Contents

PART ONE

How the brain constructs your mental health

1.

Natural highs: pleasure, pain and the brain

Some people have dramatically different experiences of pain and pleasure: heightened pleasure, chronic pain or no pain at all. In fact, one way in which pleasure is interconnected with mental health is that a cardinal symptom of several mental-health disorders, including depression and schizophrenia, is *anhedonia*: a loss of interest or pleasure in normally pleasurable activities. 'Normally pleasurable' is subjective but is not judgmental: it could include eating delicious food, reading a favourite book, having an orgasm, or other more eccentric things someone enjoys. When experiencing anhedonia, the things one typically enjoys might feel comparatively dull, less valuable, not worth the effort of obtaining. A disruption in pleasure has a debilitating effect on mental health.

Pain is also closely coupled with mental health, but in different ways. People with depression report more subjective pain in their day-to-day lives, potentially because of lower thresholds for pain.[17] This relationship runs in both directions: people with conditions that cause chronic pain, of which I am one, are more at risk for mental ill-health.[18] In general, the more frequently you experience pain and unpleasant experiences, the more likely you are to experience worse mental health.[17]

Why is mental health so closely linked to pleasure and pain? In this chapter we will discuss how the links between pain and worse mental health occur in part because of shared brain changes across chronic pain and mental health conditions. We will discuss how the brain normally processes pleasant and unpleasant things, and how this relates to differences in your likes and dislikes. Your subjective experience of things as pleasant, disgusting or painful is one major

ingredient for your mood, thoughts and behaviours – and therefore mental health. How pleasant or unpleasant you find things in the world also influences what your brain learns about (which we will discuss in Chapter 3), as well as what you are motivated to acquire or avoid in your surroundings (Chapter 4). Likewise, worse mental health can change how you experience the world, including blunting pleasure and enhancing pain. For this reason, changes to pain and pleasure could represent a warning signal of worsening mental health, and targeting the brain systems underpinning pain and pleasure might be one route to preserving good mental health.

The 'natural high' of pain

Have you ever noticed that after experiencing something rather painful or frightening, you get a sudden and paradoxical rush of giddiness? In biology this phenomenon is called *stress-induced analgesia*. You might feel this giddiness during or after something genuinely dangerous (going skydiving) or relatively mundane (stubbing your toe). In either case, the brief rush you experience also causes a temporary reduction in your pain sensitivity.

A predator is pursuing you, an enemy is attacking you – your body's only goal is to survive. At this point, when fleeing or fighting a life-threatening situation, it would be highly inconvenient to feel normal amounts of pain. It would get in the way of your survival. The last thing you need is to sit down and tend to a broken ankle or bruised eye socket. Any pain might distract you from staying alive. That is why we have stress-induced analgesia: we are more likely to survive a highly stressful encounter. Perhaps in evolutionary history, when stressful encounters were plentiful, those animals who had the special ability to suppress pain during stress were more likely to stay alive until they could pass on their useful trick to their offspring.

Even today, not everyone experiences stress-induced analgesia to the same degree, suggesting there is variation in this trait in the

population. This can be quantified by measuring people's thresholds for pain before and after stress. Some people (and some animals) show more dramatic changes in pain thresholds than others: they are much more sensitive to stress-induced analgesia.[19] For these people, acute stress might also have particularly positive effects on mood – danger might feel particularly euphoric. If, like me, you have no real inclination for high-acute-stress pursuits, you probably possess a more mundane amount of stress-induced analgesia. (Maybe you still feel it when you stub your toe, but you have no desire to repeat the action.)

Stress-induced analgesia was measured in what I think of as the 'hot and cold bath' experiments of the 1980s. Scientists studied rats swimming in various temperatures of water for precise amounts of time. After removing the rats from their hot and cold baths (and towel-drying them), the scientists then measured the rats' pain responses. Short cold-water swims, such as a 3 minute-swim in 15 degrees Celsius water, reduced the rats' responses to pain. Many of us like a nice, warm bath, but you may have heard (and been too timid to find out yourself) that cold baths or cold-water swimming can produce euphoric effects. If you're willing to brave the short-term pain, people swear by cold-water swimming.

Stress-induced analgesia exists because mammals have an in-built chemical system in the brain activated by pain and stressful experiences called the endogenous opioid system. These chemicals associated with suppressing pain (as anyone who has taken an opioid drug like codeine can attest to) also make you feel rather giddy.

