How to measure circadian rhythms in humans

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The scientific study of human circadian rhythms began when a curious sleep researcher asked clever questions and went ahead to test them on himself. Nathaniel Kleitman spent a month in a dark underground cave in 1938, having developed an "apparatus for determining and for recording motility and rectal temperature during sleep."[1] Kleitman's monitoring of bed movements by means of a primitive polygraph to produce a continuous readout of motor activity anticipated measurement techniques that have only recently become practical thanks to advances in microelectronics. He clearly demonstrated that under constant dim environmental conditions sleep did not retain its 24-hour pattern, but shifted later day by day. He also tried to live on a "28-hour day," as a test of whether the usual 24-hour cycle might simply be a reaction to the outside world. The "28-hour day" is a technique now used to separate the sleep-wake cycle (which can more or less follow this long day) from the endogenous circadian cycle (which cannot).

Two decades later, Jürgen Aschoff and Rütger Wever created a more comfortable underground "bunker" for human temporal isolation experiments, measured motility (by means of sensors in the bed and floors), rectal temperature, urine output, and many other physiological and behavioral variables, and concluded that humans have endogenous circadian cycles like plants and mice and flies.[2] They also placed subjects on days of varying lengths, and tested to what extent the biological clock could synchronize to the given periodicity. In more than 25 years of research, they laid the basis for the formal properties of the human circadian system analogous to that developed by Pittendrigh and Daan for rodents.[3]

The timing and structure of sleep and waking is considered to arise from interactions between the biological clock or circadian pacemaker (designated "process C") and a sleep homeostatic process dependent on duration of prior time awake ("process S") *(Figure 1)*.[4] This 2-process model is applicable not only to the sleep-wake cycle, but also to the understanding of the temporal patterns of nearly every neuroendocrine, physiological, and psychological function. The model has proved extremely useful for understanding a variety of sleep disturbances, and can be used to interpret apparent rhythmic abnormalities in depression, as well as providing a framework for specific therapeutic approaches.

Characteristics of the circadian clock

Biological clocks help us keep time on this rotating planet. The advantage of an internal clock to regulate sleep and wakefulness within the appropriate

Selected abbreviations and acronyms	
DLMO	dim light melatonin onset
MCTQ	Munich Chronotype Questionnaire
MEQ	Morning-Eveningness Questionnaire
SCN	suprachiasmatic nuclei

The biological clock drives all circadian rhythms in humans, whether relative to neurobehavioral function, hormones, physiology, or behavior. The most obvious rhythm is the sleep-wake cycle, which differs in timing across individuals ("chronotype"—from early-morning larks to late-night owls). However, not all changes in sleep-wake cycle behavior are a consequence of abnormal clock function. Knowledge of the formal properties of the circadian system, the role of zeitgebers for adequate synchronization to the 24-hour day, and how sleep is regulated, has led to the development of stringent protocols to investigate the characteristics of circadian rhythms and sleep. These studies have provided gold standards for estimating circadian amplitude and phase, and have identified the most useful physiological or hormonal markers. We are now at the second stage of trying to develop simpler markers for ambulatory use, which provide a reasonable estimate of circadian phase. Chronobiology requires long-term measurement over at least one 24-hour cycle, and new microchip technologies permit noninvasive and continuous data collection over many days and weeks (eg, actimetry). The next decade of research will surely yield further insights into human circadian clock function and its pathologies.

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phases is that physiology and behavior can anticipate transitions between day and night and not merely react to them. A circadian clock not only generates a cycle to match the solar day, it must also maintain an appropriate phase relation to it. This process of optimal synchronization with the environment is called entrainment, and is mediated by periodic stimuli ("zeitgebers") acting on the clock. The endogenous period of the circadian pacemaker under time-free conditions (as in a cave or a bunker) is known as τ, and the phase relation between rhythm and zeitgeber during stable entrainment is defined as ψ (eg, the difference between the phase of a given circadian rhythm such as sleep onset and the phase of a zeitgeber such as dusk or dawn) *(Figure 2)*.[2]

Individual differences in τ may lead to different ψ—the best known example is a person with short τ being a "lark" chronotype, and someone with long τ being an "owl" chronotype.[5] However, τ is not the only factor that influences phase: sensitivity to light or zeitgeber strength (when and how long a person is exposed to what wavelengths and intensities of light), and amplitude of the circadian pacemaker, are also determinants.

The most important zeitgeber is light, providing the photic signal for day and night as well as the seasons. The master circadian clock in the suprachiasmatic nuclei (SCN) consists of two coupled oscillatory systems that respond to dawn and dusk.[6] The change in daylength with seasons is mimicked in many species by changes in the duration of activity and rest (α:ρ). Three main steps are important for biological clock function *(Figure 1):* input (zeitgebers, retina) ⟹ SCN circadian pacemaker (eg, clock genes, neurotransmitters/peptides) ⟹ output (pineal melatonin synthesis, thermoregulation, etc). These factors then interact with the sleep-wake homeostat to regulate, continuously in time, sleep propensity and sleep architecture, and influence phenomena as different as mood and performance or hormonal output.

