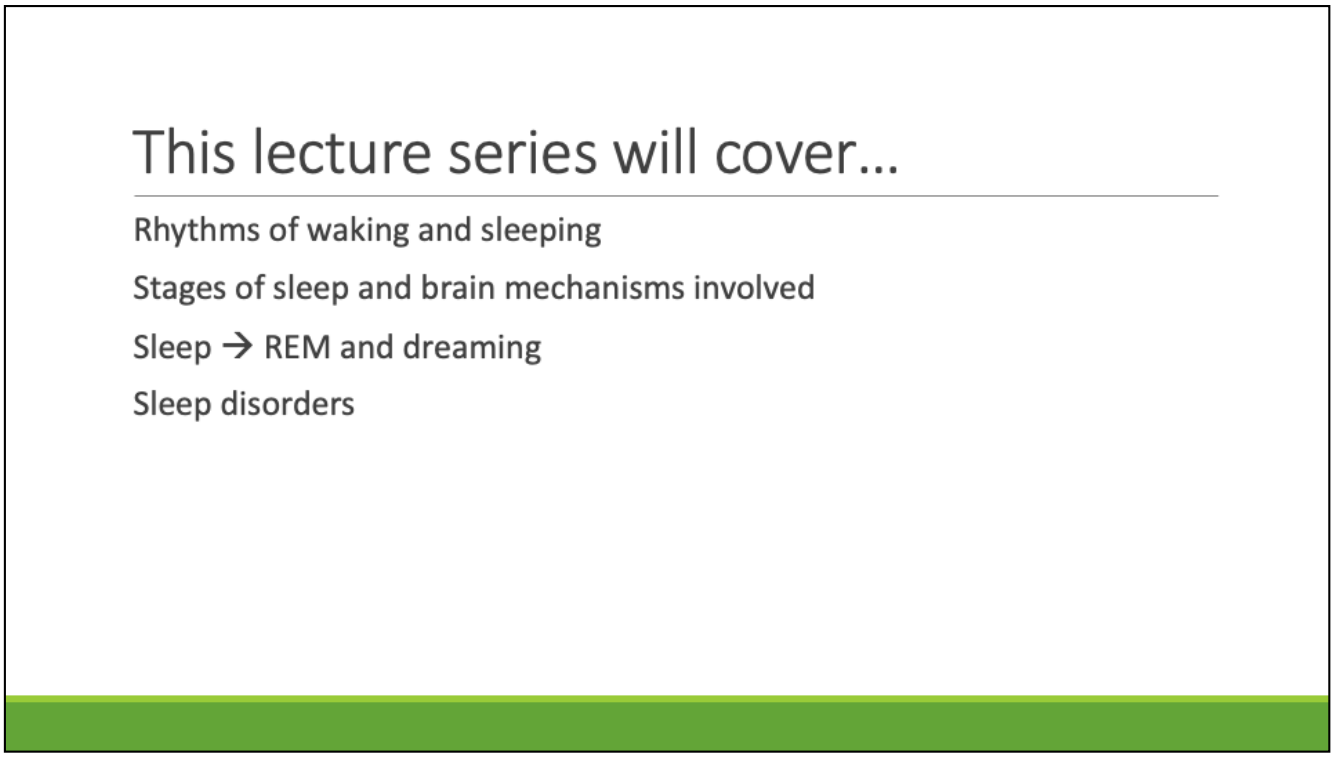
Rhythms of Waking and Sleeping

WEEK 8, LECTURE 1

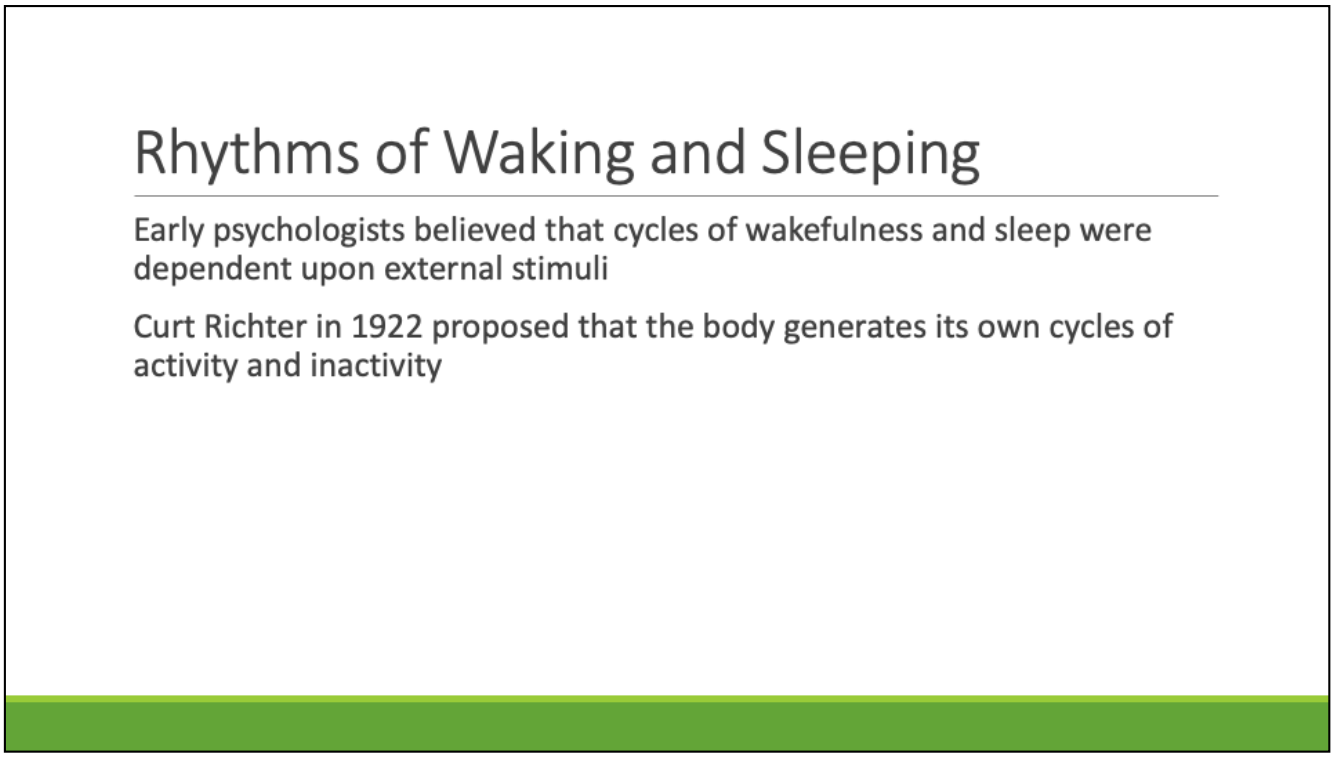
Instructor: Erin Horowitz

Welcome back everyone! Sorry to deliver another written lecture this week. Fun fact, I think in getting sick I seriously damaged my vocal cords at some point. I'm working on resting up, so my hope is that at least the last two lectures will be recorded again. But for now, you'll have to work with my notes. I hope these are clear enough – please let me know if they aren't, as this is somewhat of a new format for me.

In any case! This week's lecture is (I think) really interesting! We'll be talking about different aspects of sleep.



This is generally what we'll be covering in our lecture series this week. We'll start by talking about how sleep is regulated, and from there we'll discuss the different brain mechanisms involved in sleep. We'll have a really interesting discussion (or, written note-reading session) about the function of sleep and dreaming in particular, and we'll finish by talking about some cases where sleep can be disordered. So, let's get started.



So early on, psychologists believed that external stimuli – things like light and temperature – were the *sole* determinants of sleep and wakefulness. Being exposed to bright light makes you more awake, being in darkness makes you more sleepy, etc. etc.

It wasn't until about 1922 that a researcher named Curt Richter proposed that the body regulates its own cycles of activity and inactivity (he referred to it as the "biological clock"). We do still respond to things like light and temperature, but these external stimuli serve to signal or modulate these internal processes. Your book uses an example of pulling an all-nighter – something I'm sure we've all been through at some point in our lives. When you pull an all-nighter, you are forcing yourself to be awake. And yet, if you think back to your most recent all-nighter, you might remember that you were more tired as the night went on, but as the day started you gradually became more alter. This can happen even if you're in a small room with near-constant exposure to artificial light (say, studying for an exam), which means that *something* inside you is generating these feelings of tiredness and alertness, independent of how much or how little light you're being exposed to.

Endogenous Circannual and Circadian Rhythms

Some animals generate endogenous **circannual rhythms**, internal mechanisms that operate on an annual or yearly cycle