The reason a short, mildly stressful cold-water swim causes pain relief is because it elicits the release of the particular class of chemical called opioids.[20] You may have heard a popular term for these opioids: endorphins. This comes from the contraction of endogenous morphine (endogenous here means coming from inside the body): drugs such as opium or morphine both bind to opioid receptors in the brain. Opioid drugs simply mimic the effect of endorphins. The effect of either natural or drug opioids binding to these receptors is a cascade of cellular processes, including inhibiting some

neurons' activity and stopping the release of other brain chemicals.[21] This cascade of cellular processes then alters communication from brain regions where opioid receptors live to other brain regions and the spinal cord that blunt (or 'gate') incoming pain signals from the body.[22] Endorphins elicit a 'natural high' – giddiness, relaxation, light-headedness – that can feel pleasurable and decrease pain sensitivity. That means that under certain circumstances, moderate stress can make you feel good because it releases opioids (and other chemicals) in the brain. (If you are lucky enough to ever go to the thermal baths in Budapest, Hungary, which range in temperature from toasty to painfully chilly, you can try the hot and cold bath experiment on yourself.)

Perhaps you do not fancy trying a cold-water swim. If not, you are in luck: in humans there is a huge diversity of briefly stressful experiences that induce natural opioid release. Even activities that were not typical challenges in our evolutionary history (like dropping out of a plane) seem to harness the same opioid system as our evolutionary survival response, releasing opioids in the brain to reduce acute pain and (for some people, anyway) causing pleasurable responses to short-term stress. In one study, skydiving reduced pain sensitivity, just like the rats' cold baths, indicative of opioid release.[23] When skydivers were given a drug that stops opioid transmission right before their jump, they retained higher pain sensitivity than the group given placebo, confirming the reduction in pain sensitivity was linked to the endogenous opioid system. However, it was a small study, and pain sensitivity was not tested until after the skydivers were back on land (there are limits to what you can do mid-air, and I suppose testing someone's pain responses is a step too far even for these intrepid scientists).

Like skydiving in humans, a number of surprising things can cause stress-induced analgesia in rats. Pain itself is one: natural opioids released by a brief but painful electric shock reduce rats' pain when tested afterward.[20] Rotating rats at a certain speed has a similar effect[20] (do not try this with your pets, please!). Like with swim temperatures and skydiving, all these stressors have something in

common: they are mild and they are temporary*. Even rotating a rat too quickly (presumably a more unpleasant feeling than a rat being rotated more slowly) fails to elicit opioid release.[20] You can imagine why this is the case. Suppressing pain temporarily is useful: it might help you delay imminent death or escape from a predator when injured, for example. But if long-term extreme stress also suppressed pain we might be less inclined to escape stressful, harmful situations or avoid the sources of pain.

Pain is a useful, important signal. People who are unable to experience pain due to rare genetic conditions suffer from profound physical consequences of this insensitivity to pain – burns, broken bones, bitten-off tongues. Pain and stress might feel unpleasant but they have a hidden ability to make you feel pleasure until you are out of danger – and even when particularly unpleasant, to help you survive.

You might be wondering what stress-induced analgesia has to do with mental health. Your personal constellation of pleasure and pain (and their more minor counterparts, likes and dislikes) makes up the hedonics of your everyday life, contributing to your current mental state as well as your long-term mental health. People's differences are at their most extreme in their reactions to uncomfortable, painful situations. There is no better example of this than chronic, long-term pain, which can have a devastating effect on the mental health of sufferers.

The toll of chronic pain

If pain is prolonged, the opposite of stress-induced analgesia can occur: your brain and nervous system throughout the body become

* Some longer stressful experiences can elicit analgesia, such as longer-term shocks or longer durations of very low-temperature cold-water swimming, but the analgesia is apparently not caused by the opioid system (but instead driven by one of the other brain chemical systems involved in pain suppression).

more and more sensitive to pain. This is called *hyperalgesia* (as opposed to analgesia, the absence of pain).[24] Hyperalgesia usually develops following an injury or other physiological insult, due to localized changes in the damaged tissue. These local changes produce a hypersensitivity to pain (and sometimes touch or movement) that can keep you vigilant, preventing more injury and protecting your body. Hyperalgesia is very helpful in the short term. But in the case of long-term chronic pain, hyperalgesia can actually outlive tissue damage. You don't have an active need to protect the body from further injury but you experience heightened pain as if you did. This is thought to happen via changes in regions in your brain involved in bodily awareness, attention and emotion.[25] These regions are able to send signals to the brain's sensory regions and down through the spinal cord, causing pain in the body originating in the brain. That means that even when there is no direct painful sensation to the body (for instance, a broken bone might be entirely healed), there could still be a pain signal in the brain telling you your body is in pain.

