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Review

Seasonality in affective disorders

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ABSTRACT

Humans retain neurobiological responses to circadian day-night cycles and seasonal changes in daylength in spite of a life-style usually independent of dawn-dusk signals. Seasonality has been documented in many functions, from mood to hormones to gene expression. Research on seasonal affective disorder initiated the first use of timed bright light as therapy, a treatment since extended to non-seasonal major depression and sleep-wake cycle disturbances in many psychiatric and medical illnesses. The growing recognition that sufficient light is important for psychological and somatic well-being is leading to the development of novel lighting solutions in architecture as well as focus on a more conscious exposure to natural daylight.

> “It is chiefly the changes of the seasons which produce diseases.”
>
> [Hippocrates (5th century BC)]

1. The natural environment

Life evolved on a planet subject to a complex ever-changing pattern of light and dark that depends on latitude, season, and time of day, is dynamic in its spectral profile, and covers 9 log units of light intensity from starlight to the sun overhead at midday (Fig. 1). In mammals, retinal photoreceptors for the visual (rods and cones) and non-visual systems (intrinsically photosensitive retinal ganglion cells, ipRGCs) provide the brain with photic information. How they interact and when is an intense focus of present-day research (Schmidt et al., 2011). We know that light can phase shift the human circadian system, initiating phase advances in the morning and phase delays at night (e.g. Minors et al., 1991; Khalsa et al., 2003). What is now clear, is that humans – previously considered to be less sensitive than other mammals to the circadian phase-shifting or melatonin-suppressing effects of light – also respond physiologically to low light intensities such as occur at the twilight transition (Danilenko et al., 2000). Thus, in spite of a life-style predominantly indoors, it is feasible that changes in daylength do impact human behaviour.

2. Introduction to seasonal affective disorder

This brief overview provides examples of seasonality in humans in many domains from the biochemical to behavioural. The occurrence and nature of seasonal rhythms in humans has received renewed interest since Seasonal Affective Disorder (SAD) was diagnosed in 1984 (Rosenthal et al., 1984), following mention in many ancient medical texts. The illness was considered to involve similar photoperiodic mechanisms as seasonal reproduction and hibernation in hamsters. The discovery that bright light could influence the human circadian system (via suppression of the pineal hormone melatonin), was a crucial methodological and conceptual advance (Lewy et al., 1980). This led to the prediction that simulation of summer daylength with light could treat these patients, and remarkably, it worked (Rosenthal et al., 1984; Terman and Terman, 2005). However, none of the studies in the last 30 years can quite explain the pathophysiology of SAD, whether in terms of abnormal duration of nocturnal melatonin secretion (mirroring the long winter nights) or disturbed circadian phase relationships (dark-related phase delay), nor do they clarify how light therapy works (Kripke and Welsh, 2015). The importance of daylength has been shown in a non-human primate model of SAD: in short photoperiod conditions monkeys displayed depression-related behavioural and physiological changes which could be reversed by antidepressant treatment (Qin et al., 2015).

However, much research, in particular monoamine depletion studies, suggest similar serotonergic and catecholaminergic dysfunctions in SAD as in major depression (Neumeister et al., 2001). The dual vulnerability hypothesis indeed considers the interaction of separate factors for seasonality and depression

