Fight the fatigue

A fresh understanding of how the brain assesses bodily energy levels is revealing ways to regain your inner vitality, discovers **Caroline Williams**

THERE are many mysteries in science. What is dark matter? Why are we conscious? Are we alone in the universe? But none looms larger in the mind of the average adult than this: why am I so exhausted all the time?

It is a crucial question, not least because, according to a recent analysis of data from 32 countries, as many as 1 in 5 otherwise healthy adults complain of problematic levels of fatigue. Feeling tired all the time is one of the most common reasons to seek medical attention – so much so, in fact, that medical professionals commonly abbreviate it to TATT, perhaps to save their own energy. Often, there is no obvious medical explanation for what is causing the fatigue and not much the doctor can offer beyond blood tests to rule out any obvious deficiencies.

Despite this huge burden on our collective well-being, the question of what it means to "have energy" had, until recently, attracted surprisingly little medical research. Into the void stepped the trillion-dollar wellness industry, offering no end of ways to boost our vigour with various supplements, diets and lifestyle hacks.

Now, though, scientists are taking a fresh look at what it means to feel energised – or not – and the research is revealing that how we perceive this state largely hinges on the brain's ongoing assessment of how much energy is available to our cells. This discovery is changing how we think about our general health, opening up possible new avenues to treat clinical levels of fatigue, and suggesting practical things we can all do to stop feeling like we are running on empty.

The fact that so many otherwise healthy people feel so tired doesn't seem to make sense. Many of us, at least in the West, have easy access to far more calories than we need. If feeling good were simply a matter of calories in, energy out, we would all be bursting with vim and vigour.

So why aren't we? The short answer is that the energy we can feel – our "subjective vitality" – isn't like a simple readout on a tank of fuel. Instead, it is an ongoing body-brain estimate of how much energy is available in the body and how much is already accounted for, and an educated guess of whether we have any to spare for what we need to do next.

This feeling is an example of interoception, the ability to sense signals from within the body that tell us how well we are adapting to the world. When something is off – such as when the body feels like it is running low on energy – these signals motivate us to do something to fix the problem. As I outline in my forthcoming book *Inner Sense*, the study of interoception is revealing that our feelings, emotions and motivations are built from an ongoing, constantly changing conversation between body and brain.

Seeing energy as the output of such a process explains why boosting it isn't simply a case of eating more, or shelling out on whatever supplement is currently going viral. It is about figuring out where in the body-brain conversation the signal to conserve energy is coming from, and taking action to fix the issue.

It might be a problem with energy release in the cells, or that the brain is expecting a physical or mental challenge and wants to keep something in reserve just in case. Or it could be that something, such as stress or a fight against infection, is hogging the bulk of the body's supplies. Whatever the reason, the outcome is the same – you feel lousy – but the fix required depends on the cause.

Across large portions of the world, the idea that energy is central to well-being isn't exactly new. Eastern traditions founded thousands of years ago were built on the premise that the flow of energy around the body is key to health and vitality. Western medicine, on the other hand, grew from the foundations of anatomy and physiology – things that could be seen, measured and dissected, and could be treated with drugs or surgery. Invisible forces, not unreasonably, didn't get a look in.

The Western approach to medicine has done wonders for human life expectancy, increasing it by three decades in less than a century. But it has been less successful at extending the number of years we live in good health, our so-called healthspan. According to an estimate from 2021, globally, we are living an average of nine years beyond this, in poorer health.

Go with the flow

Martin Picard at Columbia University in New York argues that it is time to change the focus of medical research away from treating disease and towards a better understanding of health. This, he believes, requires a better understanding of how energy flows through the body. "We have veered away from it because of the tools we have had with reductionist science: if you can't sequence it, if you can't see it under the microscope or measure it on an oscilloscope, then it's not an appropriate object of study," he says. "I think that's steered us away from things that are potentially useful and important."

Picard trained in a lab run by geneticist Doug Wallace, who pioneered the study of mitochondria, the cellular factories where ›

molecules from digested food are transformed into a chemical form of energy that cells can work with. One thing that soon became clear from this research is that, when mitochondria aren't working efficiently, people feel lethargic and fatigued. Picard took this finding and ran with it, establishing a new field, mitochondrial psychobiology, to explore what energy release in mitochondria has to do with how energetic we feel, and vice versa. He and others have discovered there are many reasons why mitochondria might struggle, even in otherwise healthy people, some of which are almost certainly playing into the epidemic of TATT.

