless of the condition, could have also been influenced by factors other than a placebo effect. Notably, the circadian assessment protocol used prior to the first intervention arm involved a partial sleep deprivation in which sleep onset was delayed by one-hour to extend salivary melatonin sampling as previous studies suggested that DLMO can occur past bedtime in young people with depression (Robillard et al., 2013). Sleep deprivation is known to lead to antidepressant effects (Wirz-Justice & Van Den Hoofdakker, 1999). In the current study, mood changes in the placebo condition where apparent when the placebo condition occurred straight after the circadian assessment, but not when the placebo condition took place in the last intervention arm (i.e., four weeks after the circadian assessment, when the partial sleep deprivation effects would have subsided). Hence, the "placebo" effect may in fact reflect the effect of partial sleep deprivation, at least in part. It is also possible that partial sleep deprivation accelerated the emergence of mood improvements during light therapy, since a similar previous study without any sleep deprivation component reported mood improvements only occurring after four weeks of treatment (Nixon et al., 2021). Furthermore, studies have demonstrated that light therapy administered after sleep deprivation can prolong the antidepressant effects of sleep deprivation (e.g., Echizenya et al., 2013; Neumeister et al., 1996; Van Den Burg et al., 1990; Wehr et al., 1985). Overall, this echoes other evidence supporting the combination of sleep-based and

chronotherapeutic approaches for the management of depression (Dallaspezia & Benedetti, 2011).

Nevertheless, a significant attenuation of depression symptoms did occur when the active light intervention took place during the second arm, that is 4 weeks after the night of partial sleep deprivation, a period where the antidepressant effects of sleep deprivation are likely to have faded. Thus, our results suggest that the light exposure component of the intervention also drove significant changes in depression in the likely absence of synergistic interactions with sleep deprivation. Of note, for the subgroup who started with two weeks of active light therapy, we observed that the effects of light therapy on depression symptoms were sustained over at least 6 weeks.

Potential Mechanisms of Action

The reduction in pre-sleep intrusive thoughts across the active light intervention phase was associated with the degree of mood improvement, suggesting that this may be linked to some of the mechanisms of action underlying the antidepressant effects of light. This finding replicates preliminary results from a similar open-label study showing that individuals with worst pre-sleep thoughts were those who experienced a greater antidepressant effect from light therapy (Nixon et al., 2018). Conversely, no such association was found between improvements in mood and changes in the subjective ease of falling asleep and or changes in objective sleep efficiency. Although these findings should be interpreted with caution considering the small sample size, it may be possible that one of the main drivers of sleep-related antidepressant effects of light therapy could operate via a shift towards a mental state around bedtime that is more conducive to sleep. The means through which this could operate remain to be elucidated, but it could be

postulated that morning bright light exposure may induce a phase advance of the circadian rhythm of melatonin, which may increase sleep propensity in the evening, which may in turn attenuate concerns about difficulties falling asleep at night. Importantly, these pre-sleep concerns, often a conduit for negative ruminations, may previously have been actively contributing to adverse mood states.

The degree of improvement in the circadian rhythmicity of skin temperature across the active intervention arm was also associated with improvements in mood. The rhythmicity of mood variations has previously been found to be associated with the rhythmicity of skin temperature, whereby high subjective mood rhythmicity is associated with low skin temperature rhythmicity and vice-versa (Barbini et al., 1998). Since people with major depression have been found to experience abnormally pronounced circadian rhythms in mood, it is possible that light-related improvements in the rhythmicity of body temperature could help stabilize mood variations in this group. Of note, preliminary findings in youth with depression indicated that pre-sleep intrusive thoughts are associated with sleep disturbances and that sleep disturbances are associated with poor skin temperature rhythmicity (Nixon et al., 2022). Thus, the convergence of changes in pre-sleep cognitions and changes in the rhythm of body temperature as two factors contributing to the antidepressant response to light reinforces the notion that both sleep and circadian processes may be involved in some of the mechanisms of action underlying light therapy.

Overall, these results add to previous findings suggesting that mood improvements with light therapy may also parallel increased daytime activity, a phase advance of the rest-activity cycle, less wake time during the first third of sleep, a return to a normal mesor in core body temperature (decrease in mesor; Benedetti et al., 2007; McEnany & Lee, 2005). Previous work

on the underlying antidepressant mechanisms of light therapy reported that mood improvements parallel changes in neural responses in the medial prefrontal cortex, and a decrease in the glutamine/creatine ratio in the anterior cingulate cortex in the inter-hemispheric region (Benedetti et al., 2009; Benedetti et al., 2009; McEnany & Lee, 2005). It is also likely that light could alleviate depression symptoms via other mechanisms, including direct impacts on some of the neural circuits involved in emotional processing (e.g., LeGates et al., 2014; Vandewalle et al., 2010).

Predictors of Treatment Response

While the overall antidepressant effects of the intervention relative to the placebo and partial sleep deprivation effects were modest, the current results confirmed that individuals with certain physiological profiles responded better to the intervention than others. The proposed laboratory sleep model and ambulatory sleep model predicted 17% and 22%, respectively, of the variance in depression symptoms changes. Hence, home-based sleep measures had equivalent and even slightly better predictive value than more costly and hard to access laboratory measures. In contrast, the laboratory circadian model and ambulatory circadian model predicted 24% and 8% of the variance, respectively. This suggests that more research is needed to refine circadian measures that could be collected in the field. Furthermore, larger studies are needed to combine sleep and circadian ambulatory predictors. Herein, neither the polysomnography parameters selected as metrics of sleep quantity and quality (TST and SE), nor some of the most commonly used endogenous circadian phase markers (i.e., DLMO or the nadir of CBT) significantly predicted improvements in mood across the active light intervention. Conversely, shorter REM latency prior to treatment predicted improvements in mood. Depression-related

abnormalities in both homeostatic and circadian regulations could influence the timing of the emergence of REM sleep. From this perspective shorter REM sleep latency may be a marker of abnormal interactions between processes S and C, a phenomenon at the core of the indirect antidepressant effects of light putatively resulting from the restoration of sleep and circadian functions. Short REM latency has long been established as a marker of depression, independently of drug effects, age, and other changes in sleep (Argyropoulos & Wilson, 2005; Benca et al., 1992; Holsboer-Trachsler & Seffritz, 2000; D.J. Kupfer, 1976). It has successfully been used as a treatment predictor for trimipramine combined with light therapy or sleep deprivation (Holsboer-Trachsler & Seffritz, 2000) and other depression treatments such as tricyclic antidepressant medications (Rush et al., 1989; Svendsen & Christensen, 1981), which loosely parallels the serotonergic mechanisms of light therapy for mood improvements. Specifically, similar to what is observed with tricyclic antidepressant medications, light has been proposed to increase serotonin concentrations (Rao et al., 1992), which has been found to suppress REM sleep (Vogel et al., 1990). Although a few previous studies did not report a normalization of REM latency following light therapy (McEnany & Lee, 2005; Rosenthal et al., 1984), it would be important to further explore whether changes in REM latency along the course of light therapy is commensurate to the antidepressant response to light therapy. Further studies are also required to assess physiological predictors of treatment responses in larger samples. Past studies have identified sleep deprivation responders to predict treatment response to light therapy in people with depression (Fritzsche et al., 2001), and hypersomnia, increased eating, and a younger age to predict treatment response in people with SAD (Lam, 1994). Whether these last findings may extend to non-seasonal depression remains to be determined.

These findings have important clinical implications, as they nuance the often modest and inconsistent antidepressant effects reported in global samples with depression by highlighting identifiable subgroups of individuals for whom light therapy may be most effective. In line with models of personalized mental health care, this could inform the development of assessment tools to inform treatment plans. However, polysomnography requires considerable financial and technical resources that restrict its access in many healthcare settings. Hence, we thought it important to assess more accessible predictors of treatment response.

Accessible predictors of the antidepressant response to light therapy

In search for more accessible predictors, we observed that poor subjective sleep quality as indexed by the PSQI can predict improvements in mood following light therapy. Conversely, neither intrusive pre-sleep thoughts, the subjective ease of falling asleep, nor morningness-eveningness preference were found to predict mood improvements based on the multiple regression models.

Exploratory analyses comparing responders to non-responders to light therapy unveiled significant differences in the initial profile of core skin temperature. Compared to that of non-responders, the circadian variations in skin temperature observed in responders in the week prior to the intervention start were characterised by a lower amplitude, a lower mesor, and an elevated minima. Previous research has reported similar circadian abnormalities of skin temperature in people with depression as compared to healthy subjects (Daimon et al., 1992; Germain & Kupfer, 2008). This profile suggests that individuals who responded to light therapy may have had a weaker circadian signal prior to the intervention.

Limitations/Future Directions

Overall, the small sample size restricts the scope of this study since it is likely that the full breath of sleep and circadian profiles of depression were not captured. A larger sample is needed to better identify the possibly larger array of predictors of treatment response and mechanisms of action. Moreover, although the cross-over design of the current study allowed for within comparisons, the two-week wash-out period between both arms was likely insufficient. Specifically, when the placebo condition followed the active condition, residual effects of the active arm carried over into the placebo arm.

The tools used to quantify sleep and circadian rhythms bare their own limitations. For instance, while polysomnography is the golden standard for sleep assessment and provides in-depth sleep metrics, this approach shows only a limited picture since it is typically restricted to a single night of sleep recording in an artificial laboratory environment. Although actigraphy is less precise and remains blind to sleep architecture metrics, it can capture sleep through a wider lens of time, offering a view of variations of sleep through time. Therefore, using both approaches to compliment to each other allows for a more complete picture to emerge.

Another limitation pertains to the fact that adherence to the intervention was not perfect. Furthermore, self-reported estimates of duration in using light therapy have been found to poorly match objectively measure durations (Erin E. Michalak et al., 2007). Hence, considering that a daily log was used to measure adherence in the current study, it is possible that adherence was lower than what was documented. As suggested by Chan and colleagues (2022), motivational interviewing or cognitive behavioral therapy in combination with light therapy may represent an approach that could increase adherence. In concert with using more objective approaches to measuring adherence such as light sensors placed as a pendant or attached to the torso (M. G.

Figueiro et al., 2013; E. k. Lee et al., 2022), these two approaches could increase adherence and monitor it more accurately.

Future studies could also explore the effects of blue light considering that is has greater effects on melatonin suppression, increasing body temperature and heart rate, as well as increasing alertness and reducing subjective sleepiness as compared to green light (Cajochen et al., 2005; Lockley et al., 2006). It is possible that the effects could have been greater and/or quicker if blue light, instead of green light, was used in the current study. Although many studies have compared blue and green light, none were studied with an adequate light placebo.

2.3.5 Conclusions

This study supports the notion that poor sleep and skin temperature may play a significant role in the antidepressant effects of light therapy in the context of non-seasonal depression. Now that alternative means of creating a placebo condition for light therapy have been established as a viable option, larger studies, with a cross-sectional design or a longer wash-out period, are needed to fully disentangle the sleep and circadian predictors and mechanisms contributing to the antidepressant response to light therapy in non-seasonal depression.

Supplemental Material

Light Therapy Associated with Sleep, Circadian and Mood Improvements in People with Depression; A Randomized Control Trial

S10. α-opic Equivalent Daylight (D65) Illuminances for the Light Emitting Glasses

Photoreceptor	Photopigment	α-opic EDI
Short-wavelength cones (S)	S-cone photopsin (cyanolabe)	262.80
Medium-wavelength cones (M)	M-cone photopsin (chlorolabe)	947.25
Long-wavelength cones (L)	L-cone photopsin (erythrolabe)	617.68
Rods	Rhodopsin	1303.91
ipRGCs	Melanopsin	1318.12

Photoreceptor weighted α-opic equivalent daylight (D65) illuminance (α-opic EDI) values (in lux) as per international standard CIE 026/E:2018. (toolbox available at https://doi.org/10.25039/S026.2018.TB; CIE, S. (2018). 026/E: 2018. *CIE system for metrology of optical radiation for ipRGC-influenced responses to light. Vienna: Commission Internationale de l'éclairage*)
ipRGCs: Intrinsically photosensitive retinal ganglion cells.

S11. Light Therapy Glasses

S12.

Objective 1. Effects of Light Therapy as Compared to a Placebo

Analyses restricted to the subgroup with minimal adherence to the intervention

Results comparing depression symptoms before and after the placebo and active condition based on the order in which they occurred persisted when including only the subgroup with at least 4 days of light therapy with the target timing and duration. In both order groups, there was a significant decrease in QIDS-A17-C scores from pre-intervention to post-intervention in the first intervention arm (i.e., regardless of whether this was the placebo ($t(12) = 3.6$, $p = .004$, Cohen's $d = 1.0$) or active ($t(10)= 2.3$, $p = .041$, Cohen's $d = .71$) intervention). However, in the second intervention arm, the active condition decreased QIDS-A17-C scores ($t(13) = 2.2$, $p = .050$, Cohen's $d = 0.56$), whereas there was no such effect in the placebo condition ($t(9) < -0.1$, $p = .985$, Cohen's $d < .01$).

Analyses excluding the sleep items

Results comparing depression symptoms before and after the placebo and active condition based on the order in which they occurred persisted when excluding the sleep items of the QIDS-A17-C scores (i.e., QIDS-Sleep). In both order groups, there was a significant decrease in QIDS-Sleep from pre-intervention to post-intervention in the first intervention arm (i.e., regardless of whether this was the placebo ($t(13) = 3.9$, $p = .002$, Cohen's $d = 1.1$) or active ($t(10) = 2.3$, $p = .044$, Cohen's $d = .69$) intervention). However, in the second intervention arm, the active condition decreased QIDS-Sleep ($t(15) = 2.7$, $p = .015$, Cohen's $d = 0.68$), whereas there was no such effect in the placebo condition ($t(9) = 0.3$, $p = .801$, Cohen's $d = .08$).

Objective 2. Predictors of Treatment Response and Potential Mechanisms of Action

Results on analyses assessing predictors of treatment response and potential mechanisms of action remained similar when excluding the sleep items of the QIDS-A17-C scores (i.e., QIDS-Sleep; see tables S12 and S13).

A) Potential mechanisms of action

The model based on changes in sleep factors predicted 29% of the variance in QIDS-Sleep (adjusted $R^2 = .10$). Higher improvement in pre-sleep cognitions (i.e., decrease in GCTI scores from baseline to post-intervention) tended to be associated with higher mood improvements (i.e., decrease in QIDS-A17-C from baseline to post-intervention; $\beta = .48$, $p = .054$). Changes in depression symptoms were not significantly associated with changes in sleep efficiency ($\beta = -.01$, $p = .960$) or in the ease to fall asleep as reflected by the LSEQ GTS subscale ($\beta = -.17$, $p = .454$).

The model based on changes in circadian factors predicted 90% of the variance in depression symptoms changes (adjusted $R^2 = .77$). Higher improvement in circadian rhythmicity of peripheral body temperature (i.e., an increase in the Cosinor model fit from baseline to post-intervention) was significantly associated with higher mood improvements (i.e. decrease in QIDS-A17-C from baseline to post-intervention; $\beta = -1.18$, $p = .005$). Conversely, a lowering of circadian rhythmicity of the activity-rest cycle (i.e. an decrease in the Cosinor model fit from baseline to post-intervention) was associated with higher mood

improvements when excluding the sleep items of the QIDS-A17-C (β = .75, p = .020). There was no significant association between changes in depression symptoms and the acrophase of peripheral body temperature (β = -.10, p = .605, nor in the acrophase of the activity-rest cycle (β = .13, p = .467).

S12. Associations between depression (QIDS-A17-C minus the sleep items) improvements following active light therapy and sleep and circadian changes.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*
Sleep Model						
Intervention Order	5.84	14.66	-25.40	37.07	0.09	0.696
Sleep Efficiency (per 10%)	-0.55	10.80	-23.57	22.48	-0.01	0.960
GCTI total score (per 1 point)	0.30	0.14	-0.01	0.60	0.48	0.054
LSEQ GTS (per 1 point)	-2.12	2.76	-8.00	3.76	-0.17	0.454
Circadian Model						
Intervention Order	31.97	11.90	-1.06	65.00	0.50	0.055
Actigraphy						
Acrophase (per hour)	0.35	0.44	-0.86	1.56	0.13	0.467
Circadian Rythmicity (R^2)	58.47	15.52	15.38	101.56	0.75	0.020
Peripheral Temperature						
Acrophase (per hour)	-5.23	9.32	-31.12	20.65	-0.10	0.605
Circadian Rythmicity (R^2)	-47.31	8.31	-70.39	-24.22	-1.18	0.005

B) Predictors of treatment response

The model based on baseline polysomnographic sleep characteristics predicted 23% of the variance in improvements in depression symptoms as reflected by the QIDS-Sleep (adjusted R^2 = .11). Sleep efficiency (β =.30, p = .212) was not significantly associated with changes in QIDS-Sleep. Conversely, higher total sleep time tended to be associated with improvements in QIDS-Sleep (β = .45, p = .055),

The model based on baseline endogenous circadian characteristics predicted 24% of the variance in changes on the QIDS-Sleep (adjusted R^2 = .083). Shorter latency to REM sleep tended to be associated with higher improvements in QIDS-Sleep (β = -.42, p = .06). No significant association was found for DLMO (β = .23, p = .316) or CBT nadir (β = -.01, p = .978).

S13. Associations between initial sleep and circadian profiles and depression changes (QIDS-A17-C minus the sleep items) following active light therapy.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*
Sleep Model						
Intrervention Order	25.42	13.98	-3.75	54.59	0.40	0.084
Total Sleep Time (per min)	0.19	0.09	0.00	0.39	0.45	0.055
Sleep Efficiency (per log 10%)	14.69	11.39	-9.06	38.45	0.30	0.212

Circadian Model						
Intrervention Order	24.67	13.58	-3.74	53.08	0.39	0.085
DLMO (per log hour)	164.07	159.29	-169.32	497.46	0.24	0.316
CBTnadir (per log hour)	-3.21	113.46	-240.68	234.26	-0.01	0.978
REM Latency (per log min)	-28.81	14.56	-59.29	1.67	-0.42	0.063

Objective 3. Identify accessible predictors of the antidepressant response to light therapy

Coefficients from the multiple linear regression models assessing accessible sleep and circadian predictors of relative changes in depression symptoms during the active intervention (adjusted for the order of the intervention arms) are presented in Table S14.

The model based on sleep characteristics predicted 17% of the variance in depression symptoms changes (adjusted R^2 = .02). Worse global sleep quality as assessed by the PSQI at baseline was no longer significantly associated with higher improvements in depression symptoms when excluding the sleep items from the QIDS-A17-C (β = .42, p = .122). Baseline pre-sleep cognitions (GCTI) and ease of getting to sleep (LSEQ GTS) were not significantly linked to changes in depression symptoms.

The model based on baseline endogenous circadian characteristics predicted 8% of the variance in depression symptoms changes (adjusted R^2 < .01). None of the circadian parameters assessed in the multiple regression model were found to be significant predictors of mood changes (β < .14, p > .690). There was no significant correlation between total HO scores and mood changes following the intervention (r = -.02, p = .933).

S14. Associations between initial sleep and circadian profiles derived from accessible metrics and depression changes (excluding sleep items) following active light therapy.

			95% CI for *B*			
	B	*SE*	*LL*	*UL*	Beta	*p*
Sleep Model						
Intervention Order	7.87	13.84	-20.83	36.56	0.12	0.575
PSQI total score (per 1 point)	44.34	27.56	-12.82	101.49	0.41	0.122
GCTI total score (per 1 point)	-0.11	0.57	-1.28	1.07	-0.05	0.854
LSEQ GTS (per 1 point)	6.64	13.62	-21.61	34.89	0.11	0.631
Circadian Model						
Intervention Order	14.46	18.43	-25.69	54.61	0.23	0.448
Actigraphy						
Acrophase (per hour)	8.44	139.80	-296.16	313.04	0.02	0.953
Circadian Rythmicity (R^2)	135.96	1113.79	-2290.78	2562.70	0.05	0.905
Peripheral Temperature						
Acrophase (per hour)	4.39	20.43	-40.12	48.90	0.08	0.833
Circadian Rythmicity (R^2)	187.84	460.36	-815.20	1190.88	0.14	0.690

SECTION 3

DISCUSSION

3.1 Summary of Study Findings

Study I (Systematic review)

The objective of *study I* was to predict optimal light exposure parameters for mood in healthy individuals. Results do not support the hypothesis that melanopic EDI predicts mood improvements. Our findings cannot confirm that ipRGCs play an as important role in the mood improvements associated with light. However, this systematic review is restricted by considerable limitations of the studies that were available to date, which calls for further research in this area.

Study II (Open label trial)

The first objective of *study II* was to evaluate the time course of mood improvement following light therapy. Results support the hypothesis that mood improvements would occur after four weeks of intervention.

The second objective was to characterize the temporal dynamics of improvements in sleep, daytime functioning and mood following light therapy. Results support the hypothesis that improvements in mood would be associated with improvements in getting to sleep in the early stages of light therapy (i.e., following the first two weeks of intervention). Results also support the hypothesis that, later in the course of light therapy (i.e., after four weeks of intervention), mood improvements are associated with the alleviation of tiredness upon awakening and in the daytime.

The third objective was to identify sleep-related predictors of treatment response. Difficulties with falling asleep and waking up prior to the intervention were associated with improvements in mood following light therapy. This study supports the use of subjective sleep

characteristics as predictors of treatment response which was utilized and expanded upon in the randomized controlled trial included in this thesis (*study III*).

Study III (Randomized controlled trial)

Building on *study II*, *study III* further explored, the antidepressant effects of light therapy for non-seasonal depression in a randomized controlled trial conducted in a sample distinct from that of *Study II*. The first objective was to determine whether the antidepressant effects of light therapy surpass that of a placebo condition. Only a main effect of time was found (decrease in depression symptoms from pre- to post-intervention), which was most likely confounded by the effects of partial sleep deprivation induced in the "placebo condition". However, a non-significant trend for a Time*Condition interaction indicated that this decrease in depression symptoms was slightly more pronounced in the active compared to the placebo condition. These results somewhat support the notion that light therapy yields modest antidepressant effects in people with major depression disorder.

The second objective was to identify potential mechanisms of actions and treatment predictors. Mood improvements following light therapy were significantly associated with improvements in pre-sleep cognitions and the circadian rhythmicity of skin temperature. Shorter REM latency was found to be predictive of subsequent improvements in depression symptoms following light therapy.

The third objective sought to find more accessible self-reported measures to predict mood improvements. Subjective sleep scores on the PSQI predicted mood improvements following light therapy. Additional exploratory analyses unveiled that light therapy responders, as

compared to non-responders, had a significantly higher minima and lower amplitude and mesor of the circadian rhythm of skin temperature.

3.2 The Intertwinement of Light and Mood

3.2.1 Mood & the sub-groups of non-seasonal depression

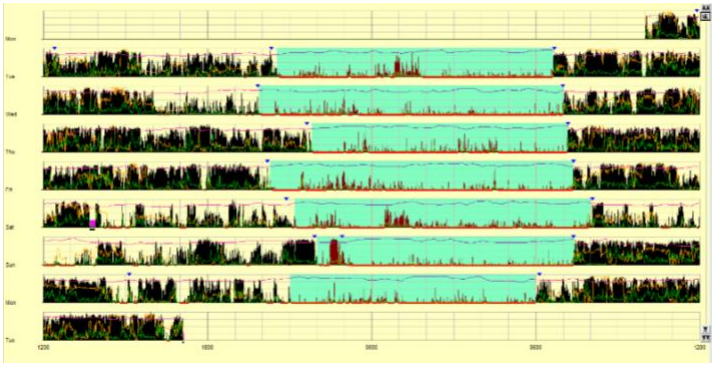
There are different mechanisms by which light influences mood, notably the indirect pathway via changes in sleep and circadian rhythms (Germain & Kupfer, 2008; Vogel et al., 1980, 1990) and the direct pathways via which light affects brain regions involved in mood and emotions processing (Legates et al., 2014). It is likely that slight variations in the functioning of these processes may lead sub-groups of individuals to respond differently to light, both in healthy individuals and in those with mood disorders. In the context of mood disorders, different studies have identified several sub-groups of individuals with homogeneous profiles of depression relating to the presence of symptoms, severity, circadian timing profiles, and mood dynamics (Goldberg, 2011; Lux & Kendler, 2010; Robillard, Carpenter, Rogers, et al., 2018; Ten Have et al., 2016; van Genugten et al., 2021). For example, one study found two MDD subgroups based on the patterns of structural network irregularities (Yang et al., 2021). These results point to the fundamental diversity of mood disorders and are aligned with the possibility that certain sub-groups may respond differently to light. Considering that most light therapy studies have grouped these different types of depression profiles as one, it is not surprising that the efficacy of light therapy for non-seasonal depression has often been found to be inconsistent (Even et al., 2008).

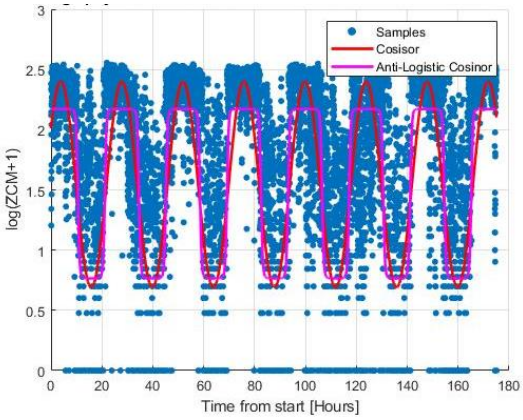
Diversity of circadian rhythms and sleep profiles linked to mood disorders

As outlined in the introduction, various studies have indicated the presence of different sleep-wake profiles, circadian rhythm abnormalities, and sleep disturbances in people with depression (Germain & Kupfer, 2008). This offers a wide net of options in determining depression sub-groups who may be more responsive to light therapy. Some authors coined the term *circadian depression* as a phenotype for mood disorders that combined various markers such as a disrupted 24hr sleep-wake cycle, weight gain, little subjective energy, and reduced motor activity (Carpenter et al., 2021). In the context of clinical mood disorders, it was also found that melatonin release may start increasing later in the evening in people with BD compared to those with unipolar depression (Robillard et al., 2013). Expanding on disrupted 24hr sleep-wake cycles, other studies are finding distinct sleep-wake profiles in depression such as 'disrupted sleep', 'long sleep', and 'delayed sleep-wake' with the latter being associated with worst mood than those with a more conventional circadian profile (Carpenter et al., 2017; Robillard, Carpenter, Rogers, et al., 2018). Other less common circadian rhythm disorders present in certain people with depression also include advanced phase disorder (Gwirtsman et al., 1989; Pflug et al., 1976), and non-24hrs sleep-wake rhythm disorder (or "free-running disorder"; Brown et al., 2011; Hayakawa et al., 2005). Importantly, some of these circadian abnormalities may be associated with deregulation of light mechanisms. Notably, it has been reported that melatonin production can be supressed by light more easily in people with BD than in controls, suggesting a heightened melatonin sensitivity to light (Dallaspezia et al., 2009).

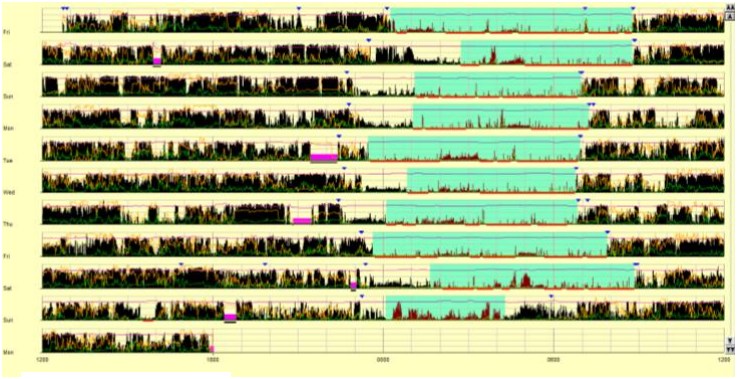
As seen in Figure 10, various sleep-wake cycles and sleep profiles were observed in the actigraphy data collected as part of *study III*. This included profiles suggestive of insomnia,

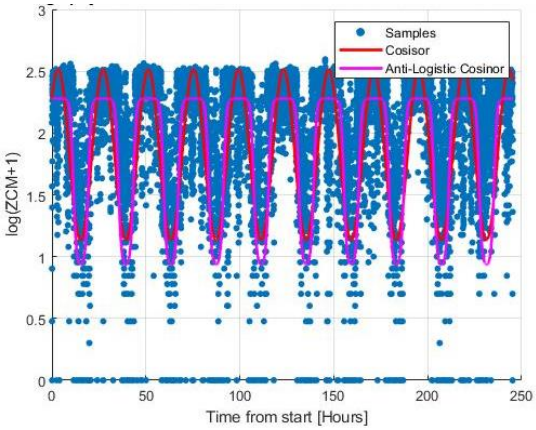
delayed sleep-wake phase, and non-24hour cycles. This highlights the level of inter-individual circadian and sleep variability across different people with non-seasonal depression.



