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Sleep behavior across the lifespan: how a model can expand our current understanding

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Models have been crucial to providing a framework within which developmental hypotheses of sleep/wake regulation can be tested (1, 2). The “Two Process Model of Sleep Regulation,” first articulated by Borbély (3) and later refined (4–7), is the most widely accepted model describing the interaction between sleep/wake homeostasis and the circadian timing system. Variations of the model cast the two systems in opposition of one another to explain consolidated bouts of wake (8) and sleep (9). With a more advanced understanding of the neurophysiological underpinnings of sleep and circadian mechanisms, more models have been developed. Phillips and Robinson (10, 11), for example, model sleep/wake regulation by incorporating the mutual inhibition of wake-active neurons (monoaminergic, MA) and sleep-active neurons of the ventro-lateral preoptic (VLPO) area to explain sleep-wake transitions, similar to a flip-flop switch (12). In this model, wake-active neurons influence the rise of homeostatic sleep pressure during wake, and in turn inform the level of the sleep drive. The circadian system also informs the sleep drive via its approximate 24-hour oscillation of sleep propensity driven by the suprachiasmatic nuclei (SCN). The interaction between sleep homeostasis and the circadian system in the Phillips-Robinson model is similar to the two-process model (13), except physiological meaning is assigned to the two processes. Importantly, the extended version of the model (11) incorporates feedback from the light/dark (wake/sleep) cycle, which determines phase of the self-sustaining circadian oscillator. In this issue of *Sleep Medicine Reviews*, Skeldon, Derks, and Dijk (14) explore how the Phillips-Robinson model (11) can explain observed changes in sleep timing and duration across the lifespan from adolescence to older adulthood. These data describe the relative impact of changes to sleep homeostasis and circadian processes on sleep behavior, continue to challenge the assumption that sleep timing is driven exclusively by the circadian system, and may provide insights into the etiology of circadian sleep-wake disorders that manifest at different ages.

The authors use the data of Roenneberg and colleagues, who show a monotonic decline of sleep duration and an “n-shaped” function in sleep timing from ages 10 to 70 years on “free” (non-work/non-school) nights (15, 16). These nights presumably reflect the natural or preferred sleep times of the individual since the external social clock is likely to have less of

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an influence than on school/work nights. Sleep timing is measured by the midpoint between self-reported sleep onset and wake-up time on free days, and therefore is called mid-sleep on free days, or MSF. This metric is adjusted for accumulated sleep debt on school/work days (17). In this large dataset of mostly Central Europeans, Roenneberg and colleagues find that midsleep time on free days shows a large delay during the adolescent years with an average MSF of about 2:30 AM at age 10 years, followed by a delay of MSF through the teen years peaking at about 5:00 AM at age 20 years, and then a subsequent advance of midsleep time to about 3:30 AM at age 70 years (15). Skeldon and colleagues aimed to simulate these data by manipulating the build-up of homeostatic sleep pressure during wake and circadian amplitude within the parameters of the Phillips-Robinson model. Circadian amplitude can be conceptualized in a few ways (18), but in this case it is presumed to indicate the synchrony of the system to produce a “robust” rhythm of consolidated sleep at night and activity during the day. Their analysis suggests that circadian amplitude impacts sleep timing across the lifespan with a decrease in circadian amplitude predicting earlier sleep times. Sleep homeostasis, however, also contributes to sleep timing, especially during the adolescent years. As homeostatic sleep pressure accumulation slows, sleep timing shifts later. These data provide additional evidence challenging the assumption that only the circadian system regulates the timing of sleep. Furthermore, these data may indicate that bio-regulatory processes underlying sleep behavior may be more or less influential at different developmental stages.

The role of sleep homeostasis in dictating sleep timing has been reported in previous studies of young healthy adults mostly in their twenties who differed on the construct of morningness/eveningness preference. Several studies have reported that sleep/wake timing and physiological circadian phase markers are earlier in morning types compared to evening types (19–22). In a series of studies, however, Mongrain and colleagues (23–26) found that some young adults who self-reported being morning types or evening types on the Morningness-Eveningness Questionnaire (MEQ) of Horne and Östberg (27), have similar circadian phases (measured by the dim light melatonin onset, DLMO). Sleep homeostatic dynamics, however, did differ between these morning and evening types. Morning types showed a faster decay rate during sleep and showed a greater homeostatic response to sleep fragmentation compared to evening types. Slow wave activity (SWA) was also higher at the beginning of recovery sleep for morning types compared to evening types, indicating that morning types start their night with more sleep pressure. This may suggest differences in the homeostatic rise during wake. Indeed, Taillard and colleagues (28) reported faster build-up of sleep pressure during wake in morning types compared to evening types. By contrast, morning and evening types who differentiate on circadian phase (early and late DLMOs) did not show these differences in sleep homeostasis, suggesting that phase preference was predominantly driven by the phase of the circadian system in this group of individuals. Thus, what was once thought to be driven exclusively by the circadian system, morningness-eveningness can also be explained by differences in sleep homeostasis, though the underlying bio-regulatory mechanisms underlying circadian phase preference may vary among individuals.

