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Circadian Rhythms, Circadian Disruption, and the Impact on Gene Expression and Health in Humans

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Chapter 6: Summary for a general audience

FOREWORD

Why I chose physiology

In August 2017, I packed up everything I owned and moved to Madison to begin my PhD in physiology at the University of Wisconsin. But it's fair to say that this story really began in 2015 when I was working on my master's degree in epidemiology (the branch of public health that studies health and disease patterns and determinants of populations). At the time, I was working on a project analyzing data from middle-aged female smokers, asking the question "does the weight gained from quitting smoking have long-term negative health impacts?" Specifically, my collaborators and I were looking at whether women in our sample who quit smoking and gained weight had more cases of stroke than those who didn't quit. While writing an article summarizing this work, we got to the discussion section where we needed to interpret our findings. In this case, we had different answers to the stroke question depending on the type of stroke, ischemic or hemorrhagic. And my collaborators and I weren't sure what to make of this finding--we'd spent months working with this data in search of these answers, but I felt limited in how well I could contextualize these results. While epidemiology was helping me understand the *who, why,* and *where* of human health and disease, I was also eager to understand more of the *how*, the molecular mechanisms underlying these patterns. It seemed to me that an understanding of all these pieces together was the most effective way to solve our most complex problems in public health.

So I had a new goal: as I completed my epidemiology degree, I decided to apply to PhD programs in physiology--the branch of biology that considers how cells, organs, and systems all work together. I met my advisor, Dr. Chris Bradfield, who shared my vision of translational health research. He was an oncologist and toxicologist at UW-Madison, and had brought together a pancreatic surgeon and epidemiologists (one of whom became my other co-advisor, Dr. Kristen Malecki) in his lab to investigate research questions pertaining to human health and environmental exposures, combining an array of

different research methodologies. After one conversation with Dr. Bradfield, I knew this lab was exactly what I'd been looking for.

Why to study circadian rhythms

When I started my PhD, I was especially eager to learn about the physiology behind the development of obesity. I was interested in factors that could be contributing to weight gain beyond diet and exercise, as millions of people were making these lifestyle changes yet were unable to shed pounds.

In my classes, a particular nutrition phenomenon that caught my attention was intermittent fasting; how individuals who changed only the timing of their meals saw positive metabolic benefits and weight loss. Food timing, it seemed, could be one of the lesser-known factors contributing to obesity. I brought these ideas to my advisors, who had similar questions about what biology might be underlying this relationship, specifically in terms of circadian rhythms (the daily patterns our bodies follow to time biological processes to match daily occurrences like eating, sleeping, or physical activity). In fact, Dr. Bradfield had been part of a research team years prior who had discovered one of the key genes that drive circadian rhythms. We were all interested in learning more about the molecular patterns of circadian rhythms in humans, and their implications for metabolism and human health.

Why I wrote this chapter

Throughout my time in graduate school, I've gotten to hear from scientists doing lots of fascinating research. I would enthusiastically share stories with my friends and family, but was disappointed that there weren't more pipelines for scientific research to get to the public.

Three years into my PhD, when the COVID-19 pandemic began, I had confidence that our public health workforce was up to the challenge. After all, we had access to advanced health and medical knowledge and technologies that positioned us much better to address a global pandemic than ever before. But it seemed like many key pieces of information—the airborne nature of the virus, the utility of high-filtration masks or maximizing indoor ventilation, for example, took *years* to reach the public. And beyond this, never in my wildest dreams did I expect that epidemiologists and public health professionals would be getting death threats for doing their jobs, or leaving their life's work out of fear for their safety.

Of course, this chaotic national divide and anti-science rhetoric had many contributing factors. But I heard a statistic years ago suggesting that very few Americans know a scientist personally. That idea has always intrigued me, and helped me make sense of the culture of distrust in science and failed science communication messaging. It's easy to imagine folks in the public questioning or even dismissing what scientists were saying when scientists were nameless, faceless groups in ivory towers.

The COVID-19 pandemic has offered a powerful example of the consequences of inadequate science communication approaches, further convincing me (along with many others) that we need to be doing more. The Wisconsin Initiative for Science Literacy at UW-Madison is doing their part by empowering PhD candidates like me to write a thesis chapter to explain my research to folks outside of my department. In academia, we need more frameworks like these, to allow us to get our work to audiences beyond our seminars and niche journals. In the meantime, we as scientists should take any opportunities we can to talk about our research. If our friends and our communities are hearing more from us, if those lines of communication are opened, it just may leave us in a better place when the public is asked to rely on science.

PART I: WHAT ARE CIRCADIAN RHYTHMS AND HOW CAN WE MEASURE THEM?

What is a circadian rhythm?

Circadian rhythms are the daily 24-hour cycles through which our bodies prepare us for recurrent activities like sleeping, eating, and physical activity, by coordinating the timing of our biological functions (e.g. drowsiness, hunger, and energy). These rhythms evolved over millions of years in tandem with our environments, when our ancestors were living outside, and were active, eating, and focused during the light hours, then inactive and resting when it was dark. Because of this evolution, exposure to sunlight serves as a major external cue for setting these rhythms, as does ambient temperature. Circadian rhythms can also be set (or reset) by behaviors such as eating or physical activity. Numerous aspects of our biology, like body temperature, metabolism, and sleep have their own unique oscillation pattern across a 24-hour day.