Which circadian clock characteristics do we want to measure?

A graphic representation of the various characteristics of the circadian system is shown in *Figure 2*. First, under entrained conditions, the sleep period remains at a stable phase angle with respect to the light-dark cycle (ψ), with a given activity-rest ratio (α:ρ); and, second, in the absence of time cues (zeitgebers), the sleep period shifts later and later each day following the frequency of the endogenous pacemaker (τ).

◆ *Freerunning period (τ)*

The freerunning period (τ) is a characteristic of the circadian pacemaker that can only be measured in humans using very elaborate protocols: either in a time-isolation environment in dim light,[2] whereby the endogenous rhythmicity reveals itself in a "free run," or in a "forced desynchrony" protocol[7] where the given sleep-wake cycle is much longer or shorter than the range to which the circadian pacemaker can entrain, and where endogenous rhythmicity retains its freerunning period (as originally shown by Kleitman, Aschoff, and Wever).

It should be noted that this natural periodicity, τ, is not only a genetically determined characteristic: τ is subject to "after-effects," ie, is changed by whatever environmental light pattern and intensity the subject was exposed to prior to the study,[2] such as

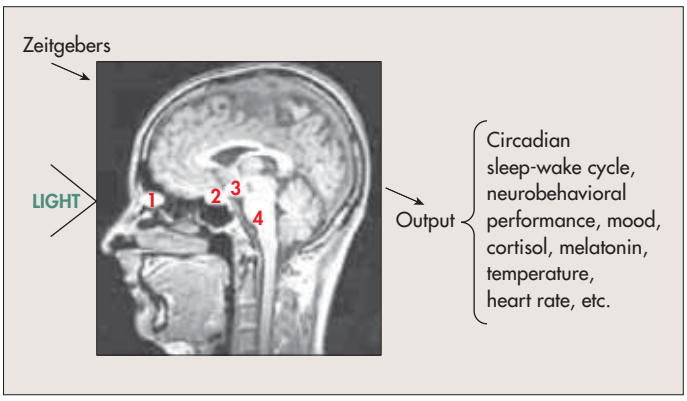

Figure 1. Circadian and homeostatic regulation of sleep. Two major processes are involved in driving the circadian sleep-wake cycle as well as all other behavioral and neuroendocrine outputs: their known anatomical correlates are schematically represented: (1) retina; **(2)** suprachiasmatic nuclei (SCN); **(3)** hypothalamus: ***anterior*** (ventrolateral preoptic nucleus—sleep-promoting); ***posterior*** (tuberomammillar nucleus—histamine; orexin [A/B]-producing neurons [wake-promoting]); **(4)** ***midbrain and pons*** (locus coeruleus [NE]; raphe nuclei [5-HT]; pedonculopontine tegmentum and laterodorsal tegmentum [ACh]).
Abbreviations: 5-HT, serotonin; ACh, acetylcholine; NE, norepinephrine.

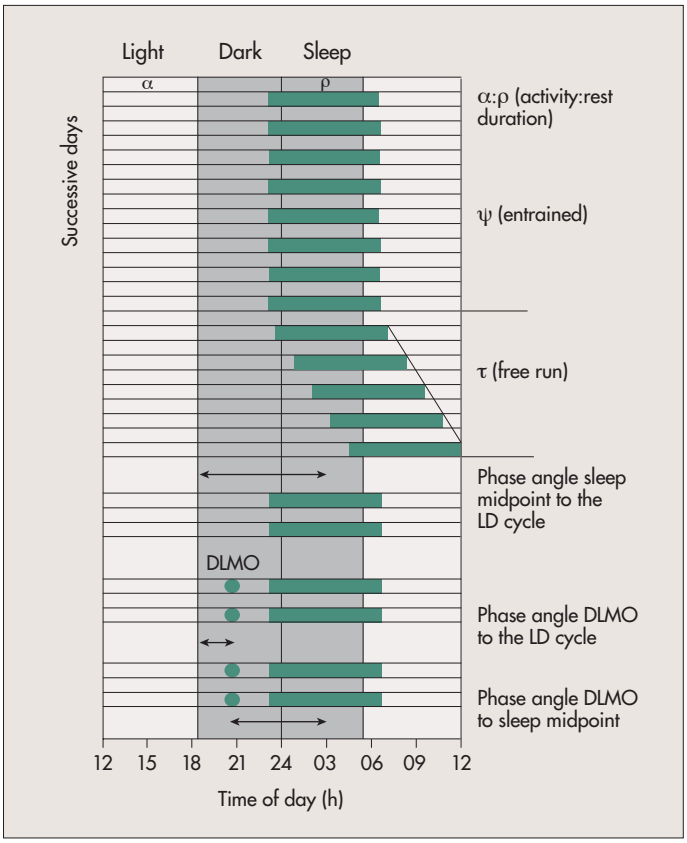

Figure 2. Schematic characteristics of the sleep-wake cycle. The sleep period (green bars) is plotted on consecutive days with respect to external time (the light:dark [LD] cycle) and internal time (the circadian phase marker dim light melatonin onset [DLMO], green circles). See text for details.

