Key Insights

Endogenous, not driven from outside. A circadian rhythm is generated inside the body and persists even without time cues from the environment

Nearly every cell carries a clock. The timing system runs throughout the body, coordinated by a master pacemaker (the SCN) in the brain

Alignment is the operative variable. What matters for everyday function is whether the many internal clocks hold their normal phase relationships with each other and with the external day

Disrupted alignment has measurable consequences. Sleep, cognition, metabolism, hormone release, and immune function are all shaped by the timing system; misalignment can degrade them

What Circadian Rhythms Are: A Primer on the Body's Timekeeping System

A circadian rhythm is an endogenous, body-wide timing system: self-sustaining cellular clocks in nearly every tissue, coordinated by a master pacemaker in the brain, set to the external day by environmental cues. This paper makes that picture available to a reader without a chronobiology background, and shows why it is the alignment of the system, not the mere presence of a rhythm, that underwrites normal sleep, alertness, hormone release, and metabolism.

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Summary

A *circadian rhythm* is an endogenous, roughly 24-hour cycle in physiology and behaviour, generated inside the body rather than imposed from outside. Almost every cell carries a self-sustaining molecular timer; those cellular timers are coordinated into a body-wide schedule by a small group of brain cells known as the suprachiasmatic nucleus, or SCN, which acts as the body's master clock and keeps the whole system set to the external day. Sleep is one output of this schedule. Alertness, hormone release, body temperature, and the timing of digestion and metabolism are others. The system is a hierarchy of clocks, not a single clock, and it is the *alignment* of those clocks (with one another, and with the external day) that underwrites normal function under realistic conditions of daily life.

The point of this paper is to make that picture available to a reader who arrives at it without a chronobiology background. There is a common conception that “circadian rhythm” is a way of saying “sleep schedule,” that the clock lives only in the brain, and that this whole subject is a wellness-only idea rather than a core biological system. None of those is right. Sleep is one downstream output of the timing system; the system itself runs in cells throughout the body; and its molecular machinery is mainstream physiology. One distinction worth naming at the outset, because it returns repeatedly: circadian timing is not the same as sleep pressure. Sleep pressure builds with time awake and discharges during sleep, largely as a function of how long someone has been up; the circadian system determines *when* the body is biologically prepared for sleep, wakefulness, digestion, and repair. The two normally cooperate, and they can be pried apart. The downstream papers in this series assume this floor. This paper establishes it.

What a circadian rhythm actually is

The defining feature of a true circadian rhythm is that it is *endogenous*: it is generated by the body, not driven by the day-night cycle outside. The way scientists prove this is to put a person, or an animal, or a single cell, into constant conditions with no time-of-day cues, and see whether the rhythm continues. It does. Under conditions of constant dim light, no clock, no scheduled meals, and no social cues, human physiology continues to oscillate with a period close to (but not exactly) 24 hours. Body temperature still rises during the biological day and falls during the biological night; melatonin still secretes on a nightly pulse; cortisol still peaks before habitual wake. The cycle persists for as long as the experiment runs. This is called *free-running*: the clock running on its own internal period, with no external time cues to pull it into step with the planet. It is what distinguishes a true endogenous rhythm from a pattern merely tracking sunrise and sunset.

The free-running period is close to but not exactly 24 hours: under careful constant conditions the intrinsic human period averages about 24.18 hours, with a tight distribution and no meaningful change with age (Czeisler et al., 1999). That small offset is why the system needs to be *set* by something external each day. We come back to that. The first point is simply that the cycle is internal: the body keeps time on its own.

The clock is in every cell

For most of the twentieth century, when people thought about biological clocks at all, they thought of a single timekeeping centre in the brain. The first surprise of modern chronobiology was that nearly every tissue in the body, and most nucleated cell types, run their own clock. A cell taken from the liver, kept alive in a dish with no input from the rest of the organism, will continue to oscillate at a ~24-hour rhythm in the activity of its genes and proteins for many cycles before slowly damping; the same is true of cells from the heart, kidney, pancreas, gut, lung, fat, muscle, and skin (Yoo et al., 2004). The clock is a cellular property, not a brain property.

At the molecular level, the clock is what biologists call a *transcription-translation feedback loop*, meaning that a handful of “clock genes” are read out into proteins, and those proteins, after a delay, regulate the reading-out of the same genes, on a roughly 24-hour cycle (Takahashi, 2017). The rest of this paper does not depend on the details of that loop; the reason to name it is to anchor the central fact that the cellular clock is mainstream biology, with a molecular mechanism worked out in detail through decades of laboratory work. The foundational discoveries of this mechanism were awarded the 2017 Nobel Prize in Physiology or Medicine to Jeffrey Hall, Michael Rosbash, and Michael Young.