Figure 1: Examples of chemical signals used to control circadian rhythms (cortisol, melatonin) and physiological states (body temperature, alertness) under circadian control. X axis shows hours of a given day, with the blue shaded areas of the bar representing night and the white representing day. Cortisol (blue line) is a hormone that impacts how alert and focused we feel, as can be seen with the alertness (yellow line)) closely following its release. Cortisol is typically highest in the morning after waking and stays high during the day, and lowest as we sleep, corresponding to when alertness is needed as a diurnal species. In contrast, melatonin (green line) is a hormone produced in our bodies, which makes us feel drowsy and promotes sleep.

Since circadian rhythms are responsible for the correct timing of many biological processes, disruption to these rhythms can throw off a lot in our bodies. But researchers are still working to understand exactly which processes are under circadian control, the full array of health impacts circadian disruption may have, and the biology behind these changes. Circadian disruption has been linked to an array of chronic diseases, including cancers, metabolic syndrome, and even allergies. Given that our modern culture has left many people exposed to some form of circadian disruption, the health impacts are broad.

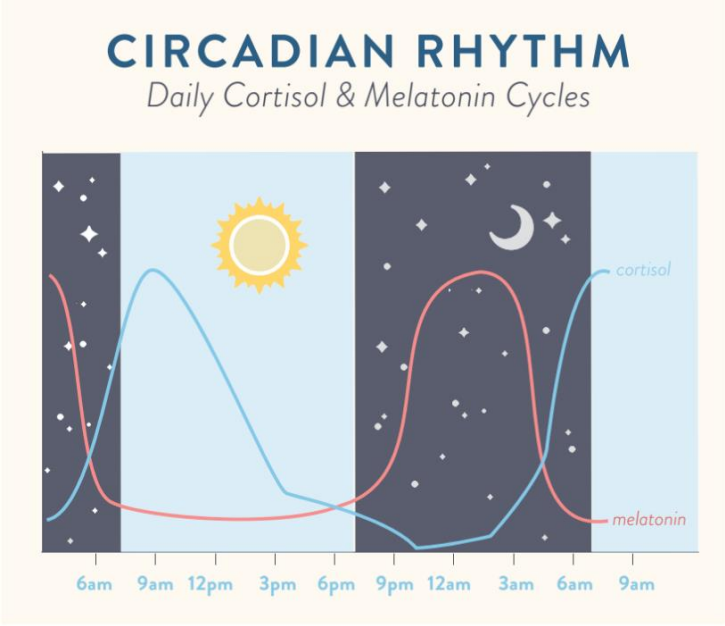
The study of circadian rhythms and circadian disruption in humans has important applications for other areas of research and medicine as well. For example, certain cancer drugs, and many other prescription or over-the-counter drugs can be more effective when taken at certain times, based on the biological processes they target, which (you guessed it) all have their own circadian rhythms.

How to measure circadian rhythms? Circadian disruption?

Since circadian rhythms are not central to any *one* aspect of biology, there is no single simple way to measure them. To understand diabetes, for example, we can measure blood sugar. But what can be measured to tell us what time a person's body thinks it is, or how well all their circadian-controlled processes are synchronized? Or if a person is disrupted? Various approaches have been developed to answer these questions. Melatonin, a hormone our bodies produce at high levels during the night to induce and maintain sleep, can be measured from blood or saliva to provide clues about circadian rhythms.. Cortisol can be similarly measured (which typically peaks in the day), to gain similar insights about incorrectly timed sleep/wake cues. To do this, researchers collect multiple samples of the melatonin or cortisol from each person over the course of a 1-2 days, and these levels can be plotted

(see figure 2). Circadian rhythms can be estimated based on each individual's peaks and valleys of the melatonin or cortisol, while irregular patterns may indicate a state of circadian disruption.

Figure 2: Illustrated example of typical cortisol and melatonin patterns over the course of two days



Ballantine, Sarah, PhD. "Regulating Circadian Rhythm (and why that's important)". *The Paleo Mom,* February 27, 2014. https://www.thepaleomom.com/regulating-circadian-rhythm/

Researchers also estimate circadian rhythms by measuring sleep patterns. (As an aside-- though sleep is often talked about in the context of circadian rhythms, it is not *itself* the circadian rhythm, it is just one of the most obvious and measurable biological functions that follows a circadian rhythm). Researchers can evaluate sleep/wake patterns via self-reported sleep diaries, or with more accuracy in a sleep study using polysomnography, when people are hooked up to electrodes and machines and spend the night sleeping in a lab. An additional method used to investigate circadian rhythms is the constant routine protocol, where participants stay a series of days and nights in a sleep lab, with the goal of keeping all circadian cues such as light, food, and sleep constant. The goal of the constant routine protocol is to look at various aspects of circadian biology in isolation (e.g. asking questions like "how do the circadian rhythms cycle without sunlight?").