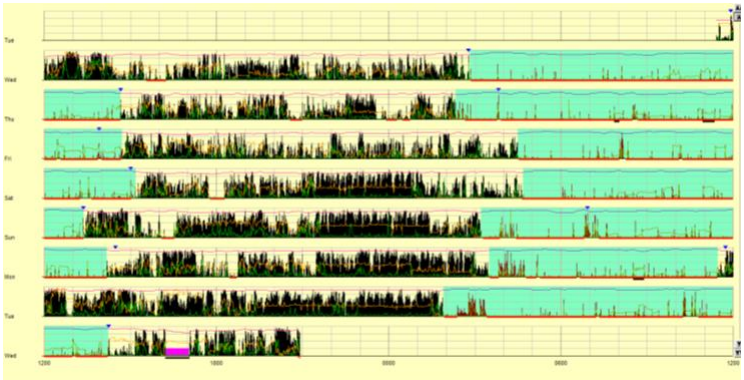


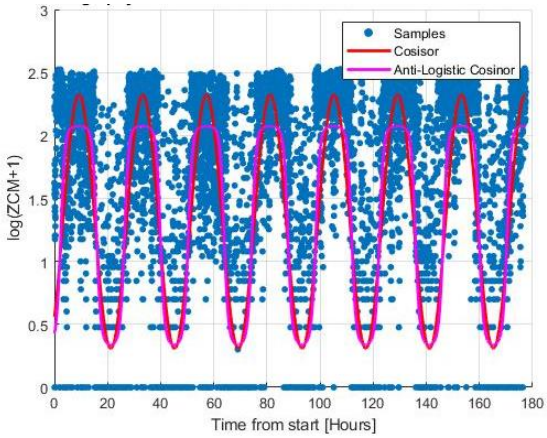
Normal



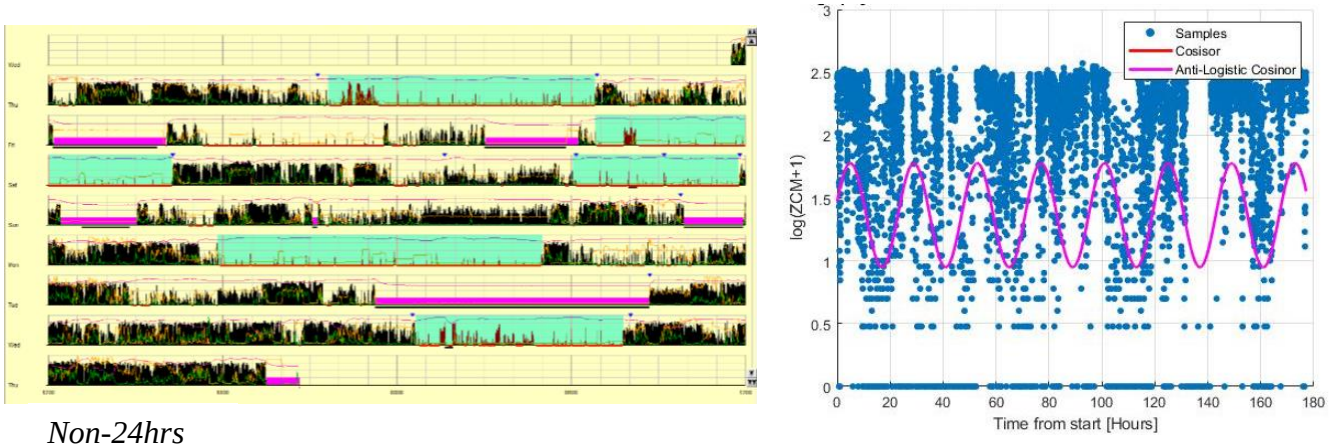


Insomnia





Delayed



Non-24hrs

Figure 10. Left panels: examples of actograms derived from actigraphy data in participants with mood disorders. Each row is a 24-hour period and clock time is on the x-axis; Black line (physical activity); Pink box (missing data); Blue box (scored as sleep); Yellow line (light level); Pink line (body temperature). Right Panels: raw activity counts (y-axis) across time (in hours – elapsed time since configuration of actigraphy) during the entire week of actigraphy monitoring. Blue dots: log-transformed datum collected for each 60sec epochs. Pink curve: extended cosinor fitted curve. Red curve: cosinor fitted curve. Cosinor analyses accounted for clock time, but figures used elapsed time in hours.

Interestingly, the sleep-related predictors of treatment response to light therapy and potential underlying mechanisms between *studies II & III* were not found to be the same which may be explained by the sleep rescheduling of *study II* or the partial sleep deprivation of *study III*. However, a third possibility is that both studies had different proportions of individuals with distinct sleep and circadian profiles in their sample. Specifically, *study II* might have had more individuals with problems fallings asleep, whereas *study III* might have had individuals with poor overall sleep prior to intervention. This highlights the need for studies with larger samples to better understand what these proportions look like at a generalizable level. Considering that the sleep profile of responders between *studies II & III* are those with sleep initiation problems

and poor overall sleep, these results may suggest that some of the responders to light therapy may initially present with insomnia or delayed sleep phase.

When examining objective sleep metrics in *study III*, a shorter REM latency was found to be a predictor of treatment response. These results are aligned with the S-Deficiency Model proposed by Borbély (Borbély et al., 2016), where the homeostatic pressure of these individuals may be disrupted creating this short REM latency (Borbely, 1987). In addition to this, naps have been found to potentially reduce REM latency (Werth et al., 1996). In addition to short REM latency being a marker of depression (Berger & Riemann, 1993), it can be speculated that those who responded to light therapy may have initially taken daytime naps which shortened REM latency. This may also be related to the daytime functioning improvements found in *study II*, whereby responders may initially take naps leading to short REM latency, and light therapy may first act on improving daytime functioning which progressively leads to mood improvements. The link between light, REM, and depression can also be influenced by the serotoninergic system, which is explained in more depth in section 3.2.2. Of note, although considered a core sleep disturbance in depression (Benca et al., 1992; Holsboer-Trachsler & Seffritz, 2000; Kupfer, 1976), not all individuals with depression have this marker of increased REM sleep pressure, suggesting another potential significant sub-group within the heterogeneous population that represent people with depression.

ipRGC sensitivity

Another potential sub-group of people with mood disorders relevant to light interventions lies at the ipRGC level. By measuring the post-illumination pupil response (PIPR), studies have found that individuals with SAD have a decreased retinal sensitivity associated with

pathways involved in the non-image-forming light input (K. Roecklein et al., 2013). Hyposensitivity of the melanopic system has also been characterized in unipolar depression, where melatonin suppression to light is lower than in people with remitted depression or healthy controls (McGlashan et al., 2019). In contrast, individuals with BD have been found to supress melatonin more easily than controls, suggesting altered melatonin sensitivity to light in the opposite direction (Dallaspezia et al., 2009). Results are not entirely consistent for bipolar disorder (Lam et al., 1990; Ritter et al., 2020; Whalley et al., 1991), however some studies have found that evening melatonin may start increasing later in people with BD compared to people with unipolar depression (Robillard et al., 2013). This may notably be influenced to the combination of electronic device use in the evening and the sensitivity in melanopsin signalling via ipRGCs in this group (Bullock et al., 2019).

Amplification of the ipRGC signal leading to discomfort has also been found in individuals with migraines (Mcadams et al., 2020), which is suggestive of possible variations in ipRGC sensitivities in healthy populations. Regarding sleep timing, one study found that healthy individuals with a later mid-sleep timing had a more pronounced PIPR which suggest a stronger response to blue light (Wisse P. van der Meijden et al., 2016). This suggest that a subgroup of healthy individuals with a more delayed sleep may also have a more sensitive melanopic system. In *study I,* the involvement of five different classes of photoreceptors based on their respective sensitivity to different types of polychromatic light were explored to see if any would predict improvements in mood in healthy individuals. Considering the melanopic involvement in the non-visual effects of light, it was expected that melanopic EDI would predict mood improvements, however no significant relationship was found between mood and the level of light-induced stimulation of any of the classes of photoreceptors.

Considering the different profiles of mood disorders and the notion that a diversity of pharmacologic agents are commonly used (various antidepressant medication such as selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors) since there is not a one fits all treatment approach, light therapy may also be a treatment approach only suitable for a subset of individuals. From a sleep perspective, this may represent those with a greater difficulty falling asleep, overall poor sleep, and shorter REM latency (*studies II & III*). In healthy individuals with normal circadian and sleep profiles, inter-individual differences in the sensitivity of mood to light may be better characterized by ipRGC sensitivities.

3.2.2 Potential mechanisms of action of light on mood

Indirect pathway

The indirect pathway through which light may influence mood, notably via improvements in circadian rhythms and sleep with downstream effects on mood, has long been the rational given to explain the mechanisms underlying the antidepressant effects of light and is the basis for *studies II & III*. Specifically, the restoration of sleep and circadian rhythms via light has long been proposed to engender mood improvements (e.g., Hickie et al., 2013; Wehr et al., 1979). Several findings issued from our studies support this notion.

Attenuating intrusive pre-sleep thoughts. It has been proposed that depression is an adaptation rather than a disease. The “analytical rumination hypothesis”, (Andrews & Thomson, 2009; Watson et al., 2002) suggests that depression is adaptive to help focus one’s attentions on solving complex social problems. Although potentially beneficial from an evolutionary

perspective, in today's day and age which includes significant social media use (i.e., creating pressure of being always connected, concerns about constant judgement, unrealistic nature of the content that is often portrayed, and social desirability), these social problems may be exaggerated and more difficult to manage. This may be one of the factors contributing to the increased presence of depression and rumination in our society.

With pre-sleep intrusive thoughts improving along the course of light therapy in *study III*, the question of how light may help with rumination arises. It is possible that improvements in both Process C and S resulting from light therapy may attenuate pre-sleep rumination. Morning bright light may result in a phase advance of melatonin rhythms (Process C), which may lead to earlier wake up times, and thus a greater build-up of sleep pressure by the evening (Process S), which may in turn attenuate concerns regarding difficulties with falling asleep.

Light therapy may also help with rumination if the daytime history of light exposure is considered. Studies have shown that increased light exposure during the day can attenuate the effects of nighttime light on melatonin suppression (Hébert et al., 2002; Rufiange et al., 2007; K. A. Smith et al., 2004). Specifically, this could mean that the negative effects on sleep (melatonin suppression) from nighttime use of light (e.g., smart phone, tv, laptop) could be attenuated by light therapy delivered in the daytime. This could lead to increased sleepiness in the evening which could reduce the risks of rumination. This phenomenon could also expand to mentally healthy individuals, whereby daytime light therapy (increased light exposure) may act as a countermeasure for nighttime light exposure, which may ultimately lead to improved sleep and mood.

Restoring sleep / circadian rhythms. The overall sleep metrics that improved with light therapy suggest a sleep-driven mechanism for mood improvement with light. Indeed, our results align with the proposition that light may produce antidepressant effects through changes in sleep regulation, notably via the homeostatic process (Stephenson et al., 2012). By alleviating sleep disruptions and promoting alertness in the morning, light therapy may, in turn, induce a better dissipation of sleep pressure during the night, and help tone down residual sleep pressure in the morning. *Study II* proposed that improvements in mood paralleled improvements in sleep in a two-step fashion across the temporal progression of the light therapy. Specifically, the first two weeks of light therapy saw improvements in sleep initiation and quality of sleep, whereas the following two weeks saw improvements in sleep-related indices of daytime functioning. Considering that the mood improvements surfaced in the last two weeks, it is possible that the most immediate effects of light pertain to sleep improvement, which then leads to improvements in sleep-related daytime function, which may be a more prominent driver of the antidepressant effects of light therapy.

In contrast, the antidepressant effects of light therapy were immediately seen in *study III*. These results should however be taken lightly since an important difference between *Studies II* and *III* is that *study III* involved partial sleep deprivation while *study II did not*. The Two-Process model (Borbély, 1982) is a helpful theoretical framework to understand the antidepressant effects of sleep deprivation. Specifically, sleep deprivation increases sleep debt by building homeostatic sleep pressure. Increased homeostatic sleep pressure has been associated with increased astrocytic signaling to adenosine receptors which alleviates low mood (Hines et al., 2013). Once the sleep debt is dissipated, the antidepressant effects of sleep deprivation may also dissipate, which could explain the short-term antidepressant effects of sleep deprivation. Another

possibility for explaining the short-term antidepressant effects is that sleep deprivation can increase cortisol levels (Wright et al., 2015), a hormone promoting arousal, which may then facilitate activation, a phenomenon known to enhance mood. The fact that this surge in cortisol stops when sleep homeostasis is re-established, may also explain why these effects would be short lived (McEwen, 2006). Since sleep deprivation may also reduce the phase-shifting capabilities of light by decreasing the strength of the signal to the SCN (Challet et al., 2001), Process C may be influenced by homeostatic sleep pressure which suggest a continued interaction between both processes (Borbély et al., 2016). Bearing in mind that improvements in skin temperature rhythmicity parallel improvements in mood and sleep, it is possible that homeostatic disruption also parallels circadian disruptions. Specifically, with both circadian and sleep changes occurring along the course of light therapy, the concept that both Process S and C are influenced by light therapy is reinforced. This also opens the door to the possibility that certain sub-groups of people with depression may benefit from light therapy more through improvements in the Process S, and others through the Process C.

Direct pathway

The direct pathway via which light affects mood (effects likely to occur in a short timeframe), can be seen at various physiological levels. In recent years, the potential involvement of photoreceptors, such as the ipRGCs, in the effects of light on mood has increasingly gained interest and is the foundation for *study I*. This mechanism likely also played a role in *studies II* & *III*; however, these studies were not designed to investigate these mechanisms. All photoreceptor types play a role in the effects of light on mood in varying degrees, but ipRGCs are most sensitive to blue light due to the increased presence of melanopsin

(Hatori & Panda, 2010). This type of light is also known to have the strongest effects on mood (Meng et al., 2018; Vandewalle et al., 2010). Furthermore, ipRGCs convey light information not only to the SCN (implications for circadian rhythms; Wahl et al., 2019), but also to other brain regions that are involved in mood such as the amygdala, the lateral habenula, the bed nucleus of the stria terminalis, and the dorsal raphe nucleus (Li & Li, 2018). This suggests that light input can influence mood independently from the master clock, thus not involving the indirect pathway. Also, blue light, as compared to green light, has been shown to increase the functional connectivity between the temporal cortex voice-sensitive area, the amygdala, as well as a hypothalamic area near a hypothalamic cluster while processing emotional stimuli (Vandewalle et al., 2010). This suggest that blue light can enhance positive and negative stimuli, which highlights the potential importance of using light in a positive behavioural context.

Overall, it is possible that the null results from *study I* regarding melanopic EDI predicting mood may stem from the lack of blue light found in the polychromatic light sources. From the perspective of the direct pathway, the results from this study may have also differed if it were done in individuals with mood disorders. This is supported by studies that demonstrated that individuals with mood disorders have abnormal melanopsin-driven PIPR responses to light (Berman et al., 2018; Feigl et al., 2018; Laurenzo et al., 2016; Maynard et al., 2017). Additionally, a study done with individuals with SAD found that blue light exposure can enhance the response in the posterior hypothalamus while listening to emotional stimuli, while green light will reduce these responses. The effects were not found in the healthy controls (Vandewalle et al., 2011).

Beyond mood, the direct pathways of light also suggest that light can influence other behavioural and physiological outputs. Specifically, light has been found to be highly involved in

cognitive functions and to increase alertness-related subcortical structures such as the hypothalamus, brainstem, and thalamus (Vandewalle et al., 2009). Bearing this in mind, the follow-up review to *study I* will investigate light profiles most prominently linked to effects on cognition. Cognition is also affected in the context of mood disorders, with low energy, fatigue, and cognitive difficulties being associated with depression and contribute to worsening mood (Corfield et al., 2016; Gotlib & Joormann, 2010). Considering that light can directly improve cognitive difficulties, it is possible that the antidepressant effects of light therapy may, in part, be driven by these improvements. Investigating cognitive difficulties prior to light intervention and their potential improvements following light therapy may inform our understanding of the potential modulating effect of cognition as another indirect pathway via which light could influence mood.

The possible involvement of serotonin in the direct and indirect effects of light on mood

None of the studies in this thesis directly measured serotonin. However, the involvement of this neurotransmitter in responses to light exposure, circadian rhythms, sleep, and depression is worth discussing as this may have some implications for the putative mechanisms underlying the antidepressant effects of light.

In terms of the direct pathways of light on mood, it has been found that a lower amount of serotonin binds to serotonin 1_A receptor sites in limbic brain regions when individuals are exposed to low levels of light, suggesting a modulation effect of light on serotonin uptake (Spindelegger et al., 2012). This may have important implications for the effects of light on mood, since serotonin influences emotional processing (Cowen & Browning, 2015), with serotonin neurons under afferent control of stress-responsive brain areas (Chaouloff, 2000) and

projecting to regions involved with mood regulation (Lowry et al., 2008). Indeed, changes in serotonin signaling are thought to play a key role in the pathophysiology of mood disorders and represent a major therapeutic target that has been widely exploited by pharmacological agents. From this perspective, light-induced modulation of the serotonergic system is likely to play a role in the direct effects of light on mood.

With respect to the indirect pathways of the effects of light on mood, serotonin is also known to have an endogenous rhythm and to peak during the active phase of the 24-hour cycle (Challet, 2007). Stressors may impact the circadian system through the bi-directional communication between the circadian system and serotonin. Since the synthesis of serotonin is mainly driven by the circadian secretion of glucocorticoids (Malek et al., 2005, 2007), serotonin follows this rhythmic release within the SCN (Cagampang & Inouye, 1994), and in turn, pharmacological manipulations of serotonin can induce phase shifts in the biological clock via the SCN and this may be time of treatment and dose-dependent (Prosser et al., 1990). Studies have also found that the endogenous production of serotonin is directly linked to the duration of sunlight and rises rapidly in brighter light (Lambert et al., 2002). Although this remains speculative, one could postulate that light-induce changes in serotonin could induce circadian phase shifts, which in turn could reinforce mood improvements via the indirect pathway. One study comparing non-seasonal depression and healthy individuals found that the serotonin mesor increased for both groups following light therapy, but that the increase was twice as high in those with depression (Rao et al., 1992). With this in mind, a greater sensitivity to the modulating effects of light on the serotoninergic system may be present in depression. From a sleep perspective, serotonin helps synthesise adenosine during the day, a sleep-promoting substance accumulating with the length of time spent awake, which is in line with the homeostatic build-up

of sleep pressure in Process S and becomes inactive at night to enable sleep (Adrien, 1995). Sleep deprivation can increase serotonin function in people with depression (Salomon et al., 1994), which may help explain its temporary antidepressant effects. Thus, the resulting sustained antidepressant effects seen in *study III*, may be a result of sleep deprivation first affecting serotonin functioning followed by light therapy helping to sustain this change in functioning after the dissipation of the acute effects of sleep deprivation.

3.2.3 Time

Circadian rhythms are a concept of time anchored in behavioral and biological patterns. When using light to manipulate these patterns, a certain number of 24-hour cycles may need to occur to observe changes at the biological, behavioral and/or psychological level, and these may take varying amounts of time. As can be seen in daylight savings, the repercussions of this transition can often be seen for up to 2 weeks (Valdez et al., 2003). In *study II* as compared to *study III*, there was a longer delay in the emergence of mood improvements, despite both studies administering the same light therapy device in the morning. It is additionally surprising that *study II* had longer delays since it had an integrated sleep rescheduling component which would conceptually help phase advance the sleep-wake cycle. One potential explanation for this difference lies in the partial sleep deprivation of an hour that was induced as part of *study III* (an artefact of the fact that bedtime was pushed back to enable later saliva sampling). It is possible that the antidepressant effects of sleep deprivation were manifested and then maintained through light therapy. This is notably likely since both conditions saw a significant improvement in mood in the first arm following this partial sleep deprivation, which was not present in the second arm. Therefore, without a partial sleep deprivation it may take four weeks for sleep/circadian

mechanisms to improve which then leads to mood improvements. This is aligned with previous work demonstrating that light therapy can be used to maintain the effects of sleep deprivation (Neumeister et al., 1996). Furthermore, despite acute effects of light, such as light stimulating emotion regulation regions of the brain (Vandewalle et al., 2010), it may subjectively take longer for individuals to feel the change in their global mood, especially for healthy individuals who presumably have overall higher and more stable mood levels to start up with. *Study I* mainly reviewed studies measuring the acute effects of light on healthy people who may have little room to improve in mood. It may thus take even longer for changes in mood to be quantified in this population. Certain sub-groups, such as those with altered light-sensitivities may explain in part the variations in response time in healthy individuals. It is also important to note that *study I* revealed a significant effect of light exposure duration which indicates that there was an effect of light on mood, even if this effect did not seem to vary based on the level of stimulation of different classes of photoreceptors. If more of the included studies had longer durations of light exposure and had a light profile that stimulated the melanopic system in a greater way, it may then be possible to see melanopic EDI and perhaps other photoreceptors predict mood.

Figure 11 depicts the contrast between the *study II & III* light source EDI profile versus *study I* EDI profiles. As can be seen, L-cone and S-cone EDI values appear to be higher than melanopic EDI in polychromatic light, even in the studies suggestive of "blue-enriched" light (study I). In contrast, the blue/green light of the Re-Timer glasses used in studies II & III is maximally targeting ipRGCs and has a higher melanopic EDI value, as expected, than the cone EDI values. Since the peak sensitivity of rhodopsin (see Figure 2) is near the wavelength of the Re-Timer glasses (500nm), it is not surprising that its EDI value was also high.

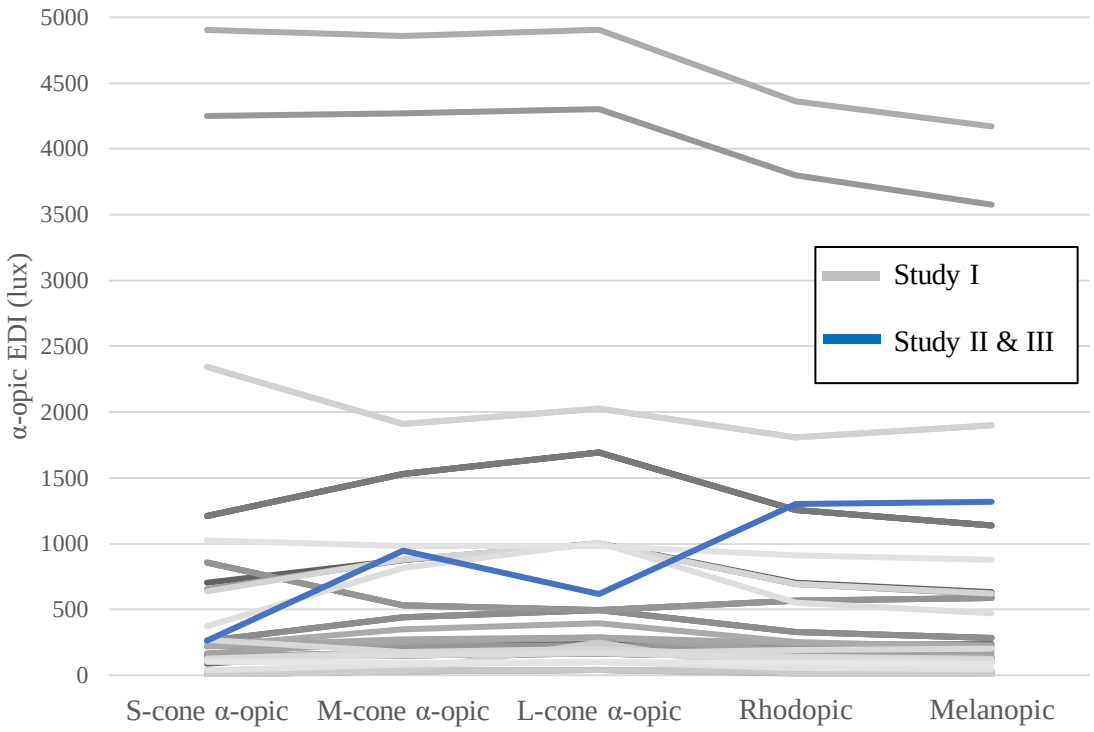
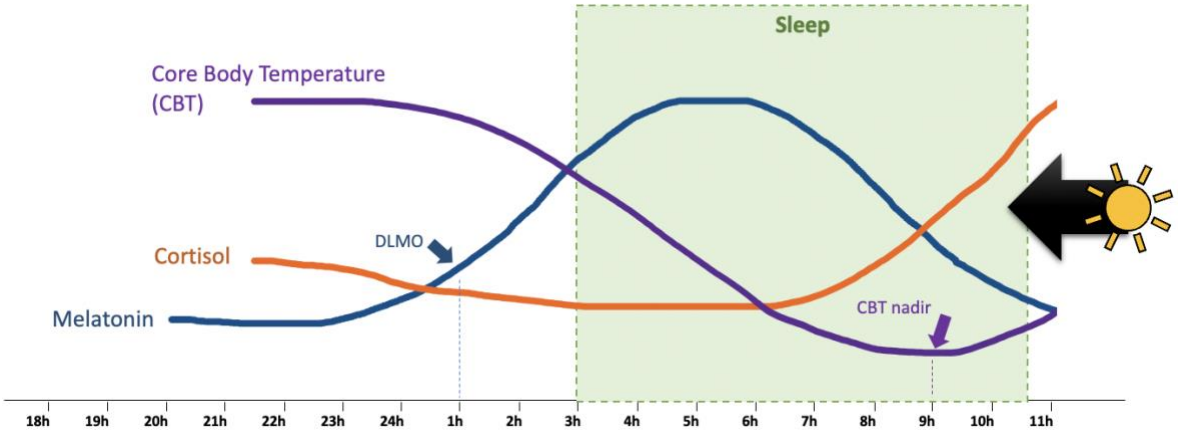


Figure 11. Profiles of α-opic EDI across the different light conditions included in *study I* in grey scale and Re-Timer glasses used in *studies II* & *III* in blue.

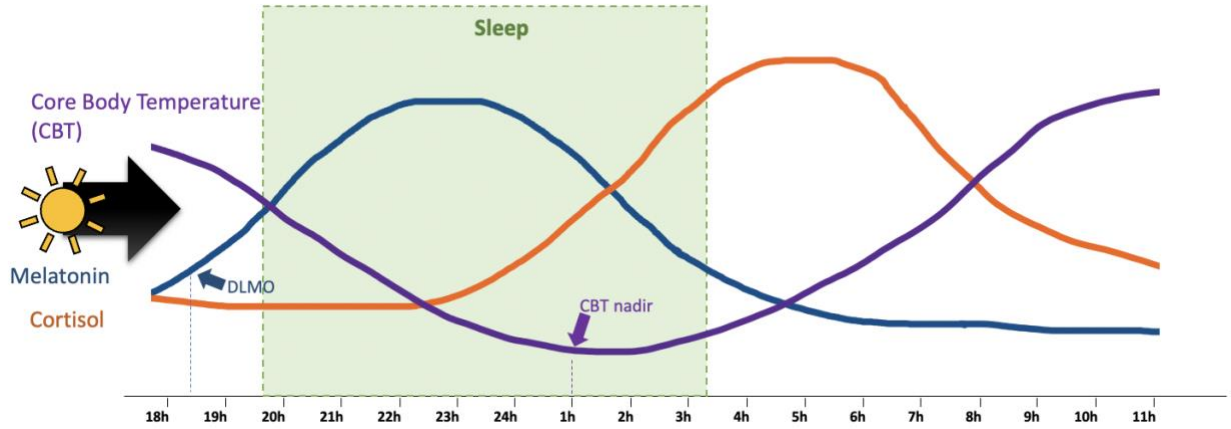
3.2.4 Treating mood disorders with chronotherapies

Circadian rhythm sleep-wake disorders (CRSWD), such as delayed and advanced sleep-wake phase disorders, are often hard to separate from insomnia which is more sleep-related than circadian. This is also often confounded in clinical practice where people are treated for initial or terminal insomnia, when in reality they have a delayed or advance sleep-wake cycle respectively. This highlights not only the importance of increasing awareness about these disorders, but also the importance of creating accessible tools to differentiate sleep- and circadian-driven disturbances and deliver the appropriate treatment.

Coming back to the point that there are different sleep/circadian profiles found across different individuals with depression (Germain & Kupfer, 2008; Hayakawa et al., 2005; Pflug et al., 1976), using light therapy in these different contexts could also require a slightly different approach. Indeed, light has different effects depending on the time of exposure (Minors et al., 1991). When aiming to induce a phase advance in someone who has a delayed phase (Figure 12 - A), using light in the morning (after the CBT_{nadir}) would help shift circadian rhythms to an earlier/more conventional time. Conversely, light exposure in the evening (before the CBT_{nadir}) would worsen/delay even more the circadian rhythms. In the case of an advanced phase (Figure 12 - B), evening light would be the treatment of choice since it would help delay the rhythms, leading to a later/normal sleep onset.