- Example: birds' migratory patterns; animals storing food for the winter

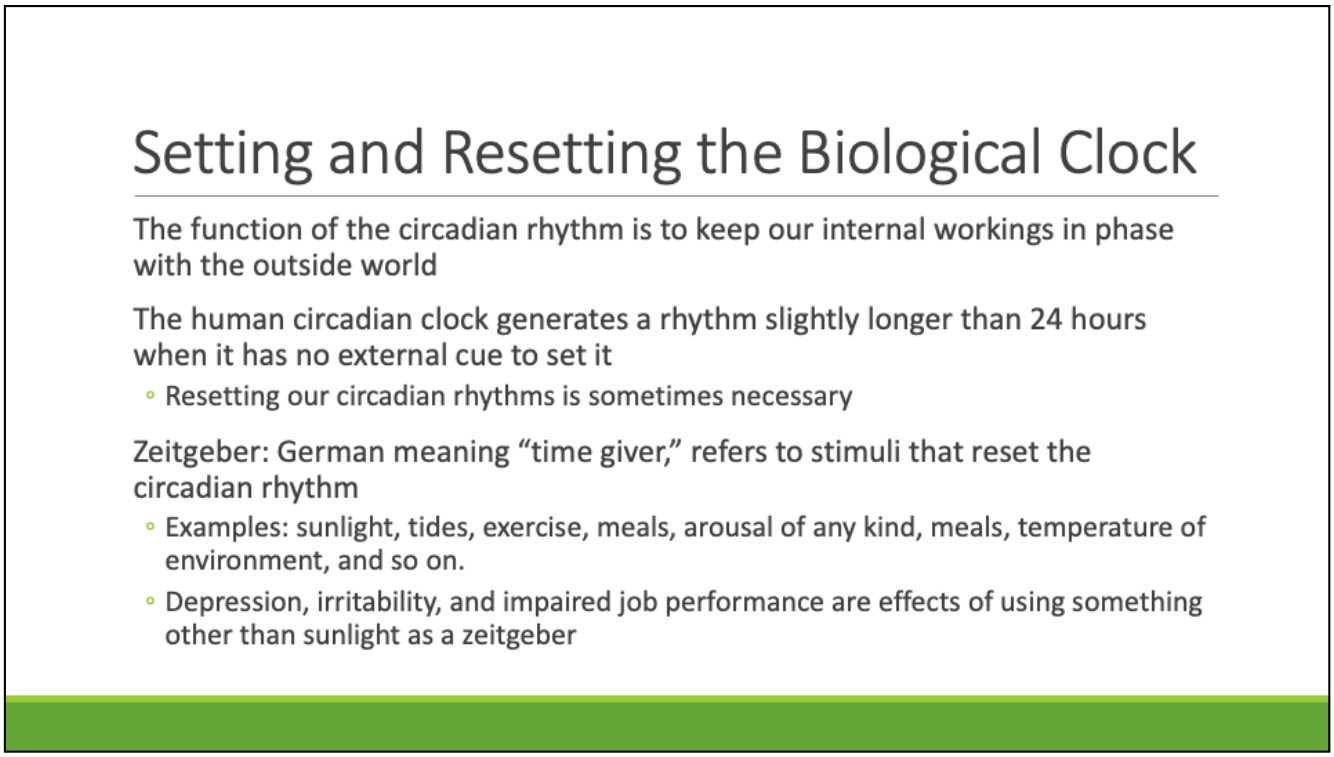
All animals produce endogenous **circadian rhythms**, internal mechanisms that operate on an approximately 24-hour cycle

- Sleep cycle
- Frequency of eating and drinking
- Body temperature
- Secretion of hormones
- Urination
- Sensitivity to drugs

What are these internal systems? Well, it can vary from species to species. Some animals have what are called circannual rhythms, which you can read about above.

ALL animals have endogenous (i.e., internally generated) circadian rhythms, which again you can read about above.

These rhythms determine not just sleep but also other regulatory processes, many (although not all) of which are listed above. Each one of these is described in more detail in your book, which I recommend you read through.