Lab studies can also be used to create states of experimental circadian disruption with various sleep protocols, such as those mimicking shift work schedules, or protocols pushing sleep back a few hours each night until schedules are reversed (called chronic jet lag). In these studies, researchers can explore the body's response to circadian disruption, for example measuring changes to metabolism, inflammation, or the circadian-relevant proteins being produced by cells.

Researchers also commonly study shift workers to understand more about the biological impact of altering circadian rhythms. Many of these studies are done by epidemiologists, who recruit large groups of shift workers and ask them questions about a range of health indicators, comparing them to non-shift-working groups.

While these existing approaches to measure circadian rhythms or their disruption have generated great insight, there are still gaps in our understanding of these topics. Each of the study approaches has limitations. For example, experimental studies which require laboratory stays and repeated measurements are complicated and limited to very small samples, and typically are limited to young,

healthy individuals. This means that their findings, though interesting, may or may not be the same for the rest of the population. Studying shift workers offers much larger sample sizes, but captures a specific, more extreme form of circadian disruption. Since life in our modern world has likely left many of us exposed to some form of circadian disruption, the ability for researchers to study circadian disruption outside of laboratory settings, in a more general population, could help us learn a lot more about its impacts.

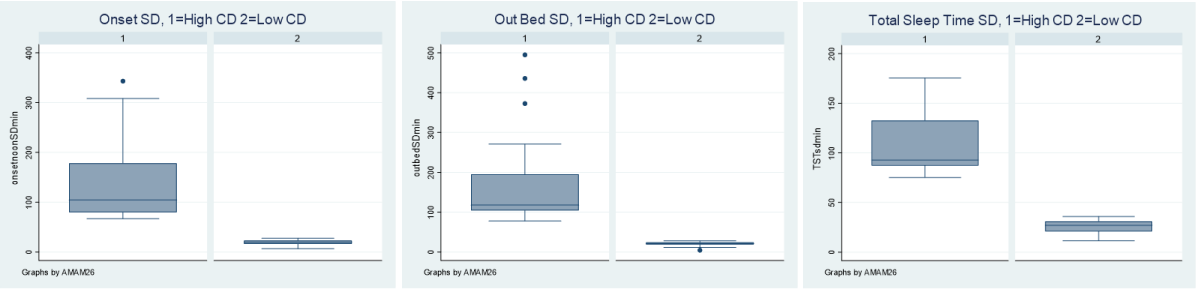
My research: an approach for estimating circadian rhythms/circadian disruption

In recent years, advances in wearable health technology have brought new opportunities for estimating circadian rhythms. Actigraph devices (smart watches) can measure sleep/wake patterns with a decent amount of accuracy, and are increasingly being utilized as a measurement tool in population health and epidemiology studies. Many epidemiological studies collect an array of health information from large sample groups (e.g. thousands of individuals), and with the addition of sleep/wake data, they offer a great opportunity to study real-world examples of circadian disruption.

For my dissertation research, I wanted to see if it was possible to differentiate circadian rhythm patterns from an epidemiological study sample. I utilized actigraph data from a Wisconsin-based population health study, the Survey of the Health of Wisconsin (SHOW), to estimate circadian rhythm patterns from a sample of 1211 Wisconsin adults. Each participant wore an actigraph device for 7 days straight, collecting sleep, wake, and activity pattern data for each individual. I used estimates of each person's daily sleep onset, out of bed time (after waking), and their total sleep time to estimate circadian rhythms. Specifically, I was interested in looking at how these times varied from day to day to understand how consistent or disrupted these rhythms were. I mapped out this variance for my study population, and split people into groups based on their level of variance. Individuals who had sleep

times that varied minimally, around 5 to 30 minutes day-to-day, were deemed “circadian consistent”, while individuals whose sleep times varied more than around 80 minutes between days were deemed “circadian disrupted”.

Figure 3: Boxplots of sleep variance. Boxplots are a useful way to compare data from two groups; in this case, we’re comparing the day-to-day variance of sleep onset (left graph), out of bed time (middle), and total sleep time (right). The left box in each graph is the disrupted group, and the right box (all smashed down at the bottom) is the consistent group. Note that the y axes are different for each graph! All are measured in minutes of variance.



Schrader, Lauren A. “Boxplots of sleep variance for disrupted and consistent circadian rhythms”. Unpublished. April 2020.

By separating my study population in this way, about 6% of folks fit criteria for circadian disruption, and about 8% fit criteria for a circadian consistent pattern. The consistent group was older than the disrupted group, most likely a reflection of work and family responsibility differences between age groups (e.g., retired people tend to have more consistent schedules). The disrupted group also had lower income than the consistent group, suggesting additional life differences, potentially indicative of less consistent work schedules or shift work. Additionally, the disrupted group had higher white blood cell counts, which could suggest a more inflamed state, warranting future research. Overall, this approach to estimating circadian rhythms to create circadian group designations from epidemiological

data was a success. It allowed us to capture real-world sleep patterns for future study, and identify a unique disrupted population whose sleep varied a couple hours from day to day.

