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COMMENTARY

Weekly and seasonal variation in the circadian melatonin rhythm in humans: A response

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Abstract

We read with interest the commentary by Skeldon and Dijk about our article "Weekly, seasonal and chronotype-dependent variation of dim light melatonin onset." The discussion points raised by Skeldon and Dijk are currently among the most hotly debated in human circadian science. What external factors determine human phase of entrainment? How great is the contribution of natural versus artificial light and sun time versus social time? Our intra-individual data add to the still limited evidence from field studies in this matter. In their commentary, Skeldon and Dijk formulate two either-or hypotheses, postulating that humans entrain either solely to the natural light-dark cycle (sun time referenced by midday) (H_1) or solely to the light selected by local clock time and social constraints (H_2). Neither hypothesis accounts for the effect of season on human light exposure. We interpreted our findings along more complex lines, speculating that the 1-h earlier melatonin rise in summer found in our sample is likely the combined result of daylight saving time (DST)-induced behavioral advances and a stronger natural zeitgeber in summer (light exposure determined by social and seasonal factors, $H_{original}$). Here, we show how the criticism by Skeldon and Dijk is based on two sentences quoted out of context (misrepresenting our hypothesis as H_1) and that their hypothesis H_2 leaves out important seasonal components in light exposure.

KEYWORDS

circadian phase, entrainment, light, melatonin, sleep

In our recent article in this journal,[1] we reported on the timing of sleep and the circadian melatonin rhythm on weekdays and weekends and in midwinter and midsummer in a sample of 33 individuals in the Netherlands. Our within-subject analyses using mixed effects models identified a ~30-min delay on weekends, dependent on chronotype, and a ~1 h advance in summer when assessed in standard time (ie, no change when assessed in local time due to daylight saving time (DST) in summer; Figure 1).

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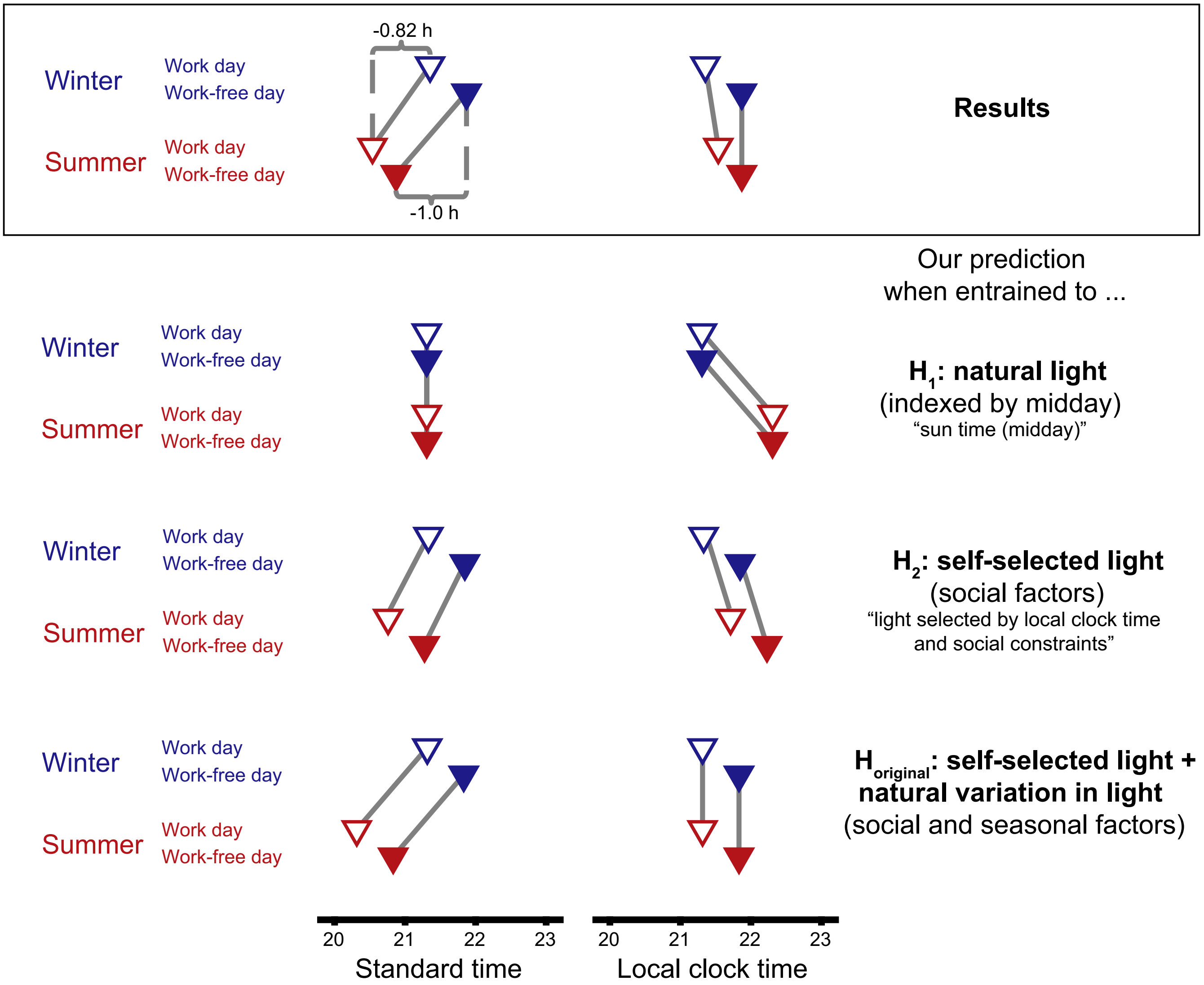