A - Delayed sleep-wake phase disorders



B - Advanced sleep-wake phase disorders

Figure 12. Phase Shifting with Light - delayed and advanced sleep-wake phase disorders. Proposed timing of light therapy for delayed (A) and advanced (B) sleep-wake phase disorders. Variations in circadian rhythms across clock time in relation to the sleep episode (in green). DLMO; Dim Light Melatonin Onset. See Figure 1 for normal circadian rhythm profile for reference.

In the case of a non-24hr circadian rhythm, one of the common interventions is to wait until the individual reaches the desired sleep onset time and then administer melatonin in the evening and bright light therapy in the morning to help stabilize the biological clock and maintain rhythms in place (Malkani et al., 2018; See figure 10, for a representation of a non-24hr sleep-wake cycle).

As can be seen in Figure 10, various circadian profiles were present in *study III*, however, the predetermined protocol for the study did not allow for modification of the timing of light therapy. Although a limitation for this study, it underlines the need for light therapy studies to create protocols that have flexibility in its application to accommodate the heterogeneous nature of mood disorders and sleep/circadian rhythm profiles.

The combination of different chronobiological approaches with light therapy may also show greater improvements in mood. Agomelatine, a melatonergic agonist (at both MT_1 and MT_2) and 5-HT_{2c} antagonist, also has antidepressant properties (Kennedy & Emsley, 2006; Loo et al., 2002). These antidepressant effects are likely due, in part, to its ability to help re-align circadian disruptions in depression (Robillard, Carpenter, Feilds, et al., 2018), and its similar effects at the serotonin receptor level as antidepressants (Kasper & Hamon, 2009). As was seen in *study III*, the combination of partial sleep deprivation and light therapy may have generated faster antidepressant effects in contrast to light therapy alone, which is aligned with previous sleep deprivation studies (Echizenya et al., 2013; Sahlem et al., 2014). One study found that combining sleep deprivation (wake therapy) with light therapy and sleep advance by 1hr was well tolerated and improved mood in hospitalized patients with non-seasonal depression (Danilenko et al., 2019). The combination of treatments operating on both the Process S and C has started to grow in the literature (Benedetti et al., 2013; Martiny et al., 2012; Wu et al., 2009), showing faster and longer-lasting effects.

Aligned with the previously mentioned benefits of combining different chronotherapies, combining light therapy with other types of treatment approaches may also yield important benefits for mood, sleep, and circadian rhythms. Specifically, combining antidepressants with light therapy is more effective than either of them alone (Benedetti et al., 2003; Benedetti et al., 2003; Lam et al., 2016), which suggests synergistic effects between circadian, sleep, and serotonergic treatments on mood. One possibility is that SSRIs increase the sensitivity of the circadian system which may lead to more effective light therapy (McGlashan et al., 2018). Combining exercise with light therapy has also been shown to enhance mood improvements

(Leppämäki, 2006; Partonen et al., 1998), and potentially even more so with cognitive behavioural therapy (Richter et al., 2014; Rohan et al., 2007).

3.3 Applications & Implications

Results from these studies open the doors to multiple application avenues with important implications for research and clinical work which extend to different groups of individuals and different settings.

3.3.1 Integrative lighting implications

Light is an important feature of our physical environment. The results of *study I* suggest that the relative role of ipRGCs (or the other photoreceptors) in improving mood in healthy individuals may not be as prominent as previously thought. Thus, this systematic review cannot justify going to great lengths to rearrange living and working lighting to target melanopic EDI (or other photoreceptors). Key limitations caution any strong conclusions. For instance, some studies used polychromatic light that was intended to be "blue-enriched", but which was found not to activate ipRGCs preferentially.

Firstly, light sources that are considered blue-enriched are created with the idea that ipRGCs would be heavily targeted since they are maximally sensitive to short wavelength light (Berson et al., 2002). The EDI profile of these light sources would be expected to maximally stimulate melanopic EDI, however, this was not found to be the case in the included studies, and likely for most blue-enriched polychromatic light sources. To keep the white appearance in light, red (long wavelength light) needs to be integrated in the spectrum of the light source, however, this creates, according to *study I*, an EDI profile that does not actually target ipRGCs (melanopic

EDI) preferentially. Although this study did not show significant effects of EDI reflective of distinct photoreceptor systems, the limited range of EDI profiles that this study was based on does not allow us to rule out the possibility that there is in fact and effect. Future studies using polychromatic light that properly targets ipRGCs are needed (see section 3.5).

Secondly, since polychromatic light is the type of electrical lighting that we are most exposed to in our daily lives, the implications of finding a statistical model to predict and then design mood enhancing polychromatic light sources is critical. Since humans spend increasing amounts of time indoors, the indoor environment should be optimized with well-being, health, and performance in mind. Certain studies have started to explore the effects of manipulating lighting in offices, schools, homes, and hospitals with promising results (Dalke et al., 2006; Gasio et al., 2003; Viola et al., 2008). As this field progresses, there is increasing recognition of the ethical implications that need to be considered. Specifically, knowing that there are light specifications that can benefit health and performance, is it ethical to continue to install light sources that do not offer these benefits? In opposition, is it ethical to install light sources that can be detrimental to health? In hospital settings where patients are trying to heal, having constant lights with high amounts of blue light may be beneficial for staff, but unfavourable for patients who are trying to sleep and keep a normal circadian rhythm (Cain & Phillips, 2021). Many research teams across the world are currently investigating best practices, such as lighting schedules mimicking natural daylight variations (Giménez et al., 2017; Volf et al., 2020) and using blue-depleted light in the evening (Vethe et al., 2021). In most cases, lighting in living spaces, offices, schools, and hospitals remain unoptimized and large-scale applications remain to be done.

3.3.2 Research implications/applications

At a research level, *study III* contributed significantly to the literature of light therapy and lighting in general by creating a novel placebo that can be accurately called a placebo. Considering the difficulties with blinding inherent to light stimulation and ensuing complexity of creating a placebo for light, other approaches were used in the past, such as red light and low light (Deltito et al., 1991; Fritzsche et al., 2001; Sit et al., 2018). Although being able to contrast the effects of these conditions, they cannot be considered true placebos since light, in all its forms, can have an effect on mood outcomes (Prayag et al., 2019). Using conditions with an absence of light may be more robust as a placebo than previous approaches focused on adjusting the intensity/spectrum of light. This can be attained by slightly leading individuals into deception by suggesting that the light source is emitting infrared light, which is invisible to the human eye, when in fact there is no light being emitted.

S*tudies II & III* suggested that light therapy may increase mood (likely by means of readjusting sleep homeostatic processes and circadian rhythms). Considering that multiple other mental health disorders have also been found to have these circadian and sleep disturbances (e.g., Cardinali et al., 2006; Poon et al., 2018; Wagner, 1999), and that *study III* demonstrated the usability of a new type of light placebo condition, a first application of these studies is extending this methodology directly into studies targeting other clinical groups. Studies have started to look at the effects of light therapy for other disorders such as PTSD (Elliott et al., 2022; Youngstedt et al., 2022; Zalta et al., 2019), Parkinson's disease (Paus et al., 2007; Rutten et al., 2019; Sonja Rutten et al., 2012), and dementia (Ancoli-Israel et al., 2002; Burns et al., 2009; Hanford & Figueiro, 2013; van Maanen et al., 2016), with mixed results. More research could explore the

differences in ipRGC sensitivities in these groups, via PIPR, and potentially uncover predictors of treatment response. Exploring these possible sub-groups within these populations and doing so with a more robust placebo may also help further uncover the benefits of light therapy.

3.3.3 Wellness enhancement and treatment implications/applications

In terms of clinical implications, *studies II* & *III* reinforce the notion that light therapy can be used to improve mood in people with formal mood disorders and that the orientation of patients towards this type of treatment could be informed by profiling sleep and circadian features that may predict therapeutic response. This is especially relevant considering the heterogenous response to light therapy in people with non-seasonal depression is diverse. Determining the best treatment approach for major depression is often a trial-and-error path to determining the optimal treatment. Having tools to determine who will and will not respond to a given treatment is beneficial to all, from the individual's perspective to a healthcare system and economic standpoint. *Studies II* & *III* have brought us one step closer to our ability to do so by proposing a predictive treatment response model for light therapy through circadian and sleep measures. In line with personalized medicine, this may facilitate more rapid and efficient orientation of patients toward treatments to which they are more likely to respond based on features of their sleep/circadian profiles. More research is needed to expand and optimize these predictive models.

Accessing treatment for depression and seeing results can take large amounts of time. This is namely true due to the long wait lists, waiting for appointments, the trial an error of finding the right therapist, and then also going through the trial and error of finding the right medication, at the right dose, and finally, the long delays in seeing clinical results. The effects of

standard antidepressant medication typically start to manifest about 10-14 weeks after treatment start (Fava, 2000; Trivedi, 2006). Light therapy may be an easily accessible option with rather rapid action of 2-4 weeks (*studies II* & *III*). It also does not yield major side effects. From this perspective, it is an appealing intervention to offer some relief while waiting for the effects of pharmacological treatments to emerge and could be maintained as an adjunctive treatment in later stages of care. As compared with the side effects of antidepressant medication, which is a common obstacle for treatment compliance (Zajecka, 2000), light therapy, which only has limited mild side effects (Benedetti, 2018; Terman & Terman, 2005), may also yield greater treatment adherence. Yet, other compliance obstacle arises with light therapy due to elements such as motivation to keep a strict wake-up schedule to administer light at the right time (Terman & Terman, 2005) and sitting in front of a light box for long periods of time. Possible solutions would be help shape light therapy into a habit which could be done with habit stacking and rewards. With regards to sitting in front of a light box for long periods of time, *studies II & III* can be used as an example where light therapy glasses, as opposed to a light box was used. This option allows people to better integrate light therapy into their morning routine which is thought to increase adherence.

Beyond the effects of light on mood, restoring sleep and circadian rhythms in people with mood disorders through light therapy has been found to have important implications for other dimensions of physical health. For instance, it has been postulated that sleep and circadian disruptions linked to altered mood states may contribute to the elevated prevalence of cardiovascular and metabolic conditions in people with mood disorders (Nixon et al., 2017). Of note, light therapy is also used to help with sleep and circadian pathologies regardless of the

presence of mood disorders (Gooley, 2008; Montgomery & Dennis, 2002; van Maanen et al., 2016).

Considering both the direct and indirect pathways of the effects of light on mood, applying light therapy as a first line of treatment in both mood and sleep clinic settings may be key. Despite the silo-like structure often characterising the different departments of hospitals, the applications of light therapy for sleep/circadian as well as mood disorders are an example of interventions well suited for integrated healthcare. This is especially true considering that relapse in depression can occur when sleep/circadian issues are left unresolved (Forest et al., 2005). Considering the high frequency of sleep and circadian disruptions in psychiatric populations, in an ideal scenario, individuals referred for mental health treatments should systematically be screened for sleep/circadian disturbances. They should be relayed to a sleep clinic if any accessible measures (such as those used in *studies II & III* e.g., sleep questionnaire, actigraphy, body temperature sensor) are suggestive of a sleep or circadian disruption so these can be addressed. Resulting from this same screening, a light therapy plan can also be put in place reflecting their circadian profile (see section 3.2.4). This combination of early mood interventions may help meet the need for safer, faster acting, more effective, and better tolerated treatment options for depression in conjunction with other therapies targeting full remissions (Möller, 2008).

3.4 Weakness/strengths

Overall strengths and weaknesses

The fact that none of the polychromatic light sources in the articles included in our systematic review (*study I)* did preferentially target ipRGCs represents a clear limitation. However, one of the review's strength lays in the fact that the focus was on polychromatic light. Monochromatic light, which is often the light source used in studies investigating the effects of ipRGCs, is not easily generalizable to typical living lighting, which tends to be polychromatic. Thus, studying typical living lighting, as was done in our review, allows for greater generalisability. Similarly, both *studies II & III* had considerable generalisability because the light therapy intervention was administered as an adjunctive treatment to participants' ongoing clinical care. Although this may induce some weaknesses, such as potentially blurring the effects of light therapy itself by diminishing or enhancing its effects through potential synergistic interactions for example with serotonin-based medications, it represents more accurately the manner in which light therapy would likely be utilized in this population, which counts many individuals already undergoing various forms of mental health treatments.

All studies also have the strength of highlighting realistic considerations for the implementation of light interventions. If replicated in further work, the findings of *study I* argue against complex manipulation of the spectrum of ambient polychromatic light to enhance mood in the general population. Furthermore, both *studies II & III* explored accessible low costs measures that can be used to predict treatment response such as self-reported questionnaires and ambulatory sleep monitoring. Although not as precise compared to tools used in a laboratory or clinical settings such as PSG and hormone sampling, which was also explored in *study III*, these types of measures may be more readily implementable in standard mental health care settings.

Finally, a great strength of *study III* is its use of a novel placebo condition which enables greater accuracy in drawing conclusions about the effects of light, as compared to previous "placebos" (i.e., based on variations in light intensity and\or spectrum which may still have yielded some effects on mood; Deltito et al., 1991; Fritzsche et al., 2001; Sit et al., 2018; Wirz-Justice et al., 1986) as discussed previously. However, the inclusion of partial sleep deprivation prior to the intervention starts in *study III*, may have hindered the capability of clearly comparing the placebo to the active condition without the confounding factor of increased sleep pressure (which may have antidepressant effects). A simple study design comparing the active to the placebo would be needed.

As a general weakness across all three studies, results may only be representative of western cultures since *study I* consisted mainly of studies done in this part of the world, and *study III* was done strictly in Canada. However, *study II* had a multisite sample (Canada & Australia) which expands the representative nature of these results. In *studies II & III*, the recruitment age range was roughly 13 to 35 years old. Although age was controlled for in the *study III* analyses, it was not for *study II*. Considering that this range spans multiple developmental periods (Salmela-Aro, 2011), it is possible that the effects of light therapy may have varied with age due to hormonal changes, brain/eye development, and changes in circadian rhythms. Unfortunately, the final sample sizes did not allow for exploring potential age-related differences. More studies are needed to better disentangle these effects. Furthermore, more females than males participated in s*tudies II* & *III*. This is however aligned with data indicating that women are twice as likely to experience depression in contrast to men (Kessler et al., 1994; Nolen-Hoeksema, 2001). Considering the influence of normal shifts in gonadal hormones in the menstrual cycle which influence neuroregulatory systems that play a role in mood disorders

(Bloch et al., 2000; Rubinow et al., 1998; W. Freeman, 2022), it is possible that the timing of light therapy within that cycle might have influenced the results. Good adherence to treatment in *studies II & III* was found, which is consistent with previous studies done with light boxes and similar to compliance rates with antidepressant medications (Michalak et al., 2002; Michalak et al., 2007). However, it important to consider how this information is collected. As was done in *studies II & III*, most studies rely on self-reported diaries which can introduce error and social desirability biases. A previous study asked participants to call a time-stamped machine when doing the light therapy sessions (Sit et al., 2018). This method, however, still relied on participants to self-report. More research is needed to determine more efficient and precise ways of measuring adherence to light therapy, an area where wearable and nearable technology may be of great value (Lee et al., 2022).

Subjective measures

Another limitation across all three studies can be found in the use of self-reported measures. Although these are easy measure to use and administer, a disadvantage is the risk of receiving answers that are untruthful or invalid. When asked to reflect on one's sleep or mood in the past month/week, it can be hard to average it together when many variations occur from day to day, which has been reported to occur more prominently in people with mental disorders (Abad & Guilleminault, 2005). This is especially true for the PSQI which asks respondents to average their sleep over the past month. Also, many items on the BDI-II may reflect sleep issues rather than depression symptoms (Carney et al., 2009) which may cloud conclusions about mood improvements. For this reason, *study II* removed certain sleep items when calculating total

scores. *Study III* opted to use the clinician rated QIDS to quantify mood improvements along treatment and analyses were also re-run after removing sleep items.

In healthy individuals, it can also be hard to capture small variations in mood through questionnaires since mood may not reach considerably low levels and may be more homogeneous from one person to the next. Additionally, in *study I*, many questionnaires measuring mood do not seem to measure the same construct of mood, which limits the ability to pull accurate conclusions about mood in meta-analyses. Typically, these questionnaires were also more simplistic than questionnaires assessing complex combinations of symptoms related to mood disorders, which may be more sensitive to slight variations.

Light history

Considering that prior light history can reduce the sensitivity of the circadian system (Chang et al., 2011; Hébert et al., 2002; Jasser et al., 2006; Smith et al., 2004), lack of reporting on or controlling for light history is a limitation that applies across all three studies. In *study I*, eight of the 14 included studies reported or controlled for light history. Bearing in mind that light history over several days, and not just a few hours prior to a study may impact results (Hébert et al., 2002), that most of the included studies that did report or control for light history did so for a short period of time, and that only a small set of variables can be controlled for in our study due to small sample size, light history was also not controlled for in the meta-analysis of *study I*. In *studies II & III*, only a short period of light exposure (30min to 1hr) was delivered to participants, which may have helped supress morning melatonin for those with a delayed phase and who were normally exposed to low levels of light. However, for those with a bright light

environment, this intervention may have had little additional effect on the circadian, sleep or mood systems.

Evening light

Considering that light exposure in the evening has been found to impact sleep, homeostatic sleep pressure, and circadian-driven aspects of sleep (Chang et al., 2015; Lastella et al., 2020; Šmotek et al., 2020; Wams et al., 2017), not controlling for variations in ambient light exposure at that time in *studies II & III* represent another limitation. Using devices that emit light before bedtime has also been associated with a delayed sleep phase and a later DLMO as compared to controls, thus suggesting that those with a delayed sleep schedule may participate in light-related behaviors that favor a later bedtime (Van der Maren et al., 2018). It is possible that this behaviour, often used as a way of distraction, may be linked to the high prevalence of intrusive pre-sleep thoughts in this population. Future studies should explore combining morning light therapy with evening dark therapy to counterbalance these effects.

3.5 Future Directions

3.5.1 Integrative lighting

Being limited by the available studies in the literature that used light with little melanopic activation, *Study I* highlights the need for studies with polychromatic light with better shorter wavelength integration. The limitation with adding more short wavelength light into polychromatic light, is that the light source no longer looks white which is why longer wavelength light is typically added in parallel. One way to counter this is with the recent development of metameric spectral tuning lighting, which can alter the non-visual impact of light

without changing the appearance of the light source (e.g., color of the light; Allen et al., 2018). The EDI profile of these light sources could be created to maximise ipRGC activations while remaining white in appearance, which has important ecological validity implications. Thus, re-running the search for *study I* in a few years, specifically on metameric lighting studies, could enable the study of more diverse EDI profiles that may be better suited to investigate whether melanopic EDI can predict mood outcomes in healthy individuals. Such studies looking to better understand the effects of metameric lighting on mood could undertake a study design that encompasses all the lessons learned from all three studies. At the light level, this would include controlling for duration of exposure, time of day, the photoperiod, and taking detailed measures of the environmental setting. Measuring mood could take different forms. In the context of healthy individuals, there would need to be standardization of mood metrics and in a clinical setting the use of more robust clinical assessments such as the QIDS-C or HAM-D. More objective measure of mood could also be used to compliment these more subjective measures. This may include an objective proxy such as brain correlates of emotional processing (e.g., through ERP or fMRI) or physiological response to emotional stimuli (e.g., heart rate, skin conductance, skin temperature, or pupil response).

Metameric lighting could also have important applications if combined with dynamic lighting (lighting that changes in spectrum/intensity across the 24hr cycle). As discussed in section 3.3.3, studies are starting to integrate dynamic lighting into settings like hospitals (Buikstra et al., 2020), nursing homes (Wahnschaffe et al., 2017), and the space station (Rahman et al., 2022) to help keep circadian rhythms aligned. Combining both approaches could allow viewers to perceive no variations while benefiting from the optimized spectrum for a given time

of day. In the context of mood disorders, this could extend into changing light therapy boxes or glasses for ambient lighting that can meet their needs at different times of day, which would not only increase adherence, but potential benefit for others in their household. At a larger scale, deployment of wearable light sensors (e.g., daysimeter) paired with experience sampling methodologies to capture mood simultaneously would enable naturalistic environment data of mood and light over long periods of time. Variations in both light and mood could also be paired with AI-based social media mood indices (Roy et al., 2020). At an even larger scale, these social media mood indices could also be paired with regional light information enabling population level research about light and mood variations.

At the other end of the spectrum, red (630-660nm), near infrared (810-850nm), and infrared (900nm) light are also shedding light on the many non-ocular benefits such as reduced pain (Haslerud et al., 2015; Huang et al., 2015; Stausholm et al., 2019), improved cognition in people with dementia (Chao, 2019; Nizamutdinov et al., 2021), and mood improvements in people with MDD (Cassano et al., 2018). This range of the light spectrum is associated with heat emission and considering the global ecological needs to reduce energy usage, windows and light bulbs (i.e., incandescent bulbs) which once allowed for and emitted infrared light, are now being modified to shield from (Wu et al., 2018) and reduce infrared light, notably through implementing LED lights. This may have important implications in settings such as hospitals or retirement homes where infrared light may be beneficial beyond enabling sight (i.e., pain). Future studies could investigate the combined effects of infrared light at a non-ocular level with short-wavelength light at the ocular level. Strictly at the ocular level, it may also be beneficial to investigate the combined effects of red light at night, which has been shown to attenuate

vigilance and accelerate the transition from wakefulness to sleep (van der Meijden et al., 2018), with morning blue light. This could result in faster re-alignment of circadian rhythms by address both pre- and post-sleep, which may lead to faster antidepressant effects.

3.5.2 What is left to investigate with regards to light therapy interventions

With the magnitude of data generated from the light intervention trials included in this thesis, there remains considerable research questions that could be further explored beyond the scope of the current thesis. It would be relevant to adapt the cosinor models applied to actigraphy and body temperature data to detect potential changes in the circadian period of these rhythms. Studies have shown that individuals with mood disorders display unstable/abnormal circadian periods (Pflug et al., 1981). Light therapy may help stabilize these variations and may thus have more prominent effects in those individuals who initially had more unstable circadian periods. As mentioned in section 3.4, re-running analyses with only females and perhaps dividing the group based on menstrual cycle phase could yield preliminary information on the influence of reproductive hormones on the effects of light on mood. Additionally, as mentioned in section 3.2.1, the presence of naps may be another variable that could be added to the predictive model. Moreover, morning cortisol was collected in study III, which would enable the characterisation of the cortisol awakening response (CAR) at pre-intervention. The literature appears to be torn between a blunted and increased CAR in depression (Dedovic & Ngiam, 2015), which may be suggestive of another sub-group profile in depression. The CAR could thus potentially be added to the predictive model of study III.

Finally, myopia has been linked to a delayed DLMO, lower melatonin output, delayed sleep onset, longer sleep onset latency, evening-type chronotype, and shorter sleep duration as

compared to emmetropes (Chakraborty et al., 2021). Considering that the axial length, anterior chamber depth, crystalline lens thickness, and citreous chamber depth of the eye also have diurnal rhythms (Chakraborty et al., 2011), myopia should also be assessed as a predictor of treatment response.

3.5.3 The need for more light therapy studies

Future studies could build on *studies II & III*, expanding on mechanisms, predictors, increasing acceptability, and exploring alternative light therapies. As was seen in *study III*, short REM latency was found to predict treatment outcome, however, no post-intervention PSG was done which means it was not possible to assess whether an improvement in REM latency may also be an underlying mechanism of light therapy. Thus, future research could leverage a study design with a pre- and post-PSG assessment to better characterize changes in sleep with adjunctive light therapy. Other predictors of treatment response also need to be explored to have a better view of who may or may not respond to light. PIPR may be an important treatment predictor since different PIPRs have been found in different forms of depression (Roecklein et al., 2013; Roecklein et al., 2021), including non-seasonal depression (Berman et al., 2018; Laurenzo et al., 2016). Finally, polymorphisms in core circadian clock genes such as, BMAL1, PERIOD3, CLOCK, and TIMELESS have been associated with mood disorders (Mendlewicz, 2009). Considering their cross-over between circadian rhythms and mood disorders, they may represent target objective treatment predictors.

To increase acceptability of light therapy, new methods of delivery are being explored such as scarves, hats, and hoods lined with LEDs (Profita et al., 2015). These different options could be integrated into clinical studies to also increase study adherence. Other areas to consider

when looking at increasing adherence is reducing associated side effects such as headaches and eyestrain, which has been reported by light therapy users (Terman & Terman, 2005). Temporal light modulation at low frequencies has been found to be associated with headaches and eyestrain, for those who tend to experience these symptoms (Wilkins et al., 1989). Flicker at a range from 3 to 70Hz can increase risks of seizures and frequencies below 165Hz can induces human biological effects such as headaches, malaise, and impaired visual performance (IEEE Power Electronics Society, 2015). The light therapy glasses used in *studies II & III* are within this low range that can create visual stress (Re-Timer are 50 to 166Hz; Re-Timer, n.d.). Future studies could explore using light sources with higher frequencies to see if these light therapy side effects are reduced. Although light pulses can have potentially negative side effects for a sub-group of individuals (e.g., epileptic, prone to headaches), pulsed light with closed eyes at night may be another avenue for delivering light therapy to a subset of individuals. One study found that pulsed blue light at night (with eyes closed) could delay circadian phase and supressed nocturnal melatonin (Figueiro et al., 2013). This may be particularly useful for those in a non-24hr cycle and advanced phase disorder. Pre-clinical work has also found that gamma entrainment using sensory stimuli (GENUS), in this case visual stimuli at 40Hz, had neuroprotective effects such as reducing neuronal and synaptic loss (Adaikkan et al., 2019). Much work is still needed, but these findings may have significant implications for neurodegenerative disorders

3.6 Conclusions

Light not only enables us to see, but it also has an important role in a diverse range of non-visual functions, including mood regulation. Influencing many of our circadian rhythms and

behaviour, light is a fundamental part of our reality. The three studies presented in this thesis lead to the conclusion that short-wavelength light has modest overall antidepressant properties in the context of non-seasonal depression, but that more work is needed to disentangle the effects of polychromatic light on mood in the general population. The heterogeneity of the response to light therapy may be influenced by the existence of different sub-groups of depression, which can be characterized, in part, by sleep and circadian rhythm profiles. These profiles also have the potential to identify and predict treatment response. A novel light placebo was also developed and successfully applied, which holds promise in helping push the boundaries of light research. Light remains at the forefront of the quickly evolving chronobiological toolkit for improving mood, however, larger studies are needed to better characterize the full profile of individuals, healthy or with a mood disorder, most likely to respond to light and to better understand the multitude of underlying mechanisms at play.

– References –

Abad, V. C., & Guilleminault, C. (2005). Sleep and psychiatry. *Dialogues in Clinical Neuroscience*, *7*(4), 291–303. https://doi.org/10.31887/dcns.2005.7.4/vabad

Abbott, K. S., Queener, H. M., & Ostrin, L. A. (2018). The ipRGC-Driven Pupil Response with Light Exposure, Refractive Error, and Sleep. *Optometry and Vision Science*. https://doi.org/10.1097/OPX.0000000000001198

Adaikkan, C., Middleton, S. J., Marco, A., Pao, P. C., Mathys, H., Kim, D. N. W., Gao, F., Young, J. Z., Suk, H. J., Boyden, E. S., McHugh, T. J., & Tsai, L. H. (2019). Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. *Neuron*, *102*(5), 929-943.e8. https://doi.org/10.1016/j.neuron.2019.04.011

Adam, E. K., Doane, L. D., Zinbarg, R. E., Mineka, S., Craske, M. G., & Griffith, J. W. (2010). Prospective prediction of major depressive disorder from cortisol awakening responses in adolescence. *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2009.12.007

Adan, A., & Natale, V. (2002). Gender differences in morningness-eveningness preference. *Chronobiology International*. https://doi.org/10.1081/CBI-120005390

Adrien, J. (1995). The serotoninergic system and sleep-wakefulness regulation. *In The Pharmacology of Sleep*, 91–116.

Akaike, H. (1987). Factor analysis and AIC. *Psychometrika*, *52*, 317–332.

Al-Karawi, D., & Jubair, L. (2016). Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. *Journal of Affective Disorders*, *198*, 64–71.