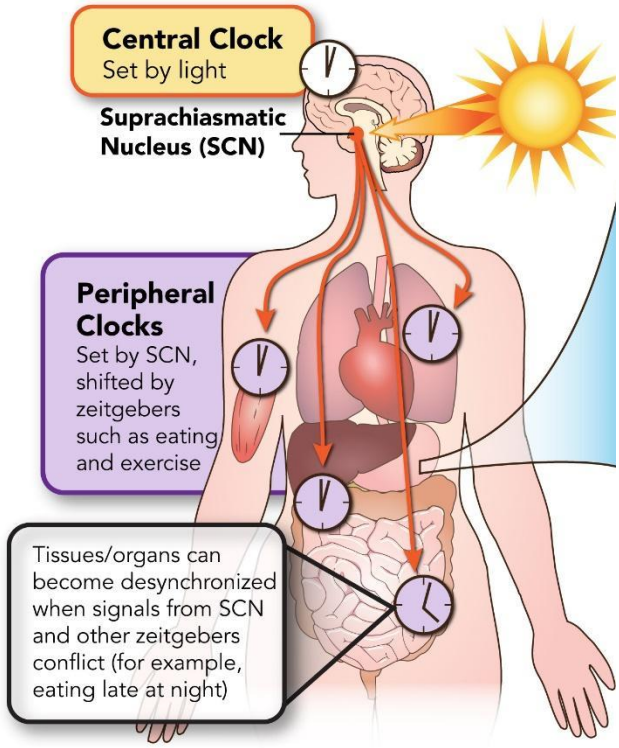
PART II: WHAT HAPPENS INSIDE THE BODY TO DRIVE CIRCADIAN RHYTHMS?

The central clock

So all humans (and animals and plants as well) have circadian rhythms. Ideally, these rhythms help us match up the timing of our bodies' functions, like digesting, sleeping, or being active, to our daily needs. But HOW do our bodies know what time it is, and HOW do these biological processes get synchronized?

To understand how our bodies know what time it is, we look to the circadian control centers: our brains. There is a small bundle of brain cells deep in each of our brains known as the suprachiasmatic nucleus, also called the central clock. This central clock is the lead timekeeper of the body, and it is primarily set by light signals it receives from the eyes. When we see bright lights during the night, our central clock tells our bodies "shut down sleeping processes, get ready for the day!" (Sunlight triggers this response best, and was a pretty great system when our ancestors lived outside. But now, with lights and phone screens, there can be a lot of mixed signals to our central clocks).

Figure 4: Illustration of the central clock in the brain, the peripheral clocks across the body, and the relationships between them. "Zeitgeber" is a German word meaning "time giver", and is the term used to describe any factors that can impact our circadian rhythms, such as sunlight, exercise, meals, etc.



Modified from Schrader, Lauren A. and Stanley, Katie. "*Central, peripheral, and molecular clocks, and the physiological processes under circadian control.*" Unpublished. March 2022.

Peripheral clocks

So our brain's central clock is the timekeeper for the body as a whole, but it gets more interesting: each organ and tissue type has its own clock, collectively called peripheral clocks. The central clock can keep all of them synchronized to its time, but sometimes, these peripheral clocks get set differently than the central clock. Why would it be useful to have peripheral clocks? Likely because of the broad range of functions that our organs perform for our bodies. Our peripheral clocks can be set by other environmental factors, helping those organs be ready as they're needed. For example, our livers, which play important roles in digestion, can have their clocks reset when we consume a meal.

