BTNacademy

MODULE 7

THE IMPORTANCE OF SLEEP

7. MODULE 7: THE IMPORTANCE OF SLEEP

7.1. Module aims

- To describe and explain the process of sleep
- To outline the function of caffeine in the sleep/wake cycle and how it can play in to poor sleep
- To explain the concept of a sleep deficit, and give the negatives that can arise
- To give practical tips for improving sleep quality

7.2. Key principles from module 6

In module 6 we spoke at length about the various methods with which you can track your food intake and other lifestyle factors along with the ways in which you can use this data to make decisions around what to do next. We then moved on to some key discussion points around the idea of dietary flexibility and clearly stated our position on these. As a brief summary, you learned:

You can consider your required tracking accuracy to fall within one of three bands:

- **Level A:** Tracking portions and adherence to your approach
- **Level B:** Tracking calories while adhering roughly to level A style meal building for the most part, unless you are proficient enough to consume your food in fewer meals or in a more sporadic and snack-based fashion while still meeting your needs
- **Level C:** Broken down into further brackets, but essentially tracking protein and calories or all three macronutrients as well as calories, probably using an app
- With all three approaches, planning your food is a good idea. This applies most for level A then less and less as your tracking becomes more accurate because you can adapt as you go more easily when you have all the available information
- You don't have to track forever, and while tracking you don't always have to use the same manner of tracking – you could be loose and then track more accurately in the run up to an event for which you'd like to lose weight, for example
- Misreporting calories is extremely common and you should be aware of it
- You can also track your weight, your measurements, your habits (desirable or undesirable), your menstrual cycle if you have one, your sleep and your gym progress. There are other things you could track, too, but this is a pretty comprehensive list of what would be useful for managing your body composition and health insofar as nutrition can impact it
- You can use the information on the food you've eaten and the impact that this has had to make informed choices on what to do next

- Being flexible with food choices is important, with a greater amount of flexibility being afforded by a greater amount of tracking rigidity

7.3. Introduction to sleep and stress

Now we are going to look at one lifestyle factor which may seem somewhat unrelated at first, but which has a huge impact not only on your general health, but your ability to make appropriate decisions around food. It therefore has a substantial influence on your ability to control your weight. In this module we will discuss sleep, meaning we will describe and explain what sleep is and what causes you to do it, we will speculate on why you do it, then we will show you the many ways which a lack of sleep can potentially result in unfavourable shifts in body composition. Finally, we will round off by giving some practical advice on improving sleep if this is something that you feel you need to do. Let's begin by talking about your brain.

7.4. How are brains studied?

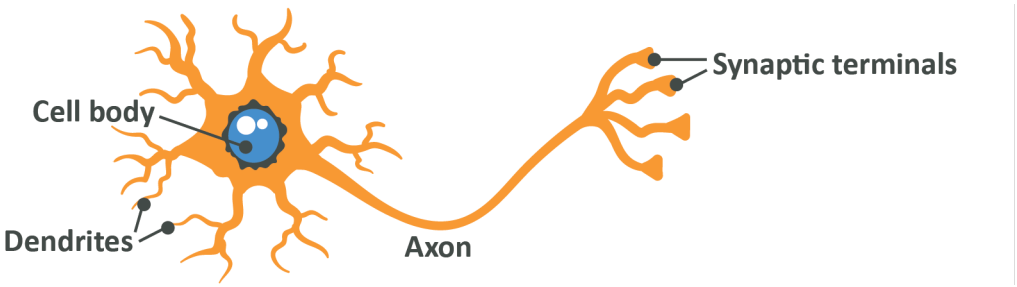
For most of our history, sleep looked something like unconsciousness because our only means of studying it was to look at a sleeping person and make assumptions based on that. When you're asleep, you're largely non-responsive and for all intents and purposes 'dead to the world', but intuitively you more than likely know that is not the case. If someone is in a coma, has passed out, is inebriated or has been sedated/anaesthetised then they can be **very** difficult to wake up. You can slap them, shout and perform surgery in some cases but nothing happens – sleeping people are comparatively easy to bring back to an awakened state.

Still, we didn't really have any means of assessing what was going on inside any brain, waking or sleeping, until the 1920's when Hans Berger, a German clinician, used emerging technology which had been tested on animals to read the electrical activity within the skull of a live human subject. What Berger measured for the first time are the now well understood and commonly spoken of 'brain waves' (though what he was looking for was a physiological basis for psychic phenomena).

7.5. What are we measuring?

Within your brain are somewhere around 86 billion specialised cells called neurons, which have a very distinctive shape. Within the cell body is a nucleus, mitochondria, endoplasmic reticulum and all of the other organelles you would expect to find in any cell, but when you look at the structure of the cell body you see some specialised structures which give the neuron certain properties.

Fig. 63

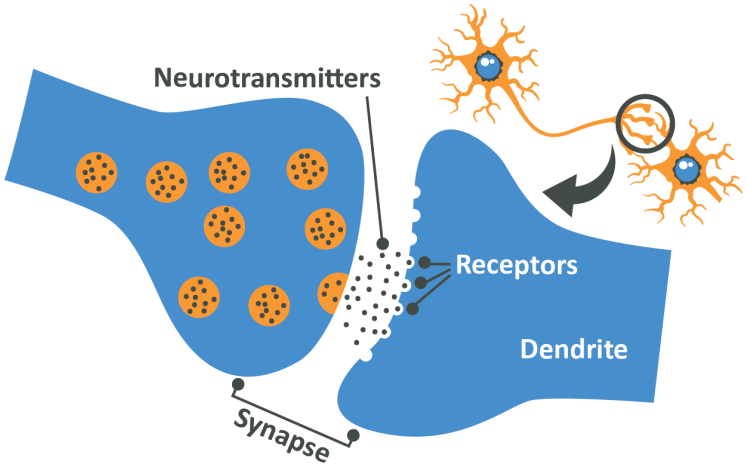


From the cell body extends two different kinds of projection, namely dendrites and an axon. The axon extends anywhere from an exceptionally short distance (say, between different neurons) anywhere to up to 15 feet in a giraffe. These exceptionally long, almost inconceivably thin thread-like projections extend all the way from the brain to various parts of the body to convey information. Your brain communicates via your spinal cord to every area of your body through nerves, which are bundles of axons, almost like humans communicate through a phone-line. A neuron is capable of sending a signal from its cell body down to a certain body part to illicit an effect (movement in somatic muscles, secretion of hormones from glands or even some amount of pain). The dendrites, on the other hand, are able to receive signals from other neurons, which is how you are able to think or perform complex tasks. Some areas of your brain are responsible for movement, some for smell, some for basic emotions, some for conscious thought and many other areas perform various different tasks; so, these areas need to be able to communicate with each other as well as to the broader body, and they do this in the following way.

In module 4 we talked about the potassium/sodium pump in terms of hydration and mineral balance, but it also plays a large role in the sending of signals via your nervous system. These signals are created thanks to a phenomenon known as 'membrane potential'. The sodium/potassium pump, as you will remember, acts to pump 3 positively charged sodium ions (positive thanks to the fact that they lack one of a stable sodium atoms negatively charged electrons) outside of the cell while pumping 2 negative potassium ions back in. This means that while the cell is in a resting state it has a significantly greater negative charge inside than out, and the opposite is true for the positive charge.

When the nerve receives a signal at one of its dendrites (in a form we'll explain momentarily), small membrane-bound proteins on the surface called protein channels will open, allowing the positively charged sodium ions to rush in, depolarising the area and reducing the charge across the membrane. This then causes a chain reaction down the dendrite, across the cell body and down the axon to either another neuron or a relevant part of the body. After the signal has passed a section of the cell body the sodium channels are closed and the sodium/potassium pumps get back to work re-creating the polarisation.

Fig. 64

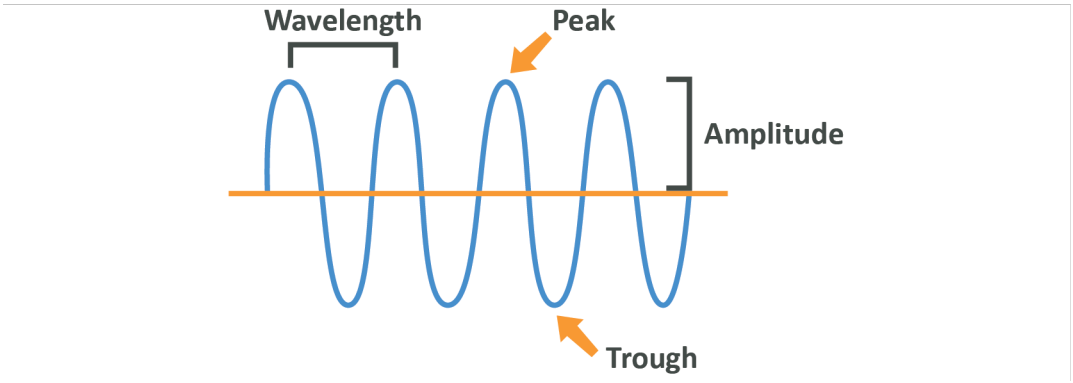


Once the signal reaches its destination it meets a problem, between the end of 1 axon and the thing with which it's trying to communicate, is a tiny gap called a synapse. When the signal reaches here the neuron sending the signal (the presynaptic neuron) secretes signalling molecules called neurotransmitters (of which dopamine is one, which we described in earlier modules). These neurotransmitters cross the gap and bind to receptor sites on the postsynaptic neuron, which then continue the signal.

7.6. What does this have to do with sleep?

The technology Berger used in the 20's was Electroencephalography or EEG. To perform an EEG a practitioner places 8-16 pairs of electrodes on specific areas of your cranium and measures electrical activity. The difference in activity between one electrode and another is translated to a line which the practitioner can then use to determine what your brain is doing, and because the lines created by these machines adopt a wave like structure, the term brainwaves has been coined. It was thanks to the electrical nature of neuron to neuron communication that we were able to measure brain activity and it was because of this activity that we were able to start to study sleep in far more detail. So how is this measured?

Fig. 65



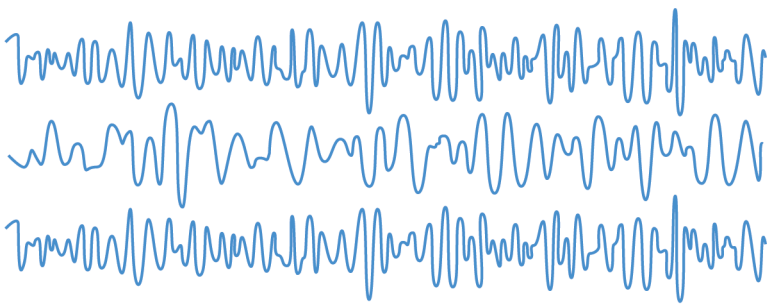
Electrical waves like the example above are measured in two dimensions:

- Amplitude, which is the difference between the peak of a wave and the centre line, and it measures the power of the wave – in soundwaves the amplitude measures the disturbance in the atmospheric air pressure and in water the amplitude would be the height of the wave. Amplitude is denoted by the symbol µV
- Frequency or wavelength is measured in hertz (Hz), and it denotes the number of cycles between peak and trough per second. The higher the frequency, the more often a peak or trough will occur in a given time period

EEG machines measure the amplitude and frequency of electrical signals in the brain and transfer them to a printout sheet which looks like the below, and it is by studying these that researchers can reach conclusions about what is occurring in your brain during the night.

Note: Fig. 66 is used to give you an idea of how EEG readouts appear. Note that true EEG measurements would contain many more lines of data.

Fig. 66



7.7. What is sleep?

Sleep is defined as "a period of rest for the body and mind, during which volition and consciousness are in partial or complete abeyance and the bodily functions partially suspended. Sleep has also been described as a behavioural [sic] state marked by characteristic immobile posture and diminished but readily reversible sensitivity to external stimuli".