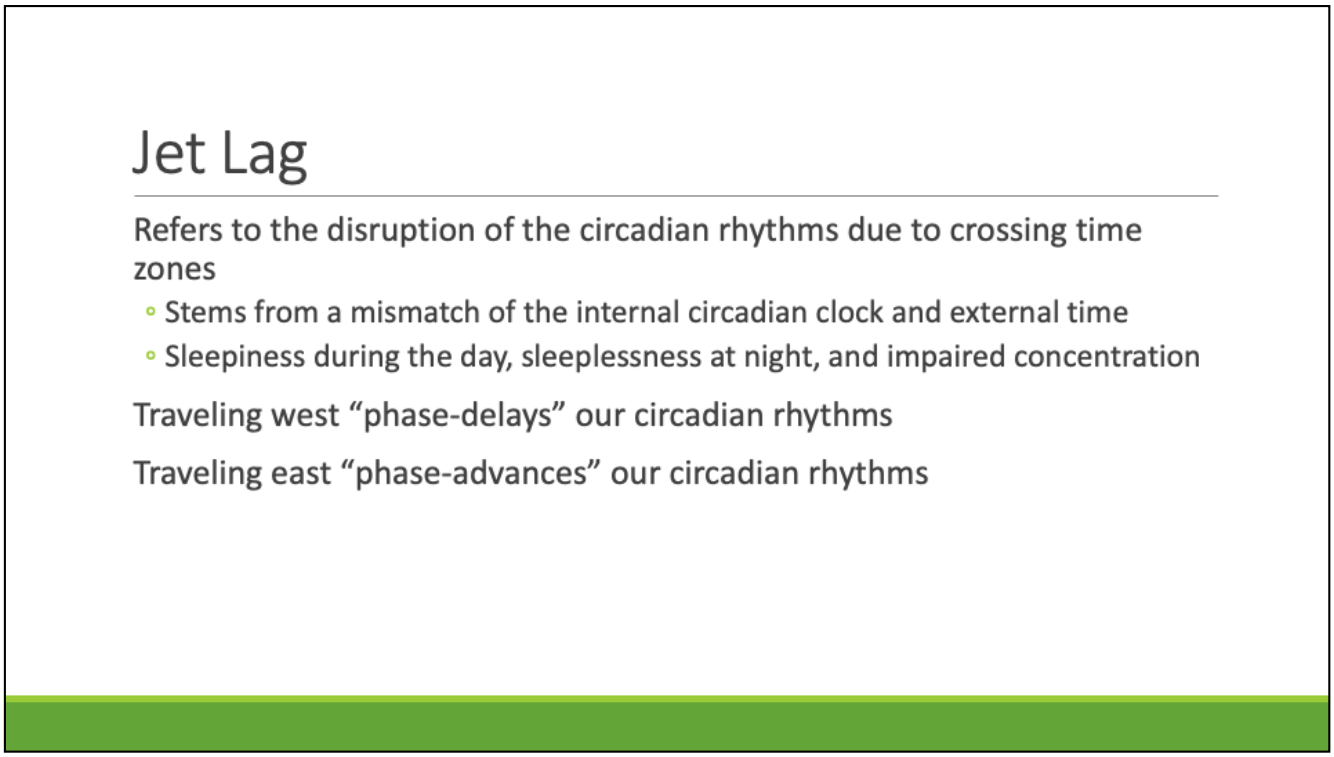


Why do we have these internal cycles? It seems like the function of these is to keep us in sync with the outside world. The reasoning for this is actually somewhat circular (this is my own opinion), but as we'll find out later in this series, it's not *entirely* clear why we sleep in the first place. So it seems like, at the very least, we have these internal cycles, and they try very hard to align with cycles of day and night in the outside world. They are actually fairly malleable, and your book has some interesting examples of when these cycles can be shifted.

And in fact, our circadian rhythms don't line up *exactly* with a 24-hour cycle. Our rhythms are actually slightly longer than that, which means that every once in awhile we need to shift or adjust them to line back up. Sometimes completely resetting these rhythms is necessary, like when you travel to a completely different time zone.

There's this German term called Zeitgeber, or "time giver", which refers to any type of stimuli that can reset your circadian rhythms. There are a bunch of examples listed above (again, your book goes into much more detail about these). Now again, these are external factors which can alter or reset your circadian rhythm. The point is that it's not *completely* determined externally.

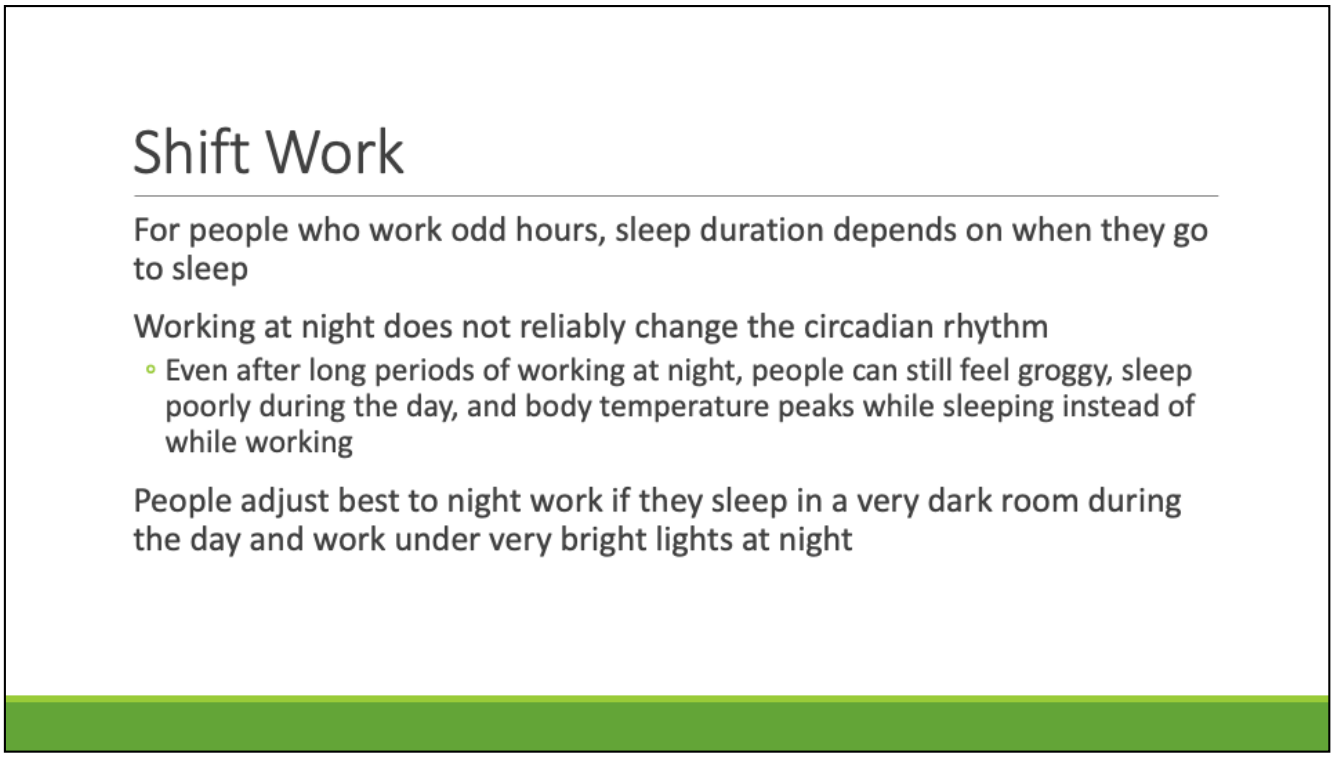
We have an internal cycle that exists in the absence of these factors, but these factors can alter that rhythm. Let’s go over some specific examples over the next few slides…



One fairly common example of a disruption in circadian rhythm is jet lag, which occurs when we cross time zones. These can be really minor, if we go somewhere that's an hour ahead… or they can be really extreme, if we go somewhere that's 12 or more hours ahead (or behind). At first, we tend to stick to the rhythm from the place we originated from – the rhythm we're used to. But as we receive cues that daytime and night time are occurring at different parts of our cycle than we're used to, this can cause shifts in tiredness and alertness.

