Models of insomnia

National Sleep Helpline

Sunlight filters through my curtains to fall softly on my face. My bed is warm, my duvet heavy. The air moves languidly, as if aware it's the start of the weekend and the day is relaxed and sweet with possibility. Outside my window, birds have begun to chirp optimistically.
I bury my head under a pillow and suppress the urge to scream. It's 8am, and I could swear I haven't slept for a minute.

Insomniac monsters have had to migrate from under the bed before cognitive behavioural therapy made its appearance

Insomnia is the most common sleep-related issue. It's defined as difficulty falling asleep, poor quality sleep and frequent awakenings. Often, people with insomnia will also perceive themselves as having slept far less than they actually have, contributing to their distress. Since insomnia is so common and can be incredibly detrimental to quality of life, it's essential to study and understand - but to talk about sleep disorders, we first have to have a basic understanding of what sleep even *is.* That seems obvious, right? I mean, it's sleep! We do it when we're tired and then we're (ostensibly) less tired. Often, we perceive it as just the 'absence of wakefulness', but it's *so much more* than that!

One of the first important tasks of sleep is to get rid of toxic waste in the brain. While we're awake, our brain is very metabolically active. The processes of brain activity (cognition, laying down new memories, sensing and responding to your environment, etc.) create waste products,

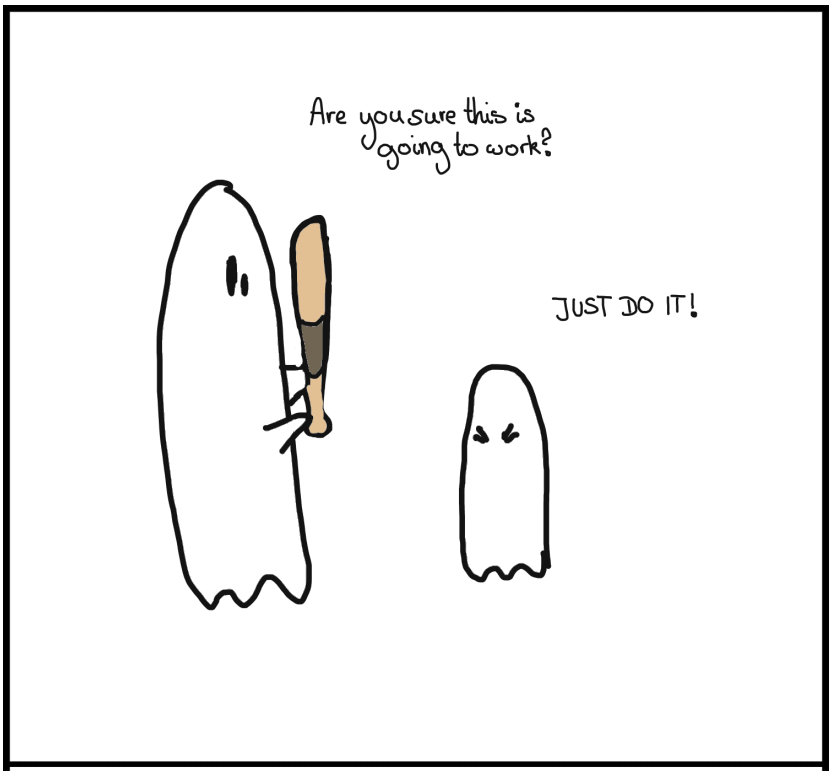
which can be toxic. Sleep clears these with the help of **glial cells.** Glial cells are non-neuronal cells in the brain that form the **glymphatic system** for waste disposal. The glymphatic system carries waste products from the brain in the **cerebrospinal fluid** to the blood system in the body, from where it can then be excreted. Sleep presumably increases the flow of the fluid and widens the spaces it flows through to aid this process. The big waste product to know about is **beta-amyloid**; you might have heard of this before, as this peptide has relatively recently been implicated in neurodegenerative diseases such as **Alzheimer's disease**.

Even if it seems like you're not doing much at all, you glia are hard at work

Sleep also helps us consolidate memory. Memory is divided into three major processes: encoding, consolidation and retrieval. Encoding includes taking the sensory information coming at us and storing it in the brain for future use. However, the memory is still fragile and has to be strengthened or *consolidated*. This consolidation involves revisiting the new memories to physically strengthen the synapses that encode them. Memories are built by remodeling **synaptic connections** in the brain. Why do we do this during sleep?
One big reason is probably so that the encoding of new memories doesn't interfere with the consolidation of older ones. If we were continually hallucinating and remembering what had just happened while we were actively going about our day, it might be a *bit* difficult to focus.