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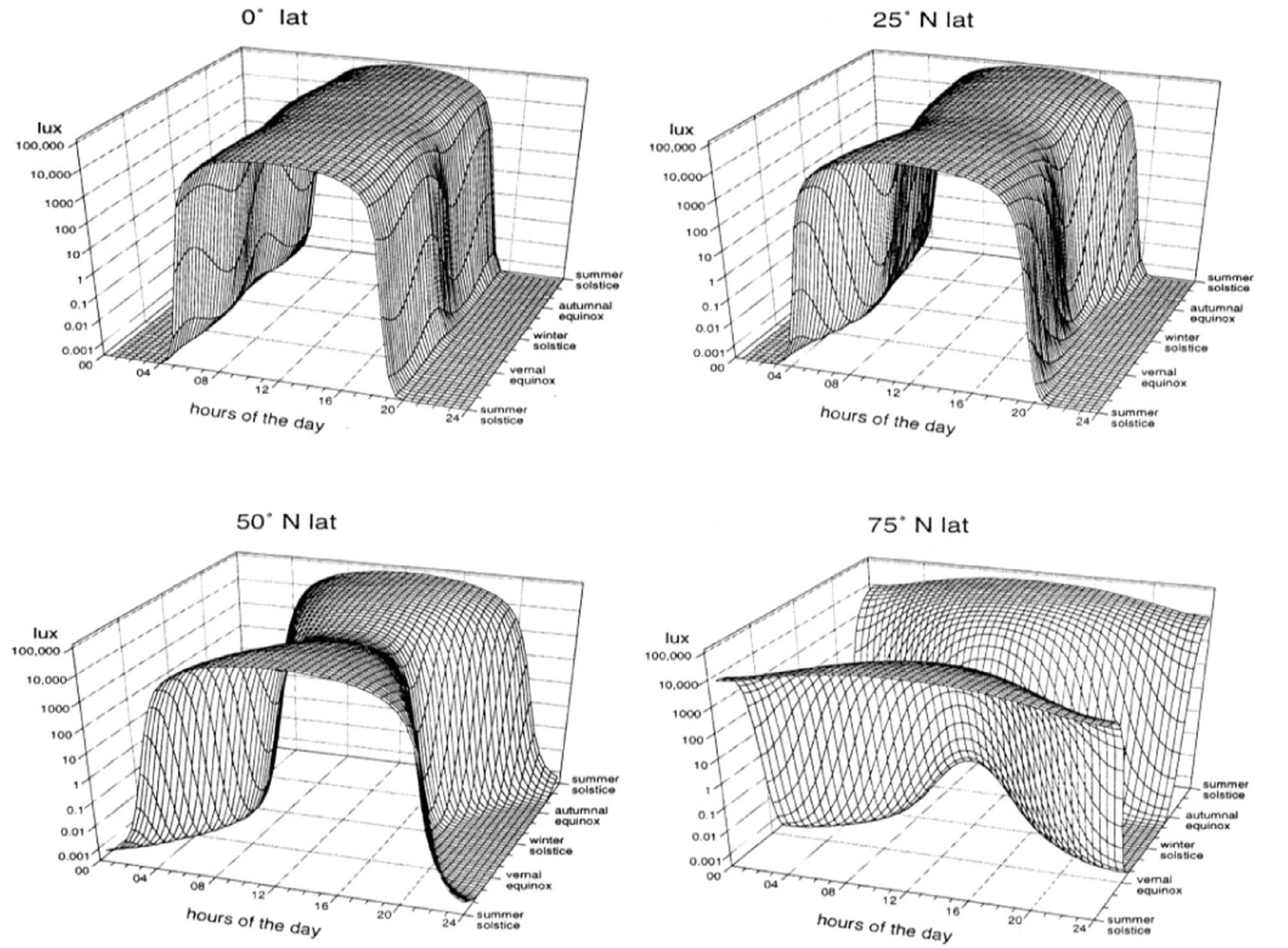

Fig. 1. Outdoor sunlight availability throughout the 24-h day across days of the year. The 3-D contour plots over 9-log units of illuminance show seasonal modulations dependent on latitude, here chosen for the equator and three equidistant latitudes north. Courtesy S. Fairhurst & M. Terman, Columbia University, New York.

(Sohn and Lam, 2005). In addition, there are genetic factors, latitude influence, and daylight-oriented behaviour to consider when looking at the prevalence of SAD.

Many studies in different latitudes and cultures have documented the prevalence of SAD. A summary of epidemiological studies (Magnusson, 2000) provided prevalence estimates of SAD ranging from 1.4 to 9.7% in Northern America, 1.3–3.0% in Europe and 0–0.9% in Asia. Although there is a latitude cline, the higher rates in the north are not found in native populations living in the same areas e.g. Lapps in Finland (Saarijärvi et al., 1999), or Icelanders in Canada (Axelsson et al., 2002), suggesting genetic and/or behavioural adaptations. Of interest, the Old Order Amish in Pennsylvania live a rural life without electric light and thus follow the natural day-night cycle and photoperiod. Their SAD prevalence is lower than observed in a nearby population: 0.84% compared with 4.3% SAD in Maryland; the difference between subsyndromal SAD prevalence even greater – 1.75% vs. 13.5% (Kasper et al., 1989), suggesting dominant environmental and behavioural effects, most probably related to their exposure to a natural pattern of outdoor light (Raheja et al., 2013).