the duration of the photoperiod (τ is longer in winter than in summer[8]). Thus, a measured τ could reflect behavioral differences with respect to light exposure, rather than just a genetic difference.

Novel techniques now in development can measure the τ of clock gene expression in tissue cultures from skin biopsies (this yields a τ for "peripheral" clocks, whose exact relationship to the τ expressed by the central clock in the SCN is not yet known).[9]

◆ *Phase angle (ψ)*

The simplest way to find out about anyone's preferred phase position is to ask their preferred sleep times on free days. Habitual bedtime and wake-up

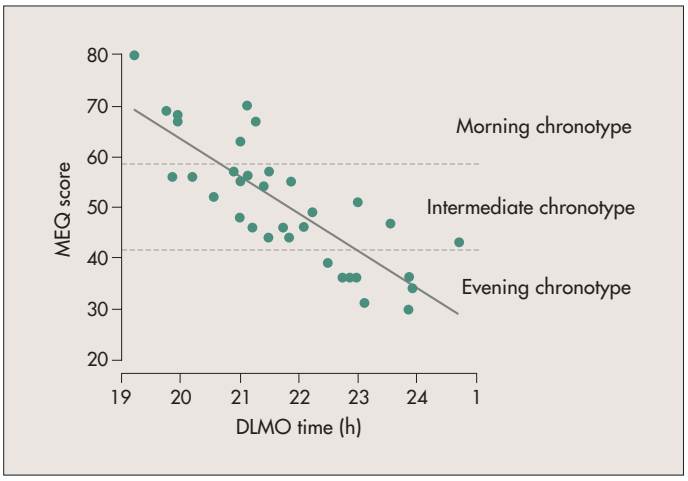

Figure 3. Correlation of internal circadian time with chronotype in winter depression. The timing of dim light melatonin onset (DLMO, threshold of 3 pg/mL) is strongly correlated with the morningness-eveningness score on the Morning-Eveningness Questionnaire (MEQ) in patients with winter depression (r=–0.81, N=35, *P*<0.001). The wide spread of chronotype is similar to that found in the general population. Redrawn from unpublished data related to reference 13 with permission from M. Terman.

time on free days are obviously chosen because this is the comfortable ψ for that individual. The sleep pattern gives a first simple estimate of a person's phase, commonly known as chronotype, which ranges from extreme early birds to extreme late-night owls. The most reliable phase marker with respect to sleep timing is the sleep midpoint (sleep onset time – wakeup time / 2). Questionnaires about sleep preferences have long been used to better quantify this characteristic. The classic Horne-Ostberg Morning-Eveningness Questionnaire (MEQ)[10] is now available as an online self-assessment (AutoMEQ) with personalized feedback (www.cet.org). Recently, the Munich Chronotype Questionnaire (MCTQ) has been developed,[5] validated against sleep logs, and also automated (www.imp-muenchen.de); it is available so far in English, German, Spanish, Italian, French, and Dutch. Objective measurement of rest-activity cycle timing can be made with actimetry.[11]

To go a step further, beyond sleep phase to internal clock phase, we need a good output of the circadian clock that can be reliably measured. The pineal hormone melatonin fulfils this role admirably.[12] All species that secrete melatonin do so at night; light immediately suppresses its synthesis. It has been well established that if samples (saliva or blood or urine) are collected under dim light and controlled posture conditions, the melatonin rhythm provides an optimal marker of circadian phase in humans. "Dim light melatonin onset" (DLMO) is the easiest marker of body clock time we have, because it can be feasibly measured in saliva before a person goes to sleep.[12] If an entire 24-hour rhythm is measured, phase can be defined as required—at the peak, the midline crossing point, offset of secretion, etc. However, many studies measure only part of the rhythm, taking evening samples under controlled conditions before sleep to measure when melatonin synthesis begins (DLMO). To understand putative abnormalities, one can measure the phase angle of the sleep midpoint to external time (in *Figure 2,* dusk; but dawn is equally valid), or the phase angle of internal time as measured by DLMO to the LD cycle or to sleep midpoint.