The hierarchy: a master pacemaker for many local clocks

A body with a clock in every cell needs some way to keep those clocks in agreement. If the liver clock ran half a day out of phase with the muscle clock, the body would try to digest a meal at the same time it was trying to mobilise stored energy for activity. The arrangement that prevents this is hierarchical. A small cluster of neurons in the hypothalamus, the SCN, acts as the system's master pacemaker. The SCN is in the brain; the rest of the system, the *peripheral clocks* (meaning the cell-autonomous clocks running in every other tissue of the body, in the liver, gut, heart, pancreas, lung, muscle, and elsewhere) are everywhere else. The SCN receives the strongest direct input from the outside world and sends timing signals, through neural and hormonal pathways, to the peripheral clocks throughout the organs and tissues, keeping them in phase with one another and with the day.

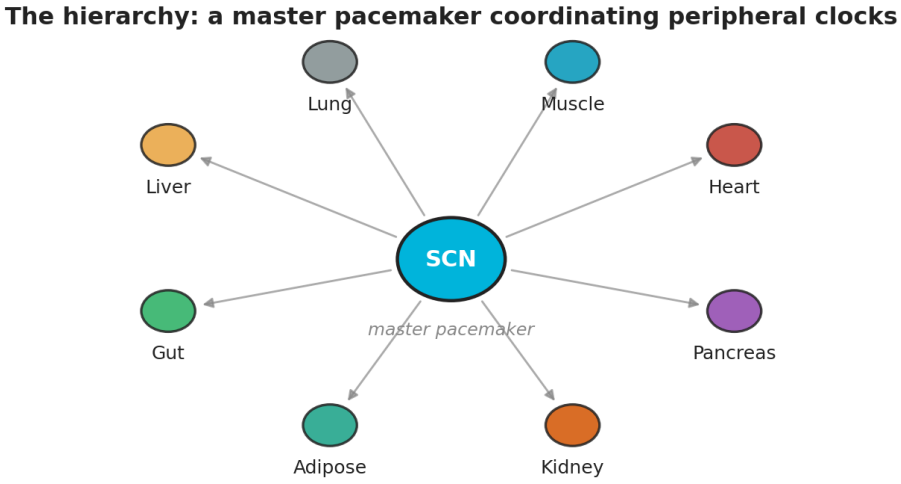

Figure 1. The hierarchy. The SCN, a small cluster of neurons in the hypothalamus, acts as the body's master pacemaker. Almost every peripheral tissue, including liver, heart, gut, pancreas, lung, muscle, adipose tissue, and kidney, runs its own cell-autonomous clock; the SCN coordinates them into a coherent body-wide schedule.

The useful analogy is an orchestra. Every instrument has its own internal sense of timing. The conductor does not produce the music; the players do. But without the conductor, the players drift apart in tempo and the music falls into incoherence. The SCN is the conductor of a body-wide orchestra of clocks. Importantly, the analogy is loose in a way that matters: peripheral clocks are not passive followers. They take their own cues from feeding times, physical activity, and tissue temperature, and they can be pulled out of phase with the SCN when those non-light cues fall at hours that conflict with the SCN's timing (Mohawk, Green, & Takahashi, 2012). This is why eating across the biological night, for example, can drag the metabolic clocks of the gut and liver toward a phase the SCN itself has not moved to. The hierarchy is real, but it is a negotiation, not a dictatorship.

Why an internal clock needs external time cues

A roughly-24-hour clock running in isolation would, over weeks, drift away from the day-night cycle of the planet. To stay useful, the internal clock has to be set, or *entrained*, by something external each day. Entrainment is the process by which an external time signal, called a *zeitgeber* (literally "time-giver"), nudges the internal clock back into alignment with real solar time. The dominant zeitgeber in humans, as in essentially all sighted mammals, is the daily light-dark cycle. Light reaches the SCN through a dedicated retinal pathway that signals

time-of-day directly to it (Berson, Dunn, & Takao, 2002; Hattar et al., 2002). Meal timing, physical activity, ambient temperature, and social cues are secondary zeitgebers, more important for peripheral clocks than for the SCN itself. This paper does not go further into the properties of light or the way it is measured; that is the subject of other papers in this series. The point here is conceptual: the internal clock is not a fixed mechanism imposing its own rhythm on the body; it is a continuously adjusted timing system, taking daily input from the world to stay set to the day it is in.