Allen, A E, Hazelhoff, E. M., Martial, F. P., Cajochen, C., & Lucas, R. J. (2018). Exploiting metamerism to regulate the impact of a visual display on alertness and melatonin suppression independent of visual appearance. *Sleep*, *41*(8). https://doi.org/10.1093/sleep/zsy100

Allen, Annette E., Hazelhoff, E. M., Martial, F. P., Cajochen, C., & Lucas, R. J. (2018). Exploiting metamerism to regulate the impact of a visual display on alertness and melatonin suppression independent of visual appearance. *Sleep*, *41*(8), 1–7. https://doi.org/10.1093/sleep/zsy100

Almeida, O. P., & Pfaff, J. J. (2005). Sleep complaints among older general practice patients: Association with depression. *British Journal of General Practice*.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders*. https://doi.org/https://doi.org/10.1176/appi.books.9780890425596.dsm05

Ancoli-Israel, S., Martin, J. L., Kripke, D. F., Marler, M., & Klauber, M. R. (2002). Effect of Light Treatment on Sleep and Circadian Rhythms in Demented Nursing Home Patients. *Journal of American Geriatrics Society*, *50*(2), 282.

Andrade, M. M., Benedito-Silva, A. A., & Menna-Barreto, L. (1992). Correlations between morningness-eveningness character, sleep habits and temperature rhythm in adolescents. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Médicas e Biológicas / Sociedade Brasileira de Biofísica ... [et Al.]*.

Andrews, P. W., & Thomson, J. A. (2009). The Bright Side of Being Blue: Depression as an Adaptation for Analyzing Complex Problems. *Psychological Review*, *116*(3), 620–654. https://doi.org/10.1037/a0016242

Angelousi, A., Kassi, E., Nasiri-Ansari, N., Weickert, M. O., Randeva, H., & Kaltsas, G. (2018). Clock genes alterations and endocrine disorders. In *European Journal of Clinical Investigation*. https://doi.org/10.1111/eci.12927

Antunes, L. C., Levandovski, R., Dantas, G., Caumo, W., & Hidalgo, M. P. (2010). Obesity and

shift work: Chronobiological aspects. *Nutrition Research Reviews*. https://doi.org/10.1017/S0954422410000016

Antypa, N., Vogelzangs, N., Meesters, Y., Schoevers, R., & Penninx, B. W. J. H. (2016). Chronotype associations with depression and anxiety disorders in a large cohort study. *Depression and Anxiety*. https://doi.org/10.1002/da.22422

Aranda, M., & Schmidt, T. M. (2021). *Diversity of intrinsically photosensitive retinal ganglion cells: circuits and functions*. *78*(3), 889–907. https://doi.org/10.1007/s00018-020-03641-5.Diversity

Argyropoulos, S. V., & Wilson, S. J. (2005). Sleep disturbances in depression and the effects of antidepressants. *International Review of Psychiatry*, *17*(4), 237–245. https://doi.org/10.1080/09540260500104458

Armitage, R. (2007). Sleep and circadian rhythms in mood disorders. *Acta Psychiatrica Scandinavica*. https://doi.org/10.1111/j.1600-0447.2007.00968.x

Aschoff, J. (1979). Circadian Rhythms: Influences of Internal and External Factors on the Period Measured in Constant Conditions. *Zeitschrift Für Tierpsychologie*, *49*(3), 225–249. https://doi.org/10.1111/j.1439-0310.1979.tb00290.x

Aschoff, J. (1983). Circadian control of body temperature. In *Journal of Thermal Biology*. https://doi.org/10.1016/0306-4565(83)90094-3

Aschoff, J., & Heise, A. (1972). Thermal Conductance in Man: Its Dependence on Time of Day and on Ambient Temperature. In *Advances in Climatic Physiology*. https://doi.org/10.1007/978-3-642-93010-2_20

Au, J., & Reece, J. (2017). The relationship between chronotype and depressive symptoms: A meta-analysis. *Journal of Affective Disorders*, *218*(October 2016), 93–104. https://doi.org/10.1016/j.jad.2017.04.021

Avery, D. H., Wildschiødtz, G., & Rafaelsen, O. J. (1982). Nocturnal temperature in affective disorder. *Journal of Affective Disorders*. https://doi.org/10.1016/0165-0327(82)90020-9

Avery, D., Wildschiodtz, G., & Rafaelsen, O. (1982). REM latency and temperature in affective disorder before and after treatment. *Biological Psychiatry*.

Baehr, E. K., Revelle, W., & Eastman, C. I. (2000). Individual differences in the phase and amplitude of the human circadian temperature rhythm: With an emphasis on morningness-eveningness. *Journal of Sleep Research*. https://doi.org/10.1046/j.1365-2869.2000.00196.x

Baglioni, C., Nanovska, S., Regen, W., Spiegelhalder, K., Feige, B., Nissen, C., Reynolds Iii, C. F., Riemann, D., & Author, P. B. (2017). SLEEP AND MENTAL DISORDERS: A META-ANALYSIS OF POLYSOMNOGRAPHIC RESEARCH HHS Public Access Author manuscript. *Psychol Bull*, *142*(9), 969–990. https://doi.org/10.1037/bul0000053

Bailes, H. J., & Lucas, R. J. (2013). Human melanopsin forms a pigment maximally sensitive to blue light (λmax ≈ 479 nm) supporting activation of Gq/11 and Gi/o signalling cascades. *Proceedings of the Royal Society B: Biological Sciences*, *280*(1759). https://doi.org/10.1098/rspb.2012.2987

Bailey, S. L., & Heitkemper, M. M. (2001). Circadian rhythmicity of cortisol and body temperature: Morningness-eveningness effects. *Chronobiology International*, *18*(2), 249–261. https://doi.org/10.1081/CBI-100103189

Balsalobre, A., Brown, S. A., Marcacci, L., Tronche, F., Kellendonk, C., Reichardt, H. M., Schutz, G., & Schibler, U. (2000). Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science*. https://doi.org/10.1126/science.289.5488.2344

Barbini, B., Benedetti, F., Colombo, C., Guglielmo, E., Campori, E., & Smeraldi, E. (1998).

Perceived mood and skin body temperature rhythm in depression. *European Archives of Psychiatry and Clinical Neuroscience*, *248*(3), 157–160.

Baron, K. G., & Reid, K. J. (2014). Circadian misalignment and health. *International Review of Psychiatry*, *26*(2), 139–154. https://doi.org/10.3109/09540261.2014.911149

Bates, D. M. (2020). *lme4 : Mixed-effects modeling with R*.

Bauer, M. S., Kurtz, J. W., Rubin, L. B., & Marcus, J. G. (1994). Mood and behavioral effects of four-week light treatment in winter depressives and controls. *Journal of Psychiatric Research*. https://doi.org/10.1016/0022-3956(94)90025-6

Baumann, B., Krell, D., Dobrowolny, H., & Bielau, H. (2004). Mechanisms of action in the prevention of recurrent mood disorders. *Pharmacopsychiatry*. https://doi.org/10.1055/s-2004-832671

Beauchemin, K. M., & Hays, P. (1997). Phototherapy is a useful adjunct in the treatment of depressed in- patients. *Acta Psychiatrica Scandinavica*, *95*(5), 424–427. https://doi.org/10.1111/j.1600-0447.1997.tb09656.x

Beck-Friis, J., Ljunggren, J. G., Thorén, M., Von Rosen, D., Kjellman, B. F., & Wetterberg, L. (1985). Melatonin, cortisol and ACTH in patients with major depressive disorder and healthy humans with special reference to the outcome of the dexamethasone suppression test. *Psychoneuroendocrinology*, *10*(2), 173–186.

Beck, A. T., Steer, R. A., & Brown, G. K. (1961). *Beck depression inventory-II*. 490–498.

Bedrosian, T. A., & Nelson, R. J. (2013). Influence of the modern light environment on mood. *Molecular Psychiatry*, *18*(7), 751–757.

Bedrosian, T. A., & Nelson, R. J. (2017). Timing of light exposure affects mood and brain circuits. *Nature Publishing Group*, *7*. https://doi.org/10.1038/tp.2016.262

Beijers, L., Wardenaar, K. J., van Loo, H. M., & Schoevers, R. A. (2019). Data-driven biological subtypes of depression: systematic review of biological approaches to depression subtyping. In *Molecular Psychiatry*. https://doi.org/10.1038/s41380-019-0385-5

Belenky, M. A., Smeraski, C. A., Provencio, I., Sollars, P. J., & Pickard, G. E. (2003). Melanopsin retinal ganglion cells receive bipolar and amacrine cell synapses. *Journal of Comparative Neurology*. https://doi.org/10.1002/cne.10652

Benca, R. M., Obermeyer, W. H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and Psychiatric Disorders: A Meta-analysis. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.1992.01820080059010

Benca, R. M., William, H., Thisted, R. A., & Gillin, J. C. (1992). Sleep and Psychiatric Disorders; A Meta-analysis. *Arch Gen Psychiatry*, *49*.

Benedetti, F., Radaelli, D., Bernasconi, A., Dallaspezia, S., Colombo, C., & Smeraldi, E. (2009). Changes in medial prefrontal cortex neural responses parallel successful antidepressant combination of venlafaxine and light therapy. *Archives Italiennes de Biologie*, *147*(3), 83–93.

Benedetti, F., Riccaboni, R., Locatelli, C., Poletti, S., Dallaspezia, S., & Colombo, C. (2013). Rapid treatment response of suicidal symptoms to lithium, sleep deprivation, and light therapy (chronotherapeutics) in drug-resistant bipolar depression. *The Journal of Clinical Psychiatry*, *74*(2), 16908.

Benedetti, Francesco. (2018). Rate of switch from bipolar depression into mania after morning light therapy: A historical review. *Psychiatry Research*, *261*(December 2017), 351–356. https://doi.org/10.1016/j.psychres.2018.01.013

Benedetti, Francesco, Calabrese, G., Bernasconi, A., Cadioli, M., Colombo, C., Dallaspezia, S.,

Falini, A., Radaelli, D., Scotti, G., & Smeraldi, E. (2009). Spectroscopic correlates of antidepressant response to sleep deprivation and light therapy: A 3.0 Tesla study of bipolar depression. *Psychiatry Research - Neuroimaging*, *173*(3), 238–242. https://doi.org/10.1016/j.pscychresns.2008.08.004

Benedetti, Francesco, Colombo, C., Pontiggia, A., Bernasconi, A., Florita, M., & Smeraldi, E. (2003). Morning light treatment hastens the antidepressant effect of citalopram: A placebo-controlled trial. *Journal of Clinical Psychiatry*, *64*(6), 648–653. https://doi.org/10.4088/JCP.v64n0605

Benedetti, Francesco, Dallaspezia, S., Fulgosi, M. C., Barbini, B., Colombo, C., & Smeraldi, E. (2007). Phase advance is an actimetric correlate of antidepressant response to sleep deprivation and light therapy in bipolar depression. *Chronobiology International*, *24*(5), 921–937. https://doi.org/10.1080/07420520701649455

Benedetti, Francesco, Serretti, A., Colombo, C., Barbini, B., Lorenzi, C., Campori, E., & Smeraldi, E. (2003). Influence of CLOCK gene polymorphism on circadian mood fluctuation and illness recurrence in bipolar depression. *American Journal of Medical Genetics*, *123B*(1), 23–26. https://doi.org/10.1002/ajmg.b.20038

Benloucif, S., Guico, M. J., Reid, K. J., Wolfe, L. F., L'Hermite-Balériaux, M., & Zee, P. C. (2005). Stability of melatonin and temperature as circadian phase markers and their relation to sleep times in humans. *Journal of Biological Rhythms*. https://doi.org/10.1177/0748730404273983

Berger, M., & Riemann, D. (1993). *REM sleep in depression an overview*. *2*(4), 211–223.

Berman, G., Muttuvelu, D., Berman, D., Larsen, J. I., Licht, R. W., Ledolter, J., & Kardon, R. H. (2018). Decreased retinal sensitivity in depressive disorder: a controlled study. *Acta Psychiatrica Scandinavica*, *137*(3), 231–240. https://doi.org/10.1111/acps.12851

Berry, R., Brooks, R., Gamaldo, C., Harding, S., Lloyd, R., & Marcus, C. (2016). American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events : Rules, Terminology, and Technical Specifications, Version 2.2. *American Academy of Sleep*, *28*(3), 391–397.

Bersani, G., Marconi, D., Limpido, L., Tarolla, E., & Caroti, E. (2008). Pilot study of light therapy and neurocognitive performance of attention and memory in healthy subjects. *Psychological Reports*. https://doi.org/10.2466/PR0.102.1.299-304

Berson, D. M., Dunn, F. A., & Takao, M. (2002). Phototransduction by retinal ganglion cells that set the circadian clock. *Science*, *295*(5557). https://doi.org/1070-1073. https://doi.org/10.1126/science.1067262.

Berson, David M, Dunn, F. A., & Takao, M. (2002). Photoransduction by retinal ganglion cells that set the circadian clock. *Science*, *295*(557), 1070–1073. %5C%5CRoot%5Cgroups%5CElectronic Library%5C300040

Bloch, M., Schmidt, P. J., Danaceau, M., Jean Murphy, M., Lynnette Nieman, M., & Rubinow, D. R. (2000). Effects of Gonadal Steroids in Women With a History of Postpartum Depression. *Am J Psychiatry*, *157*(6).

Böhmer, M. N., Hamers, P. C. M., Bindels, P. J. E., Oppewal, A., van Someren, E. J. W., & Festen, D. A. M. (2021). Are we still in the dark? A systematic review on personal daily light exposure, sleep-wake rhythm, and mood in healthy adults from the general population. *Sleep Health*, *7*(5), 610–630. https://doi.org/10.1016/j.sleh.2021.06.001

Boivin, D. B., Czeisler, C. A., Dijk, D., Duffy, J. F., Folkard, S., Minors, D. S., Totterdell, P., & Waterhouse, J. M. (1997). *Complex Interaction of the Sleep-Wake Cycle and Circadian*

Phase Modulates Mood in Healthy Subjects. *54*, 145–152.
Borbely, A. A. (1987). The S-deficiency hypothesis of depression and the two-process model of sleep regulation. *Pharmacopsychiatry*, *20*(1), 23–29. https://doi.org/10.1055/s-2007-1017069
Borbély, A. A. (1982). Two-Process Model of Sleep Regulation. *Hum Neurobiol*, *1*(3), 195–204. https://doi.org/10.1007/978-3-540-29678-2_6166
Borbély, A. A., Daan, S., Wirz-Justice, A., & Deboer, T. (2016). The two-process model of sleep regulation: A reappraisal. *Journal of Sleep Research*, *25*(2), 131–143.
Borbély, A., Daan, S., Wirz-Justice, A., & Deboer, T. (2016). The two-process model of sleep regulation: A reappraisal. *Journal of Sleep Research*, *25*(2), 131–143. https://doi.org/10.1111/jsr.12371
Borisuit, A., Linhart, F., Scartezzini, J. L., & Münch, M. (2015). Effects of realistic office daylighting and electric lighting conditions on visual comfort, alertness and mood. *Lighting Research and Technology*, *47*(2), 192–209. https://doi.org/10.1177/1477153514531518
Borragán, G., Deliens, G., Peigneux, P., & Leproult, R. (2017). Bright light exposure does not prevent the deterioration of alertness induced by sustained high cognitive load demands. *Journal of Environmental Psychology*, *51*, 95–103. https://doi.org/10.1016/j.jenvp.2017.03.008
Brainard, G. C., Hanifin, J. P., Greeson, J. M., Byrne, B., Glickman, G., Gerner, E., & Rollag, M. D. (2001). Action Spectrum for Melatonin Regulation in Humans Evidence for.pdf. *The Journal of Neuroscience*, *21*(16), 6405–6412.
Brainard, G. C., Hanifin, J. P., Rollag, M. D., Greeson, J., Byrne, B., Glickman, G., Gerner, E., & Sanford, B. (2001). Human melatonin regulation is not mediated by the three cone photopic visual system. *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jcem.86.1.7277
Brandenberger, G., & Follenius, M. (1975). Influence of timing and intensity of muscular exercise on temporal patterns of plasma cortisol levels. *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jcem-40-5-845
Brandenberger, G., Follenius, M., Hietter, B., Reinhardt, B., & Siméoni, M. (1982). Feedback from meal-related peaks determines diurnal changes in cortisol response to exercise. *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jcem-54-3-592
Brown, G. M. (1994). Light, melatonin and the sleep-wake cycle. In *Journal of Psychiatry and Neuroscience*.
Brown, M. A., Quan, S. F., & Eichling, P. S. (2011). Circadian rhythm sleep disorder, free-running type in a sighted male with severe depression, anxiety, and agoraphobia. *Journal of Clinical Sleep Medicine*, *7*(1), 93–94. https://doi.org/10.5664/jcsm.28047
Brown, T. M. (2020). Melanopic illuminance defines the magnitude of human circadian light responses under a wide range of conditions. *Journal of Pineal Research*, *February*, 1–14. https://doi.org/10.1111/jpi.12655
Brown, T. M., Thapan, K., Arendt, J., Revell, V. L., & Skene, D. J. (2021). S-cone contribution to the acute melatonin suppression response in humans. *Journal of Pineal Research*, 0–2. https://doi.org/10.1111/jpi.12719
Brzezinski, A. (1997). Melatonin in humans. In *New England Journal of Medicine* (Vol. 336, Issue 3, pp. 186–195). https://doi.org/10.1056/NEJM199701163360306
Buckley, T. M., & Schatzberg, A. F. (2010). A pilot study of the phase angle between cortisol and melatonin in major depression - A potential biomarker? *Journal of Psychiatric*

Research, *44*(2), 69–74. https://doi.org/10.1016/j.jpsychires.2009.06.012

Buikstra, N. J., Frederix, A. P. J., Heesterbeek, L. J. J., Krol, P., Schlangen, L. J., & Smolders, K. C. (2020). *The Influence of Dynamic Lighting on Sleeping Behavior, Sleep Quality and Lighting Experience of Patients at a Coronary Care Unit: report of HTI Research Project*.

Bulloch, A. G., Williams, J. V., Lavorato, D. H., & Patten, S. B. (2009). The relationship between major depression and marital disruption is bidirectional. *Depression and Anxiety*, *26*(12), 1172–1177. https://doi.org/10.1002/da.20618

Bullock, B, Burns, A., McGlashan, E., Lu, B., & Cain, S. (2019). Melanopsin signalling in the retina as a biomarker of vulnerability to bipolar disorder. *Bipolar Disorders*, *21*, 71–72.

Bullock, Ben, Mcglashan, E. M., Burns, A. C., Lu, B. S., & Cain, S. W. (2019). Traits related to bipolar disorder are associated with an increased post-illumination pupil response. *Psychiatry Research*. https://doi.org/10.1016/j.psychres.2019.05.025

Burch, J. B., Yost, M. G., Johnson, W., & Allen, E. (2005). Melatonin, sleep, and shift work adaptation. *Journal of Occupational and Environmental Medicine*. https://doi.org/10.1097/01.jom.0000177336.21147.9f

Burgess, H. J., Fogg, L. F., Young, M. A., & Eastman, C. I. (2004). Bright light therapy for winter depression - Is phase advancing beneficial? *Chronobiology International*. https://doi.org/10.1081/CBI-200025979

Burns, A., Allen, H., Tomenson, B., Duignan, D., & Byrne, J. (2009). Bright light therapy for agitation in dementia: A randomized controlled trial. *International Psychogeriatrics*, *21*(4), 711–721. https://doi.org/10.1017/S1041610209008886

Burns, A. C., Saxena, R., Vetter, C., Phillips, A. J., Lane, J. M., & Cain, S. W. (2021). Time spent in outdoor light is associated with mood, sleep, and circadian rhythm-related outcomes: a cross-sectional and longitudinal study in over 400,000 UK Biobank participants. *Journal of Affective Disorders*, *295*, 347–352. https://doi.org/https://doi.org/10.1016/j.jad.2021.08.056

Button, K. S., Kounali, D., Thomas, L., Wiles, N. J., Peters, T. J., Welton, N. J., Ades, A. E., & Lewis, G. (2015). Minimal clinically important difference on the Beck Depression Inventory-II according to the patient's perspective. *Psychological Medicine*, *45*(15), 3269–3279. https://doi.org/10.1017/S0033291715001270

Buysse, D. J., Reynolds, C. F., Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research*. https://doi.org/10.1016/0165-1781(89)90047-4

Caci, H. ., Robert, P. ., Dossios, C. ., & Boyer, P. . (2005). Morningness-Eveningness for Children Scale: Psychometric properties and month of birth effect [L'échelle de matinalité pour enfants et adolescents: Propriétés psychométriques et effet du mois de naissance]. *Encephale*.

Cagampang, F. R. A., & Inouye, S. I. T. (1994). Diurnal and circadian changes of serotonin in the suprachiasmatic nuclei: regulation by light and an endogenous pacemaker. *Brain Research*, *639*(1), 175–179.

Cagnacci, A. (1992). Melatonin: a major regulator of the circadian rhythm of core temperature in humans. *Journal of Clinical Endocrinology & Metabolism*, *75*(2), 447–452. https://doi.org/10.1210/jc.75.2.447

Cain, S. W., & Phillips, A. J. K. (2021). Do no harm: The beginning of the age of healthy hospital lighting. *Sleep*, *44*(3). https://doi.org/10.1093/sleep/zsab016

Cajochen, C. (2007). Alerting effects of light. *Sleep Medicine Reviews*, *11*(6), 453–464.

https://doi.org/10.1016/j.smrv.2007.07.009
Cajochen, C., Freyburger, M., Basishvili, T., Garbazza, C., Rudzik, F., Renz, C., Kobayashi, K., Shirakawa, Y., Stefani, O., & Weibel, J. (2019). Effect of daylight LED on visual comfort, melatonin, mood, waking performance and sleep. *Lighting Research and Technology*, *51*(7), 1044–1062. https://doi.org/10.1177/1477153519828419
Cajochen, Christian, Münch, M., Kobialka, S., Kräuchi, K., Steiner, R., Oelhafen, P., Orgül, S., & Wirz-Justice, A. (2005). High sensitivity of human melatonin, alertness, thermoregulation, and heart rate to short wavelength light. *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jc.2004-0957
Campbell, P. D., Miller, A. M., & Woesner, M. E. (2017). Bright Light Therapy: Seasonal Affective Disorder and Beyond. *The Einstein Journal of Biology and Medicine : EJBM*.
Cardinali, D. P., Furio, A. M., Reyes, M. P., & Brusco, L. I. (2006). The use of chronobiotics in the resynchronization of the sleep-wake cycle. *Cancer Causes and Control*, *17*(4), 601–609. https://doi.org/10.1007/s10552-005-9009-2
Cardinali, D. P., & Pévet, P. (1998). Basic aspects of melatonin action. *Sleep medicine reviews*, *2*(3), 175-190.
Carney, C. E., Ulmer, C., Edinger, J. D., Krystal, A. D., & Knauss, F. (2009). Assessing depression symptoms in those with insomnia: An examination of the beck depression inventory second edition (BDI-II). *Journal of Psychiatric Research*, *43*(5), 576–582. https://doi.org/10.1016/j.jpsychires.2008.09.002
Carpenter, J. S., Crouse, J. J., Scott, E. M., Naismith, S. L., Wilson, C., Scott, J., Hickie, I. B., & Merikangas, K. R. (2021). Circadian depression: a mood disorder phenotype. *Neuroscience & Biobehavioral Reviews*, *126*, 79–101.
Carpenter, Joanne S., Robillard, R., Hermens, D. F., Naismith, S. L., Gordon, C., Scott, E. M., & Hickie, I. B. (2017). Sleep-wake profiles and circadian rhythms of core temperature and melatonin in young people with affective disorders. *Journal of Psychiatric Research*, *94*, 131–138. https://doi.org/10.1016/j.jpsychires.2017.07.007
Carrier, J., Monk, T. H., Buysse, D. J., & Kupfer, D. J. (1997). Sleep and morningness-eveningness in the "middle" years of life (20-59 y). *Journal of Sleep Research*. https://doi.org/10.1111/j.1365-2869.1997.00230.x
Carskadon, M. A., Vieira, C., & Acebo, C. (1993). Association between puberty and delayed phase preference. *Sleep*. https://doi.org/10.1093/sleep/16.3.258
Carskadon, Mary A., Acebo, C., & Jenni, O. G. (2004). Regulation of adolescent sleep: Implications for behavior. *Annals of the New York Academy of Sciences*. https://doi.org/10.1196/annals.1308.032
Cassano, P., Petrie, S. R., Mischoulon, D., Cusin, C., Katnani, H., Yeung, A., De Taboada, L., Archibald, A., Bui, E., Baer, L., Chang, T., Chen, J., Pedrelli, P., Fisher, L., Farabaugh, A., Hamblin, M. R., Alpert, J. E., Fava, M., & Iosifescu, D. V. (2018). Transcranial Photobiomodulation for the Treatment of Major Depressive Disorder. the ELATED-2 Pilot Trial. *Photomedicine and Laser Surgery*, *36*(12), 634–646. https://doi.org/10.1089/pho.2018.4490
Chakraborty, R., Micic, G., Thorley, L., Nissen, T. R., Lovato, N., Collins, M. J., & Lack, L. C. (2021). Myopia, or near-sightedness, is associated with delayed melatonin circadian timing and lower melatonin output in young adult humans. *Sleep*, *44*(3), 1–12. https://doi.org/10.1093/sleep/zsaa208
Chakraborty, R., Read, S. A., & Collins, M. J. (2011). Diurnal variations in axial length,

choroidal thickness, intraocular pressure, and ocular biometrics. *Investigative Ophthalmology and Visual Science*, *52*(8), 5121–5129. https://doi.org/10.1167/iovs.11-7364

Challet, E. (2007). Minireview: Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. *Endocrinology*, *148*(12), 5648–5655. https://doi.org/10.1210/en.2007-0804

Challet, E., Turek, F. W., Laute, M. A., & Van Reeth, O. (2001). Sleep deprivation decreases phase-shift responses of circadian rhythms to light in the mouse: Role of serotonergic and metabolic signals. *Brain Research*, *909*(1–2), 81–91. https://doi.org/10.1016/S0006-8993(01)02625-7

Chan, J. W. Y., Li, S. X., Wai, S., Chau, H., Chan, N. Y., & Zhang, J. (2022). *Prediction of Dropout in a Randomized Controlled Trial of Adjunctive Light Treatment in Patients with Non-Seasonal Depression and Evening Chronotype*. 346–357.

Chang, A.-M., Aeschbach, D., Duffy, J. F., & Czeisler, C. A. (2015). Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(4), 1232–1237. https://doi.org/10.1073/pnas.1418490112

Chang, A.-M., Scheer, F. A. J. L., & Czeisler, C. A. (2011). The human circadian system adapts to prior photic history. *Journal of Physiology*, *589*(5), 1095–1102. https://doi.org/10.1113/jphysiol.2010.201194

Chang, A. M., Santhi, N., St Hilaire, M., Gronfier, C., Bradstreet, D. S., Duffy, J. F., Lockley, S. W., Kronauer, R. E., & Czeisler, C. A. (2012). Human responses to bright light of different durations. *Journal of Physiology*, *590*(13), 3103–3112. https://doi.org/10.1113/jphysiol.2011.226555

Chang, A. M., Scheer, F. A. J. L., & Czeisler, C. A. (2011). The human circadian system adapts to prior photic history. *Journal of Physiology*, *589*(5), 1095–1102. https://doi.org/10.1113/jphysiol.2010.201194

Chao, L. L. (2019). Effects of Home Photobiomodulation Treatments on Cognitive and Behavioral Function, Cerebral Perfusion, and Resting-State Functional Connectivity in Patients with Dementia: A Pilot Trial. *Photobiomodulation, Photomedicine, and Laser Surgery*, *37*(3), 133–141. https://doi.org/10.1089/photob.2018.4555

Chaouloff, F. (2000). Serotonin, stress and corticoids. *Journal of Psychopharmacology*, *14*(2), 139–151.

Chellappa, S. L., Steiner, R., Blattner, P., Oelhafen, P., Götz, T., & Cajochen, C. (2011). Non-visual effects of light on melatonin, alertness and cognitive performance: Can blue-enriched light keep us alert? *PLoS ONE*, *6*(1). https://doi.org/10.1371/journal.pone.0016429

Chung, K. I., & Song, C. H. (2001). Clinical usefulness of fatigue severity scale for patients with fatigue, and anxiety or depression. *Korean Journal of Psychosomatic Medicine*, *9*(2), 164–173.