Perhaps the biggest drain on energy production in mitochondria is – surprisingly – a surfeit of fuel. Energy is released in the mitochondria gradually, in a series of small biochemical steps that can't be rushed and have to happen in a certain order to avoid causing a metabolic pile-up. If too much fuel arrives at once, the mitochondria have to take a break from releasing energy so that the cells can concentrate on storing the excess for later. This leaves us with less energy, not more – at least in the short term. High-sugar diets are particularly problematic, with studies showing that they lead to inefficient mitochondria and people feeling moody and sluggish, rather than energised. Intriguingly, there is some evidence that challenging the mitochondria by drastically reducing sugar intake by adopting a low-carb, high-fat ketogenic diet may have the opposite effect.

Then there is stress, whether emotional or due to a physiological challenge like an infection or injury. According to a study by Picard and his colleagues, stress increases the rate at which cells burn through energy by 60 per cent. This is partly because mitochondria also produce cortisol, a stress hormone that sends out a signal that energy is needed to meet a coming challenge.

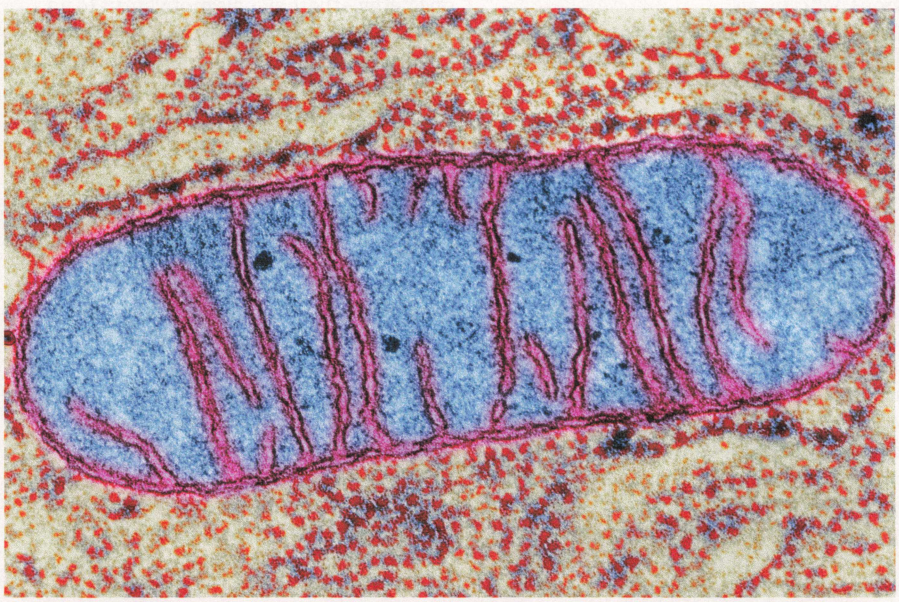
Stress isn't only literally draining, it also has broader ramifications for body-brain energy calculations. Lisa Feldman Barrett, a neuroscientist at Northwestern University in Massachusetts, coined the term "body budgeting" to describe the brain's role in managing our energy supplies in the interests of survival. She describes body budgeting in terms of predictive processing – the idea that the brain works by generating a "best guess" about what is happening in the wider world, adjusting as necessary based on incoming sensory information. When the prediction and evidence don't match, the resulting "error" signal is experienced as a feeling, whether good, bad, full of energy or in need of a nap. "We think of these as kind of like general summaries of the metabolic state of your body," she says.

"The biggest drain on your cellular energy production is, surprisingly, a surfeit of fuel"

Importantly, the brain's assessment of our metabolic state could explain why it is perfectly possible to sleep well and still feel exhausted at the thought of a long day of meetings ahead. It also explains why an unexpected piece of good news can translate into an instant energy boost. The energetic state of the body hasn't changed, but the brain's prediction of what there is to work with has transformed the situation.

Research led by Arran Davis at the University of Oxford shows how these predictions can make a measurable difference to how much energy we have to spend. When people were asked to exercise to exhaustion, those who did so in the company of a supportive friend were able to keep going for longer and to burn more calories before giving up. Davis explains this as a sign that we can dig deeper into our energy reserves when we are confident that help is at hand. "Social support signals the availability of the resources we need to recover from exercise, so we can be less cautious with our bodily resources," says Davis.