What an aligned system looks like

When the system is correctly entrained and the peripheral clocks are in step with the SCN, the body produces a familiar 24-hour pattern of outputs. Figure 2 shows the rough shape. Melatonin rises in the late evening, peaks in the middle of the biological night, and falls by morning; it is sometimes called the “darkness hormone” because its secretion is gated by the light-dark cycle and signals “night” to the body. Cortisol does the opposite: it is the morning hormone, rising in the hours before habitual wake and falling across the day, with a peak shortly after rising. Core body temperature follows its own curve, falling overnight to a minimum just before wake and rising across the day to a peak in the late afternoon or early evening. Subjective alertness tracks roughly with temperature, low in the small hours of the morning, climbing through the day, dipping slightly in the early afternoon, peaking again in the early evening, and falling as melatonin rises.

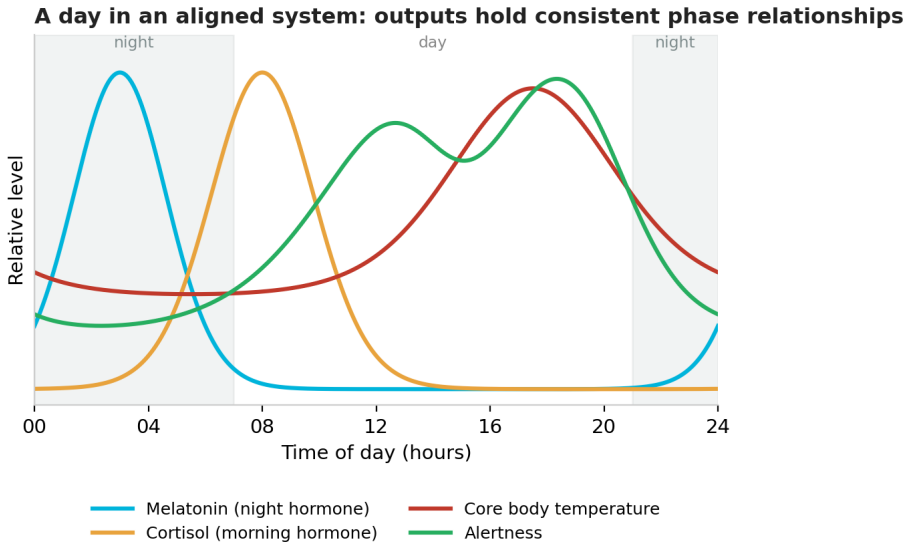

Figure 2. A day in the life of an aligned system. Idealised 24-hour curves of four well-studied outputs. The actual amplitudes vary across individuals and the precise timing depends on each person's habitual schedule; what holds across healthy adults is the set of *phase relationships* between the curves, meaning how each curve is timed relative to the others.

The point of Figure 2 is not the individual curves but the *phase relationships* between them. In an aligned system, melatonin and cortisol sit at opposite ends of the 24-hour cycle. Temperature lags slightly behind the wake/sleep axis. Alertness rises and falls together with temperature. These relationships are remarkably consistent across healthy adults, and they hold whether or not the person is currently awake at the moment in question. Alignment also contributes to consolidated sleep at the appropriate biological time, daytime alertness without need for stimulants to maintain it, glucose handling that matches when meals are typically eaten, and an immune system whose activity varies on its own daily schedule (immune-cell trafficking and inflammatory tone cycle predictably with the day; Scheiermann, Kunisaki, & Frenette, 2013). Alignment is necessary for these

outcomes but not sufficient alone: sleep, for example, also depends on accumulated sleep pressure, on a sleep-conducive environment, and on the absence of intrinsic sleep disorders, any of which can degrade sleep even when the clock is perfectly set.

Alignment is the most actionable everyday variable

A central thing the reader should take from this paper is the following distinction. The mere *presence* of a circadian rhythm is not what matters most for health under realistic conditions; what matters is whether the many internal rhythms are *aligned*, both with one another and with the external day. A person can have a perfectly intact set of cellular clocks and still feel terrible, sleep poorly, and accumulate health risk, if those clocks are pointing in different directions. (Rhythm amplitude and stability also matter, especially in ageing and in certain disorders, and the field distinguishes phase from amplitude as separate axes of circadian health; for the everyday-living case this paper is about, the most actionable axis is phase alignment.) Figure 3 illustrates the contrast with four idealised clocks.