However, melatonin assays are not (yet) a rapid or an easily available method for everyday diagnostic use. A large, carefully controlled study of melatonin rhythms and sleep timing in the same subjects has found a close phase-relationship of this marker of internal time to the sleep midpoint *(Figure 3).*[13] An algorithm was developed that is of great clinical utility, since sleep midpoint can be used as a reasonable (indirect) estimate of circadian phase (this is valid only if sleep is not too disturbed[14]). In addition, the algorithm allows calculation of when bright light therapy should be applied with respect to internal (ie, circadian) and not external (clock) time. This is the first example of applying circadian principles to determine individual timing of a treatment: the important therapeutic consequences are higher remission rates to light therapy than when prescribing the same clock time for everyone. We thus can use an everyday, straightforward determination of sleep midpoint (calculated from the MEQ, MCTQ, or a week of sleep logs) to provide a rough estimate of an individual's internal clock time. There are provocative indications that the same phase-advancing strategy with early morning light, known to be beneficial for treatment of winter depression is key to sustained improvement in non-seasonal depression. Intriguing data from a preliminary study in depressed bipolar patients (on lithium) treated by sleep deprivation, indicates that morning light therapy individually timed to maximize a circadian rhythm phase advance not only sustained the rapid sleep deprivation response, but patients continued to improve (not found with light given at 11 AM to all) (F. Benedetti, personal communication).

◆ *Amplitude*

The amplitude of a circadian oscillation is an important characteristic. When amplitude is low, a zeitgeber can theoretically elicit larger phase shifts than when amplitude is high. Measuring amplitude of clock function is, however, rather difficult in practice, and there is only indirect evidence from circadian rhythms of melatonin or temperature that amplitude can be diminished (by very specific timing of a light pulse) or augmented (by increasing light intensity/duration).

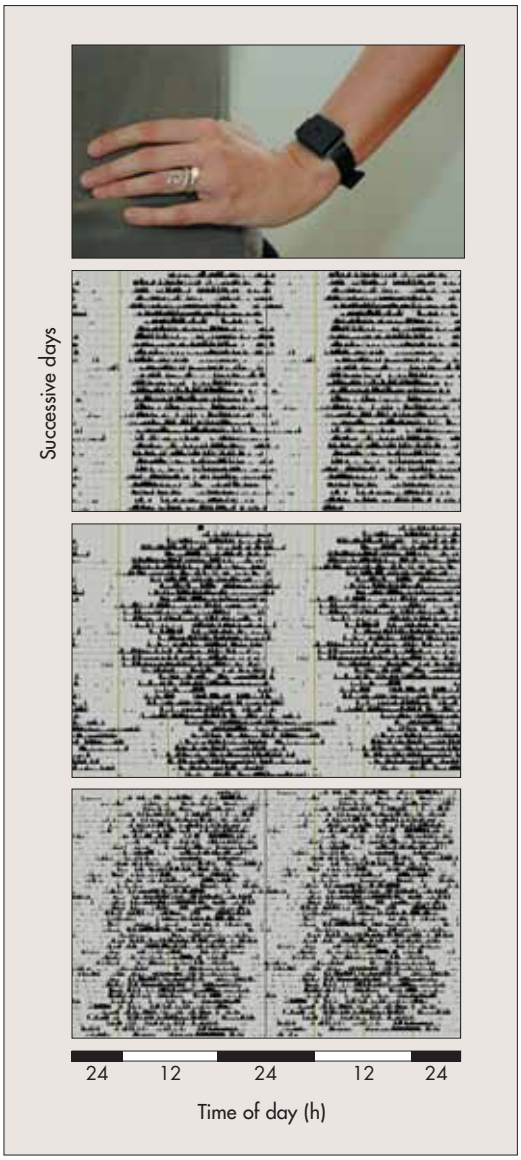

Figure 4. Long-term activity monitoring in depression. An example of an activity monitor, the size of a wristwatch (Cambridge Neurotechnology®), is shown being worn on the nondominant hand. Movements are collected at 1- to 2-minute intervals and stored until readout. The circadian rest-activity cycle is double plotted, ie, day 1 and 2 on one line, day 2 and 3 on the next line, etc. This double plot makes visualization of shifted and irregular rhythms easier. On the vertical axis of each line is the amount of activity per unit time: the higher the bar the greater the activity (blacker). **Upper panel:** 6 weeks' recording of a control pregnant woman with regular sleep patterns. **Middle and lower panels:** examples of irregular rest-activity cycles and disturbed nights in pregnant women suffering from major depression (Wirz-Justice, unpublished data).

How can we measure the circadian rest-activity cycle?