CIE. (2018). *CIE S 026/E:2018 CIE System for Metrology of Optical Radiation for ipRGC-Influenced Responses to Light.* https://doi.org/10.1002/col.22350

CIE. (2019). *Position statement on non-visual effects of light - Recommending proper light at the proper time*. https://cie.co.at/publications/position-statement-non-visual-effects-light-recommending-proper-light-proper-time-2nd

CIE. (2020). *CIE TN 011:2020: What to Document and Report in Studies of ipRGC-Influenced Responses to Light*. https://doi.org/10.25039/TN.011.2020

Cleveland, R. B., Cleveland, W. S., & Terpenning, I. (1990). STL: A seasonal-trend

decomposition procedure based on loess. *Journal of Official Statistics*, *6*(1), 3.
Commission Internationale de l'Eclairage (CIE). (2015). *Report on the First International Workshop on Circadian and Neurophysiological Photometry, 2013 (CIE TN 003:2015)*. http://www.cie.co.at/index.php?i_ca_id=978.
Corfield, E. C., Martin, N. G., & Nyholt, D. R. (2016). Co-occurrence and symptomatology of fatigue and depression. *Comprehensive Psychiatry*, *71*, 1–10. https://doi.org/10.1016/j.comppsych.2016.08.004
Correa, Á., Barba, A., & Padilla, F. (2016). Light effects on behavioural performance depend on the individual state of vigilance. *PLoS ONE*, *11*(11), 1–13. https://doi.org/10.1371/journal.pone.0164945
Cowen, P., & Browning, M. (2015). What has serotonin to do with depression? *World Psychiatry*, *14*(2), 158. https://doi.org/10.1016/0168-5597(85)90012-7
Crasson, M., Kjiri, S., Colin, A., Kjiri, K., L'Hermite-Baleriaux, M., Ansseau, M., & Legros, J. J. (2004). Serum melatonin and urinary 6-sulfatoxymelatonin in major depression. *Psychoneuroendocrinology*, *29*(1), 1–12. https://doi.org/10.1016/S0306-4530(02)00123-3
Crowe, M., Inder, M., Douglas, K., Carlyle, D., Wells, H., Jordan, J., Lacey, C., Mulder, R., Beaglehole, B., & Porter, R. (2020). Interpersonal and Social Rhythm Therapy for Patients With Major Depressive Disorder. *American Journal of Psychotherapy*, *73*(1), 29–34.
Crowley, S. J., Van Reen, E., LeBourgeois, M. K., Acebo, C., Tarokh, L., Seifer, R., Barker, D. H., & Carskadon, M. A. (2014). A longitudinal assessment of sleep timing, circadian phase, and phase angle of entrainment across human adolescence. *PLoS ONE*, *9*(11). https://doi.org/10.1371/journal.pone.0112199
Czeisler, C. A., & Klerman, E. B. (1999). Circadian and sleep-dependent regulation of hormone release in humans. *Recent Progress in Hormone Research*.
Dacey, D., Liao, H.-W., Peterson, B., Robinson, F., Smith, V., Pokorny, J., Yau, K.-W., & Gamlin, P. (2005). Melanopsin-expressing ganglion cells in primate retina signal colour and irradiance and project to the LGN. *Nature*, *433*(7027), 741–745. https://doi.org/10.1038/nature03344
Daimon, K., Yamada, N., Tsujimoto, T., & Takahashi, S. (1992). Circadian rhythm abnormalities of deep body temperature in depressive disorders. *Journal of Affective Disorders*, *26*(3), 191–198. https://doi.org/10.1016/0165-0327(92)90015-X
Dalke, H., Little, J., Niemann, E., Camgoz, N., Steadman, G., Hill, S., & Stott, L. (2006). Colour and lighting in hospital design. *Optics and Laser Technology*, *38*(4–6), 343–365. https://doi.org/10.1016/j.optlastec.2005.06.040
Dallaspezia, S., & Benedetti, F. (2011). Chronobiological therapy for mood disorders. *Expert Review of Neurotherapeutics*, *11*(7), 961–970. https://doi.org/10.1586/ern.11.61
Dallaspezia, S., Benedetti, F., Scientifi Co Ospedale, I., & Raffaele, S. (2009). Melatonin, Circadian Rhythms, and the Clock Genes in Bipolar Disorder. *Current Psychiatry Reports*, *11*, 488–493.
Damiola, F., Le Minli, N., Preitner, N., Kornmann, B., Fleury-Olela, F., & Schibler, U. (2000). Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes and Development*. https://doi.org/10.1101/gad.183500
Danilenko, K. V., Lebedinskaia, M. Y., Gadetskaia, E. V., Markov, A. A., Ivanova, Y. A., & Aftanas, L. I. (2019). A 6-day combined wake and light therapy trial for unipolar depression. *Journal of Affective Disorders*, *259*, 355–361.

https://doi.org/10.1016/j.jad.2019.08.051
Dauphinais, D. R., Rosenthal, J. Z., Terman, M., DiFebo, H. M., Tuggle, C., & Rosenthal, N. E. (2012). Controlled trial of safety and efficacy of bright light therapy vs. negative air ions in patients with bipolar depression. *Psychiatry Research*. https://doi.org/10.1016/j.psychres.2012.01.015
de Alcantara Borba, D., Reis, R. S., de Melo Lima, P. H. T., Facundo, L. A., Narciso, F. V., Silva, A., & de Mello, M. T. (2020). How many days are needed for a reliable assessment by the Sleep Diary? *Sleep Science*, *13*(1), 49–53. https://doi.org/10.5935/1984-0063.20190131
Dedovic, K., & Ngiam, J. (2015). The cortisol awakening response and major depression: Examining the evidence. *Neuropsychiatric Disease and Treatment*, *11*, 1181–1189. https://doi.org/10.2147/NDT.S62289
Deltito, J. A., Moline, M., Pollak, C., Martin, L. Y., & Maremmani, I. (1991). Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders. *Journal of Affective Disorders*, *23*(4), 231–237. https://doi.org/10.1016/0165-0327(91)90105-2
Desir, D., van Cauther, E., Golstein, J., Fang, V., Leclecq, R., Refetoff, S., & Copinschi, G. (1980). Circadian and Ultradian Variations of ACTH and Cortisol Secretion. *Horm Res*, *13*, 302–316.
DeWeerdt, S. (2022). Can resetting the body clock help with depression? *Nature*, *608*(7924), S50–S51. https://doi.org/doi: https://doi.org/10.1038/d41586-022-02211-y
Dibner, C., Schibler, U., & Albrecht, U. (2010). The Mammalian Circadian Timing System: Organization and Coordination of Central and Peripheral Clocks. In *Annual Review of Physiology* (Vol. 72, Issue 1). https://doi.org/10.1146/annurev-physiol-021909-135821
Dietzel, M., Saletu, B., Lesch, O. M., Sieghart, W., & Schjerve, M. (1986). Light Treatment in Depressive Illness; Polysomnographic, Psychometric and Neuroendocrinological Findings. *Eur Neurol*, *25*(2), 93–103.
Dijk, D.-J., & Lockley, S. (2002). Invited Review: Integration of human sleep-wake regulation and circadian rhythmicity. *J Appl Physiol*, *92*, 852–862.
Dolsen, M. R., Asarnow, L. D., & Harvey, A. G. (2014). Insomnia as a Transdiagnostic Process in Psychiatric Disorders. *Current Psychiatry Reports*, *16*(9). https://doi.org/10.1007/s11920-014-0471-y
Drake, C. L., & Wright, K. P. (2010). Shift Work, Shift-Work Disorder, and Jet Lag. In *Principles and Practice of Sleep Medicine: Fifth Edition*. https://doi.org/10.1016/B978-1-4160-6645-3.00071-2
Duffy, J. F., & Czeisler, C. A. (2009). Effect of Light on Human Circadian Physiology. *Sleep Medicine Clinics*, *4*(2), 165–177. https://doi.org/10.1016/j.jsmc.2009.01.004
Duffy, J. F., & Dijk, D. J. (2002). Getting through to circadian oscillators: Why use constant routines? In *Journal of Biological Rhythms*. https://doi.org/10.1177/074873002129002294
Duffy, J. F., Rimmer, D. W., & Czeisler, C. A. (2001). Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. *Behavioral Neuroscience*. https://doi.org/10.1037/0735-7044.115.4.895
Duncan, W. C. (1996). Circadian rhythms and the pharmacology of affective illness. In *Pharmacology and Therapeutics*. https://doi.org/10.1016/S0163-7258(96)00092-7
Echizenya, M., Suda, H., Takeshima, M., Inomata, Y., & Shimizu, T. (2013). Total sleep deprivation followed by sleep phase advance and bright light therapy in drug-resistant mood disorders. *Journal of Affective Disorders*, *144*(1–2), 28–33.

https://doi.org/10.1016/j.jad.2012.06.022
Elliott, J. E., McBride, A. A., Balba, N. M., Thomas, S. V., Pattinson, C. L., Morasco, B. J., Wilkerson, A., Gill, J. M., & Lim, M. M. (2022). Feasibility and preliminary efficacy for morning bright light therapy to improve sleep and plasma biomarkers in US Veterans with TBI. A prospective, open-label, single-arm trial. *PLoS ONE*, *17*(4 April). https://doi.org/10.1371/journal.pone.0262955
Emens, J., Lewy, A., Kinzie, J. M., Arntz, D., & Rough, J. (2009). Circadian misalignment in major depressive disorder. *Psychiatry Research*, *168*(3), 259–261. https://doi.org/10.1016/j.psychres.2009.04.009
Even, C., Schröder, C. M., Friedman, S., & Rouillon, F. (2008). Efficacy of light therapy in nonseasonal depression: A systematic review. *Journal of Affective Disorders*, *108*(1–2), 11–23. https://doi.org/10.1016/j.jad.2007.09.008
Fajutrao, L., Locklear, J., Priaulx, J., & Heyes, A. (2009). A systematic review of the evidence of the burden of bipolar disorder in Europe. *Clinical Practice and Epidemiology in Mental Health*, *5*, 1–8. https://doi.org/10.1186/1745-0179-5-3
Fares, S., Hermens, D., Naismith, S., White, D., Hickie, I., & Robillard, R. (2015). Clinical correlates of chronotypes in young persons with mental disorders. *Chronobiology International*, *32*(9), 1183–1191. https://doi.org/10.3109/07420528.2015.1078346
Fava, M. (2000). New approaches to the treatment of refractory depression. *Journal of Clinical Psychiatry*, *61*(SUPPL. 1), 26–32.
Feigl, B., Ojha, G., Hides, L., & Zele, A. J. (2018). Melanopsin-driven pupil response and light exposure in non-seasonal major depressive disorder. *Frontiers in Neurology*, *9*(SEP). https://doi.org/10.3389/fneur.2018.00764
Feigl, B., & Zele, A. J. (2014). Melanopsin-expressing intrinsically photosensitive retinal ganglion cells in retinal disease. In *Optometry and Vision Science*. https://doi.org/10.1097/OPX.0000000000000284
Fernandez, D. C., Fogerson, P. M., Lazzerini Ospri, L., Thomsen, M. B., Layne, R. M., Severin, D., Zhan, J., Singer, J. H., Kirkwood, A., Zhao, H., Berson, D. M., & Hattar, S. (2018). Light Affects Mood and Learning through Distinct Retina-Brain Pathways. *Cell*. https://doi.org/10.1016/j.cell.2018.08.004
Figueiro, M. G., Hamner, R., Bierman, A., & Rea, M. S. (2013). Comparisons of three practical field devices used to measure personal light exposures and activity levels. *Lighting Research and Technology*, *45*(4), 421–434. https://doi.org/10.1177/1477153512450453
Figueiro, Mariana G., Bierman, A., & Rea, M. S. (2013). A train of blue light pulses delivered through closed eyelids suppresses melatonin and phase shifts the human circadian system. *Nature and Science of Sleep*, *5*, 133–141. https://doi.org/10.2147/NSS.S52203
Finan, P. H., Quartana, P. J., & Smith, M. T. (2015). The effects of sleep continuity disruption on positive mood and sleep architecture in healthy adults. *Sleep*, *38*(11), 1735–1742. https://doi.org/10.5665/sleep.5154
Fischer, S., Strawbridge, R., Vives, A. H., & Cleare, A. J. (2017). Cortisol as a predictor of psychological therapy response in depressive disorders: Systematic review and meta-analysis. In *British Journal of Psychiatry*. https://doi.org/10.1192/bjp.bp.115.180653
Fonken, L. K., & Nelson, R. J. (2014). The effects of light at night on circadian clocks and metabolism. In *Endocrine Reviews*. https://doi.org/10.1210/er.2013-1051
Fontana Gasio, P., Kräuchi, K., Cajochen, C., Van Someren, E., Amrhein, I., Pache, M., Savaskan, E., & Wirz-Justice, A. (2003). Dawn-dusk simulation light therapy of disturbed

circadian rest-activity cycles in demented elderly. *Experimental Psychology*, *38*(1–2), 207–216. www.elsevier.com/locate/expgero

Forest, G., Layton, F. R., & De Koninck, J. (2005). *Polysomnographie, chronobiologie et approche cognitive dans le traitement de la dépression majeure*. 139–152.

Freedman, M. S., Lucas, R. J., Soni, B., Von Schantz, M., Muñoz, M., David-Gray, Z., & Foster, R. (1999). Regulation of mammalian circadian behavior by non-rod, non-cone, ocular photoreceptors. *Science*. https://doi.org/10.1126/science.284.5413.502

Fritzsche, M., Heller, R., Hill, H., & Kick, H. (2001). Sleep deprivation as a predictor of response to light therapy in major depression. *Fortschritte Der Neurologie Psychiatrie*, *69*(4), 156–163. https://doi.org/10.1055/s-2001-12678

Fronczek, R. (2008). *Hypocretin deficiency : neuronal loss and functional consequences*. https://hdl.handle.net/1887/12580

Gau, S. F., & Soong, W. T. (2003). The transition of sleep-wake patterns in early adolescence. *Sleep*. https://doi.org/10.1093/sleep/26.4.449

Geoffroy, P. A., Schroder, C. M., Reynaud, E., & Bourgin, P. (2019). Efficacy of light therapy versus antidepressant drugs, and of the combination versus monotherapy, in major depressive episodes: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *48*, 101213. https://doi.org/10.1016/j.smrv.2019.101213

Germain, A., & Kupfer, D. J. (2008). Circadian rhythm disturbances in depression. *Humane Psychopharmacology*, *23*(3), 571–585. https://doi.org/10.1002/hup

Giedke, H., & Bloching, B. (1989). Therapeutic sleep deprivation in a brightly lit room. *Sleep*, *88*, 245–247.

Giles, D., Jarrett, R., Roffwarg, H., & Rush, A. (1987). Reduced Rapid Eye Movement Latency: a Predictor of Recurrence in Depression. *Neuropsychopharmacology*, *1*, 33–39.

Gillin, J. C., Duncan, W., Pettigrew, K. D., Frankel, B. L., & Snyder, F. (1979). Successful Separation of Depressed, Normal, and Insomniac Subjects by EEG Sleep Data. *Archives of General Psychiatry*, *36*(1), 85–90. https://doi.org/10.1001/archpsyc.1979.01780010091010

Giménez, M. C., Geerdinck, L. M., Versteylen, M., Leffers, P., Meekes, G. J. B. M., Herremans, H., de Ruyter, B., Bikker, J. W., Kuijpers, P. M. J. C., & Schlangen, L. J. M. (2017). Patient room lighting influences on sleep, appraisal and mood in hospitalized people. *Journal of Sleep Research*, *26*(2), 236–246. https://doi.org/10.1111/jsr.12470

Glickman, G., Byrne, B., Pineda, C., Hauck, W. W., & Brainard, G. C. (2006). Light therapy for Seasonal Affective Disorder with blue narrow-band light-emitting diodes (LEDs). *Biological Psychiatry*, *59*(6), 502–507. https://doi.org/10.1016/j.biopsych.2005.07.006

Glickman, G., Hanifin, J. P., Rollag, M. D., Wang, J., Cooper, H., & Brainard, G. C. (2003). Inferior retinal light exposure is more effective than superior retinal exposure in suppressing melatonin in humans. *Journal of Biological Rhythms*, *18*(1), 71–79. https://doi.org/10.1177/0748730402239678

Glod, C. A., Teicher, M. H., Polcari, A., Mcgreenery, C. E., & Ito, Y. (1997). Circadian rest-activity disturbances in children with seasonal affective disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *36*(2), 188–195. https://doi.org/10.1097/00004583-199702000-00009

Goetze, U., & Tölle, R. (1987). Circadian rhythm of free urinary cortisol, temperature and heart rate in endogenous depressives and under antidepressant therapy. *Neuropsychobiology*. https://doi.org/10.1159/000118414

Goldberg, D. (2011). The heterogeneity of "major depression." *World Psychiatry*, *10*(3), 226–

228. https://doi.org/10.1002/j.2051-5545.2011.tb00061.x
Golden, R. N., Gaynes, B. N., Ekstrom, R. D., Hamer, R. M., Jacobsen, F. M., Suppes, T., Wisner, K. L., & Nemeroff, C. B. (2005). The efficacy of light therapy in the treatment of mood disorders: A review and meta-analysis of the evidence. *American Journal of Psychiatry*, *162*(4), 656–662. https://doi.org/10.1176/appi.ajp.162.4.656
Gooley, J. J. (2008). *Treatment of Circadian Rhythm Sleep Disorders with Light*. *37*(8), 669–676.
Gooley, J. J., Rajaratnam, S. M. W., Brainard, G. C., Kronauer, R. E., Czeisler, C. A., & Lockley, S. W. (2010). Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. *Science Translational Medicine*. https://doi.org/10.1126/scitranslmed.3000741
Gorwood, P. (2010). Restoring circadian rhythms: a new way to successfully manage depression. In *Journal of psychopharmacology (Oxford, England)* (Vol. 24, Issue 2 Suppl, pp. 15–19). https://doi.org/10.1177/1359786810372981
Gotlib, I. H., & Joormann, J. (2010). Cognition and depression: Current status and future directions. *Annual Review of Clinical Psychology*, *6*, 285–312. https://doi.org/10.1146/annurev.clinpsy.121208.131305
Güler, A. D., Ecker, J. L., Lall, G. S., Haq, S., Altimus, C. M., Liao, H. W., Barnard, A. R., Cahill, H., Badea, T. C., Zhao, H., Hankins, M. W., Berson, D. M., Lucas, R. J., Yau, K. W., & Hattar, S. (2008). Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. *Nature*. https://doi.org/10.1038/nature06829
Gwirtsman, H. E., Halaris, A. E., Wolf, A. W., DeMet, E., Piletz, J. E., & Marler, M. (1989). Apparent phase advance in diurnal MHPG rhythm in depression. *The American Journal of Psychiatry*, *146*(11), 1427–1433.
Halberg, F. (1959). Physiologic 24-hour periodicity; general and procedural considerations with reference to the adrenal cycle. *Internationale Zeitschrift Fur Vitaminforschung*, *10*, 225.
Halberg, Franz. (1969). *Chronobiology*. http://repositorio.unan.edu.ni/2986/1/5624.pdf
Haley, C. (2009). *Improving Depressive Symptom Measurement in Adolescents: A Psychometric Evaluation of the Quick Inventory of Depressive Symptomatology, Adolescent Verison*.
Hanford, N., & Figueiro, M. (2013). Light therapy and Alzheimer's disease and related dementia: Past, present, and future. *Journal of Alzheimer's Disease*, *33*(4), 913–922. https://doi.org/10.3233/JAD-2012-121645
Hannibal, J., Hindersson, P., Østergaard, J., Georg, B., Heegaard, S., Larsen, P. J., & Fabrenkrug, J. (2004). Melanopsin is expressed in PACAP-containing retinal ganglion cells of the human retinohypothalamic tract. *Investigative Ophthalmology and Visual Science*. https://doi.org/10.1167/iovs.04-0313
Harb, F., Hidalgo, M. P., & Martau, B. (2015). Lack of exposure to natural light in the workspace is associated with physiological, sleep and depressive symptoms. *Chronobiology International*, *32*(3), 368–375. https://doi.org/10.3109/07420528.2014.982757
Harrison, Y. (2013). Individual response to the end of Daylight Saving Time is largely dependent on habitual sleep duration. *Biological Rhythm Research*, *44*(3 PG-391–401), 391–401. https://doi.org/http://dx.doi.org/10.1080/09291016.2012.692255
Harvey, K. J., & Espie, C. A. (2004). Development and preliminary validation of the Glasgow Content of Thoughts Inventory (GCTI): A new measure for the assessment of pre-sleep cognitive activity. *British Journal of Clinical Psychology*, *43*(4), 409–420. https://doi.org/10.1348/0144665042388900

Hasler, B. P., Buysse, D. J., Kupfer, D. J., & Germain, A. (2010). Phase relationships between core body temperature, melatonin, and sleep are associated with depression severity: Further evidence for circadian misalignment in non-seasonal depression. *Psychiatry Research*, *178*(1), 205–207. https://doi.org/10.1016/j.psychres.2010.04.027

Hasler, B. P., Buysse, D. J., Kupfer, D. J., & Germain, A. (2011). *Phase relationships and depression*. *178*(1), 205–207. https://doi.org/10.1016/j.psychres.2010.04.027.Phase

Haslerud, S., Magnussen, L. H., Joensen, J., Lopes-Martins, R. A. B., & Bjordal, J. M. (2015). The efficacy of low-level laser therapy for shoulder tendinopathy: a systematic review and meta-analysis of randomized controlled trials. *Physiotherapy Research International : The Journal for Researchers and Clinicians in Physical Therapy*, *20*(2), 108–125.

Hatori, M., & Panda, S. (2010). The emerging roles of melanopsin in behavioral adaptation to light. *Trends in Molecular Medicine*, *16*(10), 435–446. https://doi.org/10.1016/j.molmed.2010.07.005

Hattar, S., Kumar, M., Park, A., Tong, P., Tung, J., Yau, K. W., & Berson, D. M. (2006). Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *Journal of Comparative Neurology*, *497*(3), 326–349. https://doi.org/10.1002/cne.20970

Hayakawa, T., Uchiyama, M., Kamei, Y., Shibui, K., Tagaya, H., Asada, T., Okawa, M., Urata, J., & Takahashi, K. (2005). Clinical analyses of sighted patients with non-24-hour sleep-wake syndrome: A study of 57 consecutively diagnosed cases. *Sleep*, *28*(8), 945–952. https://doi.org/10.1093/sleep/28.8.945

Hébert, M., Martin, S. K., Lee, C., & Eastman, C. I. (2002). The effects of prior light history on the suppression of melatonin by light in humans. *Journal of Pineal Research*, *33*(4), 198–203.

Hebert, M., Martin, S., Lee, C., & Eastman, C. (2002). The effects of prior light history on the suppression of melatonin by light in humans. *Journal of Pineal Research*, *33*(4), 198–203.

Hedayati, S. S., Gregg, L. P., Carmody, T., Jain, N., Toups, M., Rush, A. J., Trivedi, M. H., & Toto, R. (2017). Effect of sertraline on depressive symptoms in patients with chronic kidney disease without dialysis dependence: the CAST randomized clinical trial. *Jama*, *318*(19), 1876–1890.

Hickie, I. B., Naismith, S. L., Robillard, R., Scott, E. M., & Hermens, D. F. (2013). Manipulating the sleep-wake cycle and circadian rhythms to improve clinical management of major depression. *BMC Medicine*, *11*(1). https://doi.org/10.1186/1741-7015-11-79

Hidalgo, M. P., Caumo, W., Posser, M., Coccaro, S. B., Camozzato, A. L., & Chaves, M. L. F. (2009). Relationship between depressive mood and chronotype in healthy subjects. *Psychiatry and Clinical Neurosciences*, *63*(3), 283–290. https://doi.org/10.1111/j.1440-1819.2009.01965.x

Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savović, J., Schulz, K. F., Weeks, L., & Sterne, J. A. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Online)*, *343*(7829), 1–9. https://doi.org/10.1136/bmj.d5928

Hines, D. J., Schmitt, L. I., Hines, R. M., Moss, S. J., & Haydon, P. G. (2013). Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. *Translational Psychiatry*, *3*(October 2012). https://doi.org/10.1038/tp.2012.136

Hollandera, L. E., Freeman, E. W., Sammela, M. D., Berlina, J. A., Grisso, J. A., & Battistini, M. (2001). Sleep quality, estradiol levels, and behavioral factors in late reproductive age women. *Obstetrics and Gynecology*. https://doi.org/10.1016/S0029-7844(01)01485-5

Holsboer-Trachsler, E., & Seffritz, E. (2000). Sleep in depression and sleep deprivation: A brief conceptual review. *World Journal of Biological Psychiatry*, *1*(4), 180–186. https://doi.org/10.3109/15622970009150589

Horne, C. M., & Norbury, R. (2018). Late chronotype is associated with enhanced amygdala reactivity and reduced fronto-limbic functional connectivity to fearful versus happy facial expressions. *NeuroImage*. https://doi.org/10.1016/j.neuroimage.2018.01.025

Horne, J. A., & Östberg, O. (1976). A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International Journal of Chronobiology*.

Huang, L. U., Xi, Y., Peng, Y., Yang, Y., Huang, X., Fu, Y., ... & Ren, C. (2019). A visual circuit related to habenula underlies the antidepressive effects of light therapy. *Neuron*, *102*(1), 128-142.

Huang, Z. Y., Ma, J., Chen, J., Shen, B., Pei, F. X., & Kraus, V. B. (2015). The effectiveness of low-level laser therapy for nonspecific chronic low back pain: A systematic review and meta-analysis. *Arthritis Research and Therapy*, *17*(1). https://doi.org/10.1186/s13075-015-0882-0

Huiberts, L. M., Smolders, K. C. H. J., & de Kort, Y. A. W. (2015). Shining light on memory: Effects of bright light on working memory performance. *Behavioural Brain Research*, *294*, 234–245. https://doi.org/10.1016/j.bbr.2015.07.045

Huiberts, L. M., Smolders, K. C. H. J., & De Kort, Y. A. W. (2017). Seasonal and time-of-day variations in acute non-image forming effects of illuminance level on performance, physiology, and subjective well-being. *Chronobiology International*, *34*(7), 827–844. https://doi.org/10.1080/07420528.2017.1324471

Hur, Y. M. (2007). Stability of genetic influence on morningness-eveningness: A cross-sectional examination of South Korean twins from preadolescence to young adulthood. *Journal of Sleep Research*. https://doi.org/10.1111/j.1365-2869.2007.00562.x

Hur, Y. M., Bouchard, T. J., & Lykken, D. T. (1998). Genetic and environmental influence on morningness-eveningness2. *Personality and Individual Differences*. https://doi.org/10.1016/s0191-8869(98)00089-0

Husse, J., Eichele, G., & Oster, H. (2015). Synchronization of the mammalian circadian timing system: Light can control peripheral clocks independently of the SCN clock: Alternate routes of entrainment optimize the alignment of the body's circadian clock network with external time. *BioEssays*, *37*(10), 1119–1128. https://doi.org/10.1002/bies.201500026

IEEE Power Electronics Society. (2015). IEEE Recommended Practices for Modulating Current in High-Brightness LEDs for Mitigating Health Risks to Viewers. *In IEEE Std*, 1789–2015.