Each cell's circadian clock machinery

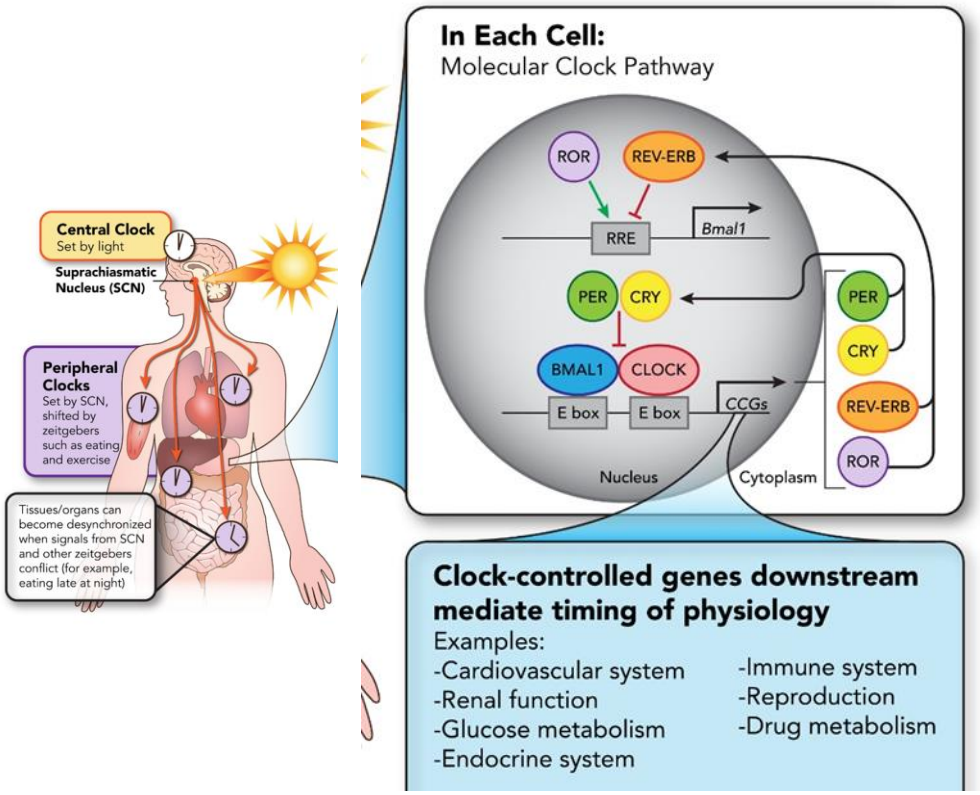
So we know that there are peripheral clocks throughout our bodies, in different organs and tissue types. But what exactly *are* these clocks, and how do they work? To answer this question, we have to go back to some high school biology. Inside nearly all of our cells, there is a full copy of our DNA, called our genome. Our genome is like a cookbook, full of recipes (genes) for thousands of different proteins, the molecules that carry out our bodies' functions. Generally speaking, each gene becomes a protein that goes out into our bodies to perform a certain function. Depending on what our bodies need in a given moment, different proteins are being produced. For example, there are genes/recipes for proteins like digestive enzymes that break down our food, collagen proteins that support the structure of our skin, or antibodies that protect us from diseases. Because genes correspond to the proteins they make, they typically have the same names—i.e. the CLOCK gene becomes the Clock protein.

Some proteins play regulatory roles in the body, serving as an on/off switch for the production of other genes. The circadian clocks in each of our cells "tick", and control circadian rhythms via a core clock loop made up of these regulatory genes/proteins, which cycle on and off at given times every 24 hours, themselves turning on and off thousands of other circadian-controlled genes. This core clock loop is made up of a dozen or so genes and their corresponding proteins, with names such as CLOCK, ARNTL, PER, and CRY. A subset of these core clock genes/ proteins are produced during the day in each of our cells, while the others are produced primarily in their absence, during the night. The core clock genes/proteins also control their own production, creating the "loop" that repeats every 24 hours (see figure 5).

Genes/proteins under circadian control

So these core clock proteins and the genes that code for them are how our bodies sense what time it is, and set their clocks. This brings us to the next question: how do our bodies synchronize our biological processes to this time? The pathways are complex, but the concept is simple: these core clock loops ticking away in our cells are also responsible for cueing on and off various biological processes by regulating the expression of other genes. When certain core clock proteins are being produced, they control the production of other proteins needed for that time of day.

Figure 5: Each cell's circadian clock machinery-- the top right diagram is a simplified illustration of the core clock loop that keeps each cell "ticking". Each colored circle is the name of a core clock gene/protein, a subset of which are produced during the day, then turn off their own production during the night--while the others are produced primarily at night. These core clock genes also act as the on/off switch for thousands of clock-controlled genes ("CCGs"), which are ramped up or down depending on the time of day.



Modified from Schrader, Lauren A. and Stanley, Katie. "*Central, peripheral, and molecular clocks, and the physiological processes under circadian control."* Unpublished. March 2022.

Interestingly, we still don't know exactly how many proteins (and thus their related biological processes) are under circadian control. Researchers have estimated that as much as half of the genes (and corresponding proteins they code for) in our genome are under circadian control, suggesting a large portion of our biological functions oscillate across each day. Though the specific circadian-controlled genes/proteins are still under investigation, research has found circadian influence in our cardiovascular systems, immune systems, reproductive functions, drug metabolism, glucose metabolism, and much more.

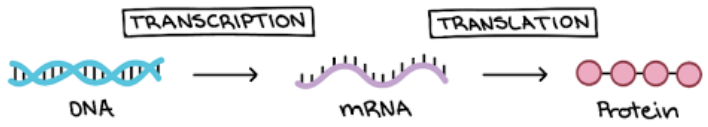
Our findings: genes under circadian control

For my project, we wanted to understand more about which genes (and their corresponding proteins and body functions) were under circadian control, and whether we could measure them in our population sample from the SHOW study. We used a common way to detect which genes are in the process of being made into proteins at a given moment in the human body, called RNA sequencing. It's a similar concept to DNA sequencing, where you're "reading" genetic material, using chemicals and machines to determine the code and generate it on a computer screen. But in the case of RNA sequencing, you're looking at mRNA, which is the intermediate material created when genes are being made into proteins.