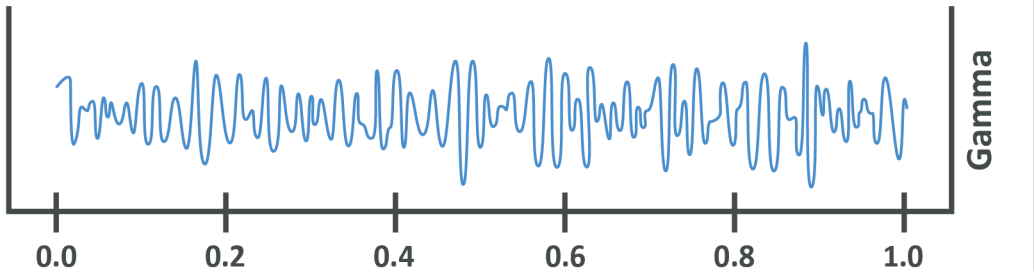
What's important is to understand that sleep is not simply a passive process that you sink in to at the end of the day, nor is it a complete blackout. As we said, we didn't know anything more than the obvious until around 1953 when Eugine Aserinsky and Nathaniel Kleitmann decided to study an unusual fact about sleep: the twitching of the eyes which is observable in sleeping individuals. Their paper "Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, During Sleep" was the first to document what we now know as (thanks to the name given by these researchers) Rapid Eye Movement or REM sleep. This is heralded by many as the birth of modern sleep science – it was shown that sleep wasn't passive or a state of complete unconsciousness which happens 'to' your brain, but rather a period during which your brain is active and which can only have been caused **by** your brain.

From there, more EEG studies have been done and so sleep has been relatively comprehensively mapped and described according to experimental findings. We now consider sleep to form 4 distinct stages spanning 3 stages of non-REM sleep and REM sleep itself. These are described below:

7.7.1. Alert awakeness

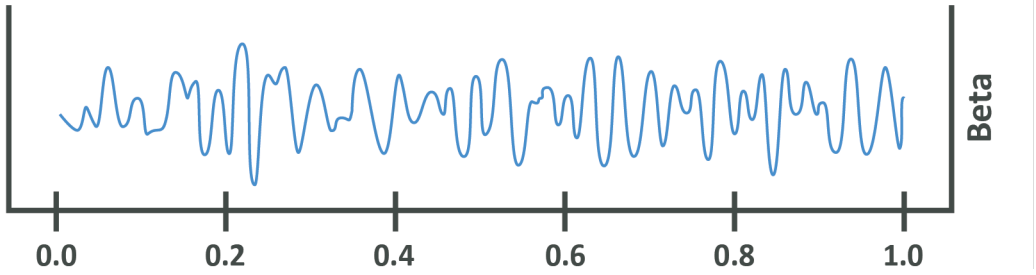
During the day your brain is, not surprisingly, at its most active. During times of extreme alertness such as when you are either hyper-aroused by an exciting event such as playing a sport or engaging in something dangerous, or when you are solving a very complex puzzle, your brain exhibits high frequency (25-50Hz), very low amplitude (0.5-2 μV) waves referred to as Gamma waves. These waves are associated with new experiences and learning, and it has been documented that individuals with learning disabilities display lower gamma frequency wave activity.

Fig. 67



During less stressful periods of wakefulness, you will display 12-25Hz, 1-5 µV waves called Beta waves. These waves are involved with conscious thought, logical thinking and moderate to high amounts of cognitively-powered problem solving. Excessive beta wave activity is, conversely, associated with stress and anxiety. The higher your beta wave frequency goes, the higher your arousal levels become.

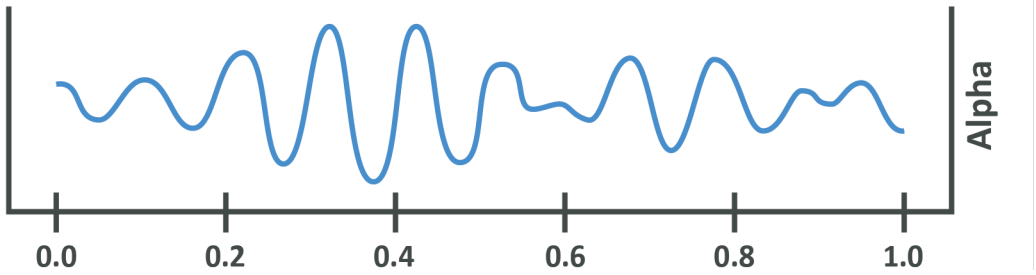
Fig. 68



7.7.2. Relaxed wakefulness

It shouldn't take too much explanation to make you aware that falling asleep very rarely happens suddenly in healthy people. We have phrases such as 'winding down' for the period of relaxation (or involuntary exhaustion) which occurs before sleep and this is displayed clearly on EEG readings. During the short time before you go to sleep you close your eyes and 'switch your brain off' to use another common phrase, and this induces Alpha wave activity of 8-12Hz and 20-80 µV. These are highly sensitive to eye opening and closing but can also be disturbed by starting to perform calculations or thinking too hard in general, which is something we will return to later in this module.

Fig. 69

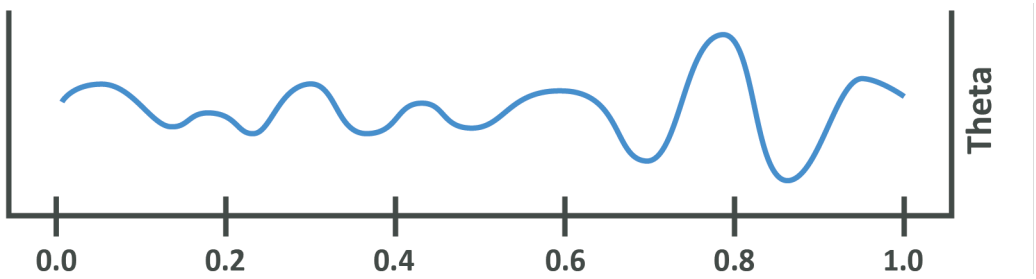


7.7.3. Falling asleep and sleep stage 1

Gradually as you relax more and more and your brain activity starts to drop further, you start to display 4-8Hz, 5-10 µV waves called theta waves and enter what is referred to as Stage 1 or non-REM stage 1 sleep, often called somnolence or drowsiness. Here your breathing starts to slow but muscles are still quite active so you can change your position and your eyes may open every now and then. To be in this state is to be able to hear conversations but to feel unwilling rather than unable to reply. It's during this time that you may also experience hynagogic jerks, which are sudden awakenings accompanied by the feeling of falling. This short stage lasts around 10 minutes and you are very easily disturbed.

Note: it's hard to tell exactly when you have fallen asleep because these things occur on a continuum of shifting frequencies and amplitudes and any distinctions we have described around them are necessarily arbitrary to a certain degree, despite being replicated across people.

Fig. 70

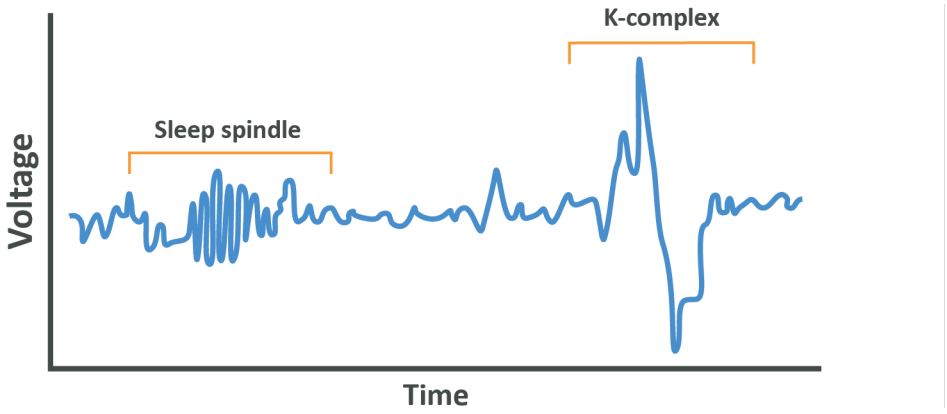


7.7.4. Stage 2 sleep

This is the first stage of definite sleep. Your muscles relax almost completely, you become almost unaware of the outside world and you start to display only Theta wave activity. Interestingly, in stage 2 sleep you show two distinct phenomena:

- Sudden and short bursts of very high frequency (12-14Hz, like low frequency beta waves) referred to as 'sleep spindles'. These are associated with activity in your thalamocortical system which is the system in which your thalamus (a region which receives sensory input) sends information to your cortex (the outer layer of your brain responsible for higher functions like memory, attention, consciousness and language). These are theorised to be critical for memory consolidation which we will come back to later
- K complexes which appear as a sudden large change in amplitude which have been shown to be absent in poor sleepers, and have been hypothesised to be part of a 'sleep defence' mechanism to keep you asleep despite environmental stimuli

Fig. 71



Because of the process by which you sleep, as we will explain later, stage 2 sleep is the stage that makes up more of your sleeping time than any other stage, accounting for 45-50% of total sleep.

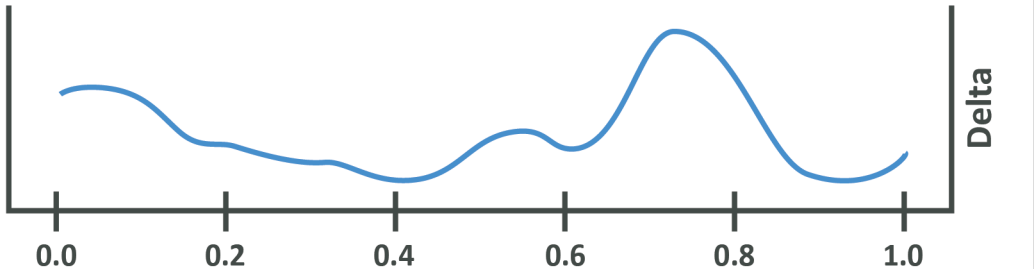
7.7.5. Stage 3 sleep

This is the stage referred to as deep sleep, and it is the time when your brain is the least active – producing slow delta waves of 0.5-4Hz but with a comparatively high 100-200µV (sometimes you will see it broken further down into stage 3 and 4). During this period your breathing, heart rate, blood pressure and body temperature drop to the lowest level during the night and you become almost completely unresponsive to outside stimuli. Deep sleep and delta waves are considered to be the most rejuvenating, restorative sleep as well as being crucial for memory consolidation – you will generally have 20-25% of your sleep being comprised of stage 3 sleep (most of this happens in the first half of the night) and a lack of delta wave sleep is what leads you to feel like you have had poor sleep quality.

On top of this, waking during delta wave sleep leads to sleep inertia, a groggy and confused feeling of near-drunkenness which can take up to 30 minutes to dissipate.

Stage 3 sleep is the period during which most sleep disturbances occur including bedwetting, sleep walking and talking, and night terrors which are described as overwhelming feelings of dread similar to a panic attack. Those who have night terrors will often sweat and show increased blood pressure and heart rate before waking. Waking someone having a night terror can cause them to lash out.

Fig. 72



7.7.6. REM sleep

This is often referred to as paradoxical sleep and for good reason. From one perspective, this is the deepest stage of sleep because you are unresponsive to stimuli and your muscles are completely paralysed but it would be a mistake to think that this is because you are completely 'out for the count'. During REM sleep your brainwaves will fall within the ranges associated with theta, alpha and even beta waves indicating brain activity which is equal to that experienced during the waking period. This is the part of the night where you dream, and the afore-mentioned paradox.

Being that you are not conscious, and so acting out your dreams with physical movement would be damaging, an area of your brainstem called the sublaterodorsal nucleus becomes active during REM sleep. This acts to inhibit skeletal motor neurons effectively shutting off your brain's ability to communicate with the wider body other than areas needed for necessary function (such as your heart and lungs). Because it's not likely that eye movements are going to cause you to hurt yourself, they have also been spared this inhibition and as you dream, your eyes are free to flicker around at will. This has been displayed elegantly in trials such as that conducted by Aserinsky, because the times of night where brain activity is at its highest (suggesting dreaming) correlate precisely to the time of night which involves jerky eye movements (as measured by an electrooculograph, which can detect activity in the muscles that control eye movements).