Iskra-Golec, I. M., Wazna, A., & Smith, L. (2012). Effects of blue-enriched light on the daily course of mood, sleepiness and light perception: A field experiment. *Lighting Research and Technology*, *44*(4), 506–513. https://doi.org/10.1177/1477153512447528

Jasser, S. A., Hanifin, J. P., Rollag, M. D., & Brainard, G. C. (2006). Dim light adaptation attenuates acute melatonin suppression in humans. *Journal of Biological Rhythms*, *21*(5), 394–404. https://doi.org/10.1177/0748730406292391

JOHNSON, M. P., DUFFY, J. F., DIJK, D. J., RONDA, J. M., DYAL, C. M., & CZEISLER, C. A. (1992). Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. In *Journal of Sleep Research*. https://doi.org/10.1111/j.1365-2869.1992.tb00004.x

Jung, C. M., Khalsa, S. B. S., Scheer, F. A. J. L., Cajochen, C., Lockley, S. W., Czeisler, C. A., & Wright, K. P. (2010). Acute effects of bright light exposure on cortisol levels. *Journal of*

Biological Rhythms, *25*(3), 208–216. https://doi.org/10.1177/0748730410368413

Jusuf, P. R., Lee, S. C. S., Hannibal, J., & Grünert, U. (2007). Characterization and synaptic connectivity of melanopsin-containing ganglion cells in the primate retina. *European Journal of Neuroscience*. https://doi.org/10.1111/j.1460-9568.2007.05924.x

Kahn-Greene, E. T., Killgore, D. B., Kamimori, G. H., Balkin, T. J., & Killgore, W. D. S. (2007). The effects of sleep deprivation on symptoms of psychopathology in healthy adults. *Sleep Medicine*, *8*(3), 215–221. https://doi.org/10.1016/j.sleep.2006.08.007

Kasper, S., & Hamon, M. (2009). Beyond the monoaminergic hypothesis: Agomelatine, a new antidepressant with an innovative mechanism of action. *World Journal of Biological Psychiatry*, *10*(2), 117–126. https://doi.org/10.1080/15622970902717024

Keenan, S. A., Hirshkowitz, M., & Casseres, H. (2013). Monitoring and Staging Human Sleep. *Encyclopedia of Sleep*, 71–79. https://doi.org/10.1016/B978-0-12-378610-4.00138-8

Keller, J., Gomez, R., Williams, G., Lembke, A., Lazzeroni, L., Murphy, G. M., & Schatzberg, A. F. (2017). HPA axis in major depression: Cortisol, clinical symptomatology and genetic variation predict cognition. *Molecular Psychiatry*. https://doi.org/10.1038/mp.2016.120

Kennedy, S. H., & Emsley, R. (2006). Placebo-controlled trial of agomelatine in the treatment of major depressive disorder. *European Neuropsychopharmacology*. https://doi.org/10.1016/j.euroneuro.2005.09.002

Kerkhofs, M., Kempenaers, C., Linkowski, P., de Maertelaer, V., & Mendlewicz, J. (1988). Multivariate study of sleep EEG in depression. *Acta Psychiatrica Scandinavica*, *77*(4), 463–468. https://doi.org/10.1111/j.1600-0447.1988.tb05152.x

Kessler, R. C., Akiskal, H. S., Ames, M., Birnbaum, H., Greenberg, P., Hirschfeld, R. M. A., Jin, R., Merikangas, K. R., Simon, G. E., & Wang, P. S. (2006). Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. *American Journal of Psychiatry*, *163*(9), 1561–1568. https://doi.org/10.1176/ajp.2006.163.9.1561

Kessler, R. C., Mcgonagle, K. A., Zhao, S., Nelson, C. B., Hughes, M., Eshleman, S., Wittchen, M. H.-U., & Kendler, K. S. (1994). Lifetime and 12-Month Prevalence of DSM-III-R Psychiatric Disorders in the United States Results From the National Comorbidity Survey Background: This study presents estimates of lifetime and 12-month prevalence of 14 DSM-III-R psychiatric dis-orders from. *Archives of General Psychiatry*, *51*(1), 8–19. https://jamanetwork.com/

Khalsa, S. B. S., Jewett, M. E., Cajochen, C., & Czeisler, C. A. (2003). A phase response curve to single bright light pulses in human subjects. In *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2003.040477

Kitamura, S., Hida, A., Watanabe, M., Enomoto, M., Aritake-Okada, S., Moriguchi, Y., Kamei, Y., & Mishima, K. (2010). Evening preference is related to the incidence of depressive states independent of sleep-wake conditions. *Chronobiology International*. https://doi.org/10.3109/07420528.2010.516705

Klein, D. C., & Weller, J. L. (1972). Rapid light-induced decrease in pineal serotonin N-acetyltransferase activity. *Science*, *177*(4048), 532-533.

Kleitman, N. (1963). *Sleep and Wakefulness*. University of Chicago Press.

Klerman, E. B. (2005). Clinical aspects of human circadian rhythms. In *Journal of Biological Rhythms*. https://doi.org/10.1177/0748730405278353

Knaier, R., Klenk, C., Königstein, K., Hinrichs, T., Rossmeissl, A., Infanger, D., Cajochen, C., & Schmidt-Trucksäss, A. (2018). Morning bright light exposure has no influence on self-

chosen exercise intensity and mood in overweight individuals–A randomized controlled trial. *Chronobiology International*, *35*(4), 477–485. https://doi.org/10.1080/07420528.2017.1414828

Koenigsberg, H. W., Teicher, M. H., Mitropoulou, V., Navalta, C., New, A. S., Trestman, R., & Siever, L. J. (2004). 24-h Monitoring of plasma norepinephrine, MHPG, cortisol, growth hormone and prolactin in depression. *Journal of Psychiatric Research*. https://doi.org/10.1016/j.jpsychires.2004.03.006

Kozaki, T., Kubokawa, A., Taketomi, R., & Hatae, K. (2015). Effects of day-time exposure to different light intensities on light-induced melatonin suppression at night. *Journal of Physiological Anthropology*, *34*(1). https://doi.org/10.1186/s40101-015-0067-1

Krauchi, K., & Wirz-Justice, A. (1994). Circadian rhythm of heat production, heart rate, and skin and core temperature under unmasking conditions in men. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, *267*(3 36-3). https://doi.org/10.1152/ajpregu.1994.267.3.r819

Kripke, D. F., Mullaney, D. J., Klauber, M. R., Craig Risch, S., & Christian Gillin, J. (1992). Controlled trial of bright light for nonseasonal major depressive disorders. *Biological Psychiatry*, *31*(2), 119–134. https://doi.org/10.1016/0006-3223(92)90199-A

Krupp, L. B., Larocca, N. G., Muir Nash, J., & Steinberg, A. D. (1989). The fatigue severity scale: Application to patients with multiple sclerosis and systemic lupus erythematosus. *Archives of Neurology*, *46*(10), 1121–1123. https://doi.org/10.1001/archneur.1989.00520460115022

Kryger, M., Roth, T., & Dement, W. C. (2014). Principles and Practice of Sleep Medicine. In *Igarss 2014*. https://doi.org/10.1007/s13398-014-0173-7.2

Kudielka, B. M., Federenko, I. S., Hellhammer, D. H., & Wüst, S. (2006). Morningness and eveningness: The free cortisol rise after awakening in "early birds" and "night owls." *Biological Psychology*, *72*(2), 141–146. https://doi.org/10.1016/j.biopsycho.2005.08.003

Kupfer, D.J. (1976). REM latency: a psychobiologic marker for primary depressive disease. *Biological Psychiatry*, *11*(2), 159–174.

Kupfer, David J, Ulrich, R. F., Coble, P. A., Jarrett, D. B., Grochocinski, V., Doman, J., Matthews, G., & Borb4ly, A. A. (1984). Application of Automated REM and Slow Wave Sleep Analysis: II. Testing the Assumptions of theTwo-Process Model of Sleep Regulation in Normal and Depressed Subjects. *Psychiatry Research*, *13*, 333535–343343.

Lack, L., Wright, H., & Paynter, D. (2007). The treatment of sleep onset insomnia with bright morning light. *Sleep and Biological Rhythms*, *5*(3), 173–179. https://doi.org/10.1111/j.1479-8425.2007.00272.x

Lam, R., & Levitt, A. (1999). Canadian Consensus Guidelines for the Intervention of Seasonal Affective Disorder. *Clinical and Academic Publishing*, 1–160.

Lam, R. W. (1994). Morning light therapy for winter depression: predictors of response. *Acta Psychiatrica Scandinavica*, *89*(2), 97–101. https://doi.org/10.1111/j.1600-0447.1994.tb01494.x

Lam, Raymond W., Levitt, A. J., Levitan, R. D., Michalak, E. E., Cheung, A. H., Morehouse, R., Ramasubbu, R., Yatham, L. N., & Tam, E. M. (2016). Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder a randomized clinical trial. *JAMA Psychiatry*, *73*(1), 56–63. https://doi.org/10.1001/jamapsychiatry.2015.2235

Lam, Raymond W, Berkowitz, A. L., Berga, S. L., Clark, C. M., Kripke, D. F., & Gillin, J. C.

(1990). Melatonin Suppression in Bipolar and Unipolar Mood Disorders. *Psychiatry Research*, *33*(2), 129–134.

Lambert, G. W., Reid, C., Kaye, D. M., Jennings, G. L., & Esler, M. D. (2002). Effect of sunlight and season on serotonin turnover in the brain. *Lancet*, *360*(9348), 1840–1842. https://doi.org/10.1016/S0140-6736(02)11737-5

Larsen, R. J., & Diener, E. (1992). Promises and problems with the circumplex model of emotion. *Emotion. Review of Personality and Social Psychology*, *13*, 25–59.

Lasko, T. A., Kripke, D. F., & Elliot, J. A. (1999). Melatonin suppression by illumination of upper and lower visual fields. *Journal of Biological Rhythms*, *14*(2), 122–125. https://doi.org/10.1177/074873099129000506

Lastella, M., Rigney, G., Browne, M., & Sargent, C. (2020). Electronic device use in bed reduces sleep duration and quality in adults. *Sleep and Biological Rhythms*, *18*(2), 121–129. https://doi.org/10.1007/s41105-019-00251-y

Laurenzo, S. A., Kardon, R., Ledolter, J., Poolman, P., Schumacher, A. M., Potash, J. B., Full, J. M., Rice, O., Ketcham, A., Starkey, C., & Fiedorowicz, J. G. (2016). Pupillary response abnormalities in depressive disorders. *Psychiatry Research*, *246*(October), 492–499. https://doi.org/10.1016/j.psychres.2016.10.039

Lazzerini Ospri, L., Prusky, G., & Hattar, S. (2017). Mood, the Circadian System, and Melanopsin Retinal Ganglion Cells. *Annual Review of Neuroscience*. https://doi.org/10.1146/annurev-neuro-072116-031324

Lee, E. k., Dion, K., Spitale, N., Nixon, A., Chun, S., & Robillard, R. (2022). *Monitoring adherence to sleep and circadian disorders treatments*.

Lee, R. S. C., Hermens, D. F., Naismith, S. L., Lagopoulos, J., Jones, A., Scott, J., Chitty, K. M., White, D., Robillard, R., Scott, E. M., & Hickie, I. B. (2015). Neuropsychological and functional outcomes in recent-onset major depression, bipolar disorder and schizophrenia-spectrum disorders: A longitudinal cohort study. *Translational Psychiatry*, *5*(4), 1–10. https://doi.org/10.1038/tp.2015.50

Legates, T. A., Altimus, C. M., Wang, H., Lee, H. K., Yang, S., Zhao, H., Kirkwood, A., Weber, E. T., & Hattar, S. (2012). Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature*. https://doi.org/10.1038/nature11673

Legates, T. A., Fernandez, D. C., & Hattar, S. (2014). Light as a central modulator of circadian rhythms, sleep and affect. In *Nature Reviews Neuroscience*. https://doi.org/10.1038/nrn3743

LeGates, T. A., Fernandez, D. C., & Hattar, S. (2014). Light as a central modulator of circadian rhythms, sleep and affect. *Nature Reviews Neuroscience*, *15*(7), 443–454.

Leichtfried, V., Mair-Raggautz, M., Schaeffer, V., Hammerer-Lercher, A., Mair, G., Bartenbach, C., Canazei, M., & Schobersberger, W. (2015). Intense illumination in the morning hours improved mood and alertness but not mental performance. *Applied Ergonomics*, *46*(Part A), 54–59. https://doi.org/10.1016/j.apergo.2014.07.001

Lépine, J. P., & Briley, M. (2011). The increasing burden of depression. *Neuropsychiatric Disease and Treatment*, *7*(SUPPL.), 3–7. https://doi.org/10.2147/NDT.S19617

Leppämäki, S. (2006). The Effect of Exercise and Light on Mood. *Publications of the National Health Institute A*. http://www.ktl.fi/portal/4043

Lewy, A.J., Rough, J. N., Songer, J. B., Mishra, N., Yuhas, K., & Emens, J. S. (2022). The phase shift hypothesis for the circadian component of winter depression. *Dialogues in Clinical Neuroscience*.

Lewy, Alfred J., Sack, R. L., Singer, C. M., Whate, D. M., & Hoban, T. M. (1988). Winter

Depression and the Phase-Shift Hypothesis for Bright Light's Therapeutic Effects: History, Theory, and Experimental Evidence. *Journal of Biological Rhythms*. https://doi.org/10.1177/074873048800300203

Lewy, Alfred J., Wehr, T. A., Goodwin, F. K., Newsome, D. A., & Markey, S. P. (1980). Light suppresses melatonin secretion in humans. *Science*. https://doi.org/10.1126/science.7434030

Li, X., & Li, X. (2018). The antidepressant effect of light therapy from retinal projections. *Neuroscience Bulletin*, *34*(2), 359–368.

Li, Y., Zhang, J., & Liu, Z. (2006). Circadian Oscillators and Phase Synchronization under a Light-Dark Cycle Model of self-sustained oscillation in a SCN neuron. *Journal of Nonlinear Science*, *1*(3), 131–138.

LINKOWSKI, P., MENDLEWICZ, J., LECLERCQ, R., BRASSEUR, M., HUBAIN, P., GOLSTEIN, J., COPINSCHI, G., & CAUTER, E. VAN. (1985). The 24-Hour Profile of Adrenocorticotropin and Cortisol in Major Depressive Illness*. *The Journal of Clinical Endocrinology & Metabolism*. https://doi.org/10.1210/jcem-61-3-429

Lockley, S. W., Brainard, G. C., & Czeisler, C. A. (2003). High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. *Journal of Clinical Endocrinology and Metabolism*. https://doi.org/10.1210/jc.2003-030570

Lockley, S. W., Evans, E. E., Scheer, F. A. J. L., Brainard, G. C., Czeisler, C. A., & Aeschbach, D. (2006). Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep*. https://doi.org/10.1093/sleep/29.2.161

Logan, R. W., & McClung, C. A. (2019). Rhythms of life: circadian disruption and brain disorders across the lifespan. *Nature Reviews Neuroscience*, *20*(1), 49–65. https://doi.org/10.1038/s41583-018-0088-y

Loo, H., Hale, A., & D'haenen, H. (2002). Determination of the dose of agomelatine, a melatoninergic agonist and selective 5-HT 2C antagonist, in the treatment of major depressive disorder: a placebo-controlled dose range study. *International Clinical Psychopharmacology*, *17*(5), 239–247.

Lovato, N., & Gradisar, M. (2014). A meta-analysis and model of the relationship between sleep and depression in adolescents: Recommendations for future research and clinical practice. *Sleep Medicine Reviews*, *18*(6), 521–529. https://doi.org/10.1016/j.smrv.2014.03.006

Lowry, C. A., Hale, M. W., Evans, A. K., Heerkens, J., Staub, D. R., Gasser, P. J., & Shekhar, A. (2008). Serotonergic systems, anxiety, and affective disorder: Focus on the dorsomedial part of the dorsal raphe nucleus. *Annals of the New York Academy of Sciences*, *1148*, 86–94. https://doi.org/10.1196/annals.1410.004

Lucas, R. J., Freedman, M. S., Muñoz, M., Garcia-Fernández, J. M., & Foster, R. G. (1999). Regulation of the mammalian pineal by non-rod, non-cone, ocular photoreceptors. *Science*. https://doi.org/10.1126/science.284.5413.505

Lucas, R. J., Peirson, S. N., Berson, D. M., Brown, T. M., Cooper, H. M., Czeisler, C. A., Figueiro, M. G., Gamlin, P. D., Lockley, S. W., O'hagan, J. B., Price, L. L. A., Provencio, I., Skene, D. J., & Brainard, G. C. (2014). Measuring and using light in the melanopsin age Open access under CC BY-NC-ND license. *Trends in Neurosciences*, *37*(1), 1–9. https://doi.org/10.1016/j.tins.2013.10.004

Lux, V., & Kendler, K. S. (2010). Deconstructing major depression: A validation study of the DSM-IV symptomatic criteria. *Psychological Medicine*, *40*(10), 1679–1690. https://doi.org/10.1017/S0033291709992157

Mackert, A., Volz, H. P., Stieglitz, R. D., & Müller-Oerlinghausen, B. (1991). Phototherapy in nonseasonal depression. *Biological Psychiatry*. https://doi.org/10.1016/0006-3223(91)90110-8

Malek, Z. S., Dardente, H., Pevet, P., & Raison, S. (2005). Tissue-specific expression of tryptophan hydroxylase mRNAs in the rat midbrain: Anatomical evidence and daily profiles. *European Journal of Neuroscience*, *22*(4), 895–901. https://doi.org/10.1111/j.1460-9568.2005.04264.x

Malek, Z. S., Sage, D., Pévet, P., & Raison, S. (2007). Daily rhythm of tryptophan hydroxylase-2 messenger ribonucleic acid within raphe neurons is induced by corticoid daily surge and modulated by enhanced locomotor activity. *Endocrinology*, *148*(11), 5165–5172. https://doi.org/10.1210/en.2007-0526

Malkani, R. G., Abbott, S. M., Reid, K. J., & Zee, P. C. (2018). Diagnostic and treatment challenges of sighted non–24-hour sleep-wake disorder. *Journal of Clinical Sleep Medicine*, *14*(4), 603–613.

Marler, M. R., Gehrman, P., Martin, J. L., & Ancoli-Israel, S. (2006). The sigmoidally transformed cosine curve: A mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. *Statistics in Medicine*, *25*(22), 3893–3904. https://doi.org/10.1002/sim.2466

Mårtensson, B., Pettersson, A., Berglund, L., & Ekselius, L. (2015). Bright white light therapy in depression: A critical review of the evidence. *Journal of Affective Disorders*, *182*, 1–7. https://doi.org/10.1016/j.jad.2015.04.013

Martiny, K., Refsgaard, E., Lund, V., Lunde, M., Sørensen, L., Thougaard, B., & Bech, P. (2012). A 9-week randomized trial comparing a chronotherapeutic intervention (wake and light therapy) to exercise in major depressive disorder patients treated with duloxetine. *The Journal of Clinical Psychiatry*, *73*(9), 22327.

Martiny, Klaus. (2004). Adjunctive bright light in non-seasonal major depression. *Acta Psychiatrica Scandinavica, Supplement*, *110*(425), 7–28. https://doi.org/10.1111/j.1600-0447.2004.00460_2.x

Mason, I. C., Grimaldi, D., Reid, K. J., Warlick, C. D., Malkani, R. G., Abbott, S. M., & Zee, P. C. (2022). Light exposure during sleep impairs cardiometabolic function. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(12). https://doi.org/10.1073/pnas.2113290119

Maynard, M. L., Zele, A. J., Kwan, A. S., & Feigl, B. (2017). Intrinsically photosensitive retinal ganglion cell function, sleep efficiency and depression in advanced age-related macular degeneration. *Investigative Ophthalmology and Visual Science*, *58*(2), 990–996. https://doi.org/10.1167/iovs.16-20659

Mcadams, H., Kaiser, E. A., Igdalova, A., Haggerty, E. B., Cucchiara, B., Brainard C □, D. H., & Aguirre, G. K. (2020). Selective amplification of ipRGC signals accounts for interictal photophobia in migraine. *Proceedings of the National Academy of Sciences*, *117*(29), 17320–17329. https://doi.org/10.1073/pnas.2007402117/-/DCSupplemental

McEnany, G. W., & Lee, K. A. (2005). Effects of light therapy on sleep, mood, and temperature in women with nonseasonal major depression. *Issues in Mental Health Nursing*, *26*(7), 781–794. https://doi.org/10.1080/01612840591008410

McEwen, B. S. (2006). Sleep deprivation as a neurobiologic and physiologic stressor: allostasis and allostatic load. *Metabolism*, *55*, S20–S23. https://doi.org/10.1016/j.metabol.2006.07.008

McGlashan, E. M., Coleman, M. Y., Vidafar, P., Phillips, A. J. K., & Cain, S. W. (2019). Decreased sensitivity of the circadian system to light in current, but not remitted depression. *Journal of Affective Disorders*, *256*(November 2018), 386–392. https://doi.org/10.1016/j.jad.2019.05.076

McGlashan, E. M., Drummond, S. P. A., & Cain, S. W. (2018). Evening types demonstrate reduced SSRI treatment efficacy. *Chronobiology International*, *35*(8), 1175–1178. https://doi.org/10.1080/07420528.2018.1458316

McKenzie, J. E., & Osgood, D. W. (2004). Validation of a new telemetric core temperature monitor. *Journal of Thermal Biology*. https://doi.org/10.1016/j.jtherbio.2004.08.020

Meesters, Y., Beersma, D. G. M., Bouhuys, A. L., & Van Den Hoofdakker, R. H. (1999). Prophylactic treatment of seasonal affective disorder (SAD) by using light visors: Bright white or infrared light? *Biological Psychiatry*. https://doi.org/10.1016/S0006-3223(98)00252-2

Meesters, Y., Duijzer, W. B., & Hommes, V. (2018). The effects of low-intensity narrow-band blue-light treatment compared to bright white-light treatment in seasonal affective disorder. *Journal of Affective Disorders*, *232*(January), 48–51. https://doi.org/10.1016/j.jad.2018.01.024

Meesters, Y., Winthorst, W. H., Duijzer, W. B., & Hommes, V. (2016). The effects of low-intensity narrow-band blue-light treatment compared to bright white-light treatment in sub-syndromal seasonal affective disorder. *BMC Psychiatry*, *16*(1), 1–10. https://doi.org/10.1186/s12888-016-0729-5

Melchior, M., Ferrie, J. E., Alexanderson, K., Goldberg, M., Kivimaki, M., Singh-Manoux, A., Vahtera, J., Westerlund, H., Zins, M., & Head, J. (2010). Does sickness absence due to psychiatric disorder predict cause-specific mortality? A 16-year follow-up of the GAZEL occupational cohort study. *American Journal of Epidemiology*, *172*(6), 700–707. https://doi.org/10.1093/aje/kwq186

Melo, M. C. A., Abreu, R. L. C., Linhares Neto, V. B., de Bruin, P. F. C., & de Bruin, V. M. S. (2017). Chronotype and circadian rhythm in bipolar disorder: A systematic review. *Sleep Medicine Reviews*, *34*, 46–58. https://doi.org/10.1016/j.smrv.2016.06.007

Mendlewicz, J. (2009). Disruption of the circadian timing systems. *CNS Drugs*, *23*(2), 15–26.

Mendlewicz, J., Linkowski, P., Branchey, L., Weinberg, U., Weitzman, E. D., & Branchey, M. (1979). Abnormal 24 Hour Pattern of Melatonin Secretion in Depression. *The Lancet*, *314*(8156–8157), 1362. https://doi.org/10.1016/S0140-6736(79)92838-1

Meng, Q., Lian, Y., Jiang, J., Wang, W., Hou, X., Pan, Y., Chu, H., Shang, L., Wei, X., & Hao, W. (2018). Blue light filtered white light induces depression-like responses and temporary spatial learning deficits in rats. *Photochemical and Photobiological Sciences*, *17*(4), 386–394. https://doi.org/10.1039/c7pp00271h

Michalak, E. E., Hayes, S., Wilkinson, C., Hood, K., & Dowrick, C. (2002). Treatment compliance in light therapy: Do patients do as they say they do? *Journal of Affective Disorders*, *68*(2–3), 341–342.

Michalak, Erin E., Murray, G., Wilkinson, C., Dowrick, C., & Lam, R. W. (2007). A pilot study of adherence with light treatment for seasonal affective disorder. *Psychiatry Research*, *149*(1–3), 315–320. https://doi.org/10.1016/j.psychres.2006.05.005

Mills, P. R., Tomkins, S. C., & Schlangen, L. J. M. (2007). The effect of high correlated colour temperature office lighting on employee wellbeing and work performance. *Journal of Circadian Rhythms*, *5*, 1–9. https://doi.org/10.1186/1740-3391-5-2

Minors, D. S., Waterhouse, J. M., & Wirz-Justicg, A. (1991). A human phase-response curve to light. *Neuroscience Letters*, *133*(1), 36–40.

Mohawk, J. A., Green, C. B., & Takahashi, J. S. (2012). Central and Peripheral Circadian Clocks in Mammals. *Annual Review of Neuroscience*, *35*(1), 445–462. https://doi.org/10.1146/annurev-neuro-060909-153128

Möller, H. J. (2008). Outcomes in major depressive disorder: The evolving concept of remission and its implications for treatment. *World Journal of Biological Psychiatry*, *9*(2), 102–114. https://doi.org/10.1080/15622970801981606

Momma, T., Okayama, H., Saitou, M., Sugeno, H., Yoshimoto, N., Takebayashi, Y., Ohki, S., & Takenoshita, S. (2017). Expression of circadian clock genes in human colorectal adenoma and carcinoma. *Oncology Letters*. https://doi.org/10.3892/ol.2017.6876

Monteleone, P., & Maj, M. (2008). The circadian basis of mood disorders: Recent developments and treatment implications. In *European Neuropsychopharmacology*. https://doi.org/10.1016/j.euroneuro.2008.06.007

Monteleone, P., Martiadis, V., & Maj, M. (2011). Circadian rhythms and treatment implications in depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *35*(7), 1569–1574. https://doi.org/10.1016/j.pnpbp.2010.07.028

Montgomery, P., & Dennis, J. A. (2002). Bright light therapy for sleep problems in adults aged 60+. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd003403

Moon, J. H., Cho, C. H., Son, G. H., Geum, D., Chung, S., Kim, H., Kang, S. G., Park, Y. M., Yoon, H. K., Kim, L., Jee, H. J., An, H., Kripke, D. F., & Lee, H. J. (2016). Advanced Circadian Phase in Mania and Delayed Circadian Phase in Mixed Mania and Depression Returned to Normal after Treatment of Bipolar Disorder. *EBioMedicine*. https://doi.org/10.1016/j.ebiom.2016.08.019

Moore-Ede, M., Sulzman, F., & Fuller, C. (1982). *The Clocks that Time Us: Physiology of the Circadian Timing System*.

Moore, R. Y., & Eichler, V. B. (1972). Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Research*. https://doi.org/10.1016/0006-8993(72)90054-6

Münch, M., Wirz-Justice, A., Brown, S. A., Kantermann, T., Martiny, K., Stefani, O., Vetter, C., Wright, K. P., Wulff, K., & Skene, D. J. (2020). The Role of Daylight for Humans: Gaps in Current Knowledge. *Clocks & Sleep*, *2*(1), 61–85. https://doi.org/10.3390/clockssleep2010008

Murphy, P. J., & Campbell, S. S. (1997). Nighttime drop in body temperature: A physiological trigger for sleep onset? *Sleep*. https://doi.org/10.1093/sleep/20.7.505

Nair, N. P. V., Hariharasubramanian, N., & Pilapil, C. (1984). Circadian rhythm of plasma melatonin in endogenous depression. *Progress in Neuropsychopharmacology and Biological Psychiatry*, *8*(4–6), 715–718. https://doi.org/10.1016/0278-5846(84)90044-7

Natale, V., & Cicogna, P. C. (2002). Morningness-eveningness dimension: Is it really a continuum? *Personality and Individual Differences*. https://doi.org/10.1016/S0191-8869(01)00085-X

Neumeister, A., Goessler, R., Lucht, M., Kapitany, T., Bamas, C., & Kasper, S. (1996). Bright light therapy stabilizes the antidepressant effect of partial sleep deprivation. *Biological Psychiatry*. https://doi.org/10.1016/0006-3223(95)00086-0

Nicolson, N. A. (2008). Measurement of cortisol. *Handbook of Physiological Research Methods*

in Health Psychology, 37–74. https://doi.org/10.4135/9781412976244.n3

Nixon, A., Bonneville, K., Leveille, C., & Robillard, R. (2022). Associations Between Pre-Sleep Intrusive Thoughts, Sleep Difficulties, and Body Temperature in Youth with Mood Disorders. *Sleep Medicine*, *100*, S211.

Nixon, A. J., Hu, C., Godbout, R., & Robillard, R. (2017). *Sleep and Cardiovascular Dysfunctions in Bipolar Disorder*. 251–261. https://doi.org/10.1007/s40675-017-0085-0

Nixon, A., Strike, M., Thatte, S., Glozier, N., Fields, K. L., De Koninck, J., & Robillard, R. (2018). Improvements in mood and subjective sleep measures along the course of adjunctive phototherapy: an open-label study. *Journal of Sleep Research*, *27*.

Nixon, Ashley, De Koninck, J., Greenham, S., Robillard, R., & Boafo, A. (2021). Psychiatric Admissions of Children and Adolescents Across School Periods and Daylight-Saving Transitions. *Journal of the Canadian Academy of Child and Adolescent Psychiatry*, *30*(4), 226–235.