3. Humans are seasonal animals

Mood is one aspect of human behaviour recognised to be affected by season. Evidence for seasonality in human cognitive brain functions suggest that this may contribute to changes in affective control at specific times of year (Meyer et al., 2016). Seasonal changes in daylength also modify human neuroendocrine function (Wehr, 1998). Humans still manifest annual rhythms in reproduction, even though the amplitude has declined over the last century and the timing has shifted (Roenneberg and Aschoff, 1990). Imaging reveals seasonal changes in brain monoamine systems, such as serotonin and dopamine e.g.(Eisenberg et al., 2010; Matheson et al., 2015; Praschak-Rieder and Willeit, 2012; and Praschak-Rieder et al., 2008), documenting with newer technologies what had been documented in post-mortem brain (Carlsson et al., 1980), cerebral spinal fluid *(Wirz-Justice, unpublished data NIMH)* and peripheral biochemical markers (Wirz-Justice and Richter, 1979). Evidence has also been gathered for a direct effect of duration of bright sunlight on serotonin turnover in the brain (Lambert et al., 2002).

In 1989, we reviewed seasonal variation in healthy individuals, in order to provide an update of variables current in depression research at that time (Lacoste and Wirz-Justice, 1989). The studies then and now vary in design and quality, given the long-term nature and related difficulty of documenting replicable rhythms over a year or many years. In general, there was evidence for seasonality in psychological variables – mood and energy, performance, aggressivity, as well as chronotype, sleep, feeding, metabolic function, thermoregulation, autonomic function, neurotransmitters, hormones and their response to stimulation. Our conclusion

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remains valid: "…The gradual recognition of the importance of seasonal rhythms in humans should not be related to the category of *'methodological problems to be controlled for'*, but used for a deeper and differentiated understanding of seasonal susceptibility to affective illness *per se*. Further research in healthy subjects may differentiate the characteristics of those individuals with susceptibility to seasonal change" (Lacoste and Wirz-Justice, 1989, p. 219).

The mythical quality that the name Andechs evokes for chronobiologists is – apart from the Klosterbier – a consequence of the unique experiments in temporal isolation that Aschoff and Wever carried out in the Max-Planck-Institute for Behavioural Physiology over 40 years. Their studies characterised the human circadian system and its zeitgebers in a unique data set (Wever, 1979). One question that arose in the early eighties with the diagnosis of SAD, was whether humans show intrinsic seasonality. The bunker data provided an opportunity to address this question: participants were isolated from time cues, natural light, daylength, etc, and one could measure any aftereffects of the photoperiod under these "pure" conditions. A retrospective analysis with respect to season of participation indicated that circadian period showed a bimodal pattern, being shorter in spring and autumn than in summer and winter, whereas sleep duration was shortest in spring compared with other times of year (Wirz-Justice et al., 1984). Women slept on average 54 min longer than men at all times of year (Fig. 2 A & B).

A further finding in this data set provides a link to seasonality in one aspect of affective disorders. Many free-running participants in the bunker experiments manifested a behaviour designated as internal desynchronisation, whereby the sleep-wake cycle broke away from the ca. 24.5 h period of the circadian temperature rhythm and exhibited either much longer (even 48 h or circabidian) or shorter days. It has been documented that the switch out of depression into mania in bipolar patients is often accompanied