The fact that there are so many inputs into the body-brain energy assessment – some physical, some psychological and



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Mitochondria are energy-producing structures inside cells

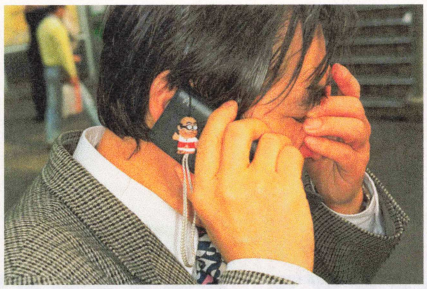
many operating unconsciously – makes it challenging to measure objectively. But there are several candidate "biomarkers" that reflect physiological processes and the subjective feeling of vitality or fatigue.

One is growth differentiation factor 15 (GDF15), a metabolic signalling molecule that cells release when under stress. This occurs in response to infections, injury and psychosocial stress. According to Stephen O'Rahilly at the University of Cambridge, GDF15 seems to function as an all-purpose distress signal to inform the brain that it needs to conserve energy.

Another line of evidence shows that GDF15 may also explain why getting older only ever seems to make us more tired. GDF15 is a reliable marker of ageing, with levels in the blood rising by up to 25 per cent as each decade passes. Picard suspects that this, too, hinges on energy budgeting. In a recent paper, he argues that many of the symptoms of ageing, including fatigue, are due to cells accumulating damage and struggling to keep up with the energy costs of repairs. As the debris piles up, the cells send distress signals to the brain, which responds by conserving energy wherever possible. "GDF15 says there's hypermetabolism: cut costs, shrink your muscles, be a little less enthusiastic, grey your hair," says Picard. "All of these things are ways to save energy."

Meanwhile, other researchers are working on different biomarkers. In 2021, the World Health Organization convened a group of health and ageing experts to thrash out a new definition of health based not on the absence of disease, but on what they call "vitality capacity" – the body's ability to extract enough energy from food to stay in good working order. The team, co-led by gerontologist Ivan Bautmans at Vrije University Brussels in Belgium, explored several potential indicators of healthy levels of vitality, from muscle strength and blood-borne inflammatory markers to simply asking people to rate how they feel. One promising option is a simple test of how quickly muscles tire based on a handheld device that stemmed from Bautmans's PhD research, 20 years ago.

Called Eforto, it computes how long it takes someone to lose 50 per cent of their maximum grip strength while holding the device as tightly as possible. This is combined with a questionnaire about the person's current energy levels to give an overall score. The final figure offers insight into their physical and mental energy levels, says Bautmans. "It is a proxy measure that tells you whether the physiology is out of balance or getting problematic," he says. In a study of nearly 1000 middle-aged people, those with the lowest overall scores were more likely to have biomarkers of low-grade inflammation in their blood than those with higher scores. This is important because chronic inflammation is a known driver of ageing, says Bautmans. Which raises the question of whether, with enough warning and the right intervention, we might be able to slow the ageing process itself.



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Stress and a high-sugar diet impact the body's energy system, leading to feelings of fatigue

Get a grip

One study by Picard and his colleagues provides hope that this might be possible. He had heard anecdotal reports of grey hair sometimes starting to regrow with colour from the roots and, intrigued, recruited 14 volunteers who had experienced this for a study. This research found that stressful periods in these people's lives could be linked with the period of greying. Then, once the stress passed, the colour returned.

Picard understands this as the body-brain system temporarily diverting the energy it would normally spend on hair pigment to something more important. "And then, when you are less stressed out, maybe that frees up some of the energy budget to spend on making colour again," he says.

Of course, this doesn't necessarily mean that going grey is optional – at some point, the challenges of ageing probably make it inevitable for those lucky enough to live that long. But it does suggest that the rate of ageing may be more malleable than we think.

Seeing fatigue as the outcome of a body-brain conversation also offers a new way to understand chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME), in which symptoms are notoriously difficult to explain. A better understanding of the pathways involved could help doctors focus on likely problem areas. For instance, recent studies have linked CFS to reduced blood flow that robs the mitochondria of fuel, with chronic inflammation that saps the body's reserves, and with a processing bottleneck in the brainstem, an interoceptive processing hub that has a hand in energy budgeting.

In our day-to-day lives, too, this updated view of vitality is revealing ways to tackle tiredness. One possibility is to take what Elissa Epel at the University of California calls "deep rest". Epel, who researches the psychological benefits of contemplative practices such as meditation and prayer, suggests that one reason these have been shown to enhance well-being is that they calm body and mind, reducing the perceived need to hunker down and save energy.