If you think of all DNA (the genome) as the cookbook, and each gene as a recipe for a given protein that carries out our bodies' functions, mRNA is like a post-it note with the recipe copied down on it to reference while cooking. The mRNA present in a sample of cells (i.e. from a blood sample) corresponds

to the genes that are currently being made into proteins, so it can provide a snapshot of what functions the body is working on at that moment. For example, if I RNA sequenced a blood sample from someone with a cold, I would see a lot of mRNA corresponding to genes/proteins for antibodies, and mRNA for genes/proteins that increase inflammation, to help that body fight the cold. In short, RNA sequencing allows us to see which genes are currently being made into proteins in a sample (or, which genes are "expressed"), and provide information about the biological functions currently underway.

Figure 6: A simplified illustration of the steps our body takes to use our DNA to make the proteins that we need for all biological functions. The middle step, where DNA is copied into mRNA, is what researchers like our group take advantage of-- by measuring and analyzing the mRNA in a sample, we can learn more about which proteins the body is in the process of making at that moment in time.

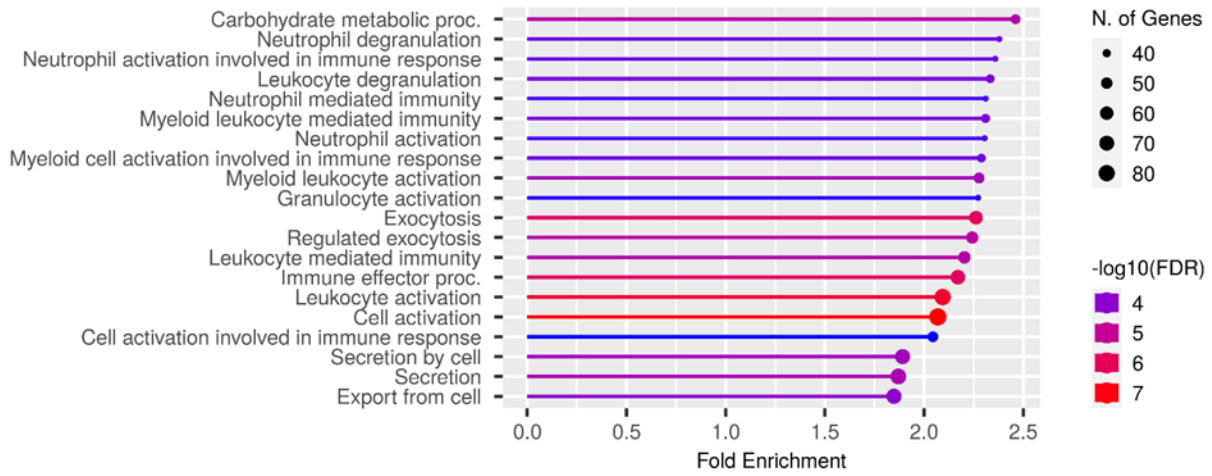


"DNA replication and RNA transcription and translation." (video). *Khan Academy.* Accessed June 15 2023. https://www.khanacademy.org/science/biology/gene-expression-central-dogma

For my project, we used RNA sequencing to learn more about which genes (and corresponding proteins) might be under circadian control. To do this, we set up a simple experiment. We took a group of people who had their blood drawn in the morning (AM), and a group of people who had their blood drawn in the evening (PM), RNA sequenced their blood, and compared the mRNA of these AM vs. PM groups.

Overall, we were excited to find mRNA corresponding to around 1200 genes that were expressed differently in the AM vs. PM groups (i.e. gene A mRNA was high in the PM group but low in the PM group, gene B mRNA was low in the PM group but high in the AM group, etc.) This suggested that these 1200 genes may be oscillating in a circadian pattern. By analyzing the functions of each of the 1200 genes, we could see that they corresponded to immune functioning and metabolism. This was an encouraging result, because evidence from other circadian research has found that both functions are circadian in nature. Thus, this research confirms these findings, showing that they are also reflected in the mRNA. Future analysis of individual genes in the set of 1200 we found can provide a greater level of detail about which specific parts of immune functioning or metabolism are altered during disruption.

Figure 7: A list of some of the biological processes we found that were reduced in the afternoon group compared to the morning group. One of the strongest signals came from carbohydrate metabolism (top), and all the processes with words like "neutrophil" and "leukocyte" are cells of the immune system



Schrader, Lauren A. "*Central, peripheral, and molecular clocks, and the physiological processes under circadian control."* Unpublished. March 2022.

We were also interested to look at the mRNA for the core clock genes in these samples. We had hypotheses for when these clock genes/proteins would be made throughout the day, based on the

patterns with which these core clock loops "tick" (e.g. BMAL1 is highest in the afternoon; PER and CRY are highest in the morning). Encouragingly, we found that the expression of these genes in our AM and PM groups matched these known oscillations of core clock genes.

Our findings: genes that go awry during circadian disruption

As another major part of this research, we wanted to use RNA sequencing to compare the circadian disrupted groups to the circadian consistent groups we identified (described above). This would make it possible to see if there were differences in the types and timing of genes/proteins that were being produced, based on whether someone was estimated to be circadian disrupted. This would help us to understand what biological processes, or their timing, might be different between the groups. For example, if certain genes/proteins were being made at high levels in the morning among the disrupted group, we could look at what function they had, and predict that they might be part of how our bodies react to circadian disruption.