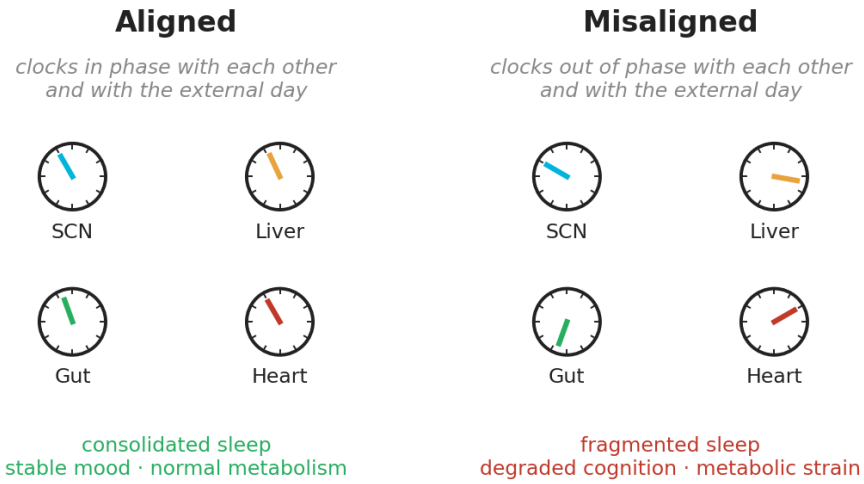

Figure 3. Alignment is the most actionable everyday axis of circadian health. Left: four representative clocks pointing in the same direction, in step with one another and with the external day. The downstream consequences are consolidated sleep, stable mood, and normal metabolism. Right: the same four clocks, now pointing in different directions because their phase relationships have been disturbed (by jet lag, an irregular schedule, eating at the wrong hours, or some combination). The biological state is misaligned even though every individual clock is still running.

This is why “your clock is fine because it is running” is the wrong question. The clocks of a sleep-deprived, jet-lagged, or chronically misaligned person are running; they are just running on different schedules. The relevant variable is whether they hold their normal phase relationships with each other and with the day. *Internal* misalignment is the state in which peripheral clocks disagree among themselves, or with the SCN. *External* misalignment is the state in which the whole system is set to the wrong time relative to the external day. The two often occur together. Both are what circadian disruption actually means.

What disruption looks like, and what it costs

Circadian disruption is a documented physiological state with consequences across multiple systems, though the strength of evidence varies by outcome, as the next paragraphs make explicit.

The clearest demonstration comes from controlled laboratory studies in which behavioural cycles are deliberately decoupled from endogenous physiology, holding everything else (diet, sleep amount, activity) constant. In one well-cited protocol of this kind, healthy adults on a forced 28-hour day showed substantial impairment of glucose handling consistent with insulin resistance, an inverted cortisol rhythm (the morning hormone peaking at the wrong biological hour), elevated mean arterial pressure (a standard summary of blood pressure across the heartbeat cycle), and a drop in leptin (a satiety hormone), purely as a consequence of moving the timing of eating and sleeping relative to internal physiology (Scheer, Hilton, Mantzoros, & Shea, 2009). The size of the experimental manipulation was much larger than anything most people produce in ordinary life. The direction of effect is also visible at lower-magnitude manipulations in observational studies: people whose work or social schedules pull their sleep timing repeatedly out of step with their internal phase ("social jet lag") show worse metabolic markers on average than those whose schedules align (Roenneberg et al., 2012), and shift workers carry elevated metabolic and cardiovascular risk over years of exposure. The acute laboratory effects are reproducible; the chronic real-life effects are smaller in any single individual and harder to disentangle from confounding lifestyle variables.

A useful way to read the literature on consequences is to split it by evidence class. *Experimentally demonstrated*, in human laboratory work: misalignment impairs sleep consolidation, reduces daytime cognitive performance, and degrades glucose handling. *Consistently observed in observational studies but not yet established as causal*: chronic circadian disruption is associated with elevated cardiovascular risk and with increased rates of mood disorders. *Suggestive but more contested*: long-term shift work is associated with an elevated risk of certain endocrine-sensitive cancers; the International Agency for Research on Cancer classifies night shift work involving circadian disruption as probably carcinogenic to humans, a Group 2A designation that reflects suggestive but not established causal evidence. Across the whole set, almost every aspect of metabolism, from glucose handling to lipid storage to mitochondrial activity, is now known to be under circadian control, and misalignment between the central clock and the peripheral clocks of metabolic tissues impairs that control in ways well-characterised at the experimental level (Bass & Takahashi, 2010). The honest summary is that the central mechanism is settled, the acute experimental effects are reproducible, and the long-term real-life associations are consistent across studies in direction but observational in nature and variable in measured magnitude (Roenneberg & Merrow, 2016).