FIGURE 1 Schematic illustrating the timing of dim light melatonin onset (DLMO) based on measurements in our sample in midwinter (standard time) and midsummer (daylight saving time)[1] or based on our predictions under various entrainment hypotheses. $H_{original}$ is our hypothesis delineated in the original article[1]; H_1 is the hypothesis purported to present our view[26]; and H_2 the hypothesis favored by Skeldon and Dijk.[26] Our prediction is that DST-induced behavioral changes (H_2) are insufficient to explain the 1-h advance in summer (in standard time) and that additional seasonal factors such as increased zeitgeber strength (more sunlight and more time spent outdoors) need to be taken into account. For this reason, DLMO is shown to be exactly 1 h earlier in summer (in standard time) when considering $H_{original}$, while DLMO is shown to be advanced by *<1 h* when considering H_2. When using local clock time as reference, we would expect DLMO to occur at the same time when considering $H_{original}$ and to be delayed in summer when considering H_2. The figure also illustrates that both reference times (standard and local time) are suited to analyze and present the results when they are clearly defined (as in our article[6]) and when the interpretation of the observed effects takes this into account. The use of standard time does not "mask the remarkable consistency of DLMO in local time" as suggested by Skeldon and Dijk [26] but underscores the presence of a shift in DLMO in relation to midday—thereby providing evidence against H_1, one of the central points Skeldon and Dijk made in their commentary.[26] Figure adapted from[26]

We performed this study to provide more empirical data on human circadian entrainment under complex, real-life light conditions. It is well established that the human circadian system entrains predominantly to light[2–6] (at least the central pacemaker in the SCN), but the jury is still out on the most important exogenous factors that determine the timing and quality of the light exposure and thus circadian entrainment. Sunlight is generally more potent than artificial light as a zeitgeber given that its intensities are orders of magnitude greater. However, modern humans tend to shield from sunlight by living and working indoors and to have access to artificial light at any time of day, which creates a noisy, low-amplitude light environment with greater inter-individual differences. Therefore, the discussion arises on the role of light exposure determined by social schedules and individual behaviors versus the role of sunlight and its seasonal variations in human entrainment. This discussion culminates in the debate about the consequences of DST,[7,8] which is practiced in many countries and which advances social schedules relative to solar midday by 1 h.

1 | OUR HYPOTHESIS AND INTERPRETATION OF THE OBSERVED EFFECTS

Based on entrainment theory and previous evidence on the importance of both artificial light and sunlight, "Our hypothesis was that DLMO [dim light melatonin onset, a marker for circadian phase of entrainment] would be earlier in summer because of the combined effect of a stronger zeitgeber and the imposed shift in social time during DST" (p.10 in[1]). We, indeed, found DLMO to be advanced by a full hour in summer (in standard time) and thus also interpreted this finding accordingly[1](Figure 1):

Original hypothesis.
entrainment to light determined by social AND seasonal factors = self-selected light + natural variation in light