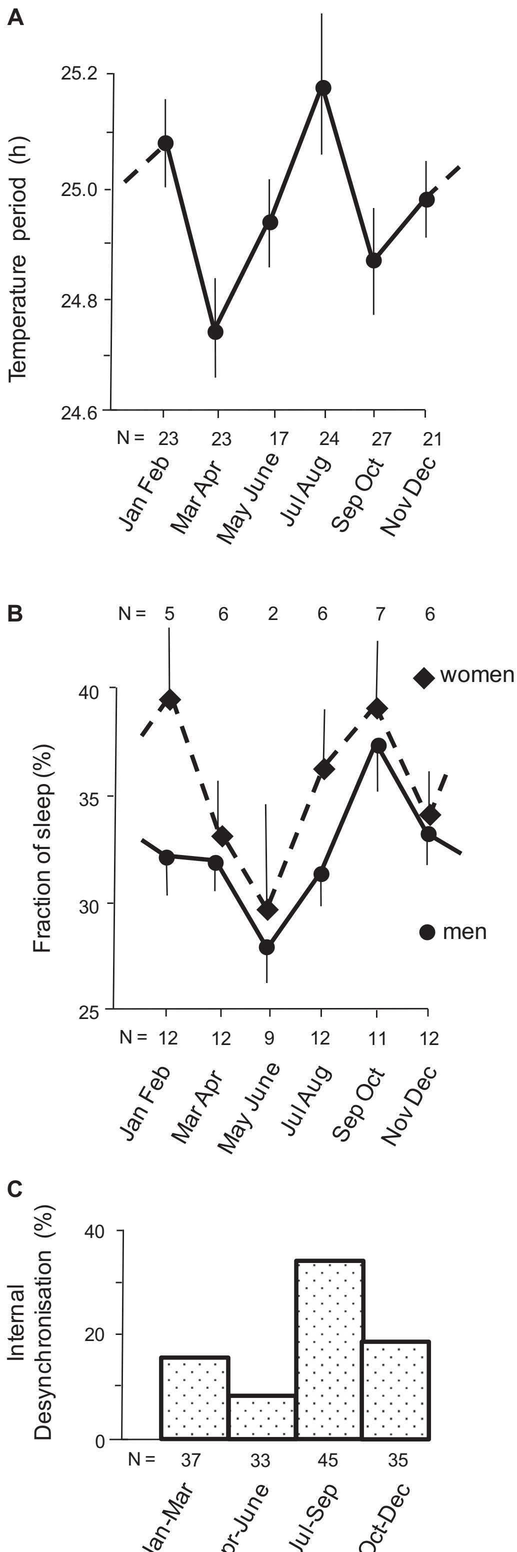

Fig. 2. Seasonal variations in data from experiments in temporal isolation. Two-monthly means ± s.e.m. for data from 15 years, N indicated at each time point. A. Circadian period of core body temperature ($p < 0.05$). B. Fraction of sleep per circadian period ($p < 0.01$ for men). C. Incidence of internal desynchronisation (%, 3-monthly means, $\chi^2 = 7.76$, df = 1, $p < 0.01$). Redrawn from Wirz-Justice et al. (1984).

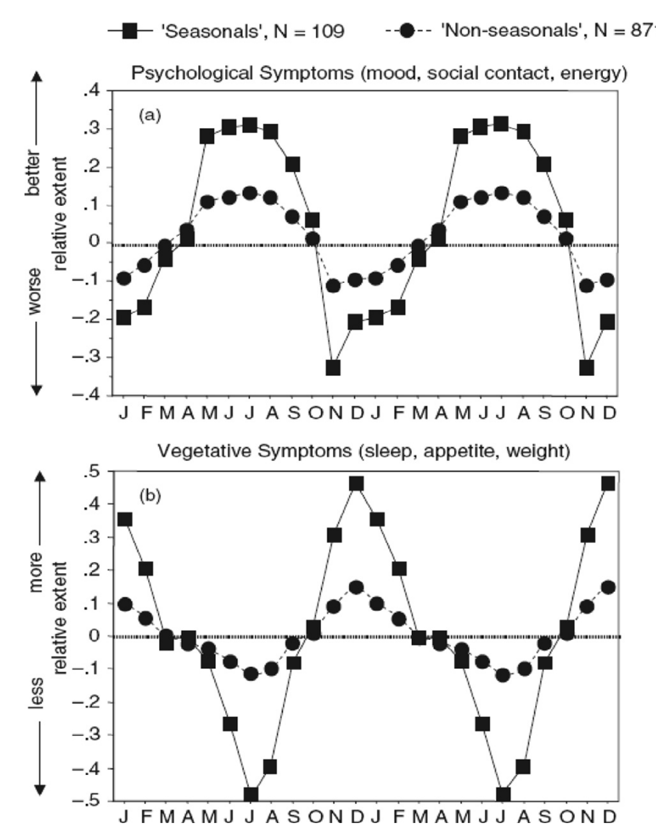

Fig. 3. Double plots of (upper panel): Σ scores for mood, social contact, energy and (lower panel): Σ scores for sleep, appetite, weight changing across the year in individuals with high seasonality or none (representative Swiss population, N = 980). Reprinted from Wirz-Justice et al. (2003), with permission.

by a spontaneous total sleep deprivation – in chronobiology terms, a circabidian day (Wehr et al., 1982). Conversely, a prescribed night awake (total sleep deprivation) is well established as antidepressant, with improvement occurring rapidly, within hours (Dallaspezia and Benedetti, 2015). Thus, in this susceptible group of patients, internal desynchronisation can take place under entrained everyday conditions and induces a clinical switch. The majority of studies report more mania episodes during spring and summer (Young and Dulcis, 2015). This has a nice parallel with the bunker data (Fig. 2 C), whereby internal desynchronisation occurred more often during the summer months compared with all other seasons (Wirz-Justice et al., 1984).