Actimetry is a noninvasive technique for ambulatory monitoring of rest-activity (which is not necessarily always congruous with sleep-wake) cycles.[11] It is the equivalent of the running wheel for hamsters and mice in human circadian biology, with the same advantages of measurement over longer periods of time than in sleep research (1 to 2 nights' polysomnography). Additionally, 24-hour monitoring can reveal unusual patterns of rest and activity that provide information quite different from the sleep EEG (eg, timing and duration of daytime naps). Familiarity with the animal literature on abnormal rest-activity cycles and the formal properties of the mammalian circadian system (eg, τ , ψ, see above)[3] can help interpret the observed phenomena. However, it must be clearly recognized that actimetry does not necessarily reflect the underlying circadian clock characteristics.

A tenet of human chronobiology is that adequate entrainment means better sleep and higher alertness, and better cognitive state and mood during wakefulness. Thus, actimetry may be used to document changes in entrainment state related to efficacy of a given treatment (whether pharmaceutical or not). Indeed, a recent study in patients with seasonal affective disorder showed a delayed rest-activity cycle and low activity when depressed, with increased activity and better synchronization following clinical improvement with light therapy.[15] There has not yet been very much long-term activity monitoring in major depression. These patients may not show a single or consistent abnormality, but rather, large interindividual differences in their rest-activity cycle patterns. This is what we are seeing in an ongoing study of 6 weeks actimetry in major depression during pregnancy *(Figure 4)*. This unstable rest-activity cycle is indicative of poor circadian entrainment, and may contribute to some aspects of the illness.

Over the years, validation of actimetry by sleep EEG in healthy subjects led to the development of analysis programs for actimetric "sleep" that provide an estimate of a number of classic parameters (sleep onset, wake-up time, wake bouts, sleep efficiency, etc). Analysis programs for circadian variables (of which there are a variety) can provide an estimate of, eg, relative amplitude (maximum-minimum), intradaily stability (estimates of strength of coupling to zeitgebers), and interdaily variability (degree of fragmentation).[16]

In conclusion, actimetry is an easy, noninvasive, and relatively inexpensive tool that deserves more use in the clinic. It provides objective verification of chronotype (time of going to bed and waking up), and documents changes in sleep-wake patterns during illness and following treatment. A minimum of 1 week's recording is recommended to compare the pattern of work and free days and to reduce variability.

Why circadian clock characteristics are not easy to see

Measuring the rest-activity cycle is a first step in looking at 24-h patterns of behavior. However, to dig deeper and look at endogenous circadian pacemaker characteristics requires special techniques and validated markers. It has long been recognized that the overtly measured rhythm of a given variable over 24 hours is not only determined by the biological clock and sleep homeostat, but also by zeitgebers such as light, or behavior, which can have direct or indirect effects on many functions, so-called "masking."[17] Some examples are shown in *Figure 5 (next page)*.[18-20]

Masking modifies the pattern of daily rhythms that are measured in naturalistic environments. As shown in *Figure 5,* postural changes rapidly affect thermoregulation,[18] as does sleep,[19] thus giving a false estimate of amplitude and phase when looking at the complete 24-hour measured curves. Light in the evening can suppress melatonin or delay its onset, even at lower intensities (>100 lux).[20] Thus, in order to elucidate the characteristics of the endogenous circadian pacemaker, it has been necessary to develop protocols that control for masking effects.