This hypothesis and the interpretation of our results are based on the simple rationale that any factor altering light exposure to a significant degree should be of relevance to circadian entrainment—and the most systematic and predictable factors altering light exposure in our sample are likely DST and season. On the one hand, DST advances social schedules by 1 h and thus also the timing of light exposure for people adhering to these schedules. Hence, we hypothesized DST as an indirect driver of an earlier phase of entrainment in summer. On the other hand, summer is usually characterized by longer, warmer, and sunnier days, which tend to drastically increase human light exposure directly and indirectly through encouraging more time spent outdoors.[1,5,9,10] Our participants, for example, were exposed to 10-fold higher light intensities in summer on average (one order of magnitude on the lux scale).[1] Such an increase in zeitgeber strength, even without substantial changes in zeitgeber timing, should also promote an earlier phase in humans, as supported by data from non-tropical and high-latitude locales without DST.[11–14] Firstly, this may be driven by the zeitgeber strength-phase dependency suggested by both mathematical models[15–18] and empirical data in various species (including some evidence in humans).[6,17,19–22] Here, exposure to stronger zeitgebers causes or is associated with earlier phases of entrainment as well as narrower population-based phase distributions. The finding that our participants showed not only a 1-h earlier DLMO but also a reduced inter-individual variance in DLMO in summer[1] is suggestive that this mechanism (stronger zeitgeber) was at play in our sample. Secondly, higher light exposure during daytime reduces the phase delaying effects of evening light.[23–25] Hence, in summer, many individuals may show a phase advance despite evening light exposure due to their prior light history. And finally, the DST-driven earlier awakening may be much more effective in producing a phase advance if natural light is available, which is the case in summer due to the early sunrise. Given the above arguments, we believe that the most likely explanation for the earlier DLMO phase in our sample in summer is a combined or even synergistic effect of social (DST) and seasonal factors on light exposure (Figure 1).

2 | THE HYPOTHESES AND INTERPRETATION OF THE OBSERVED EFFECTS BY SKELDON AND DIJK

In their commentary to our article,[26] Skeldon and Dijk do not mention our hypothesis ($H_{original}$) at all. Instead, they purport that our hypothesis and conclusion reflect entrainment to sun time (midday; their H_1, see Figure 1 and below) based on two sentences from our article quoted out of context[2]. This is most surprising since the importance of both social and seasonal factors is the dominant framework throughout our article, stated repeatedly in the background[3], our resulting hypotheses,[4] and the interpretation of our findings[5].

Skeldon and Dijk present the following two hypotheses for human circadian entrainment that are portrayed as mutually exclusive and do not explicitly incorporate seasonal effects[26] (Figure 1):

Hypothesis 1 *Entrainment to sun time (midday) = natural light.*
Hypothesis 2 *Entrainment to light selected by local clock time and social constraints = self-selected light.*

Skeldon and Dijk then elegantly demonstrate that the 1-h advance in DLMO and sleep in summer is obviously not well explained by H_1, since solar midday changes not only by 1 h but also just a few minutes over the year. Instead, they conclude the results are "most parsimoniously explained by local clock time and associated light exposure." (H_2) (p.1 in[26]).

In their commentary, Skeldon and Dijk seem to attribute the differences in DLMO between seasons solely to the 1-h advance in the timing of the light-dark cycle resulting from DST. Does this mean that one should expect a similar advance *in winter* if DST were introduced year-round (as in the model debated in many locales)? We would predict that without the light exposure typical for summer (increased daytime exposure due to less cloud cover, more outdoor activities, and earlier sunrise), the DST-induced behavioral advance would result in a phase shift of *<1 h* for most individuals (Figure 1). The strong natural light signal in summer tends to produce phase advances, both by itself (see above) and by supporting behaviorally driven advances. The latter we imagine to occur via two mechanisms: firstly, via the presence of natural morning light upon early wake up because of earlier sunrise times; secondly, via providing a strong light-dark cycle that supports realignment with the new light-dark cycle timing. Advancing a low-amplitude light-dark cycle was not enough to induce a phase shift of the melatonin, cortisol, and core body temperature rhythm in a well-controlled laboratory study by Dijk et al..[27] To us, this implies that DST in winter would be unlikely to lead to a full adaptation and that the summer-winter differences in DLMO timing in our sample likely reflect the synergistic combination of seasonal and behavioral effects on light exposure.

3 | CONCLUSION AND PERSPECTIVES

Human entrainment in real-life settings is complex, and there is a need for more field studies and scientific discussions to better understand the interplay between different signals (eg, natural and artificial light, social constraints, physical activity, meal timing) and outputs of the clock (eg, sleep, melatonin). The stability of phase of entrainment in real-life settings is, for example, still unclear. A single-entrained phase may even be a simplistic concept to start with, given the numerous circadian oscillations within each organism, which establish different phase relationships with each other under varying conditions.[28–30] We need more high-resolution longitudinal data of multiple phase markers to better comprehend how the circadian clock entrains *daily* in a world with many more zeitgebers than just light.