Similar findings on seasonality in sleep have been found under entrained conditions (particularly weekends, where a more naturalistic sleep is to be expected) (Allebrandt et al., 2014). For example, in a questionnaire survey in Switzerland, sleep was 24 min longer in winter than in summer, and women slept on average 26 min longer than men (Wirz-Justice et al., 1991). Thus, even under entrained conditions, season and gender modify sleep duration.

In this same survey, well-being (Σ scores for mood, social contact, energy) was highest in spring and summer and lowest in autumn and winter (Wirz-Justice et al., 2003) and mirrored vegetative symptoms (Σ scores for sleep, appetite and weight). These seasonal rhythms showed high amplitude in participants who fulfilled the criteria of SAD or sub-syndromal SAD, but were also present, though of much lesser extent, in "non-seasonals" (Fig. 3). Seasonality in many aspects of physiology and behaviour thus appears to be a natural phenomenon which persists in the modern-day world.

More generally, jumping to present-day epidemiology using the huge data sets of the internet, key words that searched for mental health information on Google varied across season for a wide range of diagnostic categories, all of which showed peaks in winter in both northern and southern hemispheres over a period of five years (Ayers et al., 2013) (Fig. 4).

Has seasonality, or lack of, a more general impact on health? There may be an increased health risk in individuals with high self-reported seasonality. Seasonal variations in mood and behaviour have been associated with common chronic diseases and symptoms (angina pectoris and depression), and seasonal problems or SAD with hypertension, high cholesterol levels, diabetes, other (than rheumatoid) joint diseases and other (than depressive) psychological illnesses (Øyane and Pallesen, 2010; Basnet et al., 2016).

Widespread seasonal gene expression has shown annual differences in human immunity and physiology (Dopico et al., 2015). More than 4000 protein-coding mRNAs in white blood cells and adipose tissue have seasonal expression profiles, and the immune system has a profound pro-inflammatory transcriptomic profile in winter, with increased levels of risk biomarkers for cardiovascular, psychiatric and autoimmune diseases that peak at this time of year.

4. SAD and light therapy

The concept of light therapy for SAD encountered world-wide interest – albeit sometimes extremely sceptical. Since these courageous beginnings as a somewhat 'alternative' nonpharmacological