It's not only brain activity which increases at this time. In contrast to other sleep states where your body generally slows down, your blood pressure, heart rate, breathing and metabolism will increase during this period to almost waking levels. Sexual arousal is also common with penile and clitoral erection being present (in fact REM sleep-related penile erections are one of the diagnostic tools used to determine whether erectile dysfunction is physiologically or psychologically rooted). You will likely experience short periods of wakefulness during REM sleep, too, which you are unlikely to remember. If you are over-stimulated (as we will get to later) you could wake up fully at this time, potentially then taking a long time to get back to sleep.

During brain development REM sleep appears critical. Newborns spend about 50% of their sleeping time in REM sleep, which drops to around 30% at 3 months of age and 20% by 6 months. This is associated with the maturation of your cerebral cortex (the more advanced and 'human' part of the brain) and in fact rats deprived of REM sleep during development show various neural difficulties as they age. Not only this, but infants will fall straight into REM sleep rather than following a typical adult sleeping pattern which will be explained in the next section. At age 2 REM accounts for 20-25% of sleep; a fact which lasts until adulthood. Once you reach adulthood your REM sleep percentage will drop by about 0.6% per decade of life. In short during childhood you may spend 8 hours per day in REM sleep, during early adulthood that will be around 2 hours and by age 70 it'll be approximately 45 minutes.

REM sleep is activated due to a release of 2 neurotransmitters – acetylcholine and serotonin in the pons area of your brainstem (a band of nerves which includes the abovementioned sublaterodorsal nucleus), evidenced by the fact that removal of this area eliminates REM

sleep entirely. This means that REM sleep, as for sleep in general, is not a state which you fall in to when things deactivate, but an actively 'caused' state.

As you can see, REM and non-REM sleep are hardly equivalent states and sleep itself is a hugely important part of development, but why do we need it as adults?

While deep, stage 3 sleep is necessary for rejuvenation and feeling refreshed after sleep, a lack of REM sleep (as can be caused by SSRI antidepressants and other medications) doesn't appear to have any obvious negative effects to day-to-day function. However, a lack of REM sleep does seem to impair your ability to learn complex tasks and remember things (possibly one reason it's so important during infancy – you have a lot to learn) and while we don't completely understand why, REM sleep seems important to your brain because you will compensate for a lack of it. If you have a reduced amount of REM sleep for 1 night, you will experience REM rebound sleep the following night involving REM sleep occurring earlier in the sleep cycle and for longer.

With that said, to close this section we need to explain the full state of affairs with REM sleep. Those who have complete REM sleep deprivation, as mentioned, do not experience short-term negative effects and (because of the rejuvenating nature of stage 3 sleep) may not even realise they haven't had 'normal' sleep. Additionally, these individuals may dream more in stage 3 sleep to make up for their missed opportunity. REM sleep seems to be important, but we aren't totally sure why, and it seems that your body is able to at least partially make up for any lost ground if REM sleep is absent.

During this section, we have discussed the 4 stages of sleep and mentioned sleep cycles, so let's explore that before we circle back to one important question – what's the point of sleep?

7.8. Sleep cycles

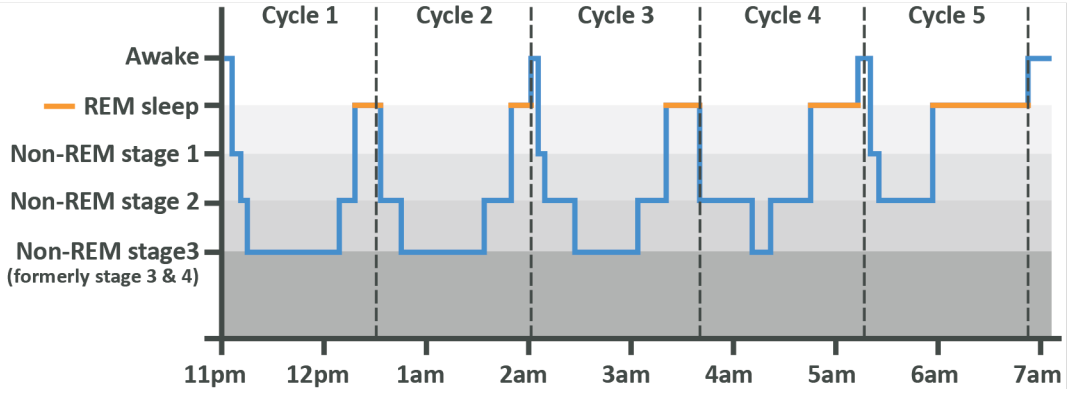
As you read above, sleep is not a homogenous experience, but rather a multi-stage process which occurs through the night. You may be thinking, that you progress from stage 1, to 2, to 3 and to REM before waking up but this is not the case. Rather, you cycle through all 4 in the first 70-100 minutes of sleep, then the following cycles repeat in loops lasting around 90-120 minutes. As each cycle occurs, REM sleep increases while stage 3 decreases meaning that the first half of the night is the sleep which helps to rejuvenate your mental abilities and feelings of being refreshed, while the latter half seems more important for learning and developing new skills. We will return to how sleep impacts this later.

The structure of these various sleep cycles is described under the term 'sleep architecture', and it changes across your lifetime in profound ways. Here we will speak only in terms of adult sleeping patterns, to avoid going into more detail than is practical.

Perhaps the most efficient way to present information about sleep patterns is via a hypnogram, which is a readout created by combining information from 3 pieces of equipment – namely the eletrooculograph which measures eye movement, the electroencephalogram (EEG) you encountered earlier and an electromyograph which detects muscle innervation as a surrogate for movement.

Below is a sample hypnogram – notice the relative length of REM and Stage 3 sleep as the night progresses.

Fig. 73



Note: Sleep doesn't function in a stepwise 1, 2, 3, REM pattern but rather 1, 2, 3, 2, REM for the first cycle, followed by cycles which either cycle as 2, 3, 2, REM (missing the falling asleep stage) or 1, 2, 3, 2, REM. Stage 2 is repeated twice per cycle, which is why it makes up so much of your total sleep.

As you can see on the above graph, due to the length of time an average adult sleeps and the duration of each cycle, most individuals will experience 5-6 sleep cycles per night if they have rested well. Waking for a short time during the night (as per the above during REM sleep) is not really a problem as waking during REM sleep allows you to slide straight into your next cycle, but if you are awake for a long period you risk missing a cycle and losing out on stage 3 and REM sleep.

So now you understand how you sleep at a basic level, let's briefly run through the key points:

- Sleep is a multi-stage process involving cycles between REM and non-REM sleep
- Non-REM sleep can be further subdivided into 3 stages (or historically 4) which are numbered in ascending order in line with 'deepness' of sleep
- Each stage can be tracked and defined judging by the frequency and amplitude of waves measured by an EEG during sleep, though due to the continual nature of these waves the categorisation is inherently somewhat arbitrary
- Each stage has a specific purpose. Stage 1 is the falling asleep stage which prepares you for sleep, stage 2 seems to be important for memory consolidation and sleep protection and stage 3 seems important for rejuvenation
- REM sleep seems important for complex learning but also infant development
- Each cycle lasts around 90 minutes
- Sleep is not a state of rest which occurs because your brain shuts down, but is rather an important state caused by the brain, and during which the brain is still active

- Waking briefly during REM sleep is not an issue but overly stimulated individuals may wake during this time and stay awake, leading to lost sleep
- Waking during stage 1-3 sleep leads to progressively worst sleep inertia

As we hope this section has shown you, sleep is a highly dynamic and complex process which potentially plays a number of roles – but why do we do it?

7.9. Why do we sleep?

An average adult needs around 7-9 hours of sleep per night meaning that with the average UK life expectancy being 79.1 for boys born between 2012-2014 and 82.8 being the life expectancy for girls born during the same period, we will spend on average over 26 years of our life asleep. Sleep is a huge part of being a living organism with every single known creature displaying some kind of sleep-like behaviour but despite the obvious importance, perhaps one of the oddest facts about sleep is that there is no solid consensus as to what the purpose is. Surely it would make far more sense from an evolutionary perspective to be able to eat, explore and procreate 24 hours per day, and a sleeping individual is one which is obviously in more danger than one which is fully alert. To this latter point, you could state that being still and hidden away during the hours of darkness may be protective but you only have to look to nocturnal animals to see that hiding in the dark is at best an incomplete picture.

There are three main theories as to why we sleep referred to as the restorative, adaptive and energy conservational theories of sleeping. We'll explain each here in turn:

7.9.1. Restoration

This is the theory that an organism needs to rest, repair and replenish its energy stores after a period of energy consumption and tissue breakdown (being awake). During sleep a large number of genes in the brain alter their expression patterns, a process which is the same across a number of species including fruit flies, rodents and birds and a number of different brain regions. These genes seem to encode proteins important for protein synthesis, intracellular transport, cholesterol synthesis and other basic cellular functions in the neurons for which expression was altered, indicating a replenishment of important macromolecules there. In contrast, being awake is associated with the expression of different genes including those responsible for RNA processing and the production of molecular chaperones which aid in the folding of proteins (both of which mean that protein synthesis is being performed in the brain during the waking period).

This all suggests that the brain uses sleep as period of recovery, leading up to a subsequent period of wakefulness. What it does not suggest, however, is that sleep is a generalised recovery period because whole body and muscle protein synthesis is typically suppressed during this time owing to the extended period of overnight fasting. There is, of course, the case that protein consumption in the middle of the night will re-stimulate muscle protein synthesis during sleeping hours (in much the same way as consuming sufficient leucine would stimulate MPS at any other time of day, as discussed in module 2) but it's extremely unlikely that this is something evolutionarily relevant.

7.9.2. Energy conservation

Wakefulness across all animals peaks at times of performance and food availability and sleep peaks at the opposite times. Animals which see by daylight and/or eat animals which are present at daytime are awake during this time and sleep when their comparative food availability is lower, while the opposite is true of nocturnal animals. This has played a large role in the evolution of the theory that animals sleep to conserve energy when they are not capable of consuming as much as they may need. This is supported by the fact that your metabolic rate is suppressed during non-REM sleep and the fact that your brain (a major energy user) reduces activity.

This theory has some key flaws, however. Firstly, the metabolic reduction during sleep only happens during non-REM sleep – during REM sleep your metabolic rate increases which would have no adaptive benefit if energy conservation was the goal. Furthermore, the actual reduction in metabolic rate, while being significant and reliable enough to measure and use as a diagnostic tool, is unlikely to actually impact on energy needs as much as you might think. Your metabolic rate drops by around 15% at most during sleeping hours (unless you are in late pregnancy where the difference is smaller) which in real terms means you might use around 100-150kcals less during the night. A very small difference.

7.9.3. Information processing and synaptic plasticity

This is the theory that sleep is vital for memory, learning and processing information, evidenced by the fact that sleep deprivation rapidly decreases these factors but also by a number of physiological events which occur during sleeping hours.

When individuals are given a memory task and then allowed to sleep before being tested, they reliably perform better at the task than groups who have undergone the same procedure without sleep (simply with rest in between learning and testing). Neuroimaging studies (a more in-depth analysis than EEG which can map out active brain areas) shows that at least some of the brain activity seen during REM sleep correlates with the brain areas involved with a task learned during prior wakefulness (so if you learn something then sleep, the brain area you used during learning is active during REM sleep) which hints at memory consolidation. How does this work?

When you learn something, synapses between neurons are created which reinforce your new knowledge, movement pattern or skill – a process called neural plasticity which is the process of physically altering brain connections to consciously learn. During waking hours, a large number of synapses are created in accordance to a task, some of which are relatively weak, in a process called Long-Term Potentiation (LTP). LTP is not sustainable, however, because an excess of connections leads to a 'noisy signal' and takes up vital space that may be needed for other new insights. During sleep, there is a synaptic downscaling which consolidates these memories to leave only the most robust connections. You may experience this when you read something which only half makes sense, go to sleep and then re-read it with perfect clarity.