A striking change in sleep timing occurs during adolescence, from about age 10 to 20 years. As described previously, Roenneberg and colleagues (15) illustrate this change using the

mid-sleep time on free days. Other studies from around the world comparing different age groups find that reported bedtimes are later on both school nights and non-school nights, and wake time is later on non-school (weekend or vacation) mornings (29–35). Longitudinal studies using actigraphically-estimated sleep times support these findings, and show that the delayed sleep pattern begins as early as the middle school years (~11 to 13 years) (36, 37). This developmental shift of sleep timing is partly driven by developmental changes to the circadian timing system. Previous studies in adolescent humans (38, 39) and in other young mammals (40) find a puberty-related delay of the circadian timing system. In human adolescents, the melatonin rhythm was later in the participants who were late or postpubertal compared to those who were pre- and early-pubertal adolescents after both groups kept the same sleep/wake (and thus dark/light) pattern for at least a week before melatonin collection. As the analysis of Skeldon and colleagues (14) in this issue would predict, however, developmental changes to sleep homeostasis also partly explains the shift to later sleep times over the course of adolescence. Previous work illustrates that the dynamics of the homeostatic sleep system are altered during adolescence. One cross-sectional study modeled the build-up of SWA using sleep before and after 36 h of sleep deprivation and found an increase in the time constant of the build-up in postpubertal teens compared to prepubertal teens (41). This suggests that mature adolescents accumulate sleep pressure at a slower rate across the waking interval compared to younger, less mature adolescents. Longer sleep onset latencies close to bedtime in mature adolescents compared to prepubertal adolescents following 14.5 and 16.5 h of wake also provides support for this developmental difference in the accumulation of sleep pressure. These changes in sleep physiology likely make it easier for an older, more mature adolescent to stay awake late to watch television, complete their homework, or send a few more text messages. The decision to go to bed later is also more likely with a reduction in parent-set bedtimes (29, 42).

In addition, we reported that self-selected sleep onset occurs later relative to the DLMO in older adolescents compared to younger adolescents (37, 43). We speculate that the developmental difference affecting the homeostatic sleep system produces this later sleep time relative to the onset of the biological night. In our proposed model (see Figure 3 in (37)), the younger adolescents, who are mostly pre- to midpubertal likely achieved their maximum sleep pressure earlier in their wake interval. By contrast, older adolescents are at a developmental stage at which sleep pressure builds more slowly across waking and their maximum sleep pressure is later. We proposed that the difference in homeostatic sleep pressure accumulation may allow the older adolescent to stay awake longer after the onset of their biological night marked by the DLMO. This extended wakefulness past the DLMO provides older adolescents a greater opportunity for evening light exposure, which likely supports a delayed circadian phase position. Hence, homeostatic sleep changes may drive the circadian phase changes observed in this age group. The extended version of the Phillips-Robinson model utilized by Skeldon and colleagues may provide a theoretical framework from which to start testing these hypotheses to understand the relative contribution of the two systems during pubertal development.

Finally, the model predictions of Skeldon and colleagues (14) could also inform the etiology of circadian rhythms sleep-wake disorders that emerge at different ages. The onset of symptoms of Delayed Sleep Phase Disorder (DSPD), for example, typically occurs during

adolescence or emerging adulthood (44–46). Patients with DSPD consistently report sleep times that are later than other individuals, and they are unable to fall asleep and wake at a clock time consistent with the earlier social schedules of school or work. Patients with DSPD show delayed circadian phase markers (46–51), suggesting that the underlying cause of the disorder is primarily driven by the circadian system. Studies have challenged this assumption, however, showing that sleep homeostasis is also altered in these patients. Watanabe and colleagues (52) reported that patients with DSPD had fewer slow waves at the beginning of the night compared to healthy controls, suggesting that the rise of sleep pressure is slowed during wake or the system is less robust in these patients. Uchiyama and colleagues (46) sleep deprived a group of patients with DSPD and an age- and sex-matched healthy control group for one night and then measured sleep propensity (minutes of stages 2, 3, 4, and REM) during an ultra-short sleep-wake cycle (10-min sleep opportunity/20-min wake) for 26 to 30 h. After sleep deprivation, the patients did not recover their sleep during the naps that occurred during their biological day, but rather most of their sleep occurred during naps that occurred during their biological night (when melatonin was high). The healthy control participants were able to sleep both during their biological day and night. The authors concluded that the patients had poor compensatory function following the night of sleep deprivation compared to the healthy controls, again, implicating a weaker homeostatic drive in the etiology of the disorder. An alternative or additional interpretation of these results is that patients with DSPD have a large circadian amplitude, making it more difficult to sleep out of phase from their circadian clock. Figure 1 of (46) shows a robust sleep propensity rhythm in patients, but not in controls after the sleep deprivation challenge. According to the model predictions of Skeldon and colleagues, a reduction in the homeostatic rise of sleep pressure across waking and a large circadian amplitude should result in later sleep timing. Furthermore, sleep timing appears to be influenced by both processes during the adolescent years, when symptoms of DSPD usually manifest. Perhaps then, the developmental slowing of homeostatic sleep pressure across waking is intact or the slowing is more exaggerated in patients with DSPD, driving the ability to fall asleep later. With later sleep/wake times, light/dark exposure also delays, which in turn increases the possibility for the circadian system to also shift to a later phase. If the circadian system is robust (large circadian amplitude), then sleeping out of phase (earlier) becomes more difficult. Thus, DSPD may be the results of an exaggerated developmental change in sleep/wake homeostasis in combination with a robust, high amplitude circadian clock. Of course, this hypothesized mechanism needs testing. Nonetheless, utilizing models to develop these types of hypotheses has the potential to challenge assumptions and expand our current understanding of sleep/wake behavior over the course of development and in the context of sleep-wake schedule disorders.

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