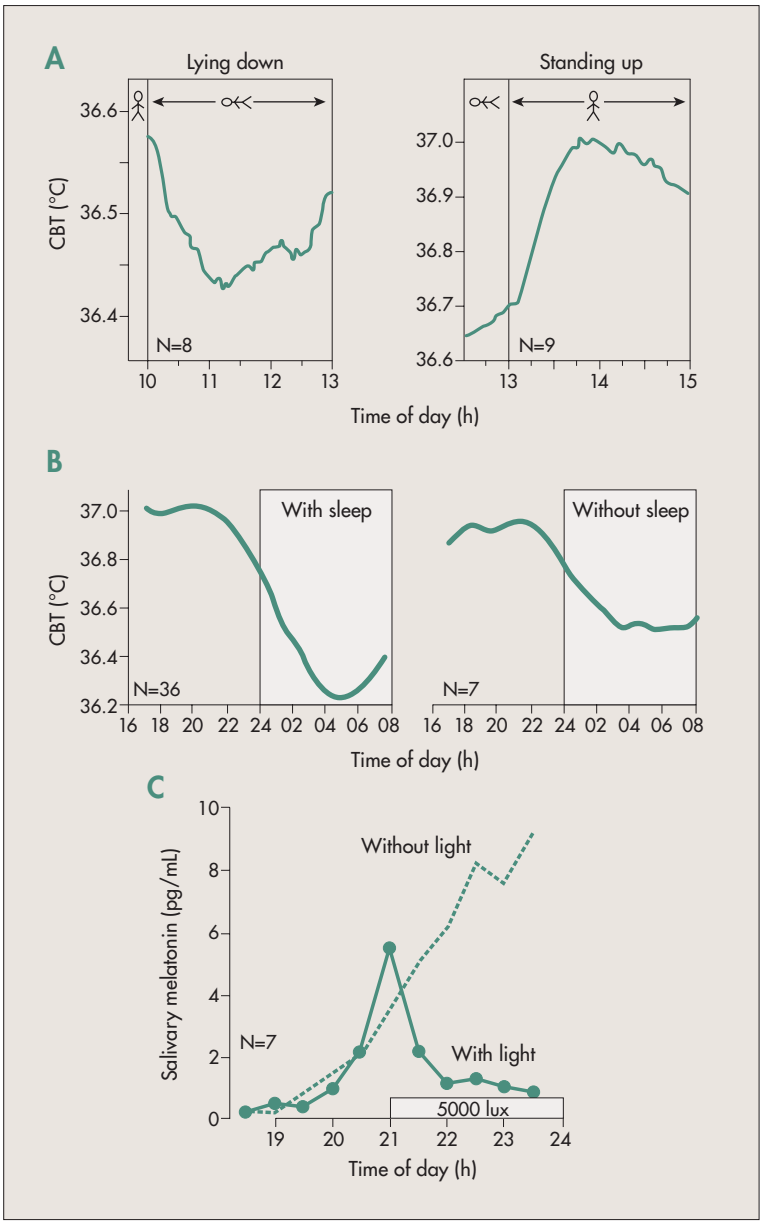

Figure 5. Examples of behavioral and environmental masking effects. Three examples of masking effects on circadian rhythms are shown: (A) posture and (B) sleep modify core body temperature (CBT); evening light suppresses melatonin secretion (C).

*Redrawn from reference 18 **(Panel A):*** Kräuchi K, Cajochen C, Wirz-Justice A. Thermophysiologic aspects of the three-process-model of sleepiness regulation. *Clin Sports Med.* 2005;24:287-300. Copyright © 2005, Elsevier; *reference 19 **(Panel B):*** Kräuchi K, Wirz-Justice A. Circadian clues to sleep onset mechanisms. *Neuropsychopharmacology.* 2001;25(5 suppl):S92-S96. Copyright © 2001, Nature Publishing Group; and *reference 20 **(Panel C):*** Wirz-Justice A, Kräuchi K, Cajochen C, Danilenko KV, Renz C, Weber J. Evening melatonin and bright light administration induce additive phase shifts in dim light melatonin onset. *J Pineal Res.* 2002;36:192-194. Copyright © 2002, Munksgaard International Publishers.

To measure endogenous circadian rhythms—back to the lab!

When attempting to document circadian rhythm disturbances, there is always the question of how much sleep "interferes" with what one measures. And often, one wants to measure sleep disturbances as well, because of their obviously important role in the illness. The 2-process model[4] is useful here in selecting the appropriate markers that reflect either the more circadian or more sleep-related homeostatic factors. The accepted "gold-standard" protocols are the:

◆ **Forced desynchrony protocol:** Under time-free conditions subjects are asked to sleep on a very short or very long cycle (eg, a 20-hour or 28-hour day).[21] The circadian system can no longer entrain to these extremes, and remains at its endogenous period (usually longer than 24 hours); this means that over the entire protocol, sleep occurs at every circadian phase. Post hoc analysis allows a "pure" circadian and a "pure" sleep homeostatic component to be educed from any variable measured (psychomotor vigilance to sleep EEG parameters[21] to subjective mood state (eg, see *Figure 3* in reference 22).

◆ **Constant routine protocol:** Under time-free conditions, subjects are kept in a constant semirecumbent posture in bed, under dim light, controlled temperature, and humidity, and given small isocaloric snacks and water every 1 to 2 hours during a period of 40 hours of total sleep deprivation.[23] This protocol minimizes masking and provides valid estimates of circadian rhythm amplitude and phase (eg, core body temperature, melatonin).[24]

Modifications of the above have been developed that are easier for patients and still reveal circadian information:

◆ **Constant bed rest protocol:** Ad libitum sleep allowed instead of sleep deprivation (easier for patients). Certain circadian rhythms can be measured under these conditions (eg, sleep propensity, rapid-eye movement [REM] sleep; see, for example, *Figure 3* in reference 25)

◆ **Multiple nap protocol:** By scheduling longer naps over the 24-hour day (eg, 150 minutes awake: 75 minutes asleep) sleep pressure (process S) does not accumulate and the circadian rhythms of many parameters thereby usually masked emerge very clearly (eg, subjective sleepiness; see *Figure 3* in reference 26).