Altogether, we appreciate the discussion inputs by Skeldon and Dijk, and we believe that our interpretation of the data is actually not that different from theirs. We all agree that light is the strongest zeitgeber for human entrainment.[2–6] Skeldon and Dijk further suggest that humans entrain to self-selected light based on local clock time and social constraints. We also fully agree that humans' exposure to light is in large parts determined by their behavior and social activities. However, the quality, intensity, and availability of especially natural light depend on factors out of human control, which are bound to have contributed to the light environment of the participants in our study. We, therefore, hypothesize that human entrainment depends both on natural changes of light, such as seasonal changes, and on social factors, such as DST and working/school schedules. Unfortunately, it is difficult to disentangle the single contributions of season and DST in our data set or in most others given their inherent confound, especially in small sample sizes, but we hope that future studies will address and clarify the mechanisms of human entrainment in real-life settings in locales where DST and seasonal effects can be separated.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

DATA AVAILABILITY STATEMENT

No datasets were generated or analyzed during the current study.

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ENDNOTES

[1] "Here, the reported differences between winter and summer are likely driven by both seasonal changes in photoperiod as well as DST (social activities are moved 1 h earlier in summer relative to sun time thus changing behavioral light exposure)." (p.5, Results)
"Overall both DLMO and sleep (onset and offset) occurred earlier in summer compared to winter. The difference in timing between summer and winter was for all variables—except for sleep onset—close to 1 h. Since clock time was converted to and expressed as standard time, this 1-h difference suggests that by late June the participants fully adapted to the 1-h shift imposed by DST in March, confirming previous studies." (p.10, Discussion)
"Based on entrainment theories and previous studies, an earlier melatonin rhythm in summer is to be expected because the zeitgeber is stronger (higher and longer light exposure)." (p.10, Discussion)
"DLMO and sleep were earlier in summer compared to winter, consistent with exposure to longer and stronger light intensities in summer, as well as the 1-h shift of social activities imposed by DST in March." (p.12, Concluding Remarks)

[2] "Synchronisation to midday" stems from a side note in our discussion where we placed our findings in context with the decades long discussion of parametric versus non-parametric entrainment –preferring midday *only in comparison with sunrise and sunset*. "The circular plots reveal how the timing of DLMO and sleep varied between seasons in relation to sun time (sunrise, midday,

sunset). The phase angle between DLMO and sunrise and between DLMO and sunset changed substantially between seasons (4–6 h difference), whereas the phase angle between DLMO and midday remained stable (only a 1-h difference). Our data therefore suggest that midday and midnight are the most stable reference points for entrainment compared to sunrise and sunset, suggesting parametric entrainment in humans—at least in our sample." (p. 10, Discussion)

"'We know that humans entrain to sun time'" was quoted from a sentence explaining the rationale for using standard time instead of local time. This (certainly suboptimal) statement was never our conclusion, but rather referred to previous studies. "From previous studies, we know that humans entrain to sun time rather than social time. We therefore used standard time, …" (p.10, Discussion)

[3] "In natural settings, light is a complex signal varying with external conditions and individuals behaviors" (p.1, Abstract)

"Yet, the light signal is dynamic, influenced by season as well as by individual behaviors." (p.1, Introduction)

"Many countries also adopt daylight saving time (DST), which must be considered in interpreting results." (p. 2, Introduction)

"This design thus incorporates considerations of the zeitgeber (light) environment, which varies substantially due to natural conditions (season) and due to self-exposure (based on core daily activities)."(p.10, Discussion)

[4] "We wished to explore how seasonal and socially dictated (work-week) light exposures impact objective measures of entrainment in humans." (p.1–2, Introduction)

"The aim of this study was to better understand how the tension between the social and biological temporal structures is interpreted by the circadian clock in humans in summer and winter." (p.9, Discussion)

"Our hypothesis was that DLMO would be earlier in summer because of the combined effect of a stronger zeitgeber and the imposed shift in social time during DST." (p. 10, Discussion)

[5] See footnote 1

[6] "Throughout the manuscript, all clock times will be reported in standard time (UCT +1)" (p.2, Methods)

"Beware that all times are expressed in standard time throughout the manuscript. Since data in summer were collected under DST, such a 1-h difference means that the timing was different in relation to sun time but the same in relation to social time (DST in summer and ST in winter) " (p.5, Results)

"We therefore used standard time" (p.10, Discussion)

"Since clock time was converted to and expressed as standard time, " (p.10, Discussion)

Most table captions and graph axis titles

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