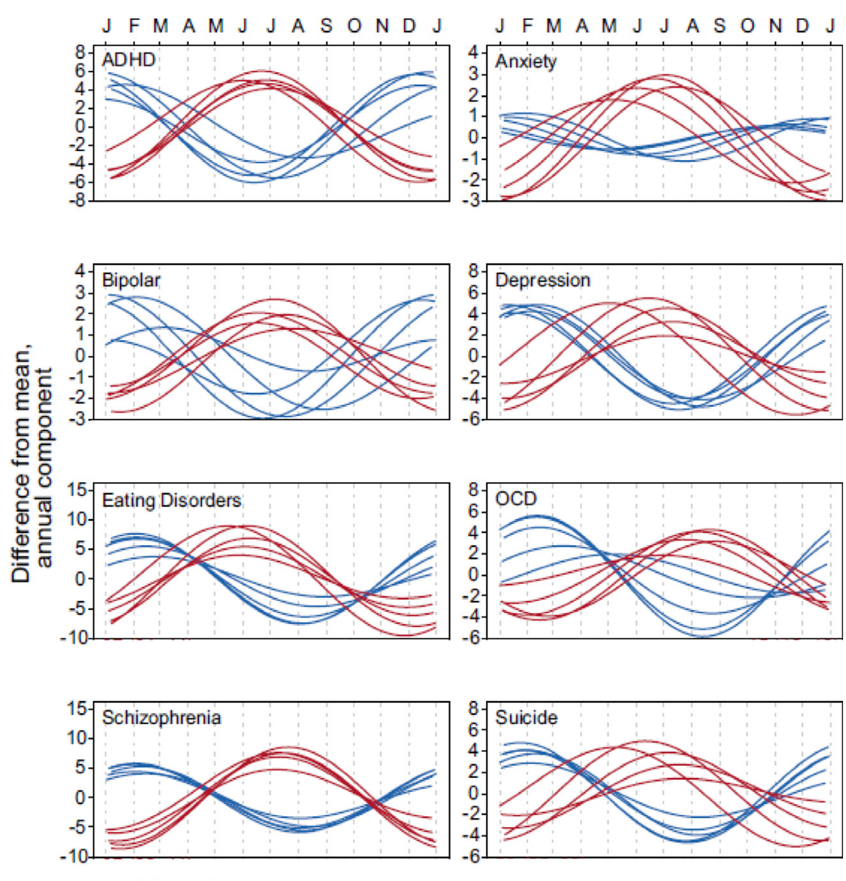

Fig. 4. Seasonal change in Google search queries for various mental illnesses and problems, U.S. and Australia. *Note: Each wavelet plot is on its own Y axis to highlight variability over years. For statistics, see original paper. ADHD, attention deficit hyperactivity disorder; OCD, obsessive-compulsive disorder.* Reprinted from Ayers et al. (2013), with permission.

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approach, light has become established as the treatment of choice for SAD (Terman and Terman, 2005). This has been a remarkable example of translational psychiatry, the first treatment of depression in fact based on a neurobiological model. Since 30 years, the Society for Light Treatment and Biological Rhythms (www.sltbr.org) has brought together basic researchers, clinicians, and manufacturers, to develop standards and coordinate the field, and the non-profit website www.cet.org offers information on chronotherapy to the public and professionals.

From the initial clumsy light boxes, several generations of devices have been developed for the market, only a few of which have actually undergone clinical trials. The main evidence for efficacy has been gained with white light lamps with a smooth diffusing screen that filters out UV rays, of sufficient size for a broad visual field, and 10,000 lx illumination at eye level at a comfortable sitting distance. White light lamps include blue wavelengths in the spectrum; the use of blue wavelength-only light devices has not been demonstrated to be more efficacious, and may have ophthalmological side effects. Head visors are a possible technique, and dawn simulation may also be useful (see Wirz-Justice et al., 2013 for overview).

Recent *meta*-analyses also indicate efficacy of light therapy in non-seasonal major depressive disorder and bipolar illness (Al-Karawi and Jubair, 2016; Penders et al., 2016; Perera et al., 2016). Broader applications are developing – such as light for premenstrual, pregnancy /post-partum depression and geriatric depression, as well as improving sleep-wake cycle disturbances in ADHD, schizophrenia, borderline personality disorder, and even in some medical illnesses (kidney transplant patients, cirrhosis) (Wirz-Justice et al., 2013).

The more we learn about the circadian system in ageing, the more specific and important becomes the use of enhanced light exposure to maintain and improve daytime vigilance, cognitive function, mood, and consolidate nighttime sleep, particularly in dementia (Riemersma-van der Lek et al., 2008; Wirz-Justice et al., 2013). In recent years, it has become clear that the non-visual functions of light have wide-spread implications for general well-being and long-term health outcomes. This has led to a rapid development of novel lighting solutions and implementation of chronobiological principles in architectural and lighting design, together with care for appropriate darkness at night (Wirz-Justice and Fournier, 2010). One interesting offshoot of this knowledge has been a return to consider the importance of natural daylight in everyday life.

Daylight influences nearly every aspect of human physiology: visual, non-visual ocular input to the circadian clock, and direct skin absorbance (the necessity of some UV light on the skin for Vitamin D synthesis, but not too much given its potential for melanoma). A Daylight Academy (www.daylight.academy) has been founded to coordinate research and applications in these diverse fields ranging from medicine to the built environment to solar energy, together with the publication of a first "white paper" with a future research agenda (Sanders and Oberst, 2017).

5. Is seasonality important?

In conclusion, the research on human seasonality that grew out of the discovery of SAD and its treatment with light, is an extension of basic studies of the circadian system. We could not have predicted the remarkably diverse applications of light as therapy, nor the expansion of the lighting industry to include the non-visual aspects of the photic signal. Our 7/24 society certainly will not return to a naturalistic environment, living according to the dawn-dusk signal and following the seasons. Hopefully, however, the importance of adequate synchronisation to the outdoor light-dark cycle for health will be recognised. Not only should our work and home environments be adapted to meet these essential needs, but also our daylight-oriented behaviour.

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