It's generally less disruptive to travel west. We "phase-delay" our rhythms; the time at the place we arrive at is slightly earlier than the one we left, and so we end up staying awake later and sleeping later until we adjust.

It's more disruptive to travel east. In this case, we "phase-advance" our rhythms, meaning we arrive in a place that has a later time than we're used to. If we leave in the morning and arrive at night, we're likely not going to be sleepy until our internal cycle tells us it's "nighttime," which is still based on where we originated from. In this case, we have to essentially force ourselves to adhere to the new rhythm – by sleeping when it's dark and waking when it's light – even if our internal cycles are telling us otherwise.



Another example is shift work – and specifically, people who work irregular shifts (e.g., night shifts). For these individuals, the amount of time they sleep depends on when they go to sleep. If they go to sleep in the morning, for example, they tend to only sleep for a few hours before waking up automatically.

You might think that someone who consistently works, say, a night shift would eventually shift their circadian rhythm to match an awake-at-night-asleep-during-the-day cycle. But this actually isn't the case, and you can read about some of the problems these individuals have above.

The best solution to this – at least for people who work night shifts – is to sleep in a very dark room during the day and work under very bright lights at night – essentially simulating "normal" day/night cycles.

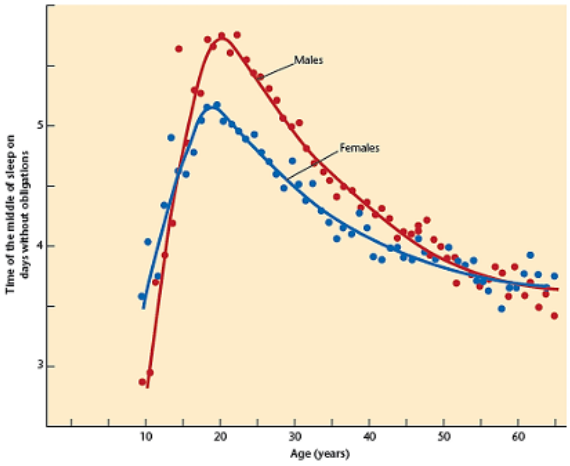
Morning People and Evening People

Cycles can differ between people and lead to different patterns of wakefulness and alertness

Change as a function of age…

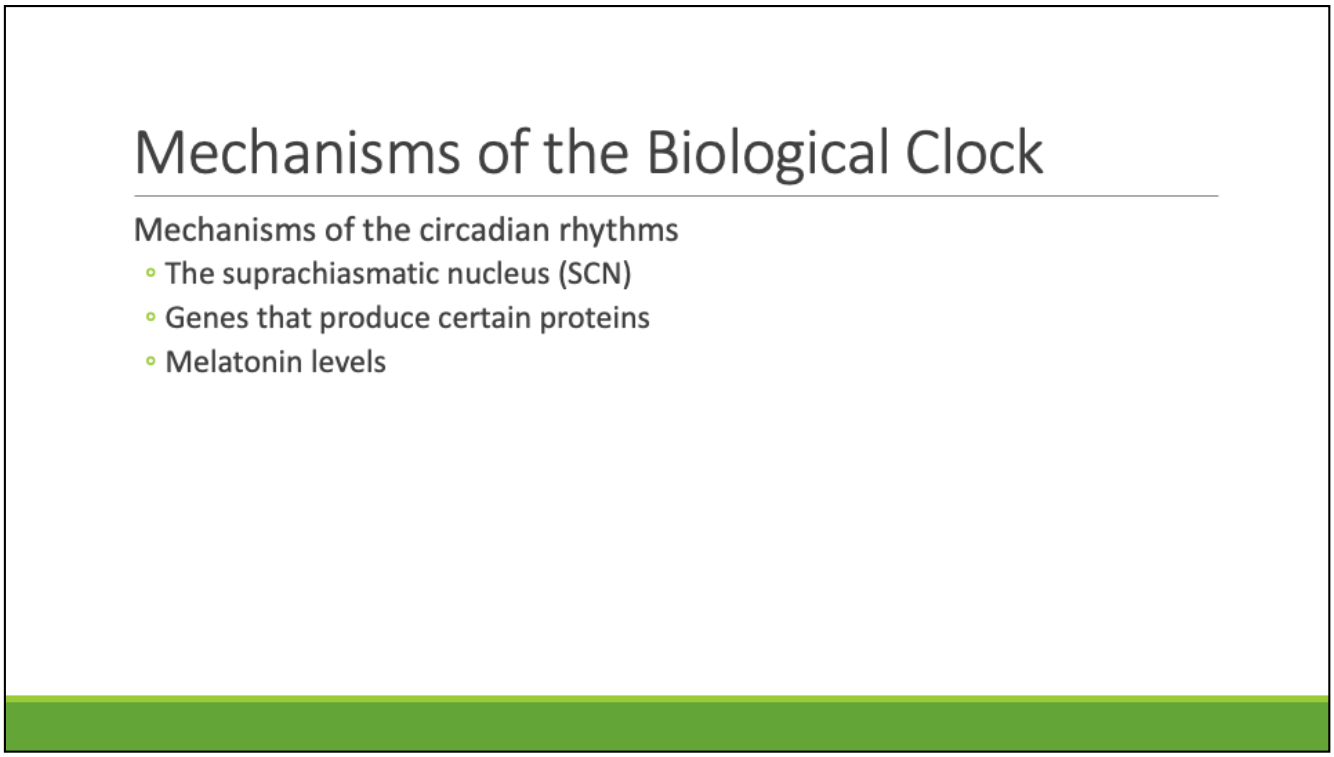
- Young children tend to be morning people
- Adolescents are often night people