The forced desynchrony protocol in particular has dissected out the relative contributions of the sleep-wake homeostat and circadian pacemaker to a large number of neurobehavioral and physiologic functions, which provide the basis for suggested measures in *Table I*. These are exhaustive and long protocols, and thus expensive in terms of recruitment effort, time in the laboratory, and 24-hour continuous monitoring. Each has its respective advantages, and elegant studies over the last decade have consolidated the database, established standard values, and led to a qualitative hierarchy of "which measures are suitable for which question." The major questions of what changes in ψ , phase relationships between dawn and dusk (α:ρ), or circadian amplitude occur in major depression require laboratory studies that will help elucidate whether clock dysfunction is a core feature of the illness.

Markers of the clock

In summary, *Table I* provides a short list of putative clock markers for researchers and clinicians. The list additionally contains external zeitgebers, since these impact on the structure of sleep and wake—from the important role of social zeitgebers to putative conflicting zeitgebers as found in shift

CIRCADIAN CHARACTERISTICS	Ideal lab protocol	Shorter (less perfect) alternatives
τ	Temporal isolation (free running) Forced desynchrony	DLMO over 3 consecutive weeks
ψ (chronotype)		Sleep midpoint (MEQ, MCTQ, sleep logs, actimetry)
ψ	Constant routine (circadian rhythms of core body temperature, melatonin, cortisol, heart rate, etc)	DLMO
Amplitude	Constant routine (circadian rhythm of core body temperature?)	Actimetry (relative amplitude highest-lowest activity)
α:ρ	Actimetry	Sleep logs
Stability of entrainment	DLMO over successive days or weeks	Actimetry for at least 7 days (intradaily stability)
Retinal function	Melatonin suppression test	Ophthalmology checkup: (does not necessarily test circadian photoreceptor function)
Measured light input (zeitgeber strength)	Ambulatory light monitoring	Light logs (time outdoors)
Social zeitgebers		Social Rhythm Metric Questionnaire

SLEEP HOMEOSTAT	EEG characteristics
Decline in process S during sleep	Slow-wave activity (eg, 0.75-4.5 Hz) in NREM sleep
Rise in process S during wake	◆ θ/α activity in wake EEG (particularly frontal) ◆ Slow eye movements in wake EEG

Table I. Markers of circadian rhythms and the sleep homeostat.
Abbreviations: DLMO, dim light melatonin onset; MCTQ, Munich Chronotype Questionnaire; MEQ, Morning-Eveningness Questionnaire; NREM, nonrapid eye movement (sleep).

workers. Zeitgeber strength (eg, how much light does an individual receive and at what time of day) is an important factor for entrainment. Retinal input is a further factor; since light is the major zeitgeber, eye problems may diminish photic input to the clock. Blind persons, for whom this signal is absent, cannot usually synchronize well: they show phase-delayed or even free-running sleep-wake cycles, indicating that social zeitgebers are not always sufficient for entrainment.

Thanks to more than a decade of elegant studies carried out in healthy humans in forced desynchrony and constant routine protocols, we have valid data about the best markers of the clock. Together with the development of new technologies that allow noninvasive measurement of physiology and behavior over many days (eg, i-buttons for skin temperatures,[27] actimetry), we have reached the stage where chronobiology theory meets ambulatory research practice. The next decade will surely bring insights into the complexity of temporal organization in humans and examples of pathophysiology of clock function. ❐

Many of these approaches are being developed within the EU 6th Framework Project EUCLOCK (#018741).

REFERENCES

1. Kleitman N. *Sleep and Wakefulness*. Revised and enlarged edition. Chicago, Ill; The University of Chicago Press; 1987.
2. Wever RA. *The Circadian System of Man: Results of Experiments Under Temporal Isolation*. New York, NY: Springer Verlag; 1979.
3. Pittendrigh CS, Daan S. A functional analysis of circadian pacemakers in nocturnal rodents. *J Comp Physiol (A)*. 1976;106:233-355.
4. Borbély AA, Achermann P. Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia, Pa: WB Saunders Company; 2000:377-390.
5. Roenneberg T, Wirz-Justice A, Merrow M. Life between clocks: daily temporal patterns of human chronotypes. *J Biol Rhythms*. 2003;18:80-90.
6. Moore RY. Circadian rhythms: basic neurobiology and clinical applications. *Ann Rev Med*. 1997;48:253-266.
7. Dijk DJ, Edgar DM. Circadian and homeostatic control of wakefulness and sleep. In: Turek FW, Zee PC, eds. *Regulation of Sleep and Circadian Rhythms*. New York, NY: Marcel Dekker, Inc; 1999:111-147.
8. Wirz-Justice A, Wever RA, Aschoff J. Seasonality in freerunning circadian rhythms in man. *Naturwissenschaften*. 1984;71:316-319.
9. Brown SA, Fleury-Olela F, Nagoshi E, et al. The period length of fibroblast circadian gene expression varies widely among human individuals. *PLoS Biol*. 2005;3:e338.
10. Horne JA, Östberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *Int J Chronobiol*. 1976;4:97-110.
11. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. *Sleep*. 2003;26:342-392.
12. Lewy AJ, Cutler NL, Sack RL. The endogenous melatonin profile as a marker for circadian phase position. *J Biol Rhythms*. 1999;14:227-237.
13. Terman M, Terman JS. Light therapy for seasonal and nonseasonal depression: efficacy, protocol, safety, and side effects. *CNS Spectr*. 2005;10:647-663.
14. Wright H, Lack L, Bootzin R. Relationship between dim light melatonin onset and the timing of sleep in sleep onset insomniacs. *Sleep Biol Rhythms*. 2006;4:78-80.
15. Winkler D, Pjrek E, Praschak-Rieder N, et al. Actigraphy in patients with seasonal affective disorder and healthy control subjects treated with light therapy. *Biol Psychiatry*. 2005;58:331-336.
16. Van Someren EJ. Actigraphic monitoring of movement and rest-activity rhythms in aging, Alzheimer's disease, and Parkinson's disease. *IEEE Trans Rehabil Eng*. 1997;5:394-398.
17. Mrosovsky N. Masking: history, definitions, and measurement. *Chronobiol Int*. 1999;16:415-429.