We were excited to find that a set of genes was expressed differently (at higher or lower levels) between the groups. While the number of these differentially expressed genes wasn't in the hundreds like when we compared AM to PM groups, there were a few interesting genes that came up. One of these was a gene for a type 2B activin receptor. This gene codes for the activin type 2B receptor, a protein that plays a number of roles, including growth and differentiation processes in tissues across the body. For example, activin 2B receptors help regulate muscle growth. We found that this gene was produced at higher levels in folks from the circadian disrupted group. Could this mean that circadian disruption leads to altered growth and differentiation in a specific cell or tissue type? It's hard to interpret exactly what to make of this yet, but findings like these provide clues and pave the way for future research. To understand more, researchers could look at other circadian disrupted populations to measure whether

they have high expression of this same gene compared to non-disrupted groups, and if so, in which tissue types. Is activin type 2B expressed at high levels in muscle? Urine? Skin cells? Knowing these answers could offer more information about what role any upregulated activin type 2B receptors may be playing during circadian disruption.

PART IV: APPLYING WHAT I LEARNED IN PURSUIT OF CIRCADIAN HEALTH

Throughout my dissertation research over the past 5 years, I learned a number of things that I apply regularly to my own life. Here are a few examples of how we can apply findings from circadian rhythm research to optimize our lives and health.

Chronotypes and schedules to fit them

An interesting concept in the world of circadian rhythm research is the idea of "chronotypes". Chronotypes are a way of classifying people based on when they are naturally most active, like a scientific version of early birds and night owls. But recent research has suggested that it's not just personal preference that makes someone a morning person or not—there are likely genetic underpinnings that contribute to these patterns.

A few different systems have been created to classify people in this way—"morningness" vs. "eveningness" preference is used in some research, or "larks" and "owls" in others, but the basic idea is the same: you ask individuals a series of questions about when they feel most active, most groggy, most likely to fall asleep, etc., and you can fairly well capture which camp they fall into. Next, researchers compare the genetics of these groups to see if patterns emerge. While there isn't one specific gene that makes you a morning person or not, various studies have found real biological differences between chronotype groups, suggesting the idea that some bodies truly are biologically predisposed to function better in the morning, and others later in the day. Evolutionary biologists have proposed that this natural variation would have been an advantage for early humans: as we roamed around savannas and dodged predators, having our entire clan asleep at the same time would leave us awfully vulnerable, so having a degree of variation in everyone's schedules would make sense.

With this in mind, it's interesting to consider our culture, which is built to reward morning people, and leaves night owls at a disadvantage. In fact, night owls (called eveningness chronotypes in the research) are much more likely to experience circadian disruption and its negative health effects, since they're often fighting against the sleep pattern most natural for their bodies to start workdays, childcare responsibilities, etc. on the early birds' schedule.

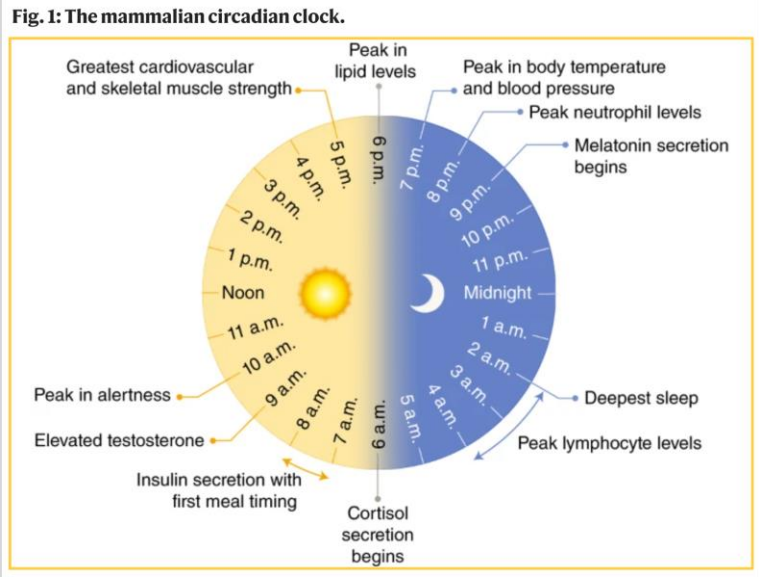
While a total overhaul of established social schedules is probably unlikely, increased work flexibility and remote work options provide more opportunities to tailor work timing to fit individuals. For those who have the privilege of tailoring their daily schedules, it may be helpful to consider their natural chronotypes. So, for example, if you're someone who has always struggled to wake up early, it may be more beneficial to start your day slightly later when your body and brain are more active and ready to go, working with your biology instead of against it.

Optimizing daily schedules based on circadian rhythms in your body

Beyond these early or late preferences for sleeping, through my research I've gotten curious about the circadian timing of many other processes in my body throughout the day. As someone who works remotely, I have lots of flexibility to optimize my schedule. I started paying attention to patterns—what time in the morning did I start feeling hungry? When did I feel calmest? Most irritable? Groggy? Most effective at writing my dissertation?"