As an adult, it partially depends upon genetics



There are also individual differences in people's sleep cycles. Some people are "night owls" and some people are "morning larks" (which is a term I wasn't aware of until I read this textbook… I've just been calling them "morning people"…), and some people are neither. Generally speaking, young children tend to be morning people and adolescents tend to be night people. Personally, I'm a night person, but I've noticed that's changed as I've gotten older. Now I'm much more comfortable waking up early, whereas 5 or 6 years ago I would have been incredibly upset if I had to wake up before 8am.

This graph is based on a study that looked at the variance of individuals' sleep/wake cycles in terms of both gender and age. They asked individuals to record the "middle" of their sleep on days on which they had no obligations ("middle" here means finding the midpoint between the time they fell asleep and the time they woke up). You can see a few things by looking at the graph: first, that there is a lot of individual variance (by looking at the dots). There also appears to be a gender difference, in which males report sleeping much later than females on average. And there's also an age difference – both of the sexes recorded here report a peak in sleep time around the age of 20, and that steadily declines (and the gender difference becomes smaller) as age increases.



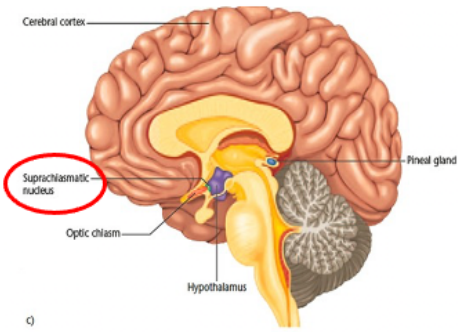
So those are some examples of different factors that can shift one's circadian rhythms. Let's move on and talk about the physiological components that underlie this mechanism.

The Suprachiasmatic Nucleus (SCN)

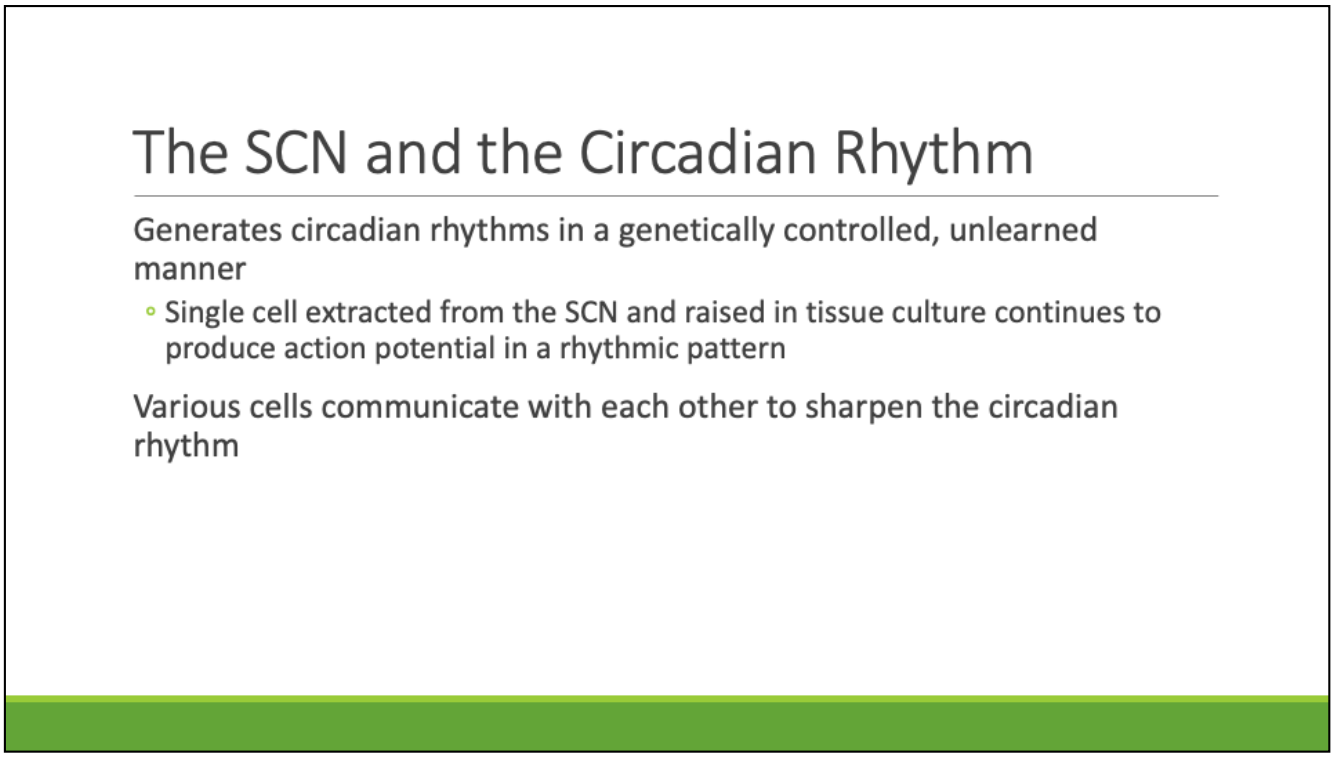
The main control center of the circadian rhythms of sleep and temperature

- Located above the optic chiasm and part of the hypothalamus

Damage to the SCN results in less consistent body rhythms that are no longer synchronized to environmental patterns of light and dark



We'll start with an area called the suprachiasmatic nucleus (SCN), which you can read about above.