The two big **neurotransmitters** involved in the onset of sleep are **adenosine** and **GABA**. Both are inhibitory neurotransmitters, meaning they act as depressants (like alcohol, but that doesn't mean that alcohol will make you sleep better. Just because it also shuts down certain processes

in the brain doesn't make it suitable to promote sleep. That's like saying getting hit on the head by a baseball bat and falling unconscious is a great way to get some rest).

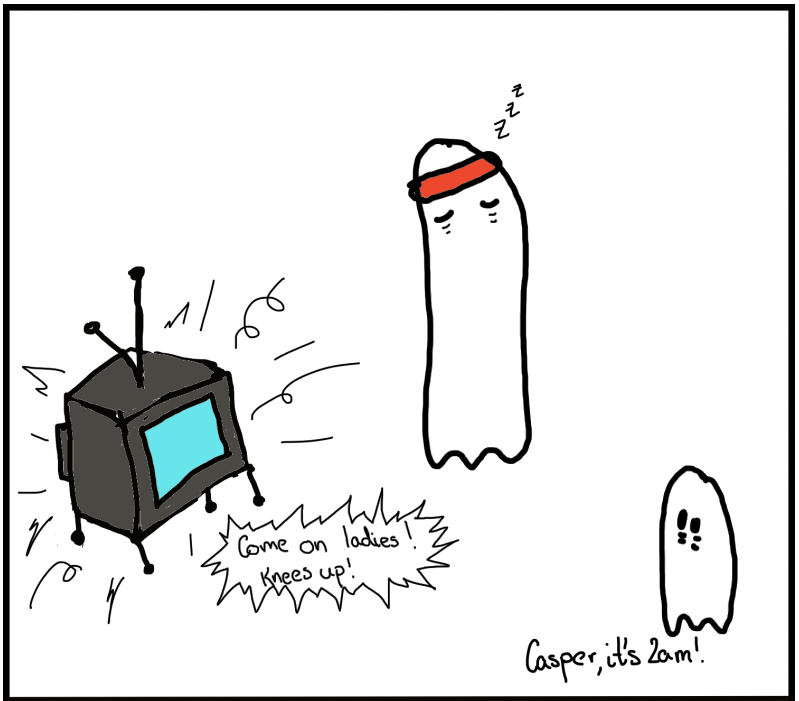


Funnily enough, this is exactly how Cara became a ghost in the first place.

GABA is released by the hypothalamus and inhibits regions of the brain promoting wakefulness. **ATP** breaks down in the brain into **adenosine**, a nucleoside which builds up while your brain is metabolically active. Adenosine exerts 'sleep pressure' as it builds up, inhibiting arousal in the brain, and is then metabolized while we sleep. Caffeine is actually an adenosine receptor antagonist, blocking the receptors which adenosine would bind to and thus making us feel as if we don't need to sleep. However, when caffeine breaks down, we might feel a 'crash' because further adenosine has accumulated in the meantime. There are many excitatory neurotransmitters involved in wakefulness, including **acetylcholine (ACh)**, **noradrenaline** (NA - another name for this is norepinephrine, NE), **dopamine (DA)**, **serotonin** (or 5-HT, which stands for 5-hydroxytryptamine) and **orexin (**also called **hypocretin**), which form the **arousal system**. The hormone cortisol, often associated with stress, also contributes to wakefulness.