Evidence for this process lies in the following – Brain Derived Neurotrophic Factor which is a Growth Factor (growth factors are chemicals which bind to specific cellular receptors to cause

growth), activity regulated cytoskeleton-associated protein (a plasticity protein), Nerve Growth Factor and P-CREB (Phospho-cAMP response element binding protein) which is important for spatial memory, are all increased proportionally with sleep debt, indicating that an increased amount of time awake leads to an increased amount of non-consolidated neural plasticity. Furthermore, the higher these markers become, the longer you spend in stage 3 sleep which is the stage most associated with net consolidation.

This is a very strong theory, though it still raises some questions. For example, the above theory focuses only on the parts of the brain which form from the telencephalon (the telencephalon in humans develops during the pre-natal period into the cerebral cortex and the basal ganglia – two of the most important brain areas). Some animals do not have a telencephalon such as fruit flies, but these animals still display sleep or sleep-like behaviour.

Because no one theory is wholly correct, and because all three have good evidence to justify them to at least some degree, it's very likely that the truth is all three played a small role during the evolution of sleep. Whatever the reason why we sleep, it's evidently important and your body agrees. Sleep is one of the strongest urges we have, and maintaining sleeplessness for more than a few days is extremely difficult. There are two primary drivers to sleep, the circadian pathway and the adenosine pathway which are both fascinating and intricate. Let's look at those now.

7.10. What makes us sleep?

Of the two pathways thought to control sleep, it is far more likely that you will have heard of the circadian rhythm pathway so it is here that we will start. Circadian (sir-KAY-dee-an) comes from the Latin Circa Diem which means "around a day", because a circadian rhythm runs in approximately 24 hour cycles. Crucially, a circadian rhythm is endogenously determined, meaning that it would operate without external cues, but it is entrainable which means that some external cues influence it, though it will operate at different temperatures.

The circadian rhythm which operates to control the human sleep/wake cycle is an example of one such rhythm. You may have experienced yourself that your body will want to be awake during certain approximate hours and want to sleep during other ones, and the frame never shifts all that much in one direction or other. However, after a certain period of adjustment which is colloquially known as jet lag, you can indeed move your waking frame to a different place in the cycle. This is a perfect illustration of the in-built yet modifiable nature of human circadian cycling which controls not only sleeping and waking but also a number of other aspects of physiology and behaviour according to the day/night diurnal pattern in which we live. Below is a table indicating the changes which occur due to circadian rhythmic control in humans.

Fig. 74

Behavioural and physiological changes in humans over 24 hours	Day	Night
Mood	Higher	Lower
Core body temperature	Higher	Lower
Urine production	Higher	Lower
Growth hormone	Lower	Higher
Blood pressure	Higher	Lower
Alertness	Higher	Lower
Melatonin	Lower	Higher
Cortisol	Higher	Lower
Sleep	Lower	Higher

Here you can see that a huge number of factors alter throughout the 24 hour cycle. For example, your core body temperature will vary by about 1 degree across the day, starting to dip at 10pm at night in anticipation of sleep, it will hit its lowest point at 4am and then start to rapidly increase in anticipation of waking up. This isn't just small physiology, though – our ability to perform mathematical equations between 4am and 6am is so poor that it's considered worse than it would be at another time of the day, after you had consumed enough alcohol to be legally classed as drunk. Similarly, although it is possible to force yourself to stay awake your mental alertness at 2am will never be what it would have been during daytime – it's no coincidence that the Chernobyl disaster occurred during a night shift and that there is a disproportionate amount of car accidents at around 3am than at any other time of day, even when fatigue is taken into account.

Interestingly, however, if you manage to stay awake all night you will start to feel better and would perform better in cognitive tests at around 10am, just like you always would. This shows that the 2am disasters and 3am car accidents cannot just be down to fatigue or tiredness – this is under some form of control.

As you have just learned, these rhythmic changes are controlled endogenously by something within us. Interestingly, although the mechanism by which they are controlled changes the same holds true for life forms as distant from us as Synechoccus elongates, also known as cyanobacteria which display behavioural changes according to the day/night cycle even without the influence of light or temperature. This tells us that 24 hour cycling of behaviour is extremely well conserved across evolutionary time, most likely as this allows an individual to maintain proper sleeping and waking hours despite variable periods of light and darkness according to seasonality and location. But the question remains – how is the 24 hour cycle controlled in humans, and how can the environment entrain it?

7.11. The SCN

Evidence for the fact that the human sleep/wake cycle is innately controlled comes from studies in participants who live for the duration of the experiment in an environment removed from external cues. It would be very easy to argue, for example, that we wake and sleep according only to light conditions or temperature but that does not seem to be the case. In these experiments caves or bunkers are often used to remove all natural light or temperature interference. In one such study participants underwent a 5 day period of living in dim artificial light which included radio or TV usage, thus allowing them to have some temporal cues as to the time, and when this was the case they maintained a 24 hour sleep/wake cycle. After these cues were removed the subjects started to awaken later in the day and each whole cycle started to last around 28 hours rather than the usual 24, but it still seemed that the subjects lived in a rhythmic fashion and when cues were restored they reverted to a 24 hour cycle almost immediately. This indicates that a cyclical process is occurring but it is imperfect in isolation as we will discuss later. Below is a graph which shows their sleep/wake periods according to the availability of temporal cues (the blue arrow on each line is an indication of rectal temperature – remember that it's not only waking and sleeping which is controlled by a circadian rhythm).

Fig. 75

(Image taken from Purves D, Augustine GJ, Fitzpatrick D, et al., editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. The Circadian Cycle of Sleep and Wakefulness. Available from: https://www.ncbi.nlm.nih.gov/books/NBK10839/).

Many regions in your body are operating in a rhythmic fashion, and researcher's hypothesise that every single cell within your body has some amount of rhythmic action, varying hour-to-

hour over a given period. As a result, your heart, liver, digestive tract and many other areas all 'know' when it's night or daytime, but if this was left unchecked and able to run freely it would mean that trillions of clocks would need to line up independently – somewhat unlikely, so what's controlling it all? Deep inside your brain is one of the oldest parts, evolutionarily speaking – the hypothalamus. This area is responsible for an enormous amount of our major functions by being the area which can connect your nervous system to your endocrine system. For example, in order for your body to release the hormone cortisol, the hypothalamus receives a signal from your nervous system then sends a signal to the pituitary gland, which in turn signals your adrenal glands, which ultimately secrete cortisol into the bloodstream.

Inside this brain region, close to the optic nerve are two small areas totalling around 20,000 neurons called the suprachiasmatic nuclei (SCN), and it is this area that is referred to as your 'master body clock'. This is an example of an oscillator which is distinct from the usual homeostatic mechanisms about which we have spoken so far. A homeostatically regulated system always tries to fight to return to or stay at a predefined ideal, but an oscillator instead attempts to move towards something in particular. An example of a homeostatic system is a thermostat which turns on heating when the temperature drops but an example of an oscillator is a clock on your wall, always moving in one direction. So how does this group of neurons perform this task?

The neurons in the SCN are able to maintain their 24 hour cycle independently of each other and your body. When isolated and placed in a culture in a lab, a single SCN neuron will create spontaneous action potentials at predictable times of day despite being disassociated from any other neurons or other bodily systems, which means that these action potentials are created within the SCN itself. The way that these neurons are able to do this comes down to a gene expression feedback loop.

In the nucleus of the neuron, like that of every other cell, is a complete copy of your DNA. On that DNA are nucleotides in a particular order, with certain sections of nucleotides being called genes. These genes can do a number of things, one of which being coding for proteins. 2 proteins which are coded for by genes expressed within the nucleus of SCN neurons are PER proteins and CRY proteins. Two other proteins known as BMAL1 and CLOCK bind together and enter the nucleus of the cell to promote the transcription of PER and CRY genes. The resultant PER and CRY proteins combine to create a dipepdide which enters the nucleus and inhibits the action of BMAL1 and CLOCK, thus preventing its own expression. As PER and CRY build-up, their transcription decreases until you end up with a lot of PER and CRY but very little synthesis.

Over time, the PER:CRY complex degrades and allows CLOCK and BMAL1 to start to do their job again. This whole cycle takes around 24 hours and this is the molecular central bodily clock. The SCN then uses various signals to communicate with other areas of the body, aligning the clock that each of those has. It's not that the SCN actively makes your heart beat differently at day and night, it's the case that the SCN tells your heart when day and night is so that it's able to change its beating pattern accordingly. When the SCN is removed or damaged, peripheral structures still display a rhythmic pattern of activity but they are all dis-regulated.

Furthermore, alterations in the genes which code for these proteins (amongst others) are what drive some people to be morning people or evening people. This is not due to laziness, preference or practice – it is simply the case that some people operate better or worse around 2 hours later or earlier than others.

The SCN is obviously manipulated by certain inputs. If this was set in stone you would not be able to recover from jet lag and you would not be able to alter your sleeping pattern according to different times of year or perhaps different working conditions requiring you to stay awake during the night. The wake/sleep circadian rhythm and more broadly the action of the SCN are entrainable owing to their sensitivity to light exposure.

The SCN receives information from your retina. Until recently it was thought that your eyes contained only rods and cones, as these are the photosensitive cells which can translate light energy into visual information, but studies using completely blind individuals indicated that the ability of a person to visually experience light was not a prerequisite for this. Rather, specialised light-sensing, non-visual cells on your retina translate light into information which is used by the SCN to calibrate to the day/night conditions in a given location. The removal of this calibration is why the individuals in the experiment above found that their sleep/wake cycle became dis-regulated.

Coming back to focus only on sleep – how is it that the SCN controls the sleep/wake cycle? The SCN calibrates to the current daytime/night time cycle and then signals for the pineal gland, a small, pinecone-shaped endocrine gland in the brain, to produce melatonin which has a sleep-promoting effect, but also, via a number of cascades, impacts on various other phenomena influenced by circadian rhythms including immune function, antioxidant defence action and glucose metabolism. Though the exact mechanism for this action of melatonin remains to be comprehensively elucidated, the fact remains that melatonin secretion corresponds precisely to the onset of sleep, while reduced melatonin secretion corresponds with wakefulness. Not only this, but impaired melatonin secretion is associated with insomnia while exogenous melatonin can induce sleepfulness.

Please note that it is not only melatonin involved in sleep. Many other neurotransmitters and hormones (remember, the difference between a neurotransmitter and a hormone isn't within the chemical itself but the location of it – neurotransmitters impact neurons, hormones impact other cells, so some chemicals are both) are involved in sleep and wakefulness. The full extent of this is beyond the scope of this manual, but briefly:

- Glutamate is the most commonly found neurotransmitter in the brain, and the primary excitatory neurotransmitter, meaning that it 'activates' neurons and promotes the production of action potentials. Glutamate seems to regulate sleep duration to some degree, but it can also be converted into the following chemical (GABA)
- A neurotransmitter known as GABA is released to suppress action in the posterior hypothalamus. This area is responsible for wakefulness and so GABA secretion correlates with the onset of sleep

- The neurotransmitter orexin, produced in the hypothalamus, seems responsible for the regulation of many different aspects of sleep including processes involving dopamine, noradrenaline, histamine and acetylcholine. An impairment of orexin production is responsible for a lot of instances of the sleep disorder narcolepsy, which sees people becoming overwhelmingly tired at seemingly random parts of the day
- Dopamine, the 'reward' neurotransmitter, seems to regulate sleep/wake cycles, potentially by downregulating melatonin
- Acetylcholine seems to be important for REM sleep. The areas in which it is used as a key neurotransmitter are associated with the onset of REM sleep, and it's highest overall during REM and wakefulness, but lowest during non-REM sleep
- Noradrenaline and serotonin both act to instigate wakefulness in the morning, working to increase and then maintain arousal and cortical function
- Cortisol is often referred to as 'the stress hormone' as it is released from the adrenal glands (small glands sitting on top of (ad-) your kidneys (-renal) in response to stressful situations. Cortisol's main role is to promote glycogenolysis, lipolysis and protein breakdown to release glucose, fatty acids and amino acids into the bloodstream to use during a fight or flight scenario. Cortisol, however, is also partly responsible for waking you up in the morning. The usual secretion pattern for cortisol is to be high in the morning and then progressively reduce during the day until sleep, of course intermittently spiking in accordance with stress, exercise and other stimuli in between
- Growth Hormone Releasing Hormone's (GHRH) main role, as the name suggests, is to promote the release of Growth Hormone (GH). It's released during sleep and correlates to deep sleep. GHRH promotes this deep sleep, but it's product, GH, can also help to maintain normal structure and metabolism. GH deficiency can lead to muscle loss and a relatively higher level of fat mass than is seen in individuals who have healthy GH production and though poor sleep is unlikely to cause clinically low GH secretion this is worth consideration

In sum, the SCN regulates the internal clock of every cell within your body via interactions with various endocrine structures including but not exclusively the pineal gland, which releases melatonin around the time that it starts to get dark and the adrenal glands which promote the release of cortisol to instigate wakefulness. The way that this is calibrated is through specialised retinal cells which are able to relay information about light conditions to the SCN, but the SCN itself is self-regulatory to some degree also.