The SCN is genetically controlled, meaning its behavior is completely unlearned. Interestingly, if you remove cells from the SCN and keep them alive in a tissue culture, they'll continue to fire in response to the body's circadian rhythm. The same thing will happen if you remove SCN cells from one organism and transplant them to another whose SCN has been completely removed: the recipient will take on the circadian rhythms of the donor organism! So this area is *incredibly* genetically specified.

This effect can be produced by a single SCN cell, although having more SCN cells attuned to one cycle will sharpen or enhance the rhythm.

The SCN and the Retinohypothalamic Path

Light resets the SCN via a small branch of the optic nerve called the retinohypothalamic path

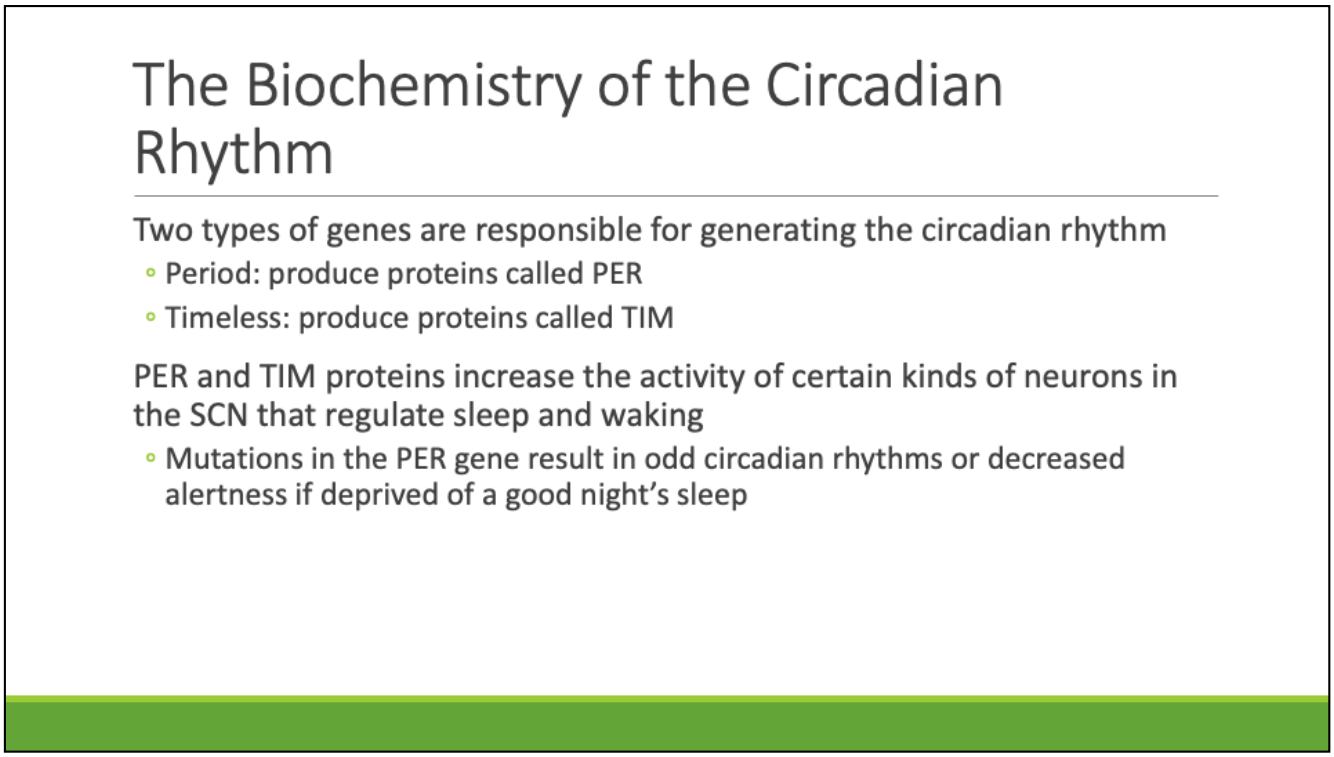
- Travels directly from the retina to the SCN

The **retinohypothalamic path** comes from a special population of ganglion cells that have their own photopigment called **melanopsin**

- The cells respond directly to light and do not require any input from the rods or cones

Since the SCN is one of the primary determinants of the circadian rhythm, it is relatively sensitive to light. The SCN is connected to a branch of the optic nerve called the retinohypothalamic pathway. This pathway contains a special type of ganglion cell that does not respond to photoreceptors; rather it responds directly to light via a photopigment called melanopsin (recall from our lecture on methodology that "opsins" are chemicals that respond especially well to light).

