Weekly and seasonal variation in the circadian melatonin rhythm in humans: Entrained to local clock time, social time, light exposure or sun time?

Anne C. Skeldon1,2 | Derk-Jan Dijk2,3

1Department of Mathematics, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford, UK
2UK Dementia Research Institute Care Research & Technology Centre at Imperial College London and the University of Surrey, Guildford, UK
3Surrey Sleep Research Centre, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Correspondence
Anne C. Skeldon, Department of Mathematics, Faculty of Engineering and Physical Sciences, University of Surrey, Guildford GU2 7XH, UK. Email: a.skeldon@surrey.ac.uk

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UK Dementia Research Institute

Abstract
A recent elegant study published in this journal (Zerbini, Winnebeck & Merrow, J Pineal Res, e12723, 2021) reported data on weekly and seasonal changes in circadian timing, as assessed by the melatonin rhythm in dim light in a population that was exposed to a change from standard time to day light saving time. The authors highlight a one hour earlier timing of melatonin onset in summer compared with winter and a 20 minutes delay on work-free days compared with work days. The variations in the timing of the melatonin rhythm are reported in standard time and the authors imply that the data are consistent with synchronization to midday and that “we know that humans entrain to sun time.” Here, we show that their extensive data are most parsimoniously explained by entrainment to local clock time and associated light exposure rather than “sun time,” indexed by either dawn or midday.

KEYWORDS
circadian phase, entrainment, light, melatonin, sun time

Recently, Zerbini et al reported an extensive and carefully executed study to quantify “Weekly, seasonal and chronotype-dependent variation of dim-light melatonin onset” in humans. The study provides much-needed data to answer the fundamental questions about entrainment of the human circadian pacemaker: Is it entrained to local clock time, social time, light exposure or sun time? However, we feel that their analyses and conclusions are at some points contradictory and confusing. Here, we seek to clarify some of their findings and suggest an alternative interpretation of their data.

In their within-participant study, dim-light melatonin onset (DLMO), which is considered a gold standard marker of circadian phase, was assessed in the winter (December) and again in the summer (June). In each season, DLMO was assessed on Wednesday or Thursday to estimate circadian phase during work days, and on Sunday to estimate circadian phase at the end of a 2-day work-free.

The study took place in Groningen, the Netherlands, and therefore, local clock time was standard time in the winter and daylight saving time in the summer. Since local clock time determines many of our daily activities Zerbini et al chose to refer to it as “social time.”

In their analyses, Zerbini et al state that “we know that humans entrain to sun time rather than social time” and, therefore, report all DLMO times in standard time, rather than local clock time. What is meant by “sun time” is in general ambiguous since it has been variously defined by others as the timing of the zenith of the sun or dawn or dusk. In the context of Zerbini et al, we take “sun time” to mean solar midday since in the summary of their findings they state...
“… that it [DLMO] relates to midday or midnight rather than sunrise or sunset.” To explain why we disagree with their assumption that humans entrain to sun time, the use of standard time in their analyses and consequent interpretation of their data, we compare the data to the predictions of two hypotheses (See Figure 1).

**Hypothesis 1** Participants were entrained to sun time (midday).

**Hypothesis 2** Participants were entrained to light selected by local clock time and social constraints.

## 1 | DLMO IN WINTER AND SUMMER VERSUS HYPOTHESES 1 AND 2

During work days, the DLMO occurred at 20:27 (standard time), that is 21:27 (local clock time) for summer and 21:16 (standard time/local clock time) for winter. During work-free days, the corresponding reported times are 20:47 (standard time) in summer and 21:47 (standard time/local clock time) in winter which corresponds to 21:47 and 21:47 when measured in local clock time. So, when expressed in local clock time, DLMO does not change across seasons, (Table 1 of,1 also see Figure 1, central panels).

By reporting in standard time, Zerbini et al mask the remarkable consistency of DLMO timing in local clock time between seasons. These data and the reported mixed model analysis in which the effect of season was estimated as being approximately one hour are consistent with hypothesis 2 that the timing of DLMO associates with local clock time. The observed one hour effect of season is then a direct consequence of changing local clock time to standard time (see Figure 1, lower panels).

We do agree with the authors that the data show that the timing of DLMO does not associate with sunrise or sunset. Association of DLMO with sunrise/sunset has only been observed in environments without access to electrical light.2,3 But, in our opinion, the current data do not support the conclusion that DLMO associates with midday (solar noon), hypothesis 1. Under hypothesis 1, when expressed in standard time, there should not have been a one hour seasonal advance (see Figure 1, upper panels).