Though this is fascinating and it answers a lot of questions it still leaves a few unanswered.

If sleep is regulated solely through circadian rhythms, why is it that after a few days of reduced sleep you feel the need to catch up? If it's only circadian rhythms why is it that after a particularly difficult day you sleep much more deeply or for longer? Let's look at the other, perhaps more intuitive mechanism for the manifestation of sleep.

7.12. The homeostat sleep pathway

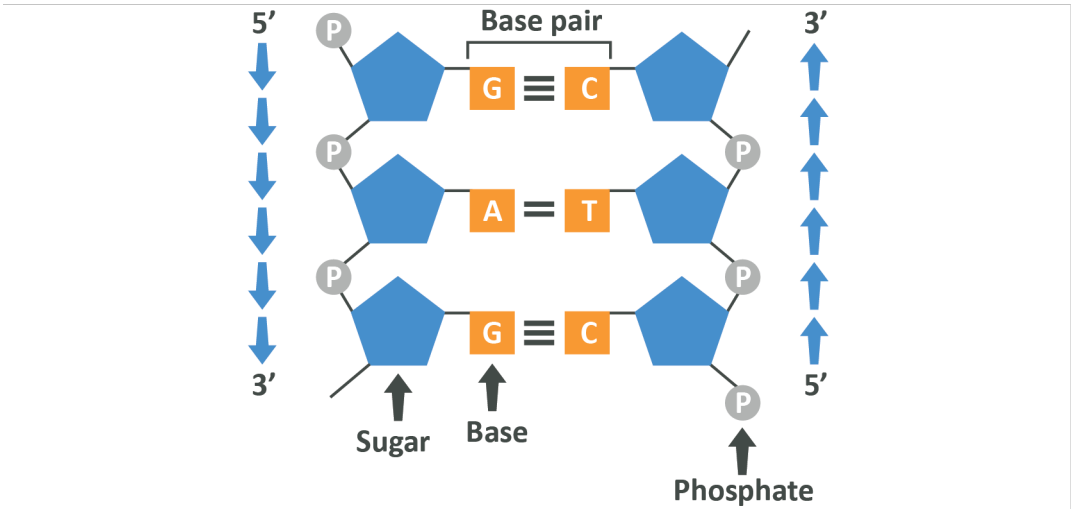
The homeostat sleep pathway is the one which makes a great deal more sense from a simple logical standpoint. The longer you have been awake, the more sleep pressure you will experience, but because this pathway works in tandem with the circadian pathway you are able to stay awake during the day despite being fatigued, and you are able to go to sleep at night even if you slept in until 1pm. Of course, this simplistic view is lacking somewhat – if you are extremely fatigued you are going to struggle to stay awake during the day in any warm, dark, comfortable environment and you may struggle to sleep at night if you take a long nap at 6pm, but the general trend holds true thanks to a combination of both of these factors. Let's explore the homeostat mechanism, which takes us back to module 2 and ATP.

Adenosine Triphosphate (ATP) is the 'energy currency' of the body. We break down glucose and fatty acids to make it, and then we break the weak phosphate bond to release energy to perform functions. This results in ADP and a spare phosphate molecule. Respiration then uses food energy to replace the phosphate and recycle ATP.

However, this isn't the only possible outcome, though. Adenylate kinase is an enzyme which can take a phosphate from 1 ADP and add it to another, leaving 1 Adenosine with only 1 phosphate – this is Adenosine Monophosphate (AMP). ADP can also be broken down to AMP to release energy. This AMP is then broken down into free adenosine by enzymes called ecto-5'-nucleotidase in the cytosol of a cell. Finally, adenosine can be produced by the breakdown of RNA, which is a chain of sub-units similar to DNA, used in various different cellular actions including DNA transcription and translation into proteins.

Adenosine is a nucleoside, meaning that it is a nucleobase linked to a sugar molecule. Nucleobases are the units of DNA code, as you see in the image below.

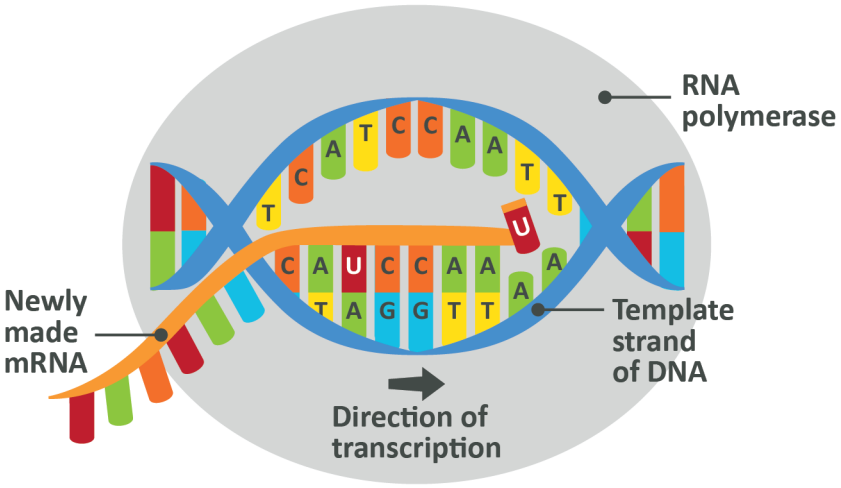
Fig. 76



What you are looking at here is a simplified image of DNA structure. Each side has a number of phosphate molecules (P), linked to a pentagonal shape which represents a sugar, ribose and a base denoted A, T, G or C. This is the DNA code. The 'A' stands for adenine (along with guanine, thymine and cytosine – uracil is another nucleobase found only in RNA), which when combined to the ribose sugar becomes adenosine. During protein synthesis, RNA strings are

formed when the cell 'reads' the DNA code and matches corresponding RNA nucleobases to DNA bases. In the image below, the DNA (blue) is separated from each other and then the RNA (red) is created, unit by unit, in accordance with a very simple pattern (U corresponds to A, A to T, C to G and G to C) by an enzyme called RNA Polymerase in a process called transcription.

Fig. 77



This new RNA (called messenger RNA or mRNA) is then used by cellular machinery to piece together amino acids which the DNA 'codes' for.

This is not wholly important for our purpose here and you don't need to remember it, but it should give you an understanding of both the importance of adenosine as a molecule, and the incredible way in which your body is able to use the same few substances to perform a huge number of different functions.

7.13. How adenosine is involved with sleep and wakefulness

Free adenosine is, as you have just learned, produced in your cells via the processes involved with energy production (as you may have guessed, it can also be produced by the breakdown of RNA). As such, the amount of adenosine produced within a cell is directly proportionate to the amount of work that the cell has done. This includes neurons and the closely associated cells also found in your brain, glial cells. As you have learned, your brain is an obligate glucose user and also a highly energy expensive mass. If you look back to module 1 you will see that it uses more calories per hour, per pound, than almost any other tissue which means that a lot of ATP is being broken down during the day, especially if that day requires a great deal of mental work.

Adenosine is readily broken down to adenine and free ribose under normal conditions by the enzyme adenosine desaminase, but during wakefulness the breakdown of glycogen and glucose in the brain, therefore the usage of ATP far outreaches this and adenosine levels gradually build-up during wakefulness. Adenosine concentration within the neuronal cytoplasm increases, meaning that a concentration gradient starts to occur and the adenosine eventually crosses the membrane barrier and enters the extracellular space within the brain.

The adenosine can bind to neuronal synapses and adenosine receptors. There are a number of different ways in which this induces sleep, including:

- When adenosine binds to one form of adenosine receptor in a synapse, it initiates a cascade of effects resulting in the reduced secretion of various neuro-transmitters associated with wakefulness including but not limited to dopamine
- When it binds to another form of adenosine receptor, it initiates a cascade of events which inhibit the release of factors which themselves inhibit the secretion of GABA

Injecting exceedingly small amounts of adenosine into the brain of rats induces sleep, meaning that we can safely postulate that adenosine is indeed involved directly with sleep onset. Interestingly, one of the area's most strongly associated with adenosine build up during the day is, as you might expect, the frontal cortex which is the region involved with complex cognitive tasks. This is why you feel extremely tired after hard study or learning, and why you sleep so deeply after these activities.

During non-REM sleep (especially stage 3 sleep), brain activity is heavily reduced meaning that adenosine clearance is significantly higher than production, and so you wake refreshed. During REM sleep you use a lot of ATP within your brain for the activity associated with this stage to occur but because this stage is relatively short, you wake refreshed after a long sleep. This is why incidentally, we mentioned that REM sleep deprivation does not seem to create the feeling of fatigue that inhibition of stage 3 sleep does.

It follows that adenosine build up is not something that will necessarily go away over time, nor is it something that will be reduced by one night of good sleep if this follows a period of deprivation. One study took two groups of participants – 1 group had two nights of 8 hour sleep while the other had a night with 2 hours of sleep and a night with 8 hours of sleep – though the second group slept well during the recovery sleep, they still displayed cognitive difficulties during a prescribed task on day 3. This indicates what should now be somewhat obvious, the build-up of adenosine in neuronal synapses is cumulative and therefore regular good sleep rather than the usual pattern of midweek poor sleep and weekend lie ins is a far more preferable approach.

As a final note, this is the primary mechanism by which caffeine exerts is effects alongside some others, including interaction with GABA receptors and enzymes involved with the breakdown of a molecule known as cAMP (that, in the brain, has involvement in the production of noradrenaline and norepinephrine amongst others, therefore raising heart rate and alertness). Caffeine effectively blocks adenosine receptors and therefore reduces adenosine's ability to make you feel fatigued for a certain period of time, and in a very effective manner. Not only this, because some of the areas affected by adenosine are typically related to dopamine this can create a mood-boosting effect. This is not perfect, however.

Firstly, habitual caffeine intake does not remove adenosine from the brain, rather it prevents it's binding to receptors. Once caffeine is metabolised and becomes inactive the adenosine is able to re-bind and fatigue sets back in. Caffeine consumption can therefore 'mask' a sleep debt but this is only temporary. As you have seen, reducing fatigue is not the only function of

proper sleep and therefore using caffeine to mediate this behaviour can have far reaching affects. Moreover, chronic and habitual caffeine intake can result in an up-regulation of the adenosine system, meaning that over time you need more caffeine to have the same affect and, of course, upon cessation the symptoms of fatigue come on much more quickly.

Fortunately, individuals will adjust to a lower caffeine intake after a few weeks but this period can be uncomfortable, creating headaches amongst other things. Because of the ability of caffeine to mask a sleep debt and improve your mood by stimulating dopaminergic activity, it can be considered to be somewhat addictive and it is possible to fall victim to caffeine dependence syndrome. This will be mentioned to some degree later in this module but for now the take home is that, although caffeine can have obvious benefits, those benefits are not without side effects and habitual high intakes should possibly be avoided.

So far, we have discussed the role and mechanism of sleep, but how much do we need, and what happens when we don't get enough?