These cells respond to gradual changes in light, which helps the SCN determine the time of day, and subsequently help regulate tiredness/wakefulness. Interestingly, these cells respond especially strongly to short-wavelength (i.e., blue) light, which is one of the reasons why staring at your phone right before you fall asleep will actually result in lower quality sleep (or a general delay in falling asleep).

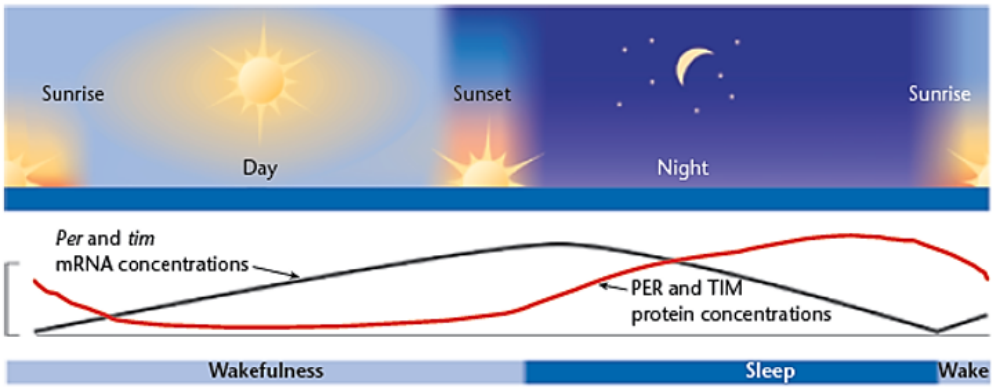


So to sum up what we've talked about so far: the retinohypothalamic pathway transmits light information to the SCN, which helps the SCN determine the time of day. From there, the SCN regulates circadian rhythms. Now the question is, how does it actually *do* that?

There are two types of genes that are responsible for generating these rhythms: period (which produces proteins called PER) and timeless (which produces proteins called TIM)

These two proteins interact to regulate sleep and wakefulness by activating certain neurons in the SCN, which you can read more about above.

Interaction of mRNA with PER and TIM Proteins



How do these proteins work, exactly? Your book gives an example from fruit flies, but the principle is generally the same for humans.

There are two processes at work here: 1) mRNA coding for the production of PER and TIM (indicated by the black line) and 2) the actual concentration of PER and TIM (indicated by the red line). You can see from looking at the image above that coding comes first, and concentration is slightly delayed (it takes time for these proteins to be produced, after all).

mRNA begins to code for the production of PER and TIM early in the morning, when their concentrations are at their lowest. mRNA will continue to ramp up its coding throughout the day, and the result is that by the evening, the actual concentration of PER and TIM is at its highest. At this point, when PER and TIM are at their peak, they'll send a signal back to mRNA to decrease production. mRNA concentrations decrease, and over the course of the evening, PER and TIM concentrations slowly decrease as well. By morning, PER and TIM concentrations are at their lowest, and the cycle starts back up again.

Now, I realize I haven't really told you what PER and TIM do with regards to circadian rhythms. Part of the reason is that it's beyond the scope of this class, but another is because, like I mentioned, PER and TIM are present in fruit flies, and are not present in the same way in humans. We possess genes *similar* to PER and TIM, and their functioning is… complicated. Your book provides several examples of how mutations or malfunctions in these proteins can lead to disordered sleep. This is a great way to study how these proteins function – if one of them malfunctions and causes, say, delays in sleep, we know that that protein must be involved in the part of the circadian rhythm that makes you sleepy as the day ends.

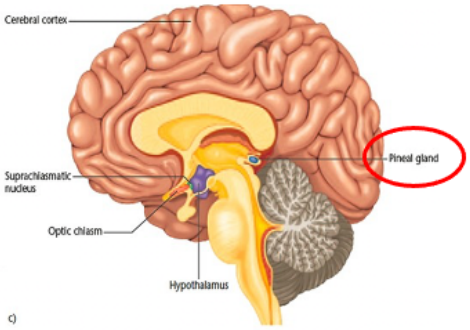
Melatonin

The SCN regulates waking and sleeping by controlling activity levels in other areas of the brain

- The SCN regulates the pineal gland, an endocrine gland located posterior to the thalamus
- The pineal gland secretes **melatonin**, a hormone that increases sleepiness

Melatonin secretion usually begins two to three hours before bedtime

- Melatonin feeds back to reset the biological clock through its effects on receptors in the SCN
- Melatonin taken in the afternoon can phase-advance the internal clock and can be used as a sleep aid



The SCN also regulates an area of the brain known as the pineal gland – and specifically, it leads to the release of a hormone called melatonin, which you can read about above.

Melatonin can actually be used as an effective sleep aid – and it's sold over the counter (and now in gummy form!). It's most effective when taken a few hours before bedtime (you can also take it in the afternoon, but this might cause you to become sleepy closer to sunset)..

Questions for your discussion group...

1. How does the SCN work with PER, TIM, and Melatonin to regulate circadian rhythms?

Okay, that does it for this first lecture! I have just one question for you for this lecture, because it was fairly short. Our next lecture will look at sleep cycles and the brain mechanisms that regulate them. See you then!