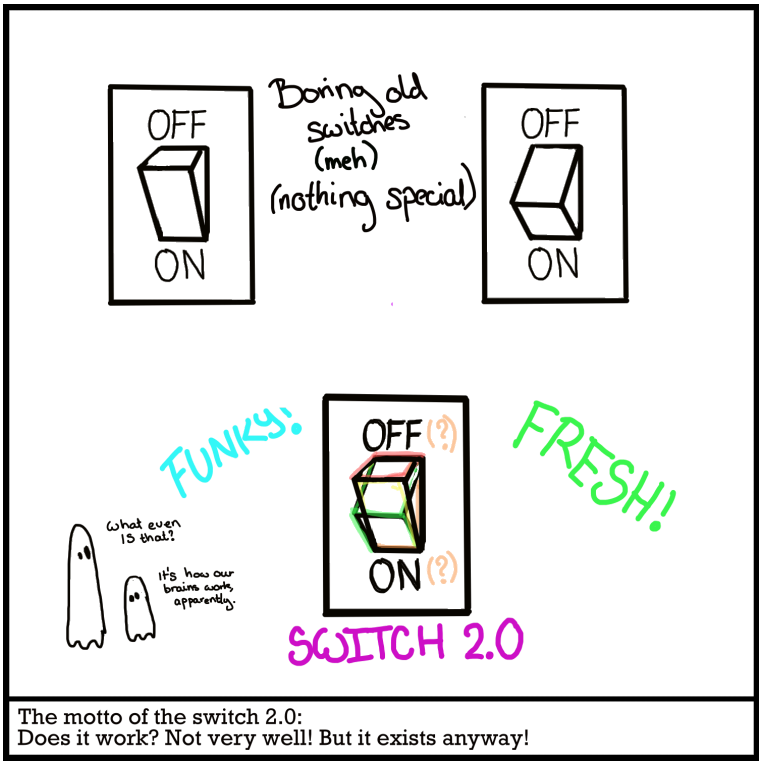
We can think of sleep as a process regulated by two main systems: the inhibitory **hypothalamus** and the **arousal system**. The hypothalamus contains areas which work to inhibit wakefulness and promote sleep. The first is the **suprachiasmatic nucleus (SCN)**; this receives information from light-sensitive proteins in the eye that isomerize and tell the SCN "Hey! It's getting dark, you should produce more melatonin", thereby regulating the circadian rhythm. The second is the **VLPO**, a collection of neurons in the hypothalamus that inhibit the

arousal system. The VLPO and the arousal system act as a **switch**, both mutually inhibiting the other.



Parasomnias include sleepwalking or sleep paralysis. They can occur because of a failure to suppress the usual atonia (i.e. muscle paralysis) which normally occurs during REM sleep and prevents you from acting out your dreams.

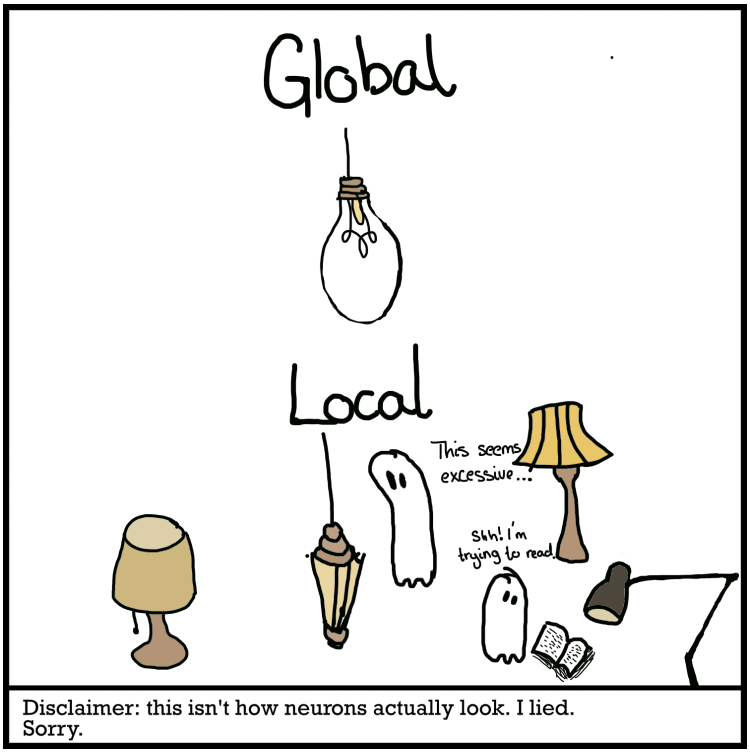
One proposed model of insomnia, the Cano-Saper model, depicts insomnia as a dysfunction in this switch. In Cano's experiments on stress-induced sleep issues in rats, their brains showed expression of **cFos** (a marker of neural activity) in both the brain's sleep circuitry *and* in the arousal system - which you wouldn't expect if the switch was fully in sleep mode. Additionally,