Some of these daily occurrences have fairly predictable patterns for all humans. For example, the cortisol and other hormones released as we wake up mean that we tend to be most alert and focused a few hours after getting up in the morning.

Figure 8: Examples of the average times when selected biological processes peak. This illustration assumes the individual is waking with the light, and not in a state of circadian disruption.



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I've experienced first-hand that the work I can get done at 11:00 AM comes much more naturally than what I produce at 3:30, when I feel groggy and ready for a nap (this is around the time that the morning boost of alert/awake chemical signals are fading). With this in mind, I usually try to do my most mentally challenging work first thing in the morning, and often take a break or do something physical in the afternoon, like chores or going for a walk.

Another part of my daily routine that I try to optimize with my circadian rhythms is my meal timing. Unsurprisingly, our metabolisms are highest during the day, while we're active. Because of our circadian rhythms, the timing of our food consumption plays a role in our metabolic health. Studies have shown that even when eating the same number of calories, groups that eat later in the day tend to gain weight,

while those eating earlier in the day do not. Intermittent fasting (IF) has been a recent diet trend based on these ideas. Research into IF has also shown benefit for pancreatic health/those with diabetes, as a fast period helps to give many metabolic processes a robust off switch/break (likely strengthening and aligning circadian rhythms in our bodies). This makes evolutionary sense that our bodies would do well with this, as the 24-hour food availability many of us currently enjoy was not the case for our ancestors, who'd have larger gaps without food.

A quick Google search will return many IF diet plans (some more science-backed than others), one of the most common being 16:8—16 hours of fasting, followed by 8 hours of eating. This is roughly what I do each day, trying to time my 8 hours of eating with my active/day period and not eating less than 4 hours before I go to bed.

Healthy sleep patterns vs. acceptable sleep patterns

Throughout my PhD research, I've also considered my own sleep/wake health. For example, I've been paying a lot more attention to my light exposure at night. We've all heard that it's better for sleep to minimize light before and while sleeping—but why is this? Melatonin, the hormone responsible for cueing and maintaining our sleep state, is inhibited when light hits our eyes. This includes even quick light exposure—like a trip to the bathroom, or dim light exposure—like a street light outside a window. I've become more aware of this in my routines, turning off all sources of light while I'm sleeping, and using plug in night lights so that I don't have to turn on overhead lights if I'm up at night.

Conversely, this also means that bright light can be used as a tool when we want to be feeling awake and alert. Sleep health experts suggest exposure to sunlight—outside, or by a window—soon after waking, to really drive home the "it's daytime!" message for our bodies. For those of us in more northern cities with less sunlight in the winter, light therapy lamps can offer similar benefits.

In the past few years doing this research, I've also reevaluated my own sleep schedule. For as long as I can remember, I've never been sleeping or waking up when I was supposed to (shout out to my mom, who for years had the task of waking me up for school). I've always been active in the evenings and at night. No matter how early I'm waking up, around the time everyone else is going to sleep, I feel like I've got a few more hours before I could wind down—I'm just not tired. I imagine for non-night owls, this would feel about like asking them to go to bed at 7 pm.

Like many night owls, this creates a constant struggle of attempting to go to sleep early, occasionally succeeding, (usually failing), and waking up as close as possible to the early-risers. This leads to a very frustrating cycle of sleep debt, grogginess, and wild oscillations in sleep times--a.k.a. circadian disruption. For many folks with 9-to-5 jobs or other morning responsibilities, this is the only option. This form of circadian disruption has been deemed "social jetlag", based on the idea that many individuals are waking before they are ready to fulfill social obligations, and based on self-reported data, a large portion of working adults fit these criteria.

But as someone fortunate enough to make my own schedule, I began to consider whether acceptance of my natural sleep inclinations would ultimately be healthier and simpler. From my study of circadian rhythms, I knew that going to sleep and waking up as close to the same times each day was ideal, so if I could find a bedtime and wake time that was reasonable for my body and stick to it, I could likely have more consistency than trying to sleep like an early-riser. Though this approach isn't ideal for early-morning obligations, it's led to less circadian disruption overall.

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Looking back, I never would have expected my academic journey would have taken me to circadian rhythms. As someone who started grad school keen to find new answers in the obesity epidemic, I anticipated joining a lab that was studying something like fat cell signaling or high sugar diets. But when

I consider everything I've learned studying human bodies in my 14 years of college, this path makes a lot of sense. Because as much as the wellness industry, high school biology classes, even existing medical guidance distills health messages to make them seem simple ("just eat fewer calories and exercise and you'll lose the weight!"), in reality none of it is. Not only is the physiology of our bodies more complex than we may ever fully appreciate, our health is impacted by an elaborate, tangled web of external factors, from the air we breathe to the neighborhoods we live in to the amount of stress we face each day in our jobs. The good news is that scientists and healthcare providers are considering this bigger picture now more than ever. So here's hoping that this research is one piece of the puzzle, helping lead us to more answers about what it really takes to be healthy in this modern world.