## 2 | DLMO ON WORK DAYS AND WORK-FREE DAYS VERSUS HYPOTHESES 1 AND 2

Dim-light melatonin onset assessed on Sunday evenings was on average 20 minutes later in the summer, and 31 minutes later in the winter, than DLMO assessed on Wednesday or

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**FIGURE 1** Dim-light melatonin onset (DLMO) and hypotheses on how it should change with season. Triangles show the time of DLMO with open symbols used for work days and filled symbols for work-free days. Blue (red) symbols are for winter (summer). Central panels: data as reported in.1 Top panels: Hypothesis 1: Participants were entrained to sun time as indexed by solar noon. Since solar noon varied by less than a minute from day-to-day and by an average of six minutes between December and June, DLMO should remain approximately constant when expressed in standard time (top left). When expressed in local time, that is standard time in winter and daylight saving time in summer, DLMO times in the summer appear to move later by approximately one hour (top right). Bottom panels: Hypothesis 2: Participants were entrained to the light selected by local time/social constraints. Under this hypothesis, DLMO tracks local time so remains approximately constant when expressed in local time (bottom right) but appears to move earlier by one hour in the summer when expressed in standard time (bottom left). Later sleep timing on work-free days results in later timing of light exposure and later DLMO times.
Thursday. Sun time does not change between work days and work-free days and, therefore, cannot explain the observed shift.

Social constraints do change between work days and work-free days. Indeed, on work-free days, the participants went to bed approximately one hour later and got up approximately one hour and 40 minutes later than on work days. The delayed DLMO on Sunday evening is consistent with delays in the timing of light exposure as a result of delayed sleep timing. Similar delays have been observed in a carefully controlled study of a simulated weekend,\(^4\),\(^5\) in the field,\(^6\) and have been predicted by mathematical models of sleep and the effect of light on the circadian pacemaker.\(^7\) Thus, the data do not need to be explained by the ad-hoc hypothesis that DLMO is an “unstable” marker of the circadian clock, but are in accordance with hypothesis 2, that is that participants were entrained to light selected by local clock time and social constraints.

**3 | CONCLUSION/PERSPECTIVE**

Overall, both the seasonal variation and work day-work-free day data reported by Zerbini et al are in accordance with those from other recent studies,\(^8\)-\(^10\) and with the hypothesis that humans in industrialized societies are entrained to light exposure, which is determined by local clock time and social constraints. Available light may in addition be modulated by season and by geographic position. In this scenario, DLMO is a sensitive indicator of week day to weekend changes in circadian phase and driver of variation in sleep propensity.\(^4\) No further explanation is required to explain the observed sleep and circadian timing.

Our interpretation is not at odds with the notion that stronger zeitgebers yield earlier circadian phases than weak zeitgebers. As in previous studies,\(^8\),\(^11\) Zerbini et al found that participants were exposed to more light in summer than in winter and imply that this average higher level of light exposure drives the observed phase shifts when expressed in standard time. However, most of the effects of light exposure were only significant in their mixed model when “season” was removed as a factor. Since the dependent variables were expressed in standard time, this implies that this analysis provides no evidence that the observed phase shift in DLMO is driven by seasonal differences in the light exposure beyond the change induced by changing the timing of social constraints. The mixed-model approach has many strengths but as applied in Zerbini et al, is not based on entrainment theory, that is it does not take the differential effects of light at different circadian phases into account. A proper analysis would consider both the intensity and timing of light over the 24 hours period, and further analysis would be needed to substantiate their claim. In fact, in our student population,\(^8\) we found that the time of the mid-point of half the daily light exposure moved with local clock time and sleep timing and was not associated with solar noon.

Our interpretation of the Zerbini et al data, that is DLMO does not entrain to sun time, appears inconsistent with large scale population studies of the variation of behaviour within a time zone.\(^12\),\(^13\) These studies provide compelling evidence that sleep timing is later in people living near the west border of a time zone, where solar noon occurs at a later local clock time, compared with those living close to the east border. These findings imply that human sleep timing, and presumably the circadian pacemaker, is at least partially entrained to sun time. The discrepancy may be explained by the very different timescales on which seasonal changes from standard to daylight saving time and the position in a time zone act.

Our interpretation does not negate some of the arguments against annual changes from standard time to daylight saving time.\(^14\) These changes are associated with disruptions of the alignment of circadian phase and the timing of sleep which are, however, temporary. Indeed, in spite of their hypothesis, Zerbini et al acknowledge “the participants fully adapted to the 1 hour shift.”

Additional studies especially when combined with epidemiological, statistical\(^12\) and entrainment theory-based modelling\(^15\) are essential to fully understand human entrainment and for robust policies and recommendations about light exposure and the timing of our work and sleep schedules.

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**ORCID**

Anne C. Skeldon [ORCID: 0000-0001-6387-4766]

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