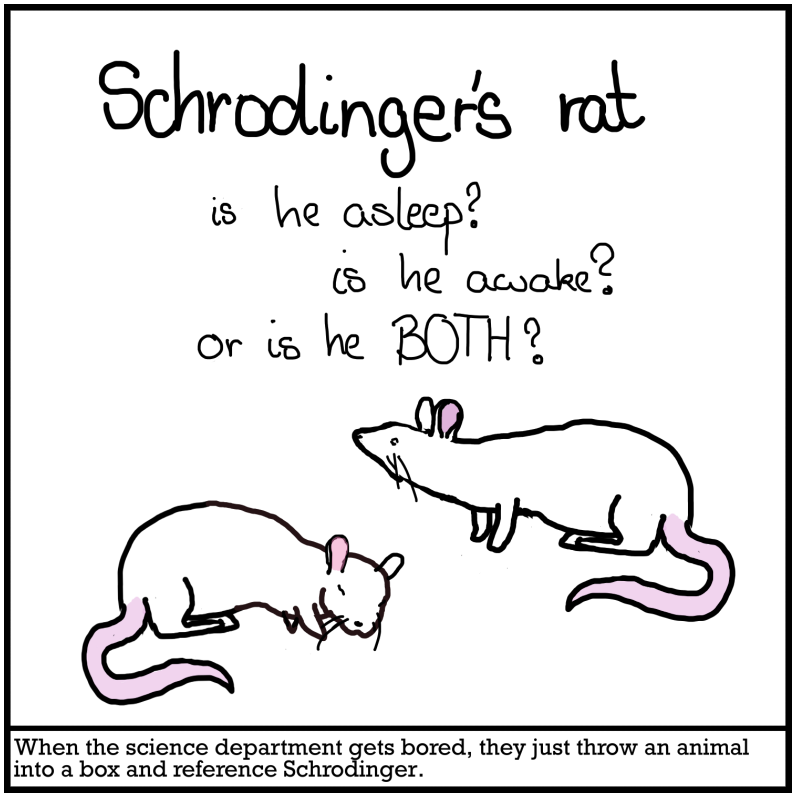
The motto of the switch 2.0:
Does it work? Not very well! But it exists anyway!

the stressed rats still had **high-frequency EEG activity** during nREM sleep. High-frequency EEG activity is indicative of **cortical activity**, therefore showing that sensory and cognitive processing was going on. Even though other parts of their brain seem asleep, they haven't put their cognitive functioning (their 'thinking' processes) to sleep. So were they both awake and asleep?
The 'flip-flop switch' hypothesis argues that sleeping is a continual fight between the VLPO and the arousal system. If one gets the slightest advantage over the other, the switch gets pushed over into the other direction. In Cano's theory, the switch becomes unstable in insomniac brains and 'flip-flops' often due to an issue with one or both sides of the system.

Another theory, proposed by Daniel Buysse, hinges on the idea that sleep is not a **global** phenomenon, but a **local** one (which explains very little).
Rather than sleep being dependent on one big switch that turns sleep ON for the whole brain and wakefulness OFF, it's proposed that sleep is a characteristic intrinsic to neurons or clusters of neurons. It can be defined as a "statistical phenomenon".
This isn't making things easier to understand.
Let's look at an analogy:
In a dim room, you're trying to make out a book you're reading. The idea of sleep as a fully global phenomenon is like having one big light with one switch - you turn it on and it you can read. You can't have *some* illumination, you either have it or you don't.
But maybe you have a whole lot of lights and they each have their own switch. You have to flip enough switches to read your book. Maybe you've even rigged up some system where flipping one switch will flip another switch and another, until a master switch is flipped that lights up the room.



In the Buysse model, instead of one switch rapidly flipping from awake to asleep, the idea is that there's a lot of switches, with some flipped ON and others OFF. In other words, you can essentially be awake and asleep *at the same time*! Or more accurately, parts of your brain exhibit a 'sleep-state' and others a 'wake-state'. The central/global and the local mechanisms of sleep aren't necessarily mutually exclusive. It might be that the growing proportion of 'asleep' neurons triggers a switch that causes central sleep-regulatory centers to cause essentially the whole brain to go to sleep. This model might help explain why studies on insomnia often find the patients to be asleep, despite the insomniacs adamantly arguing that they *couldn't have been asleep*, they were awake the *whole time*. Maybe neither of them got it wrong. It's just that their arousal system wasn't being fully shut off, and parts of their brain really *were* awake, even if other parts were showing signs of sleeping!



When the science department gets bored, they just throw an animal into a box and reference Schrodinger.

This could potentially alter how we should view and treat insomnia as well. What if insomnia isn't an issue with turning the sleep system ON, but with turning the wake system OFF?
A lot more research has to be done into both the psychology and neurobiology of insomnia, but I hope I've emphasized what's important - that the brain is a weird, strange, complicated and *awesome* hunk of fat.

It's 2am. I'm exhausted, but I can't sleep. My mind is buzzing.

I sigh and clamber out of bed. I sit in the kitchen and eat a slice of apple pie, doodling idly.
I tell myself:
It's okay.
You can be tired.
You're allowed to be tired.
Slowly, the bed stops becoming a menacing ghost haunting my mind. I trip up and I get worse, but I know how to get better now, too. Maybe I'm (slowly, painfully, step by exhausting step) healing.

Further reading

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