Counterarguments and clarifications

"A circadian rhythm is just your sleep schedule." It is not. Sleep is one of the most visible outputs of the circadian system, but the system itself coordinates hormone release, metabolism, temperature, immune function, and gene expression across most of the body's tissues. A person can have a textbook sleep schedule and still be circadian-disrupted in other ways; conversely, sleep disturbance is one of the first downstream signs that the timing system is in trouble. The cellular clocks in the liver and gut do not stop existing when their owner is awake.

"You can adjust it on the weekend." The system does adjust, but slowly, and the cost of repeated adjustment is non-trivial. After a substantial phase shift, such as flying across multiple time zones or staying up many hours later than usual, realignment often takes days. The SCN commonly shifts on the order of about a day per time zone or hour of phase shift, but the rate depends on direction (eastward usually slower than westward), on the timing of light exposure during recovery, and on individual chronotype; the peripheral clocks lag further, re-entraining one tissue at a time. Habitually staying up late on weekends and reverting to a normal schedule on Monday produces a small, repeated version of jet lag every week, a pattern known in the chronobiology literature

as “social jet lag” (Roenneberg et al., 2012), with the SCN and the peripheral clocks chronically chasing each other rather than ever settling. The depth of this phenomenon and its specific consequences are the subject of other papers in the series; the high-level point is that re-entrainment is real but not free.

“This is soft wellness, not hard biology.” The legitimate part of this concern is that some popular framings of circadian health overshoot what the science supports for chronic-disease outcomes. The illegitimate part is the implication that the underlying biology is soft. The cellular clock has been mapped at the molecular level, its workings can be measured directly in laboratory preparations, and its mechanism was awarded a Nobel Prize in 2017. For the outcome claims, where the evidence ranges from mechanistic to experimental to observational, the place to look is the previous section: the experimental work in laboratory misalignment protocols is reproducible, and the observational chronic-disease associations are honestly labelled as such.

“If I feel fine staying up, my clock is fine.” Subjective feeling and physiological alignment are separable variables. The cortisol rhythm, the body-temperature curve, the metabolic phase of the liver, and the immune-cell rhythms of the gut do not depend on conscious awareness. They run on their own time. Misalignment protocols in the laboratory typically do not produce acute subjective distress proportional to the physiological changes measured, which is precisely the point: feeling alert at an inappropriate biological hour is not the same as being aligned. It is the same alerting machinery being driven by a sufficiently strong external prompt (caffeine, stress, social stimulation, a startling experience) to compensate, in the short term, for a clock that is telling the rest of the body to wind down.

What supports alignment, in one line

In ordinary life, the principal cues that the circadian system reads from the environment are the daily light-dark cycle, the timing of sleep and wake, the timing of meals, and the timing of physical activity. Holding those cues consistent helps the SCN and the peripheral clocks stay set to the same day. Later papers in this series examine these signals in detail, especially the role of light, where the modern environment has changed most. This paper does not address them further; the present floor is *what is being aligned*, not how to align it.

What this paper has established

Circadian rhythms are an endogenous, body-wide timing system. They are generated by self-sustaining cellular clocks present in nearly every tissue. Those clocks are coordinated by a master pacemaker in the brain, the SCN, into a coherent body-wide schedule. The system is entrained to the external day by environmental time cues, of which the daily light-dark cycle is the dominant one. When everything is in place, the system produces a familiar 24-hour pattern of sleep, alertness, hormone release, body temperature, metabolism, and immune function, held together by stable phase relationships between many distributed oscillators. *Alignment*, not the mere existence of those oscillators, is the most actionable everyday variable. When alignment is disturbed, the consequences appear across the systems the clocks govern, with strength of evidence ranging from settled mechanism to consistent observational association. The biology underlying all of it is well-characterised, mainstream physiology.

That is the floor on which the rest of the Korrus circadian materials rest. Subsequent papers in this series address how the system is perturbed in particular environments and how it can be supported by design. They assume the picture above; this paper made it.

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