Diet and exercise also play an important role in our energy budgeting. Sugary snacks have been shown to crash mood and energy levels – as demonstrated in relation to mitochondria – while short periods of activity, or "exercise snacks", can do the opposite. And regular exercise forces the body to increase energy production by clearing out inefficient mitochondria and replacing them with fresh ones that work better.

Finally, it is worth keeping in mind that the people you surround yourself with affect your energy levels in a very real sense. So, no matter how much you have on your plate, and even if you occasionally fall off the diet and exercise wagon, it is good to know that our bodies and brains are wired so that, in the right company, there is usually enough energy to go around. ▮

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Mythology-ology

The new science of myths and folktales is revealing what makes some stories run and run, finds **Laura Spinney**

ONCE upon a time, a strong, attractive hero lost one or both of his parents. He then overcame a series of obstacles and faced off against a monster that had terrorised his community. The hero vanquished the monster and was celebrated.

If this story sounds familiar, that's because it is the road travelled by Superman, Harry Potter, Luke Skywalker and countless other fictional heroes stretching back centuries. Its enduring appeal has puzzled researchers for nearly as long. However, in recent years, the study of storytelling has been revitalised, as linguists, psychologists and experts in cultural evolution have begun probing the subject using large databases of myths and folktales, powerful algorithms and an evolutionary mindset. We are finally starting to get answers to key questions, including what makes a good story, why some are more enduring than others and exactly how far back we can trace the roots of the most popular ones – as well as how stories have traversed time and space.

It is an epic quest, but there has never been a better time to undertake it. Unlike the Brothers Grimm and other early folktale collectors, modern surveyors of storytelling needn't do painstaking fieldwork – they don't even have to stray from their computer screens to chart the emergence and evolution of stories. "Social media is almost a natural experiment in storytelling that, through its very platform, does the collection," says folklorist and ethnographer Timothy Tangherlini at the University of California, Berkeley. What's more, this new scientific approach can illuminate some phenomena that appear to be modern, including the power of conspiracy theories to sometimes lead us down rabbit holes.

The study of myth and folktales has long had a bad reputation, with scholars in generations past trying to co-opt ancient stories as evidence of the march of societies from "primitive" to "civilised" states. Bringing a more data-driven, evolutionary perspective to bear was a breakthrough, not least in providing new ideas about why we tell stories.

One leading hypothesis holds that storytelling emerged as humanity's first data management system, a way of faithfully and memorably transmitting information that would enhance the recipients' chances of survival. For anthropologist Michelle Scalise Sugiyama at the University of Oregon, this explains why the stories that hunter-gatherers tell are so concerned with the local landscape, climate and animals. "They're told for their ecological relevance and utility," she says. As for narrative – the way we structure stories by embedding agents and their actions into a causal sequence – that grew out of a much older aspect of human cognition: the agency-detection mechanism, our tendency to interpret ambiguous cues as evidence of living beings with their own intentions.

But storytelling has traditionally taken place in a group setting, and other researchers have stressed this social aspect. Two decades ago, evolutionary psychologist Robin Dunbar at the University of Oxford proposed that storytelling is a form of gossip, or "vocal grooming", that allows people to keep track of who is cooperative and who is a free rider in the community. For Tangherlini, it is a way of building consensus on a world view – the norms and values that the group adheres to. And psychologist Adrian Bangerter at the University of Neuchâtel, Switzerland, sees its purpose as making sense of non-routine events, which also demands consensus, because people must agree on an interpretation. There is evidence that the brain activity of people listening to a story becomes synchronised and that this manifests in feelings of "groupiness", says Bangerter. A good storyteller encourages these feelings using devices such as re-enactment, reported speech and audience participation, creating a collaborative, immersive experience.

Ghosts and gremlins

As well as helping us understand an exceptional event, storytelling may also anchor the memory of it by keeping the visceral emotion of eyewitnesses alive. One way to enhance memorability is to incorporate elements that are minimally counterintuitive, such as a 100-year flood or a ghost, which violate listeners' expectations to a small degree. The violation activates our agency-detection mechanism, grabbing attention and raising the heart rate, which then increases neural activity, strengthening the memory. Since it does so across all those in earshot, groupiness is likely to be a by-product. Anyone who regularly goes to a church, mosque or synagogue and listens to stories of the prophets experiences this. "The original protagonists are long gone," says Bangerter, "but for millions of people, these stories are highly vivid and meaningful."

These ideas aren't mutually exclusive: a story might tell us something essential, help us bond and perpetuate the strong emotion of an eyewitness. If it is to stand the test of time, it should also, ideally, be entertaining. Some of ›