7.14. Sleep deprivation, more common than we think?

According to the Sleep Foundation, individuals need to get the following amount of sleep per night to be in peak health:

- **Newborns (0-3 months):** 14-17 hours
- **Infants (4-11 months):** 12-15 hours
- **Toddlers (1-2 years):** 11-14 hours
- **Pre-schoolers (3-5):** 10-13 hours
- **School age children (6-13):** 9-11 hours
- **Teenagers (14-17):** 8-10 hours (teenagers really do need to have a lie in!)
- **Younger adults (18-25):** 7-9 hours
- **Adults (26-64):** 7-9 hours
- **Older adults (65+):** 7-8 hours

This is unfortunate because according to the National Sleep Foundation Bedroom Poll of 2013 adults in the UK only get an average of 6 hours, 49 minutes sleep while needing 7 hours and 20 minutes. 51% report getting less sleep than needed on workdays, and only 42% report getting a good night's sleep most nights. This is the average and it's not great, but what happens if you get progressively less sleep?

Sleep deprivation is a complete lack, or suboptimal amount of sleep either acutely or over a long period, though sleep restriction is probably a more accurate term for incomplete rather than completely absent sleep. As you read earlier, sleep occurs in cycles and each individual's cycles will last 90-120 minutes or so. In order to have a full, restful night's sleep the ideal situation is to have the correct number of cycles for you (usually 4-5) and allow them to run to completion. Waking up and feeling tired is one obvious sign of some degree of sleep deprivation but this could in fact have multiple causes:

- You are indeed sleep deprived, therefore you have not undergone enough stage 3 sleep to allow the complete clearance of adenosine, and so you still feel fatigued
- You are indeed sleep deprived and although you had the optimal amount of sleep last night you have built up a sleep debt over time to mean that you need multiple nights to catch up
- You are not sleep deprived, but in fact woke up during non-REM stage 2 or 3 sleep and therefore experiencing sleep inertia which will pass. This is the cause for the often made claim that people have slept too much, and why you may wake up at 5am and feel great (because you woke during REM sleep), but fall back asleep until 6:30am when your alarm goes off and feel terrible even though you have slept for longer. This sleep inertia typically dissipates after up to 30 minutes

This also goes the other way, if you have woken up feeling great but have not slept for long, you may have simply woken during REM sleep at the appropriate time of day and, according to your circadian rhythm you will wake and feel alert. This is often short-lived, however, and you are likely to feel a great deal of sleep pressure earlier in the day than you usually would. In general, sleeping from 7-9 hours as an adult is needed, though of course there will be outliers at either end of that range. Aiming to sleep well for this duration is the most effective way of avoiding sleep debt and it can be assumed that sleeping for much less than this will lead to a degree of sleep deprivation even if you subjectively feel OK (especially if you habitually drink caffeine upon waking).

There are three primary causes of sleep deprivation as detailed below:

Fig. 78

Type of sleep reduction	Causes	Comments/examples
Commonly observed reduction in sleep time	Daily sleep time reduction below the level an individual needs	This is common in contemporary lifestyles
	Single omission of a full night's sleep, or the majority of a night's sleep	This could be due to being on duty at work, partying or studying
	Shifting sleeping period in relation to the circadian rhythm, resulting in reduced and poor sleep	In shift workers and regulars on long-haul flights, the different sleep stages become dis-regulated along with a number of other physiological functions. This is largely unavoidable
Considerable reduction in sleep time	Wakefulness prolonged to several days	Experimental conditions, torture, tribal rites
	Selective sleep-stage deprivation	Seen in experimental conditions
	Total prolonged sleep deprivation	Only in experimental animals. Total deprivation in rats causes death after 16-21 days
Sleep reduction due to pathology	Depression, anxiety	In these disorders, sleep onset is suppressed, leading to reduced sleep time

Substance abuse or addiction	Alcohol eliminates REM sleep, sleep medication reliance can result in physical dependence
Somatic disease or pain	Restless leg syndrome, sleep related breathing issues (sleep apnoea) and some metabolic diseases can impact sleep severely
Primary sleep disorders	Genetic determinants intensified by old age and improper sleep hygiene, chronic stress, traumatic experience, difficult life situations and inadequate subjective assessment of the duration of one's sleep can lead to insomnia

The longest recorded period of sleep deprivation in a volunteer study is 203 hours (around 8.5 days). During this period, the subjects showed a complete lack of usual alpha wave function, and in fact waking brainwave activity resembled that of stage 1 sleep. The longest period of wakefulness on record at the time of writing is 268 hours, held by a 42 year old man from Cornwall, England.

While this is extreme, multiple-day waking experiments have been performed with some amount of regularity. The results from one can be found below:

Fig. 79

Duration of deprivation	Symptoms
Night 1	Most people are capable of withstanding 1 night of complete sleep deprivation, although discomfort may be experienced. 24 hour sleeplessness does not alter behaviour. However, tremor and increased muscle tone are observed which can lead to impairment in precise movements
Night 2	A feeling of fatigue and stronger need for sleep is persistent, especially between 3-5 am, during the time when body temperature is at its lowest
Night 3	Performing tasks that require concentration and calculating may be impaired, particularly if these are dull and repetitive. The volunteers become irritated and impolite in any instance of disagreement, potentially as areas of the brain responsible for emotional regulation are inhibited. During early hours participants experienced an overwhelming need for sleep, and remaining wakeful is only possible with the help of observers who wake the volunteers up if necessary
Night 4	Prolonged microepisodes of sleep occur: the subjects discontinue their activities and stare into space – delta waves are recorded via EEG even though subjects are apparently awake. Sleep microepisodes impair performance of the tasks that require attention over a prolonged period

	of time. Subjects may also experience perception disorders, illusions, hallucinations, irritation, inaccuracy and 'the hat phenomenon' where a waking participant will feel a pressure on their head like a hat, and may try to take it off
Night 5	The symptoms become more intense and include disturbances in reasoning and orientation, visual and tactile hallucinations, fatigue, irritability and delusions. The subjects may exhibit distrust, suspecting that someone attempts to murder them is a characteristic symptom at this stage. Intellectual and problem-solving skills are considerably impaired
Night 6	Participants develop symptoms of depersonalisation and are no longer capable of interpreting reality. This syndrome is known as sleep deprivation psychosis (which subsides after a sufficient time of sleeping)

Most people will never be awake this long. In fact, it would be very unusual for someone to stay awake for more than 36 hours at any point in their lifetime (skipping 1 full night of sleep) but recent research has indicated that alterations to behaviour and experience accumulate across days of partial sleep loss, resulting in symptoms similar to those associated with acute 1-3 day restriction.

This topic is enormously complex because, as you have seen, sleep is not uniform and therefore when people are restricted to shorter than optimal amounts of sleep, each stage is differentially affected. Adults restricted to 4 hours sleep per night experienced a reduction in non-REM stage 2 sleep and REM, and almost absent stage 1 sleep but experienced no difference in the duration of non-REM stage 3 sleep, and actually saw an increased intensity of it compared to those sleeping 8 hours. With that said, this did not mediate cognitive impairment or other symptoms of sleep deprivation.

Additionally, there is data to suggest that while the range of 7-9 hours may be ideal and while reducing sleep to 6 hours will impair subjective 'freshness' upon waking, after a short time this effect disappears and there are no other symptoms, indicating a form of adaptation.

On top of this complexity is a sparsity of actual data. While studying complete sleep deprivation is comparatively simple, to perform experiments to test cumulative sleep debt, subjects would need to be monitored for 24 hours per day for 1-3 weeks in a lab. Because of this, only a few studies have been done. What must be noted, however, is that before these studies were done, anecdotal research suggested that the real sleep need was 4-6 hours of 'core sleep' and that anything beyond this was optional. More recent data, what little of it there is, refutes this. Daily insufficient sleep, contrary to older belief, gradually amounts to a sleep debt with the following symptoms.

7.14.1. An increased tendency to involuntarily fall asleep

This is probably the most obvious result of sleep insufficiency, but it causes you to find staying awake difficult. There is a dose-response relationship starting at around 6.75 hours per night of increased risk of falling asleep, with risk increasing as hours of sleep decline. This is accompanied by oculomotor activity alterations, with involuntary eye closure and eye rolling being part of the initial sleeping transition. The less sleep you get, the more often your eyelids will 'force' themselves closed which has obvious consequences for driving but also performance on tasks involving vigilance.

7.14.2. Behavioural alertness and cognitive performance

Performance on tests for psychomotor vigilance (a sustained-attention, reaction-timed task) is so sensitive to reduced sleep that your score on these tests is used as a marker of fatigue. Sleep deprivation increases behavioural lapses during performance which increase in duration from 0.5-10 seconds, and are thought to reflect 'microsleeps'. These microsleeps are thought to reflect wake state instability, and are likely caused by the action of adenosine on neurotransmitters such as dopamine associated with maintaining wakefulness. Again, these can be exceedingly dangerous when driving.

In one study on truck drivers, those restricted to 3, 5, 7 or 9 hours in bed had their reaction times tested and those in the 3 or 5 hour group displayed a marked decline over the 14 day testing period. Another study kept participants in a lab for 20 days, and for 14 consecutive nights they were only afforded 4, 6 or 8 hours of sleep. Not unsurprisingly the 4 and 6 hour groups (but not 8) displayed a poorer performance on psychomotor vigilance tests and reduced cognitive output. What may be surprising, was that when compared to the effects of complete deprivation the results seen were equal to up to 3 nights of complete sleep deprivation, meaning that even though the participants were sleeping somewhat, their sleep debt quickly amounted to a far more impactful level than might be intuitively expected.

7.14.3. Subjective sleepiness and mood

Interestingly, while performance in various tests of reaction time and cognitive performance drop off relatively quickly from long-term sleep restriction, subjective sleepiness and mood do not. Complete sleep deprivation for 1-3 days and chronic sleep restriction both result in similar levels of cognitive impairment but while the former also comes with extreme levels of sleepiness and pronounced impacts on mood, in the latter subjects only report moderate levels of sleepiness. This indicates that it is very easy to underestimate the impact of sleep restriction and overestimate your readiness for performance at complex tasks.

7.14.4. Driving performance

As has been hinted at in this section already, sleep restriction severely impacts driving performance (real world and simulated for experimental purposes). Driving performance has been shown in numerous studies to be severely decreased (meaning more crashes) with sleep being restricted to 4-6 hours per night.

7.14.5. Altered appetite

Appetite is not something often thought about or considered to be 'real' but this is a mistake. Far from being a subjective phenomenon, appetite is a physiologically mediated process governed by your endocrine system. Two of the most impactful hormones for appetite are grehlin, considered to stimulate hunger, and leptin, considered to mediate general appetite overall. This can be conceptualised as such: leptin controls your background hunger to keep you at a given energy balance (it is leptin which decreases day-to-day when you lose fat beyond your set-point, and this is what initiates a lot of the fight back against dieting) and grehlin acts to induce acute hunger at meal times. With sleep restriction, overall leptin secretion is suppressed which in turn can lead you to adopt a higher set point, while grehlin

secretion becomes more regular and far greater upon secretion. All of this means that sleep restriction causes a greater amount of hunger, a mechanism supported by the epidemiological evidence that low sleeping hours are correlated closely to obesity and diabetes. Increased BMI is correlated with poor sleep in individuals as young as 3-8 years old.

7.14.6. Impaired decision making and self-control

One of the areas of the brain most strongly affected by sleep restriction is the prefrontal cortex, which is responsible for personality expression, planning complex cognitive behaviour and decision making. Because of this, sleep restriction makes it far harder to avoid acting on impulse which, when combined with the above appetite alterations, can severely impact your success with controlling your food intake.

7.14.7. Immune response

It is relatively well documented that complete sleep deprivation impairs immune function but the impacts of restriction on the immune system are at present poorly studied. What can be taken from the limited research is that sleep restriction to 6 hours per night results in an increase of IL-6 in both sexes and TNF-alpha in men, both of which are markers of systemic inflammation. Systemic inflammation is associated with insulin resistance, cardiovascular disease and osteoporosis, so this should not be ignored.

7.14.8. Cardiovascular health

Epidemiological (observational) studies indicate an increased risk of cardiovascular events when sleep is restricted to less than 7 hours per night but as yet no direct mechanism can be noted; there are too many co-variables such as a relationship between poor sleep and weight gain.