Nixon, Ashley, Strike, M. K., Feilds, K. L., Glozier, N., Thatte, S., Hickie, I. B., De Koninck, J., & Robillard, R. (2021). Temporal dynamics of subjective sleep profiles predicting mood improvements during adjunctive light therapy combined with sleep rescheduling. *Journal of Affective Disorders Reports*, *4*(November 2020), 12–15. https://doi.org/10.1016/j.jadr.2021.100106

Nizamutdinov, D., Qi, X., Berman, M. H., Dougal, G., Dayawansa, S., Wu, E., Yi, S. S., Stevens, A. B., & Huang, J. H. (2021). Transcranial near infrared light stimulations improve cognition in patients with dementia. *Aging and Disease*, *12*(4), 954–963. https://doi.org/10.14336/AD.2021.0229

Nolen-Hoeksema, S. (2001). Gender Differences in Depression. *Current Directions in Psychological Science*, *10*(5), 173–176. https://doi.org/10.1111/1467-8721.00142

Okamoto-Mizuno, K., & Mizuno, K. (2012). Effects of thermal environment on sleep and circadian rhythm. In *Journal of Physiological Anthropology*. https://doi.org/10.1186/1880-6805-31-14

Oren, D. A., Levendosky, A. A., Kasper, S., Duncan, C. C., & Rosenthal, N. E. (1996). Circadian profiles of cortisol, prolactin, and thyrotropin in seasonal affective disorder. *Biological Psychiatry*. https://doi.org/10.1016/0006-3223(95)00079-8

Pachito, D. V., Eckeli, A. L., Desouky, A. S., Corbett, M. A., Partonen, T., Rajaratnam, S. M. W., & Riera, R. (2018). Workplace lighting for improving alertness and mood in daytime workers. *Cochrane Database of Systematic Reviews*, *2018*(3). https://doi.org/10.1002/14651858.CD012243.pub2

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews*, *10*(1), 1–11. https://doi.org/10.1186/s13643-021-01626-4

Paine, S. J., Gander, P. H., & Travier, N. (2006). The epidemiology of morningness/eveningness: Influence of age, gender, ethnicity, and socioeconomic factors in adults (30-49 years). *Journal of Biological Rhythms*, *21*(1), 68–76. https://doi.org/10.1177/0748730405283154

Pan, A., Schernhammer, E. S., Sun, Q., & Hu, F. B. (2011). Rotating night shift work and risk of type 2 diabetes: Two prospective cohort studies in women. *PLoS Medicine*. https://doi.org/10.1371/journal.pmed.1001141

Pandi-Perumal, S. R., Smits, M., Spence, W., Srinivasan, V., Cardinali, D. P., Lowe, A. D., & Kayumov, L. (2007). Dim light melatonin onset (DLMO): A tool for the analysis of circadian phase in human sleep and chronobiological disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(1), 1–11. https://doi.org/10.1016/j.pnpbp.2006.06.020

Parrott, A. C., & Hindmarch, I. (1980). The leeds sleep evaluation questionnaire in psychopharmacological investigations-a review. *Psychopharmacology*, *71*(2), 173–179. https://doi.org/10.1007/BF00434408

Partonen, T., Leppämäki, S., Hurme, J., & Lönnqvist, J. (1998). Randomized trial of physical exercise alone or combined with bright light on mood and health-related quality of life. *Psychological Medicine*, *28*(6), 1359–1364. https://doi.org/10.1017/S0033291798007491

Partonen, Timo, & Lönnqvist, J. (2000). Bright light improves vitality and alleviates distress in healthy people. *Journal of Affective Disorders*, *57*(1–3), 55–61. https://doi.org/10.1016/S0165-0327(99)00063-4

Paus, S., Schmitz-Hübsch, T., Wüllner, U., Vogel, A., Klockgether, T., & Abele, M. (2007). Bright light therapy in Parkinson's disease: A pilot study. *Movement Disorders*, *22*(10), 1495–1498. https://doi.org/10.1002/mds.21542

Payne, J. D., & Nadel, L. (2004). Sleep, dreams, and memory consolidation: The role of the stress hormone cortisol. *Learning and Memory*, *11*(6), 671–678. https://doi.org/10.1101/lm.77104

Peeters, F., Nicolson, N. A., & Berkhof, J. (2004). Levels and variability of daily life cortisol secretion in major depression. *Psychiatry Research*. https://doi.org/10.1016/j.psychres.2003.12.010

Penders, T. M., Stanciu, C. N., Schoemann, A. M., Ninan, P. T., Bloch, R., & Saeed, S. A. (2016). Bright light therapy as augmentation of pharmacotherapy for treatment of depression: A systematic review and meta-analysis. *Prim. Care Companion J. Clin. Psych*, *18*(5). https://doi.org/10.4088/PCC.15r01906

Perera, S., Eisen, R., Bhatt, M., Bhatnagar, N., de Souza, R., Thabane, L., & Samaan, Z. (2016). Light therapy for non-seasonal depression: systematic review and meta-analysis. *British Journal of Psychiatry Open*, *2*(2), 116–126. https://doi.org/10.1192/bjpo.bp.115.001610

Pevet, P., & Challet, E. (2011). Melatonin: Both master clock output and internal time-giver in the circadian clocks network. In *Journal of Physiology Paris*. https://doi.org/10.1016/j.jphysparis.2011.07.001

Pflug, B., Erikson, R., & Johnsson, A. (1976). Depression and daily temperature A LONG-TERM STUDY. *Acta Psychiatrica Scandinavica*, *54*(4), 254–266.

Pflug, B., Johnsson, A., & Ekse, A. T. (1981). Manic-depressive states and daily temperature: SOME CIRCADIAN STUDIES. *Acta Psychiatrica Scandinavica*, *63*(3), 277–289. https://doi.org/10.1111/j.1600-0447.1981.tb00675.x

Pillai, V., Kalmbach, D. A., & Ciesla, J. A. (2011). A meta-analysis of electroencephalographic sleep in depression: Evidence for genetic biomarkers. *Biological Psychiatry*. https://doi.org/10.1016/j.biopsych.2011.07.016

Pittendrigh, C. (1993). Temporal Organization: Reflections of a Darwinian Clock-Watcher. *Annual Review of Physiology*, *55*(1), 17–54. https://doi.org/10.1146/annurev.physiol.55.1.17

Polo, A., Singh, S., Crispo, A., Russo, M., Giudice, A., Montella, M., Colonna, G., & Costantini, S. (2017). Evaluating the associations between human circadian rhythms and dysregulated

genes in liver cancer cells. *Oncology Letters*. https://doi.org/10.3892/ol.2017.7109

Poon, Y. P. Y. P., Kan, C. K., Yeung, W. F., & Chung, K. F. (2018). Delayed sleep-wake phase disorder and delayed sleep-wake phase in schizophrenia: Clinical and functional correlates. *Schizophrenia Research*, *202*, 412–413. https://doi.org/10.1016/j.schres.2018.06.057

Posener, J. A., DeBattista, C., Williams, G. H., Kraemer, H. C., Kalehzan, B. M., & Schatzberg, A. F. (2000). 24-Hour monitoring of cortisol and corticotropin secretion in psychotic and nonpsychotic major depression. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.57.8.755

Prayag, A., Münch, M., Aeschbach, D., Chellappa, S., & Gronfier, C. (2019). Light Modulation of Human Clocks, Wake, and Sleep. *Clocks & Sleep*, *1*(1), 193–208. https://doi.org/10.3390/clockssleep1010017

Prayag, A. S., Najjar, R. P., & Gronfier, C. (2019). Melatonin suppression is exquisitely sensitive to light and primarily driven by melanopsin in humans. *Journal of Pineal Research*, *66*(4), 1–8. https://doi.org/10.1111/jpi.12562

Profita, H., Roseway, A., & Czerwinski, M. (2015). Lightwear: An exploration in wearable light therapy. *In Proceedings of the Ninth International Conference on Tangible, Embedded, and Embodied Interaction*, 321–328.

Prosser, R. A., Miller, J. D., & Craig Heller, H. (1990). A serotonin agonist phase-shifts the circadian clock in the suprachiasmatic nuclei in vitro. *Brain Research*, *534*(1–2), 336–339. https://doi.org/10.1016/0006-8993(90)90153-3

Pruessner, J. C., Wolf, O. T., Hellhammer, D. H., Buske-Kirschbaum, A., Von Auer, K., Jobst, S., Kaspers, F., & Kirschbaum, C. (1997). Free cortisol levels after awakening: A reliable biological marker for the assessment of adrenocortical activity. *Life Sciences*. https://doi.org/10.1016/S0024-3205(97)01008-4

Quitkin, F. M., Rabkin, J. G., Ross, D., & Mcgrath, P. J. (1984). Duration of Antidepressant Drug Treatment: What Is an Adequate Trial? *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.1984.01790140028003

R Core Team. (2021). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.r-project.org/

Rahman, S. A., Kent, B. A., Grant, L. K., Clark, T., Hanifin, J. P., Barger, L. K., Lockley, S. W., Charles, C., Brainard, G., & Hilaire, M. (2022). Effects of dynamic lighting on circadian phase, self-reported sleep and performance during a 45-day space analog mission with chronic variable sleep deficiency. *Journal of Pineal Research*.

Randler, C., Bilger, S., & Díaz-Morales, J. F. (2009). Associations among sleep, chronotype, parental monitoring, and pubertal development among German adolescents. *Journal of Psychology: Interdisciplinary and Applied*. https://doi.org/10.3200/JRL.143.5.509-520

Rao, M. L., Müller-Oerlinghausen, B., Mackert, A., Strebel, B., Stieglitz, R. -D, & Volz, H. -P. (1992). Blood serotonin, serum melatonin and light therapy in healthy subjects and in patients with nonseasonal depression. *Acta Psychiatrica Scandinavica*, *86*(2), 127–132. https://doi.org/10.1111/j.1600-0447.1992.tb03240.x

Re-Timer. (n.d.). *Technical Specifications Re-Timer Glasses*. https://www.re-timer.com/specifications/

Revell, V. L., Arendt, J., Fogg, L. F., & Skene, D. J. (2006). Alerting effects of light are sensitive to very short wavelengths. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2006.01.032

Revell, V. L., Arendt, J., Terman, M., & Skene, D. J. (2005). Short-wavelength sensitivity of the

human circadian system to phase-advancing light. In *Journal of Biological Rhythms*. https://doi.org/10.1177/0748730405275655

Rhebergen, D., Korten, N. C. M., Penninx, B. W. J. H., Stek, M. L., van der Mast, R. C., Oude Voshaar, R., & Comijs, H. C. (2015). Hypothalamic-pituitary-adrenal axis activity in older persons with and without a depressive disorder. *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2014.10.005

Richter, K., Myllymaeki, J., Scharold-Schaefer, S., Tomova, I., Mayrer, R., & Niklewski, G. (2014). Treating Comorbid Insomnia in Older Adults via Cognitive-Behavioural Treatment, Bright Light and Exercise. *Health*, *06*(10), 960–968. https://doi.org/10.4236/health.2014.610121

Rietveld, W J. (1996). General introduction to chronobiology. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Medicas e Biologicas*, *29*(1), 63—70. http://europepmc.org/abstract/MED/8731333

Rietveld, Wop J., Minors, D. S., & Waterhouse, J. M. (1993). Circadian rhythms and masking: An overview. *Chronobiology International*, *10*(4), 306–312. https://doi.org/10.1080/07420529309059713

Ritter, P., Wieland, F., Skene, D. J., Pfennig, A., Weiss, M., Bauer, M., Severus, E., Güldner, H., Sauer, C., Soltmann, B., & Neumann, S. (2020). Melatonin suppression by melanopsin-weighted light in patients with bipolar i disorder compared to healthy controls. *Journal of Psychiatry and Neuroscience*, *45*(2), 79–87. https://doi.org/10.1503/jpn.190005

Robillard, R., Naismith, S., Smith, K., Rogers, N., White, D., Terpening, Z., Ip, T., Hermens, D., Whitwell, B., Scott, E., & Hickie, I. (2014). Sleep-Wake Cycle in Young and Older Persons with a Lifetime History of Mood Disorders. *PLoS ONE*, *9*(2), e87763. https://doi.org/10.1371/journal.pone.0087763

Robillard, R, Carpenter, J., Feilds, K., Hermens, D., White, D., Naismith, S., Bartlett, D., Whitwell, B., Southan, J., Scott, E., & Hickie, I. (2018). Parallel Changes in Mood and Melatonin Rhythm Following an Adjunctive Multimodal Chronobiological Intervention With Agomelatine in People With Depression: A Proof of Concept Open Label Study. *Frontiers in Psychiatry*, *9*(December), 1–8. https://doi.org/10.3389/fpsyt.2018.00624

Robillard, R, Carpenter, J. S., Rogers, N. L., Fares, S., Grierson, A. B., Hermens, D. F., Naismith, S. L., Mullin, S. J., Feilds, K. L., Glozier, N., Scott, E. M., & Hickie, I. B. (2018). Circadian rhythms and psychiatric profiles in young adults with unipolar depressive disorders. *Translational Psychiatry*, *8*(1), 213. https://doi.org/10.1038/s41398-018-0255-y

Robillard, R, Hermens, D., Naismith, S., White, D., Rogers, N., Ip, T., Mullin, S., Alvares, G., Guastella, A., Smith, K., Rong, Y., Whitwell, B., Southan, J., Glozier, N., Scott, E., & Hickie, I. (2015). Ambulatory sleep-wake patterns and variability in young people with emerging mental disorders. *Journal of Psychiatry and Neuroscience*, *40*(1), 28–37. https://doi.org/10.1503/jpn.130247

Robillard, R, Naismith, S. L., Rogers, N. L., Scott, E. M., Ip, T. K. C., Hermens, D. F., & Hickie, I. B. (2013). Sleep-Wake cycle and melatonin rhythms in adolescents and young adults with mood disorders: Comparison of unipolar and bipolar phenotypes. *European Psychiatry*, *28*(7), 412–416. https://doi.org/10.1016/j.eurpsy.2013.04.001

Robillard, Rebecca, Carpenter, J., Rogers, N., Fares, S., Grierson, A., Hermens, D., Naismith, S., Mullin, S. J., Feilds, K.-L., Glozier, N., Scott, E. M., & Hickie, I. B. (2018). Circadian rhythms and psychiatric profiles in young adults with unipolar depressive disorders Running title: Circadian rhythms in depression Rébecca Robillard. *Translational*

Psychiatry, *In press*.

Robillard, Rébecca, Naismith, S. L., Rogers, N. L., Ip, T. K. C., Hermens, D. F., Scott, E. M., & Hickie, I. B. (2013). Delayed sleep phase in young people with unipolar or bipolar affective disorders. *Journal of Affective Disorders*, *145*(2), 260–263. https://doi.org/10.1016/j.jad.2012.06.006

Rodenbeck, A., Huether, G., Rüther, E., & Hajak, G. (2002). Interactions between evening and nocturnal cortisol secretion and sleep parameters in patients with severe chronic primary insomnia. *Neuroscience Letters*. https://doi.org/10.1016/S0304-3940(02)00192-1

Roecklein, K. A., Franzen, P. L., Wescott, D. L., Hasler, B. P., Miller, M. A., Donofry, S. D., DuPont, C. M., Gratzmiller, S. M., Drexler, S. P., Wood-Vasey, W. M., & Gamlin, P. D. (2021). Melanopsin-driven pupil response in summer and winter in unipolar seasonal affective disorder. *Journal of Affective Disorders*, *291*, 93–101. https://doi.org/10.1016/j.jad.2021.04.084

Roecklein, K., Wong, P., Ernecoff, N., Miller, M., Donofry, S., Kamarck, M., Wood-Vasey, W. M., & Franzen, P. (2013). The post illumination pupil response is reduced in seasonal affective disorder. *Psychiatry Research*, *210*(1), 150–158. https://doi.org/10.1016/j.psychres.2013.05.023

Roenneberg, T., Kuehnle, T., Juda, M., Kantermann, T., Allebrandt, K., Gordijn, M., & Merrow, M. (2007). Epidemiology of the human circadian clock. In *Sleep Medicine Reviews* (Vol. 11, Issue 6, pp. 429–438). https://doi.org/10.1016/j.smrv.2007.07.005

Roenneberg, T., Kuehnle, T., Pramstaller, P. P., Ricken, J., Havel, M., Guth, A., & Merrow, M. (2004). A marker for the end of adolescence. *Current Biology*, *14*(24), 1038–1039. https://doi.org/10.1016/j.cub.2004.11.039

Rohan, K. J., Roecklein, K. A., Tierney Lindsey, K., Johnson, L. G., Lippy, R. D., Lacy, T. J., & Barton, F. B. (2007). A randomized controlled trial of cognitive-behavioral therapy, light therapy, and their combination for seasonal affective disorder. *Journal of Consulting and Clinical Psychology*, *75*(3), 489–500.

Rosenthal, N. E., Sack, D. A., Gillin, J. C., Lewy, A. J., Goodwin, F. K., Davenport, Y., Wehr, T. A., Mueller, P., & Newsome, D. (1984). Seasonal affective disorder: a description of the syndrome and preliminary findings with light therapy. *Archives of General Psychiatry*, *41*(1), 72–80.

Rosenthal, Norman E, Sack, D. A., Skwerer, R. G., Jacobsen, F. M., & Wehr, T. A. (1988). Phototherapy for Seasonal Affective Disorder. *Journal of Biological Rhythms*, *3*(2), 101–120. https://doi.org/10.1177/074873048800300202

Roy, A., Nikolitch, K., McGinn, R., Jinah, S., Klement, W., & Kaminsky, Z. A. (2020). A machine learning approach predicts future risk to suicidal ideation from social media data. *Npj Digital Medicine*, *3*(1), 1–12. https://doi.org/10.1038/s41746-020-0287-6

Ru, T., de Kort, Y. A. W., Smolders, K. C. H. J., Chen, Q., & Zhou, G. (2019). Non-image forming effects of illuminance and correlated color temperature of office light on alertness, mood, and performance across cognitive domains. *Building and Environment*, *149*(December 2018), 253–263. https://doi.org/10.1016/j.buildenv.2018.12.002

Rubin, R., Heist, K., McGeoy, S., Hanada, K., & Lesser, I. (1992). Neuroendocrine aspects of primary endogenous depression. XI. Serum melatonin measures in patients and matched control subjects. *Arch Gen Psychiatry*, *49*(7), 558–567.

Rubinow, D. R., Schmidt, P. J., & Roca, C. A. (1998). Estrogen-Serotonin Interactions: Implications for Affective Regulation. *Biological Psychiatry*, *44*(9), 839–850.

Rufiange, M., Beaulieu, C., Lachapelle, P., & Dumont, M. (2007). Circadian light sensitivity and rate of retinal dark adaptation in indoor and outdoor workers. *Journal of Biological Rhythms*, *22*(5), 454–457. https://doi.org/10.1177/0748730407305375

Rüger, M., Gordijn, M. C. M., Beersma, D. G. M., De Vries, B., & Daan, S. (2005). Nasal versus temporal illumination of the human retina: Effects on core body temperature, melatonin, and circadian phase. *Journal of Biological Rhythms*, *20*(1), 60–70. https://doi.org/10.1177/0748730404270539

Rüger, M., St Hilaire, M. A., Brainard, G. C., Khalsa, S. B. S., Kronauer, R. E., Czeisler, C. A., & Lockley, S. W. (2013). Human phase response curve to a single 6.5 h pulse of short-wavelength light. *Journal of Physiology*, *591*(1), 353–363. https://doi.org/10.1113/jphysiol.2012.239046

Rupp, A. C., Ren, M., Altimus, C. M., Fernandez, D. C., Richardson, M., Turek, F., Hattar, S., & Schmidt, T. M. (2019). Distinct ipRGC subpopulations mediate light's acute and circadian effects on body temperature and sleep. *ELife*. https://doi.org/10.7554/eLife.44358

Rush, a J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., Markowitz, J. C., Ninan, P. T., Kornstein, S., Manber, R., Thase, M. E., Kocsis, J. H., & Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), Clinician Rating (QIDS-C), and Self-Report (QIDS-SR): A Psychometric Evaluation in Patients with Chronic Major Depression. *Depression*, *54*(5), 573–583. https://doi.org/10.1016/S0006-3223(03)01866-8

Rush, A. J., Erman, M. K., Giles, D. E., Schlesser, M. A., Carpenter, G., Vasavada, N., & Roffwarg, H. P. (1986). Polysomnographic Findings in Recently Drug-Free and Clinically Remitted Depressed Patients. *Archives of General Psychiatry*, *43*(9), 878–884. https://doi.org/10.1001/archpsyc.1986.01800090068009

Rush, A. J., Giles, D. E., Jarrett, R. B., !-,Ldman-Koffler, F., Debus, J. R., Weissenburger, J., Orsulak, P. J., & Roffwarg, H. P. (1989). Reduced REM Latency Predicts Response to Tricyclic Medication in Depressed Outpatients. *Biological Psychiatry*, *26*(1), 61–72.

Rutten, S., Vriend, C., Smit, J. H., Berendse, H. W., Van Someren, E. J., Hoogendoorn, A. W., Van Den Heuvel, O. A., Twisk, J., & van der Werf, Y. (2019). Bright light therapy for depression in Parkinson disease: A randomized controlled trial. *Neurology*, *92*(11), e1145–e1156.

Rutten, Sonja, Vriend, C., Van Den Heuvel, O. A., Smit, J. H., Berendse, H. W., & Van Der Werf, Y. D. (2012). Bright light therapy in parkinson's disease: An overview of the background and evidence. *Parkinson's Disease*. https://doi.org/10.1155/2012/767105

Sahlem, G. L., Kalivas, B., Fox, J. B., Lamb, K., Roper, A., Williams, E. N., Williams, N. R., Korte, J. E., Zuschlag, Z. D., El Sabbagh, S., Guille, C., Barth, K. S., Uhde, T. W., George, M. S., & Short, E. B. (2014). Adjunctive triple chronotherapy (combined total sleep deprivation, sleep phase advance, and bright light therapy) rapidly improves mood and suicidality in suicidal depressed inpatients: An open label pilot study. *Journal of Psychiatric Research*, *59*, 101–107. https://doi.org/10.1016/j.jpsychires.2014.08.015

Salmela-Aro, K. (2011). Stages of adolescence. *Encyclopedia of Adolescence*, 360–368.

Salomon, R. M., Delgado, P. L., Licinio, J., Krystal, J. H., Heninger, G. R., & Charney, D. S. (1994). Effects of Sleep Deprivation on Serotonin Function in Depression. *Biological Psychiatry*, *36*(12), 840–846.

Schlangen, L. J. M., & Price, L. L. A. (2021). The Lighting Environment, Its Metrology, and Non-visual Responses. *Frontiers in Neurology*, *12*(March).

https://doi.org/10.3389/fneur.2021.624861
Schmidt, T. M., & Kofuji, P. (2010). Differential cone pathway influence on intrinsically photosensitive retinal ganglion cell subtypes. *Journal of Neuroscience*. https://doi.org/10.1523/JNEUROSCI.3656-10.2010
Shahid, A., Wilkinson, K., Marcu, S., & Shapiro, C. M. (2011). Karolinska Sleepiness Scale (KSS). In *STOP, THAT and One Hundred Other Sleep Scales*. https://doi.org/10.1007/978-1-4419-9893-4_47
Shanahan, T. L., Zeitzer, J. M., & Czeisler, C. A. (1997). Resetting the Melatonin Rhythm with Light in Humans. *Journal of Biological Rhythms*, *12*(6), 556–567. https://doi.org/10.1177/074873049701200610
Sheehan, D. (2016). *The MINI international neuropsychiatric interview,(Version 7.0. 2) for DSM–5*.
Sheehan, David V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*.
Simonneaux, V., & Ribelayga, C. (2003). Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. *Pharmacological reviews*, *55*(2), 325-395.
Siraji, M. A., Kalavally, V., Schaefer, A., & Haque, S. (2022). Effects of Daytime Electric Light Exposure on Human Alertness and Higher Cognitive Functions: A Systematic Review. *Frontiers in Psychology*, *12*(January), 1–17. https://doi.org/10.3389/fpsyg.2021.765750
Sit, D. K., McGowan, J., Wiltrout, C., Diler, R. S., Dills, J., Luther, J., Yang, A., Ciolino, J. D., Seltman, H., Wisniewski, S. R., Terman, M., & Wisner, K. L. (2018). Adjunctive bright light therapy for bipolar depression: A randomized double-blind placebo-controlled trial. *American Journal of Psychiatry*, *175*(2), 131–139. https://doi.org/10.1176/appi.ajp.2017.16101200
Smith, C. S., Reilly, C., & Midkiff, K. (1989). Evaluation of Three Circadian Rhythm Questionnaires With Suggestions for an Improved Measure of Morningness. *Journal of Applied Psychology*. https://doi.org/10.1037/0021-9010.74.5.728
Smith, K. A., Schoen, M. W., & Czeisler, C. A. (2004). Adaptation of human pineal melatonin suppression by recent photic history. *Journal of Clinical Endocrinology and Metabolism*, *89*(7), 3610–3614. https://doi.org/10.1210/jc.2003-032100
Smolders, K. C. H. J., de Kort, Y. A. W., & Cluitmans, P. J. M. (2012). A higher illuminance induces alertness even during office hours: Findings on subjective measures, task performance and heart rate measures. *Physiology and Behavior*, *107*(1), 7–16. https://doi.org/10.1016/j.physbeh.2012.04.028
Smolders, K. C. H. J., De Kort, Y. A. W., & Cluitmans, P. J. M. (2016). Higher light intensity induces modulations in brain activity even during regular daytime working hours. *Lighting Research and Technology*, *48*(4), 433–448. https://doi.org/10.1177/1477153515576399
Smolders, K. C. H. J., De Kort, Y. A. W., & van den Berg, S. M. (2013). Daytime light exposure and feelings of vitality: Results of a field study during regular weekdays. *Journal of Environmental Psychology*, *36*, 270–279.
Smolders, K., & de Kort, Y. (2014). Bright light and mental fatigue: Effects on alertness, vitality, performance and physiological arousal. *Journal of Environmental Psychology*, *39*, 77–91. https://doi.org/10.1016/j.jenvp.2013.12.010

Šmotek, M., Fárková, E., Manková, D., & Kopřivová, J. (2020). Evening and night exposure to screens of media devices and its association with subjectively perceived sleep: Should "light hygiene" be given more attention? *Sleep Health*, *6*(4), 498–505. https://doi.org/10.1016/j.sleh.2019.11.007

Solomon, D. A., Leon, A. C., Endicott, J., Mueller, T. I., Coryell, W., Shea, M. T., & Keller, M. B. (2004). Psychosocial impairment and recurrence of major depression. *Comprehensive Psychiatry*, *45*(6), 423–430. https://doi.org/10.1016/j.comppsych.2004.07.002

Souêtre, E., Salvati, E., Belugou, J. L., Pringuey, D., Candito, M., Krebs, B., Ardisson, J. L., & Darcourt, G. (1989). Circadian rhythms in depression and recovery: Evidence for blunted amplitude as the main chronobiological abnormality. *Psychiatry Research*. https://doi.org/10.1016/0165-1781(89)90207-2

Souman, J., Borra, T., de Goijer, I., Schlangen, L., Vlaskamp, B. N. S., & Lucassen, M. P. (2018). Spectral Tuning of White Light Allows for Strong Reduction in Melatonin Suppression without Changing Illumination Level or Color Temperature. *Journal of Biological Rhythms*, *33*(4), 420–431. https://doi.org/10.1177/0748730418784041

Souman, J., Tinga, A. M., te Pas, S. F., van Ee, R., & Vlaskamp, B. N. S. (2018). Acute alerting effects of light: A systematic literature review. *Behavioural Brain Research*, *337*(September 2017), 228–239. https://doi.org/10.1016/j.bbr.2017.09.016

Spindelegger, C., Stein, P., Wadsak, W., Fink, M., Mitterhauser, M., Moser, U., Savli, M., Mien, L. K., Akimova, E., Hahn, A., Willeit, M., Kletter, K., Kasper, S., & Lanzenberger, R. (2012). Light-dependent alteration of serotonin-1A receptor binding in cortical and subcortical limbic regions in the human brain. *World Journal of Biological Psychiatry*, *13*(6), 413–422. https://doi.org/10.3109/15622975.2011.630405

Spitschan, M., Stefani, O., Blattner, P., Gronfier, C., Lockley, S., & Lucas, R. (2019). How to Report Light Exposure in Human Chronobiology and Sleep Research Experiments. *Clocks & Sleep*, *1*(3), 280–289. https://doi.org/10.3390/clockssleep1030024

Srinivasan, V., Smits, M., Spence, W., Lowe, A., Kayumov, L., Pandi-Perumal, S., Parry, B., & Cardinali, D. (2006). Melatonin in mood disorders. In *World Journal of Biological Psychiatry*. https://doi.org/10.1080/15622970600571822

St Hilaire, M. A., Gooley, J. J., Khalsa, S. B. S., Kronauer, R. E., Czeisler, C. A., & Lockley, S. W. (2012). Human phase response curve to a 1 h pulse of bright white light. *Journal of Physiology*, *590*(13), 3035–3045. https://doi.org/10.1113/jphysiol.2012.227892

Staner, L., Cornette, F., Maurice, D., Viardot, G., Le Bon, O., Haba, J., Staner, C., Luthringer, R., Muzet, A., & Macher, J.-P. (2003). Sleep microstructure around sleep onset differentiates major depressive insomnia from primary insomnia. *Journal of Sleep Research*, *12*(4), 319–330.

Statistics Canada. (2019). *Table 13-10-0096-18 Mood disorders, by age group*. https://doi.org/https://doi.org/10.25318/1310009601-eng

Stausholm, M. B., Naterstad, I. F., Joensen, J., Lopes-Martins, R. Á. B., Sæbø, H., Lund, H., Fersum, K. V., & Bjordal, J. M. (2019). Efficacy of low-level laser therapy on pain and disability in knee osteoarthritis: Systematic review and meta-analysis of randomised placebo-controlled trials. *BMJ Open*, *9*(10). https://doi.org/10.1136/bmjopen-2019-031142

Steckler, T., Holsboer, F., & Reul, J. M. H. M. (1999). Glucocorticoids and depression. *Bailliere's Best Practice and Research in Clinical Endocrinology and Metabolism*, *13*(4), 597–614. https://doi.org/10.1053/beem.1999.0046

Steiger, A., & Holsboer, F. (1997). Nocturnal secretion of prolactin and cortisol and the sleep

EEG in patients with major endogenous depression during an acute episode and after full remission. *Psychiatry Research*, *72*(2), 81–88. https://doi.org/10.1016/S0165-1781(97)00097-8

Stephan, F. K., & Zucker, I. (1972). Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.69.6.1583

Stephenson, K. M., Schroder, C. M., Bertschy, G., & Bourgin, P. (2012). Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story. *Sleep Medicine Reviews*, *16*(5), 445–454.