18. Kräuchi K, Cajochen C, Wirz-Justice A. Thermophysiologic aspects of the three-process-model of sleepiness regulation. *Clin Sports Med*. 2005;24:287-300.
19. Kräuchi K, Wirz-Justice A. Circadian clues to sleep onset mechanisms. *Neuropsychopharmacology*. 2001; 25(5 suppl):S92-S96.
20. Wirz-Justice A, Kräuchi K, Cajochen C, Danilenko KV, Renz C, Weber J. Evening melatonin and bright light administration induce additive phase shifts in dim light melatonin onset. *J Pineal Res*. 2002;36: 192-194.
21. Dijk DJ, Duffy JF, Riel E, Shanahan TL, Czeisler CA. Ageing and the circadian and homeostatic regulation of human sleep during forced desynchrony of rest, melatonin and temperature rhythms. *J Physiol*. 1999;516:611-627.
22. Boivin DB, Czeisler CA, Dijk DJ, et al. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. *Arch Gen Psychiatry*. 1997;54:145-152.
23. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (Type 0) resetting of the human circadian pacemaker. *Science*. 1989;244: 1328-1333.
24. Duffy JF, Dijk DJ. Getting through to circadian oscillators: why use constant routines? *J Biol Rhythms*. 2002;17:4-13.
25. Wirz-Justice A, Cajochen C, Nussbaum P. A schizophrenic patient with an arrhythmic circadian rest-activity cycle. *Psychiatry Res*. 1997;73:83-90.
26. Cajochen C, Knoblauch V, Kräuchi K, Renz C, Wirz-Justice A. Dynamics of frontal EEG activity, sleepiness and body temperature under high and low sleep pressure. *NeuroReport*. 2001;12:2277-2281.
27. van Marken Lichtenbelt WD, Daanen HA, Wouters L, et al. Evaluation of wireless determination of skin temperature using iButtons. *Physiol Behav*. 2006;88: 489-497.

COMMENT MESURER LES RYTHMES CIRCADIENS CHEZ L'HOMME

L'horloge biologique contrôle tous les rythmes circadiens chez l'homme, que ce soit pour les fonctions neurocomportementales, les sécrétions hormonales, la physiologie ou le comportement. Le rythme le plus évident est celui du cycle veille-sommeil dont la synchronisation diffère selon les individus (« chronotype » – du lève-tôt « au chant du coq », au couche-tard « au cri du hibou »). Cependant, les altérations du cycle veille-sommeil ne sont pas tous une conséquence d'un fonctionnement anormal de l'horloge circadienne. La connaissance des propriétés formelles du système circadien, du rôle des synchroniseurs (zeitgebers) pour la bonne synchronisation des 24 heures de la journée et de la façon dont le sommeil est régulé, a permis le développement de protocoles rigoureux pour la recherche des caractéristiques des rythmes circadiens et du sommeil. Ces études ont fourni des critères de référence pour l'estimation de l'amplitude et de la phase circadiennes et ont permis l'identification des marqueurs physiologiques et hormonaux les plus utiles. Nous en sommes maintenant à la deuxième étape, celle du développement de marqueurs plus simples à usage ambulatoire pour une estimation raisonnablement exacte de la phase circadienne. La chronobiologie nécessite des mesures à long terme sur au moins un cycle de 24 heures et les nouvelles technologies à micropuce permettent le recueil continu de données, de façon non invasive et sur de nombreux jours et semaines (par ex., l'actimétrie). Au cours des prochaines dix années, la recherche permettra sûrement une compréhension plus approfondie du fonctionnement de l'horloge circadienne humaine et de sa pathologie.