7.14.9. Muscle growth and loss

Sleep restriction alters the secretion patterns of testosterone, estrogen and cortisol negatively, as well as that of growth hormone (and therefore IGF-1 which is related to GH). This can result in an environment that promotes an increase in muscle protein breakdown and an impairment of muscle protein synthesis. Additionally, the restoration theory of sleep importance indicates that a reduction in sleep duration can impair the neural pathways which lead to muscle contractions and therefore exercise performance. This all adds up to meaning that exercise performance and recovery may be impaired, leading to far slower progress.

As you can see, the impacts of poor sleep can be far-reaching, but it would be a mistake to think that everyone will get every issue noted. Inter-individual variability in sleep requirements and circadian rhythm ‘settings’ is quite pronounced in some cases and this reflects on the responses that individuals experience when they don’t sleep as much as they ideally would. Sleep which is restricted to less than 7 hours leads to pronounced neurobehavioural alterations in most healthy adults but not everyone experiences issues in experimental conditions. Similarly, some people will experience severe effects with mild restriction while others will not experience any difference until restriction becomes severe. Additionally, people will experience each effect to a different degree, so while some may find

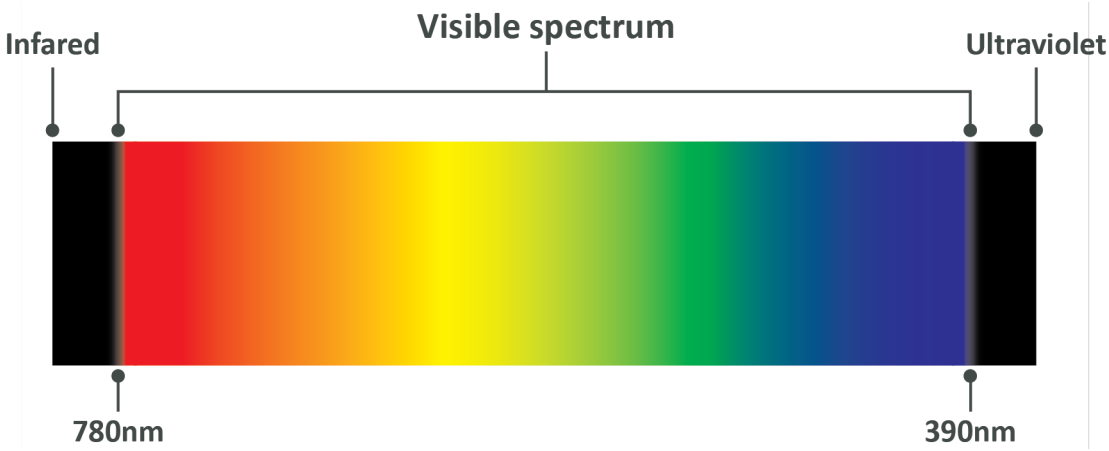
that their memory is profoundly reduced, but reaction time is unaltered, others may feel no sleepiness but notice that their reaction time is greatly increased. Interestingly and importantly, though effects change between people they seem stable within individuals across different instances of restriction and therefore become predictable, implying that they are inherent to that person's genetic makeup.

Wherever you fall on the spectrum and whatever symptoms you experience, it should be self-evident that avoiding sleep restriction is a very good idea. Sleep, however, does not come easily to some, especially in the modern world in which distractions and daily stresses are high while sleep is looked upon almost as a waste of time. Of course, there are pathologies listed in the table earlier in this module such as sleep apnoea and insomnia, as well as interactions with medications which can alter sleep and the treatment of these is largely beyond the scope of this course, but there are general principles and activities you can do to give yourself the greatest possible chance of having sufficient, high quality sleep.

7.15. Improving your sleep – light exposure

Sleep improvement doesn't start when you get into bed, it starts a long time before that. The first key aspect of getting good sleep is accurately calibrating your SCN by exposing yourself early to natural light. Exposing your eyes to natural light early in the morning has a re-setting effect on your circadian rhythm known as phase advancement which can not only wake you up due to suppression of melatonin release, but can create an earlier onset of melatonin release later in the day. Light exposure close to sleep is unadvisable, as this can both alter your SCN calibration and directly impair melatonin release meaning that late-night light exposure can impair your natural sleep processes.

Fig. 80



Visible light occurs on a spectrum of different wavelengths ranging from very short wavelength purple light to very long wavelength red light, and it seems that it is the short-wavelength blue light (which is that emitted by the sun) which creates a phase-shifting effect in your SCN via your retina. If you are unable to expose yourself to natural light in the morning (perhaps you work shifts or it's simply not light when you travel to work due to short winter days) various blue-light emitting lamps can be purchased which, when used for 5-10 minutes,

have the same effect. Just looking out of a window on a bright day can have a similar effect – ideally this should be repeated as often as is possible throughout the day.

Unfortunately, TV sets, tablets and mobile phones all emit the same blue light and this can alter melatonin release late in the day. Wearable blue light blocking goggles are available and many devices have apps which can cut the blue light out of their screens, but by far the most effective method is to turn off screens an hour before planned sleep and undergoing a relaxing night time routine.

7.16. Set a routine

Sleep is managed in part by your circadian rhythm which will start to prepare your body for sleep at roughly the same time each day, meaning that doing this each day is a good thing. While it is common for many people to sleep, and wake later at weekends, this can lead to circadian misalignment and a phenomena referred to in one research paper as 'social jet lag'.

As well as keeping sleep times relatively consistent, it pays to have a set sleep schedule which prepares you for sleep and allows you to wind down. Daily stress and busy minds which won't shut off are two of the most common subjective causes for sleep disturbance and this makes a lot of sense in the context of what you have learned.

- Daily stress causes the release of the hormones cortisol and adrenaline as well as the neurotransmitter noradrenaline, all of which are associated with wakefulness and alertness. If stress is not allowed to dissipate before going to bed this can cause difficulty in slowing brain activity down to theta wave levels. Managing stress is far beyond the scope of this course other than to say that talking to people, creating actionable plans and even writing a journal and 'to do' list for the next day can help to silence your thoughts to some degree. This is something we explore in greater detail in the BTN Practical Academy
- Along with the final point from the above, because stage 1 sleep is easily disturbed by conscious thought, going to sleep with a lot on your mind can self-evidently affect this important transitional stage and make sleep elusive. An effective strategy here is to first avoid stimulating entertainment such as exciting movies or video games within an hour of bed in lieu of reading with a dim light, and writing a journal or to do list to empty your mind of thoughts which can be picked up in the morning

7.16.1. Avoid stimulants and excessive alcohol

Stimulants such as alcohol and nicotine can cause a very alert state not conducive to sleeping. Caffeine is especially effective here as it has a half life ranging from 1.5-9.5 hours depending on your size, genes and other factors (smoking increases this). Half life in pharmacology means the time that ½ of an active compound takes to clear your system, so if your caffeine half-life time is 6 hours then taking 200mg at 10am would leave 100mg at 4pm, 50mg at 10pm and 25mg at 4am.

Of course, that is not to say that caffeine being in your system at any level will impact on sleep, but it has been documented that 400mg taken 6 hours before sleep causes sleep

disturbance, and that 300mg taken 15 minutes before bed did not impact REM sleep, but significantly reduced stage 3 sleep and increased stage 2 sleep (indicating an inability for the adenosine-clearing shutting down of brain areas to occur). Ultimately the recommendation to reduce habitual caffeine intake in the afternoon and eliminate within 6 hours of sleep (or more if possible) seems an important one.

Alcohol when consumed in moderate amounts seems to induce relaxation and therefore leads to greater onset of sleep, but doses over 0.32g/kg of bodyweight (so around 19g or 2 units for a 60kg individual) seem to impair sleep quality. A dose of 0.49g/kg in the hour before bedtime seems to impair REM sleep onset and alter wave amplitude in non-REM sleep indicating increased sleep intensity. Overall, it would seem that a small amount of pre-bed alcohol may be beneficial but larger amounts are to be avoided.

7.16.2. Ensure your bed and room is comfortable

It should be relatively obvious that a comfortable room is one which is more conducive to good sleep. Sleepfoundation.org recommend that the room should be cool to allow for the natural drop in your core temperature to occur, with 16-19C being their recommended ambient range. Your mattress, pillows and duvet should be clean, comfortable and breathable, and you would ideally have blackout curtains, minimal electronics (switched off at the mains to reduce noise and standby lights), a fan or white noise machine if you prefer these and ear plugs if needed near busy roads. Many of these are optional so ensure that whatever your room is like suits you, but consider these suggestions as a good place to start.

7.16.3. Avoid excessive liquid consumption

During the night, you transition your sleep between different stages, and during REM sleep you can often experience short awakenings, typically lasting a few seconds, which you don't remember. If, however, you are stimulated (either by caffeine, by mental stress or by light in the room) you can become fully awake and it can take a long time to get back to sleep.

Perhaps one of the biggest culprits here is needing the toilet. During the progressively deeper stages of sleep and REM sleep your urine production is switched off so as to prevent night time accidents, but upon waking this is not the case and excessive liquid consumption before bed can lead you to becoming fully awake in the middle of the night and being forced to get up, turn on a bathroom light and interrupt melatonin secretion, relieve yourself and then return to bed where you may struggle to return to proper sleep.

The amount of liquid that could be classed as excessive is always going to vary individual to individual and day-to-day, but it's worth keeping an eye on your intake and noticing at what point you're forced to get up during the night.

7.16.4. Engage in exercise

Exercise alters endocrine, nervous system and somatic functions so it makes sense that it would impact sleep. The exact form which this impact takes is largely dependent on the type

of exercise undertaken and the amount of time between the exercise bout and sleep, but the effects are relatively consistent.

Exercise undertaken during the day has a small positive impact on sleep, evident because a greater amount of stage 3 sleep is seen. Late evening training, on the other hand, seems to have the opposite effect. This is likely to be due to the impact exercise can have on cortisol, dopamine, adrenaline and noradrenaline. Interestingly, chronic exercisers also experience shorter sleep onset latency (they fall asleep faster), reduced time awake during the night and significantly longer total sleep time. It has yet to be elucidated at the time of writing, whether this is because of the impact of acute exercise sessions, or the somatic responses to chronic exercise including improved body composition, cardiac function, glucose control and immune function.

Note: Aerobic exercise is the modality typically used in research that seeks to explore the association between sleep and exercise, but it is likely that resistance training would have the same effects.

7.16.5. Consider your food choices

Large meals or foods which cause indigestion for individuals would ideally be avoided. Sleepfoundation.org recommend avoiding spicy, very rich or very 'heavy' meals, and it's worth noting that many chocolate bars contain some natural caffeine.

With that said, consumption of a higher carbohydrate food prior to bed can reduce sleep onset time due to a phenomenon called postprandial somnolence (which many experience after larger meals).

7.16.6. Take naps

Finally, it is possible to improve performance during periods of sleep restriction by engaging in short (sub 30 minute) naps. While this may result in some amount of immediate sleep inertia, after this has dissipated, workers show an increase in performance when compared with workers who have not napped, as well as reduced subjective tiredness. Napping should not be considered a replacement for sleep because, as you have seen, a full sleep cycle can take up to 120 minutes. With that said it is worth noting that there is evidence a nap during sleep debt situations may not impact night time sleep but may improve waking function. Being that the human circadian rhythm naturally dips at both 2-3am and 2-3pm, and therefore it could be argued that we evolved to take an afternoon nap, for those who struggle to complete a full night's sleep due to their schedule (shift workers, for example) this could be a viable option.

7.17. In summary

In this module, we have covered everything you need to know about sleep. What it is and what it is not, why we need it, how our bodies make us do it, what happens when we don't get enough and what you can do about it.

Next, we will look at supplements. We'll go through what works and how, what may not be as effective as we are led to believe, and how you can discern fact from fiction when presented with something we didn't mention.