Stetler, C., & Miller, G. E. (2005). Blunted cortisol response to awakening in mild to moderate depression: Regulatory influences of sleep patterns and social contacts. *Journal of Abnormal Psychology*. https://doi.org/10.1037/0021-843X.114.4.697

Stokkan, K. A., Yamazaki, S., Tei, H., Sakaki, Y., & Menaker, M. (2001). Entrainment of the circadian clock in the liver by feeding. *Science*. https://doi.org/10.1126/science.291.5503.490

Sundberg, I., Ramklint, M., Stridsberg, M., Papadopoulos, F. C., Ekselius, L., & Cunningham, J. L. (2016). Salivary melatonin in relation to depressive symptom severity in young adults. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0152814

Surridge-David, M., Maclean, A., Coulter, M. E., & Knowles, J. 6. (1987). Mood Change Following an Acute Delay of Sleep. *Psychiatry Research*, *22*(2), 149–158.

Svendsen, K., & Christensen, P. G. (1981). Duration of REM sleep latency as predictor of effect of antidepressant therapy A PRELIMINARY REPORT. *Acta Psychiatrica Scandinavica* , *64*(3), 238–243.

Tanaka, Y., Akiyoshi, J., Kawahara, Y., Ishitobi, Y., Hatano, K., Hoaki, N., Mori, A., Goto, S., Tsuru, J., Matsushita, H., Hanada, H., Kodama, K., Isogawa, K., Kitamura, H., & Fujikura, Y. (2011). Infrared radiation has potential antidepressant and anxiolytic effects in animal model of depression and anxiety. *Brain Stimulation*, *4*(2), 71–76. https://doi.org/10.1016/j.brs.2010.04.001

Tao, L., Jiang, R., Zhang, K., Qian, Z., Chen, P., Lv, Y., & Yao, Y. (2020). Light therapy in non-seasonal depression: An update meta-analysis. *Psychiatry Research*, *291*(June), 113247. https://doi.org/10.1016/j.psychres.2020.113247

Tarrasch, R., Laudon, M., & Zisapel, N. (2003). Cross-cultural validation of the Leeds sleep evaluation questionnaire (LSEQ) in insomnia patients. *Human Psychopharmacology*, *18*(8), 603–610. https://doi.org/10.1002/hup.534

Taub, J. M., & Berger, R. J. (1973). Performance and Mood Following Variations in the Length and Timing of Sleep. *Psychophysiology*. https://doi.org/10.1111/j.1469-8986.1973.tb00805.x

te Kulve, M., Schlangen, L. J. M., & van Marken Lichtenbelt, W. D. (2019). Early evening light mitigates sleep compromising physiological and alerting responses to subsequent late evening light. *Scientific Reports*, *9*(1). https://doi.org/10.1038/s41598-019-52352-w

Ten Have, M., Lamers, F., Wardenaar, K., Beekman, A., De Jonge, P., Van Dorsselaer, S., Tuithof, M., Kleinjan, M., & De Graaf, R. (2016). The identification of symptom-based subtypes of depression: A nationally representative cohort study. *Journal of Affective Disorders*, *190*, 395–406. https://doi.org/10.1016/j.jad.2015.10.040

Terman, M., Lewy, A. J., Dijk, D. J., Boulos, Z., Eastman, C. I., & Campbell, S. S. (1995). Light

Treatment for Sleep Disorders: Consensus Report: IV. Sleep Phase and Duration Disturbances. *Journal of Biological Rhythms*, *10*(2), 135–147. https://doi.org/10.1177/074873049501000207

Terman, M., & Terman, J. S. (2005). Light therapy for seasonal and nonseasonal depression: Efficacy, protocol, safety, and side effects. *CNS Spectrums*, *10*(8), 647–663. https://doi.org/10.1017/S1092852900019611

Thalén, B. -E, Kjellman, B. F., Mørkrid, L., Wibom, R., & Wetterberg, L. (1995). Light treatment in seasonal and nonseasonal depression. *Acta Psychiatrica Scandinavica*, *91*(5), 352–360. https://doi.org/10.1111/j.1600-0447.1995.tb09794.x

Thalén, B. E., Mørkrid, L., Kjellman, B. F., & Wetterberg, L. (1997). Cortisol in light treatment of seasonal and non-seasonal depression: Relationship between melatonin and cortisol. *Acta Psychiatrica Scandinavica*. https://doi.org/10.1111/j.1600-0447.1997.tb09934.x

Thapan, K., Arendt, J., & Skene, D. J. (2001). An action spectrum for melatonin suppression: Evidence for a novel non-rod, non-cone photoreceptor system in humans. *Journal of Physiology*, *535*(1), 261–267. https://doi.org/10.1111/j.1469-7793.2001.t01-1-00261.x

Trivedi, M. H. (2006). Major depressive disorder: Remission of associated symptoms. *Journal of Clinical Psychiatry*, *67*(SUPPL. 6), 27–32.

Tsai, J. F., Hsiao, S., & Wang, S. Y. (2007). Infrared irradiation has potential antidepressant effect. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *31*(7), 1397–1400. https://doi.org/10.1016/j.pnpbp.2007.06.006

Tsuno, N., Besset, A., & Ritchie, K. (2005). Sleep and depression. In *Journal of Clinical Psychiatry*. https://doi.org/10.4088/JCP.v66n1008

Tuunainen, A., Df, K., Endo, T., Tuunainen, A., Kripke, D. F., & Endo, T. (2009). Light therapy for non-seasonal depression (Review) Light therapy for non-seasonal depression. *Sleep*, *3*, 3–5. https://doi.org/10.1002/14651858.CD004050.pub2.Copyright

Tuunainen, A., Kripke, D. F., Elliott, J. A., Assmus, J. D., Rex, K. M., Klauber, M. R., & Langer, R. D. (2002). Depression and endogenous melatonin in postmenopausal women. *Journal of Affective Disorders*, *69*(1–3), 149–158. www.elsevier.com/locate/jad

Tylee, A., Gastpar, M., Lepine, J.-P., & Mendlewicz, J. (1999). DEPRES II (Depression Research in European Society II): a patient survey of the symptoms, disability and current management of depression in the community. *International Clinical Psychopharmacology*, *14*(3).

Ulrike, S., Reinhold, L., & Dirk, H. (2013). Major depression in young girls is related to altered cortisol awakening response. *European Child and Adolescent Psychiatry*. https://doi.org/10.1007/s00787-012-0371-9

Urbán, R., Magyaródi, T., & Rigó, A. (2011). Morningness-eveningness, chronotypes and health-impairing behaviors in adolescents. *Chronobiology International*. https://doi.org/10.3109/07420528.2010.549599

Valdez, P., Ramírez, C., & García, A. (2003). Adjustment of the sleep-wake cycle to small (1-2 h) changes in schedule. *Biological Rhythm Research*, *34*(2), 145–155. https://doi.org/10.1076/brhm.34.2.145.14494

Van Cauter, E., Sturis, J., Byrne, M. M., Blackman, J. D., Leproult, R., Ofek, G., L'Hermite-Baleriaux, M., Refetoff, S., Turek, F. W., & Van Reeth, O. (1994). Demonstration of rapid light-induced advances and delays of the human circadian clock using hormonal phase markers. *American Journal of Physiology - Endocrinology and Metabolism*. https://doi.org/10.1152/ajpendo.1994.266.6.e953

Van Cauter, Eve, & Refetoff, S. (1985). Multifactorial control of the 24-hour secretory profiles of pituitary hormones. In *Journal of Endocrinological Investigation: Official Journal of the Italian Society of Endocrinology*. https://doi.org/10.1007/BF03348519

Van Den Burg, W., Bouhuys, A. L., Van Den Hoofdakker, R. H., & Beersma, D. G. M. (1990). Sleep deprivation in bright and dim light: antidepressant effects on major depressive disorder. *Journal of Affective Disorders*, *19*, 109–117.

Van der Maren, S., Moderie, C., Duclos, C., Paquet, J., Daneault, V., & Dumont, M. (2018). Daily Profiles of Light Exposure and Evening Use of Light-emitting Devices in Young Adults Complaining of a Delayed Sleep Schedule. *Journal of Biological Rhythms*, *33*(2), 192–202. https://doi.org/10.1177/0748730418757007

van der Meijden, W P, Te Lindert, B. H. W., Ramautar, J. R., Wei, Y., Coppens, J. E., Kamermans, M., Cajochen, C., Bourgin, P., & Van Someren, E. J. W. (2018). Sustained effects of prior red light on pupil diameter and vigilance during subsequent darkness. *Proc Biol Sci*, *285*(1883). https://doi.org/10.1098/rspb.2018.0989

van der Meijden, Wisse P., Van Someren, J. L., te Lindert, B. H. W., Bruijel, J., van Oosterhout, F., Coppens, J. E., Kalsbeek, A., Cajochen, C., Bourgin, P., & Van Someren, E. J. W. (2016). Individual Differences in Sleep Timing Relate to Melanopsin-Based Phototransduction in Healthy Adolescents and Young Adults. *Sleep*, *39*(6), 1305–1310. https://doi.org/10.5665/sleep.5858

van Genugten, C. R., Schuurmans, J., van Ballegooijen, W., Hoogendoorn, A. W., Smit, J. H., & Riper, H. (2021). Discovering different profiles in the dynamics of depression based on real–time monitoring of mood: a first exploration. *Internet Interventions*, *26*. https://doi.org/10.1016/j.invent.2021.100437

van Maanen, A., Meijer, A. M., van der Heijden, K. B., & Oort, F. J. (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *29*, 52–62. https://doi.org/10.1016/j.smrv.2015.08.009

Vandewalle, G., Collignon, O., Hull, J., Daneault, V., Albouy, G., Lepore, F., Phillips, C., Doyon, J., Czeisler, C., Dumont, M., Lockley, S., & Carrier, J. (2015). Blue Light Stimulates Cognitive Brain Activity in Visually Blind Individuals. *J Cogn Neurosci*.

Vandewalle, G., Schwartz, S., Grandjean, D., Wuillaume, C., Balteau, E., Degueldre, C., Schabus, M., Phillips, C., Luxen, A., Dijk, D. J., & Maquet, P. (2010). Spectral quality of light modulates emotional brainresponses in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(45), 19549–19554. https://doi.org/10.1073/pnas.1010180107

Vandewalle, Gilles, Hébert, M., Beaulieu, C., Richard, L., Daneault, V., Garon, M. Lou, Leblanc, J., Grandjean, D., Maquet, P., Schwartz, S., Dumont, M., Doyon, J., & Carrier, J. (2011). Abnormal hypothalamic response to light in seasonal affective disorder. *Biological Psychiatry*, *70*(10), 954–961. https://doi.org/10.1016/j.biopsych.2011.06.022

Vandewalle, Gilles, Maquet, P., & Dijk, D. J. (2009). Light as a modulator of cognitive brain function. In *Trends in Cognitive Sciences*. https://doi.org/10.1016/j.tics.2009.07.004

Veitch, J. (1997). Revisiting the performance and mood effects of information about lighting and flourescent lamp type. *Journal of Environmental Psychology*, *17*(3), 253–262. https://doi.org/10.1006/jevp.1997.0059

Vethe, D., Scott, J., Engstrøm, M., Salvesen, Ø., Sand, T., Olsen, A., Morken, G., Heglum, H. S., Kjørstad, K., Faaland, P. M., Vestergaard, C. L., Langsrud, K., & Kallestad, H. (2021). The evening light environment in hospitals can be designed to produce less disruptive effects on

the circadian system and improve sleep. *Sleep*, *44*(3). https://doi.org/10.1093/sleep/zsaa194

Vilches, N., Spichiger, C., Mendez, N., Abarzua-Catalan, L., Galdames, H. A., Hazlerigg, D. G., Richter, H. G., & Torres-Farfan, C. (2014). Gestational chronodisruption impairs hippocampal expression of NMDA receptor subunits Grin1b/Grin3a and spatial memory in the adult offspring. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0091313

Viola, A. U., James, L. M., Schlangen, L. J. M., & Dijk, D.-J. (2008). Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scandinavian Journal of Work, Environment and Health*, *34*(4), 297–306. https://doi.org/10.5271/sjweh.1268

Viola, Antoine U., James, L. M., Schlangen, L. J. M., & Dijk, D. J. (2008). Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. *Scandinavian Journal of Work, Environment and Health*, *34*(4), 297–306. https://doi.org/10.5271/sjweh.1268

Visser, E. K., Beersma, D. G. M., & Daan, S. (1999). Melatonin suppression by light in humans is maximal when the nasal part of the retina is illuminated. *Journal of Biological Rhythms*, *14*(2), 116–121. https://doi.org/10.1177/074873099129000498

Vogel, G. W., Buffenstein, I. A., Minter, K., Hennessey, A., Buffenstein, A., Hennessey, A., & Vogel, G. W. (1990). Drug Effects on REM Sleep and on Endogenous Depression. *Neuroscience & Biobehavioral Reviews*, *14*(1), 49–63.

Vogel, G. W., Vogel, F., McAbee, R. S., & Thurmond, A. J. (1980). Improvement of depression by REM sleep deprivation. *Arch Gen Psychiatry*, *37*, 247–253.

Voiculescu, S. E., Le Duc, D., Roșca, A. E., Zeca, V., Chiţimuș, D. M., Arsene, A. L., Drăgoi, C. M., Nicolae, A. C., Zăgrean, L., Schöneberg, T., & Zăgrean, A. M. (2016). Behavioral and molecular effects of prenatal continuous light exposure in the adult rat. *Brain Research*. https://doi.org/10.1016/j.brainres.2016.08.031

Volf, C., Aggestrup, A. S., Svendsen, S. D., Hansen, T. S., Petersen, P. M., Dam-Hansen, C., Knorr, U., Petersen, E. E., Engstrøm, J., Hageman, I., Jakobsen, J. C., & Martiny, K. (2020). Dynamic LED light versus static LED light for depressed inpatients: Results from a randomized feasibility trial. *Pilot and Feasibility Studies*, *6*(1). https://doi.org/10.1186/s40814-019-0548-9

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., Charlson, F., Davis, A., Degenhardt, L., Dicker, D., Duan, L., Erskine, H., Feigin, V. L., Ferrari, A. J., Fitzmaurice, C., Fleming, T., Graetz, N., Guinovart, C., Haagsma, J., … Murray, C. J. L. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *386*(9995), 743–800. https://doi.org/10.1016/S0140-6736(15)60692-4

W. Freeman, E. (2022). Treatment of depression associated with the menstrual cycle: premenstrual dysphoria, postpartum depression, and the perimenopause. *Dialogues in Clinical Neuroscience*, *4*(2), 177–191. https://doi.org/10.31887/dcns.2002.4.2/efreeman

Wagner, D. R. (1999). Circadian rhythm sleep disorders. *Current Treatment Options in Neurology*, *1*(4), 299–307.

Wahl, S., Engelhardt, M., Schaupp, P., Lappe, C., & Ivanov, I. V. (2019). The inner clock—Blue light sets the human rhythm. *Journal of Biophotonics*, *12*(12), 1–14. https://doi.org/10.1002/jbio.201900102

Wahnschaffe, A., Nowozin, C., Haedel, S., Rath, A., Appelhof, S., Münch, M., & Kunz, D.

(2017). Implementation of dynamic lighting in a nursing home: impact on agitation but not on rest-activity patterns. *Current Alzheimer Research*, *14*(10), 1076–1083.

Walther, C. P., Shah, A. ., & Winkelmayer, W. C. (2017). Treating depression in patients with advanced CKD: Beyond the generalizability frontier. *JAMA*, *318*(19), 1873–1874.

Wams, E. J., Woelders, T., Marring, I., Van Rosmalen, L., Beersma, D. G. M., Gordijn, M. C. M., & Hut, R. A. (2017). Linking light exposure and subsequent sleep: A field polysomnography study in humans. *Sleep*, *40*(12). https://doi.org/10.1093/sleep/zsx165

Wang, J. L., Williams, J., Lavorato, D., Schmitz, N., Dewa, C., & Patten, S. B. (2010). The incidence of major depression in Canada: The National Population Health Survey. *Journal of Affective Disorders*, *123*(1–3), 158–163. https://doi.org/10.1016/j.jad.2009.07.016

Wang, Y. P., & Gorenstein, C. (2013). Psychometric properties of the Beck Depression Inventory-II: A comprehensive review. *Revista Brasileira de Psiquiatria*, *35*(4), 416–431. https://doi.org/10.1590/1516-4446-2012-1048

Watson, D., & Clark, L. . (1988). Development and Validation of Brief Measures of Positive and Negative Affect: The PANAS Scales. *Journal of Personality and Social Psychology*, *54*(6), 1063–1070. https://doi.org/10.4135/9781483398839.n13

Watson, P. J., Badcock, P., & Andrews, P. W. (2002). Toward a revised evolutionary adaptationist analysis of depression: the social navigation hypothesis. *Journal of Affective Disorders*, *72*(1), 1–14. www.elsevier.com/locate/jad

Weaver, D. R. (1998). The Suprachiasmatic Nucleus: A 25-Year Retrospective. *Journal of Biological Rhythms*. https://doi.org/10.1177/074873098128999952

Weaver, E., Laizner, A. M., Evans, L. K., Chugh, D. K., Lyon, K., Smith, I. L., Schwartz, I. R., Pack, H., & Dinges, D. F. (1997). An Instrument to Measure Functional Status Outcomes for Disorders of Excessive Sleepiness. *Sleep*, *20*(10), 835–843. https://doi.org/10.1093/sleep/20.10.835

Wehr, T A, Rosenthal, N. E., Sack, D. A., & Gillin, J. C. (1985). Antidepressant effects of in bright and dim light. *Acta Psychiatr. Scand*, *72*, 161–165.

Wehr, Thomas A, Wirz-Justice, A., Goodwin, F. K., Duncan, W., & Gillin, J. C. (1979). Phase Advance of the Circadian Sleep-Wake Cycle as an Antidepressant. *Source: Science, New Series*, *206*(9), 710–713. http://www.jstor.org/stable/1749063

Weil, T., Daly, K. M., Castillo, H. Y., Thomsen, M. B., Wang, H., Mercau, M. E., Hattar, S., Tejeda, H., & Fernandez, D. C. (2022). Daily changes in light influence mood via inhibitory networks within the thalamic perihabenular nucleus. *Science Advances*, *8*(23), 1–14. https://doi.org/10.1126/sciadv.abn3567

Weinberger, A. H., Gbedemah, M., Martinez, A. M., Nash, D., Galea, S., & Goodwin, R. D. (2018). Trends in depression prevalence in the USA from 2005 to 2015: Widening disparities in vulnerable groups. *Psychological Medicine*, *48*(8), 1308–1315. https://doi.org/10.1017/S0033291717002781

Werth, E., Dijk, D. J., Achermann, P., & Borbély, A. A. (1996). Dynamics of the sleep EEG after an early evening nap: Experimental data and simulations. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, *271*(3 40-3). https://doi.org/10.1152/ajpregu.1996.271.3.r501

Whalley, L. J., Perini, T., Shering, A., & Bennie, J. (1991). Melatonin response to bright light in recovered, drug-free, bipolar patients. *Psychiatry Research*, *38*(1), 13–19. https://doi.org/10.1016/0165-1781(91)90048-T

Wickersham, L. (2006). Time-of-Day Preference for Preschool-Aged Children. *Annual Review*

of Undergraduate Research, *5*, 259–268.
Wilhelm, I., Born, J., Kudielka, B. M., Schlotz, W., & Wüst, S. (2007). Is the cortisol awakening rise a response to awakening? *Psychoneuroendocrinology*. https://doi.org/10.1016/j.psyneuen.2007.01.008
Wilkins, A. J., Nimmo-Smith, I., Slater, A. I., & Bedocs, L. (1989). Fluorescent lighting, headaches and eyestrain. *Lighting Research & Technology*, *21*(1), 11–18.
Wirz-Justice, A. (2006). Biological rhythm disturbances in mood disorders. *International Clinical Psychopharmacology*. https://doi.org/10.1097/01.yic.0000195660.37267.cf
Wirz-Justice, A. (2007). Chronobiology and psychiatry. In *Sleep Medicine Reviews*. https://doi.org/10.1016/j.smrv.2007.08.003
Wirz-Justice, A. (2009). From the basic neuroscience of circadian clock function to light therapy for depression: On the emergence of chronotherapeutics. *Journal of Affective Disorders*, *116*(3), 159–160. https://doi.org/10.1016/j.jad.2009.04.024
Wirz-Justice, A., Bader, A., Frisch, U., Stieglitz, R. D., Alder, J., Bitzer, J., Hösli, I., Jazbec, S., Benedetti, F., Terman, M., Wisner, K. L., & Riecher-Rössler, A. (2011). A randomized, double-blind, placebo-controlled study of light therapy for antepartum depression. *Journal of Clinical Psychiatry*. https://doi.org/10.4088/JCP.10m06188blu
Wirz-Justice, A., & Van Den Hoofdakker, R. H. (1999). Sleep deprivation in depression: What do we know, where do we go? *Biological Psychiatry*, *46*(4), 445–453. https://doi.org/10.1016/S0006-3223(99)00125-0
Wirz-Justice, A., Bucheli, C., Graw, P., Kielholz, P., Fisch, H. -U, & Woggon, B. (1986). Light treatment of seasonal affective disorder in Switzerland. *Acta Psychiatrica Scandinavica*, *74*(2), 193–204. https://doi.org/10.1111/j.1600-0447.1986.tb10606.x
Wolfson, A., & Carskadon, M. (1998). Sleep Schedules and Daytime Functioning in Adolescents. *Breaking the Language Barrier: An Emergentist Coalition Model for the Origins of Word Learning*, *69*(4), 875–887. http://www.jstor.org/stable/1132351
Wong, K. Y., Dunn, F. A., Graham, D. M., & Berson, D. M. (2007). Synaptic influences on rat ganglion-cell photoreceptors. *Journal of Physiology*. https://doi.org/10.1113/jphysiol.2007.133751
Wright, K., Drake, A., Frey, D., Fleshner, M., Desouza, C., Gronfier, C., & Czeisler, C. (2015). Influence of Sleep Deprivation and Circadian Misalignment on Cortisol, Inflammatory Markers, and Cytokine Balance. *Brain Behav Immu.*, *47*, 24–34. https://doi.org/10.1016/j.bbi.2015.01.004
Wu, J. C., Kelsoe, J. R., Schachat, C., Bunney, B. G., DeModena, A., Golshan, S., Gillin, J. C., Potkin, S. G., & Bunney, W. E. (2009). Rapid and Sustained Antidepressant Response with Sleep Deprivation and Chronotherapy in Bipolar Disorder. *Biological Psychiatry*, *66*(3), 298–301. https://doi.org/10.1016/j.biopsych.2009.02.018
Wu, M., Shi, Y., Li, R., & Wang, P. (2018). Spectrally Selective Smart Window with High Near-Infrared Light Shielding and Controllable Visible Light Transmittance. *ACS Applied Materials and Interfaces*, *10*(46), 39819–39827. https://doi.org/10.1021/acsami.8b15574
Wüst, S., Federenko, I., Hellhammer, D. H., & Kirschbaum, C. (2000). Genetic factors, perceived chronic stress, and the free cortisol response to awakening. *Psychoneuroendocrinology*. https://doi.org/10.1016/S0306-4530(00)00021-4
Xiao, H., Cai, H., & Li, X. (2021). Non-visual effects of indoor light environment on humans: A review. *Physiology and Behavior*, *228*(October 2020), 113195. https://doi.org/10.1016/j.physbeh.2020.113195

Xiong, H., Yang, Y., Yang, K., Zhao, D., Tang, H., & Ran, X. (2018). Loss of the clock gene PER2 is associated with cancer development and altered expression of important tumor-related genes in oral cancer. *International Journal of Oncology*. https://doi.org/10.3892/ijo.2017.4180

Yamada, N., Martin-Iverson, M. T., Daimon, K., Tsujimoto, T., & Takahashi, S. (1995). Clinical and chronobiological effects of light therapy on nonseasonal affective disorders. *Biological Psychiatry*, *37*(12), 866–873. https://doi.org/10.1016/0006-3223(94)00221-N

Yang, X., Kumar, P., Nickerson, L. D., Du, Y., Wang, M., Chen, Y., Li, T., Pizzagalli, D. A., & Ma, X. (2021). Identifying Subgroups of Major Depressive Disorder Using Brain Structural Covariance Networks and Mapping of Associated Clinical and Cognitive Variables. *Biological Psychiatry Global Open Science*, *1*(2), 135–145. https://doi.org/10.1016/j.bpsgos.2021.04.006

Yerevanian, B. I., Anderson, J. L., Grota, L. J., & Bray, M. (1986). Effects of bright incandescent light on seasonal and nonseasonal major depressive disorder. *Psychiatry Research*, *18*(4), 355–364. https://doi.org/10.1016/0165-1781(86)90020-X

Yoo, S.-H., Yamazaki, S., Lowrey, P. L., Shimomura, K., Ko, C. H., Buhr, E. D., Siepka, S. M., Hong, H.-K., Oh, W. J., Yoo, O. J., Menaker, M., & Takahashi, J. S. (2004). PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(15), 5339 LP – 5346. https://doi.org/10.1073/pnas.0308709101

Yoon, I. Y., Kripke, D. F., Elliott, J. A., Youngstedt, S. D., Rex, K. M., & Hauger, R. L. (2003). Age-related changes of circadian rhythms and sleep-wake cycles. *Journal of the American Geriatrics Society*. https://doi.org/10.1046/j.1532-5415.2003.51356.x

Yoshiike, T., Honma, M., Ikeda, H., & Kuriyama, K. (2019). Bright light exposure advances consolidation of motor skill accuracy in humans. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2019.107084

Youngstedt, S. D., Kline, C. E., Reynolds, A. M., Crowley, S. K., Burch, J. B., Khan, N., & Han, S. Y. (2022). Bright Light Treatment of Combat-related PTSD: A Randomized Controlled Trial. *Military Medicine*, *187*(3–4), E435–E444. https://doi.org/10.1093/milmed/usab014

Zaidi, F. H., Hull, J. T., Peirson, S. N. N., Wulff, K., Aeschbach, D., Gooley, J. J., Brainard, G. C. C., Gregory-Evans, K., Rizzo, J. F. F., Czeisler, C. A., Foster, R. G. G., Moseley, M. J., & Lockley, S. W. (2007). Short-Wavelength Light Sensitivity of Circadian, Pupillary, and Visual Awareness in Humans Lacking an Outer Retina. *Current Biology*. https://doi.org/10.1016/j.cub.2007.11.034

Zajecka, J. M. (2000). Clinical issues in long-term treatment with antidepressants. *Journal of Clinical Psychology*, *61*, 20–25.

Zalta, A. K., Bravo, K., Valdespino-Hayden, Z., Pollack, M. H., & Burgess, H. J. (2019). A placebo-controlled pilot study of a wearable morning bright light treatment for probable PTSD. *Depression and Anxiety*, *36*(7), 617–624. https://doi.org/10.1002/da.22897

Zandi, B., Stefani, O., Herzog, A., Schlangen, L. J. M., Trinh, Q. V., & Khanh, T. Q. (2021). Optimising metameric spectra for integrative lighting to modulate the circadian system without affecting visual appearance. *Scientific Reports*, *11*(1), 1–14. https://doi.org/10.1038/s41598-021-02136-y

Zeitzer, J. M., Friedman, L., & Yesavage, J. A. (2011). Effectiveness of evening phototherapy for insomnia is reduced by bright daytime light exposure. *Sleep Medicine*, *12*(8), 805–807.

https://doi.org/10.1016/j.sleep.2011.02.005
Zhao, J., Zhou, X., Tang, Q., Yu, R., Yu, S., Long, Y., Cao, C., Han, J., Shi, A., Mao, J. J., Chen, X., & Chen, L. (2018). BMAL1 Deficiency Contributes to Mandibular Dysplasia by Upregulating MMP3. *Stem Cell Reports*. https://doi.org/10.1016/j.stemcr.2017.11.017
Zhou, X., Yu, R., Long, Y., Zhao, J., Yu, S., Tang, Q., & Chen, L. (2018). BMAL1 deficiency promotes skeletal mandibular hypoplasia via OPG downregulation. *Cell Proliferation*. https://doi.org/10.1111/cpr.12470