7.18. References

- Cornel, D. and Lupu, A. (2015). *Simple Circuit for Monitoring Brain Activity*. 6th International Conference: Computational Mechanics and Virtual Engineering. [online] pp.395-400. Available at: http://aspeckt.unitbv.ro/jspui/bitstream/123456789/1958/1/70%20395-400%20Lucrare%202%20%20COMEC%202015%20Druga.pdf [Accessed 14 Jun. 2017].
- Berger, H. (1933). Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten*, 98(1), pp.231-254.
- Azevedo, F., Carvalho, L., Grinberg, L., Farfel, J., Ferretti, R., Leite, R., Filho, W., Lent, R. and Herculano-Houzel, S. (2009). Equal numbers of neuronal and non-neuronal cells make the human brain an isometrically scaled-up primate brain. *The Journal of Comparative Neurology*, 513(5), pp.532-541.
- Aserinsky, Eugene, and Nathaniel Kleitman. (1953). Regularly Occurring Periods of Eye Motility, and Concomitant Phenomena, during Sleep. *Science*. 118 (3062). pp. 273–274. [Online] *JSTOR*, [Available at www.jstor.org/stable/1680525].
- Lüthi, A. (2014). Sleep Spindles. *The Neuroscientist*, 20(3), pp.243-256.
- The Role of the Spontaneous and Evoked K-Complex in Good-Sleeper Controls and in Individuals with Insomnia. (2011). *Sleep*.
- Akerstedt, T., Hume, K., Minors, D. and Waterhouse, J. (1997). Good sleep - its timing and physiological sleep characteristics. *Journal of Sleep Research*, 6(4), pp.221-229.
- Tassi, P. and Muzet, A. (2000). Sleep inertia. *Sleep Medicine Reviews*, 4(4), pp.341-353.
- Fraigne, J., Torontali, Z., Snow, M. and Peever, J. (2015). REM Sleep at its Core Circuits, Neurotransmitters, and Pathophysiology. *Frontiers in Neurology*, 6.
- Floyd, J., Janisse, J., Jenuwine, E. and Ager, J. (2007). Changes in REM-Sleep Percentage Over the Adult Lifespan. *Sleep*, 30(7), pp.829-836.
- Tarullo, A., Balsam, P. and Fifer, W. (2010). Sleep and infant learning. *Infant and Child Development*, 20(1), pp.35-46.
- Sandyk, R. (1992). Melatonin and maturation of REM sleep. *International Journal of Neuroscience*, 63(1-2), pp.105-114.
- Tarullo, A., Balsam, P. and Fifer, W. (2010). Sleep and infant learning. *Infant and Child Development*, 20(1), pp.35-46.
- Siegel, J. (2011). REM sleep: A biological and psychological paradox. *Sleep Medicine Reviews*, 15(3), pp.139-142.
- Colten, H., Altevogt, B. and Research, I. (2017). *Sleep Physiology*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK19956/ [Accessed 17 May 2017].

- Ons.gov.uk. (2017). *National Life Tables, United Kingdom- Office for National Statistics*. [online] Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2015-09-23 [Accessed 27 Feb. 2017].
- Sleepfoundation.org. (2017). *National Sleep Foundation - Sleep Research & Education*. [online] Available at: https://sleepfoundation.org [Accessed 27 Feb. 2017].
- Tononi, G. (2001). Modulation of Brain Gene Expression during Sleep and Wakefulness A Review of Recent Findings. *Neuropsychopharmacology*, 25(5), pp.S28-S35.
- Mackiewicz, M., Shockley, K., Romer, M., Galante, R., Zimmerman, J., Naidoo, N., Baldwin, D., Jensen, S., Churchill, G. and Pack, A. (2007). Macromolecule biosynthesis: a key function of sleep. *Physiological Genomics*, 31(3), pp.441-457.
- Goldberg, G., Prentice, A., Davies, H. and Murgatroyd, P. (1988). Overnight and basal metabolic rates in men and women. *European Journal of Clinical Nutrition*, 42(2), pp.137-144.
- Vyazovskiy, V., Cirelli, C., Pfister-Genskow, M., Faraguna, U. and Tononi, G. (2008). Molecular and electrophysiological evidence for net synaptic potentiation in wake and depression in sleep. *Nature Neuroscience*, 11(2), pp.200-208.
- Mignot, E. (2008). Why We Sleep: The Temporal Organization of Recovery. *PLoS Biology*, 6(4), p.e106.
- Kondo, T. (2007). A Cyanobacterial Circadian Clock Based on the Kai Oscillator. *Cold Spring Harbor Symposia on Quantitative Biology*, 72(1), pp.47-55.
- Cohen, S. and Golden, S. (2017). *Circadian Rhythms in Cyanobacteria*.
- Purves, D., Augustine, G., Fitzpatrick, D., Hall, W., LaMantia, A. and White, L. (2012). *Neuroscience*. 2nd ed. Sunderland, Massachusetts.: Sinauer Associates, Inc.
- Gonze, D., Bernard, S., Waltermann, C., Kramer, A. and Herzel, H. (2005). Spontaneous Synchronization of Coupled Circadian Oscillators. *Biophysical Journal*, 89(1), pp.120-129.
- Li, Y., Liu, Z., Wang, R., Chen, L. and Zhang, J. (2009). Synchronisation mechanisms of circadian rhythms in the suprachiasmatic nucleus. *IET Systems Biology*, 3(2), pp.100-112.
- Claustrat, B. and Leston, J. (2015). Melatonin: Physiological effects in humans. *Neurochirurgie*, 61(2-3), pp.77-84.
- Velloso, C. (2008). Regulation of muscle mass by growth hormone and IGF-I. *British Journal of Pharmacology*, 154(3), pp.557-568.
- Watson, C., Lydic, R. and Baghdoyan, H. (2011). Sleep duration varies as a function of glutamate and GABA in rat pontine reticular formation. *Journal of Neurochemistry*, 118(4), pp.571-580.

- Dzirasa, K., Ribeiro, S., Costa, R., Santos, L., Lin, S., Grosmark, A., Sotnikova, T., Gainetdinov, R., Caron, M. and Nicolelis, M. (2006). Dopaminergic Control of Sleep-Wake States. *Journal of Neuroscience*, 26(41), pp.10577-10589.
- Portas, C., Bjorvatn, B. and Ursin, R. (2000). Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. *Progress in Neurobiology*, 60(1), pp.13-35.
- Krueger, J. and Obál Jr, F. (1993). Growth hormone-releasing hormone and interleukin-1 in sleep regulation. *FASEB*, 7(8), pp.645-652.
- Nitz, D. and Siegel, J. (1996). GABA release in posterior hypothalamus across sleep-wake cycle. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology*, 271(6), pp.1707-1712.
- McGregor, R., Wu, M., Barber, G., Ramanathan, L. and Siegel, J. (2011). Highly Specific Role of Hypocretin (Orexin) Neurons: Differential Activation as a Function of Diurnal Phase, Operant Reinforcement versus Operant Avoidance and Light Level. *Journal of Neuroscience*, 31(43), pp.15455-15467.
- Huang, Z., Urade, Y. and Hayaishi, O. (2011). The Role of Adenosine in the Regulation of Sleep. *Current Topics in Medicinal Chemistry*, 11(8), pp.1047-1057.
- Durmer, J. and Dinges, D. (2005). Neurocognitive Consequences of Sleep Deprivation. *Seminars in Neurology*, 25(01), pp.117-129.
- Sallinen, M., Holm, A., Hiltunen, J., Hirvonen, K., Härmä, M., Koskelo, J., Letonsaari, M., Luukkonen, R., Virkkala, J. and Müller, K. (2008). Recovery of Cognitive Performance from Sleep Debt: Do a Short Rest Pause and a Single Recovery Night Help?. *Chronobiology International*, 25(2-3), pp.279-296.
- Ribeiro, J. and Sebastião, A. (2010). Caffeine and Adenosine. *Journal of Alzheimer's Disease*, 20(s1), pp.S3-S15.
- Duffy, J. and Czeisler, C. (2009). Effect of Light on Human Circadian Physiology. *Sleep Medicine Clinics*, 4(2), pp.165-177.
- Meredith, S., Juliano, L., Hughes, J. and Griffiths, R. (2013). Caffeine Use Disorder: A Comprehensive Review and Research Agenda. *Journal of Caffeine Research*, 3(3), pp.114-130.
- International Bedroom Poll, (2013). *National Sleep Foundation*. [online] Available at: https://sleepfoundation.org/sites/default/files/RPT495a.pdf [Accessed 13 Mar. 2017].
- Foster, R. and Kreitzman, L. (2013). The rhythms of life: what your body clock means to you!. *Experimental Physiology*, 99(4), pp.599-606.
- Czeisler, C. and Gooley, J. (2007). Sleep and Circadian Rhythms in Humans. *Cold Spring Harbor Symposia on Quantitative Biology*, 72(1), pp.579-597.

- Pilcher, J., Morris, D., Donnelly, J. and Feigl, H. (2015). Interactions between sleep habits and self-control. *Frontiers in Human Neuroscience*, 9.
- Friedman, J. (2002). The function of leptin in nutrition, weight, and physiology. *Nutrition Reviews*, 60(10), pp.S1-14, S68-87.
- Miller, E., Freedman, D. and Wallis, J. (2002). The prefrontal cortex: categories, concepts and cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 357(1424), pp.1123-1136.
- Dattilo, M., Antunes, H., Medeiros, A., Mônico Neto, M., Souza, H., Tufik, S. and de Mello, M. (2011). Sleep and muscle recovery: Endocrinological and molecular basis for a new and promising hypothesis. *Medical Hypotheses*, 77(2), pp.220-222.
- Orzeł-Gryglewska, J. (2010). Consequences of sleep deprivation. *International Journal of Occupational Medicine and Environmental Health*, 23(1).
- Wright, H., Lack, L. and Kennaway, D. (2004). Differential effects of light wavelength in phase advancing the melatonin rhythm. *Journal of Pineal Research*, 36(2), pp.140-144.
- Figueiro, M., Wood, B., Plitnick, B. and Rea, M. (2011). The impact of light from computer monitors on melatonin levels in college students. *Neuro Endocrinology Letters*, 32(2), pp.158-163.
- Hasler, B., Dahl, R., Holm, S., Jakubcak, J., Ryan, N., Silk, J., Phillips, M. and Forbes, E. (2012). Weekend–weekday advances in sleep timing are associated with altered reward-related brain function in healthy adolescents. *Biological Psychology*, 91(3), pp.334-341.
- Research, I. (2017). *Pharmacology of Caffeine*. [online] Ncbi.nlm.nih.gov. Available at: https://www.ncbi.nlm.nih.gov/books/NBK223808/ [Accessed 30 Mar. 2017].
- Březinová, V. (1974). Effect of caffeine on sleep. *British Journal of Clinical Pharmacology*, 1(3), pp.203-208.
- Van Reen, E., Jenni, O. and Carskadon, M. (2006). Effects of Alcohol on Sleep and the Sleep Electroencephalogram in Healthy Young Women. *Alcoholism: Clinical and Experimental Research*, 30(6), pp.974-981.
- Stone, B. (1980). Sleep and low doses of alcohol. *Electroencephalography and Neurophysiology*, 48(6), pp.706-709.
- Uchida, S., Shioda, K., Morita, Y., Kubota, C., Ganeko, M. and Takeda, N. (2012). Exercise Effects on Sleep Physiology. *Frontiers in Neurology*, 3.
- Nehme, P., Marqueze, E., Ulhôa, M., Moulatlet, E., Codarin, M. and Moreno, C. (2014). Effects of a carbohydrate-enriched night meal on sleepiness and sleep duration in night workers: A double-blind intervention. *Chronobiology International*, 31(4), pp.453-460.

- Ruggiero, J. and Redeker, N. (2013). Effects of Napping on Sleepiness and Sleep-Related Performance Deficits in Night-Shift Workers: A Systematic Review. *Biological Research For Nursing*, 16(2), pp.134-142.
- Campbell, S., Murphy, P. and Stauble, T. (2005). Effects of a Nap on Nighttime Sleep and Waking Function in Older Subjects. *Journal of the American Geriatrics Society*, 53(1), pp.48-53.