People with chronic pain are far more likely to experience a mental health disorder. A large study by the World Health Organization found that people who experienced persistent pain for more than six months showed a fourfold increase in anxiety or depressive disorders. As I see it, there are two possible explanations for the close relationship between chronic pain and mental health. The first (perhaps the most obvious, the one you think of right away) is that being in pain is *clearly* uncomfortable, unpleasant and disruptive to life, and that such a miserable experience must naturally lead to poor mental health. I am sympathetic to this explanation. I experience intermittent chronic pain from osteoarthritis in my foot after an accident sixteen years ago. Anyone who has experienced chronic pain has felt the mental toll of being subject to your body's whims: it is substantial, it forces your willpower to be secondary to your pain's ultimate command. It is inescapable. It is not surprising that it can worsen mental health. But this is not the only direction of causality.

Across countries and cultures,[26] the association between chronic

pain and mental health runs in both directions. People with chronic pain are more likely to develop depression but people with depression are *also* much more likely to develop chronic pain in the future.[27] What could explain this?

Chronic pain might be more common in people with depression if susceptibility to depression also confers a susceptibility to chronic pain, and/or if current depression changes the way the brain responds to pain. There is evidence for both of these possibilities. The biological mechanisms causing chronic pain share many characteristics in common with those involved in depression. Most tellingly, in the brain, there is substantial anatomical overlap between the brain regions disrupted in people with chronic pain and those disrupted in people with depression or anxiety[28] (and likely other mental health disorders). Many of the physiological processes thought to support chronic pain, such as heightened inflammation, are also thought to play a causal role in mental health disorders.[29] This fact also reveals something about chronic pain itself. In my long experience with chronic pain, I have found that doctors who speak to you about it as a patient think it is very important to emphasize that chronic pain is not 'all in your head' – it is *real*. But in my experience, as a scientist and as a patient, this is not quite the truth.

Neuroscientific studies of chronic pain show that this disability may have more in common with a mental health disorder than with short-term pain. When you experience short-term pain following from an injury or other damage to the body, pain receptors called nociceptors are activated, and transmit information about tissue damage via nerves to your spinal cord. From the spinal cord, information is propagated up to the sensory-pain circuitry of the brain. You can think of this as the 'bottom-up' pain pathway, sending signals about pain somewhere in your body to your brain. Over time, pain receptors can become sensitized or habituated, increasing or decreasing pain responses, respectively.[30] But once the signal from nociceptors reaches the brain, the amount of pain you eventually feel is not a direct reflection of the information transmitted up via nociceptors. In addition to the physical *sensation* of pain, you also

have a much wider emotional and cognitive experience: something upsetting, distracting and attention-grabbing, which also forms part of what we call pain. So the experience of chronic pain might originate from pain sensations but it also could originate from somewhere else entirely – from other cognitive processes in your brain.

This concept is hard to wrap your head around when you are the person in pain. When you can point to something on your body that hurts, describe what causes and what relieves its pain, it seems impossible that the pain is from anything other than the source you identified. But pain experience is influenced by hunger, arousal, stress, distraction, your previous experiences with pain and your genetics, among other factors.[30,31] The pain you actually experience originates in the brain, via unconscious processes including expectations and predictions about the body. And sometimes, these processes are so powerful that they no longer require input from the nociceptors in the body to send pain signals to your sensory systems.

In chronic pain, your brain's expectations about the significance of pain magnify its severity.[31] For instance, interpreting pain as a potential threat can enhance pain perception.[31] Previous sensations associated with pain can begin to evoke pain on their own, overgeneralizing the pain response to a non-painful input.[30] That is how chronic pain can even be entirely caused or maintained by the state of the brain: you can perceive pain without any information travelling up from the nociceptors; it can genuinely be 'all in your head'.

If, like me, you experience chronic pain, there is also an upside to this news. If pain can be maintained by processes very similar to mental health disorders then it does not always require painkillers: it can also be treated by changing your expectations about pain.

I experienced this phenomenon by accident a number of years ago when I was seeing an orthopaedic surgeon who sent me for steroid injections in the location of my old injury in case they relieved my pain enough that I could delay surgery (otherwise I needed a joint replacement in my foot). He had diagnosed my osteoarthritis

on an MRI scan and it was relatively severe, but steroids work very effectively for some people's pain by decreasing inflammation at the site of the pain. I went for the steroid injection and was one of those lucky people – it worked.

But it turned out I was extra lucky. Although the steroid injection was supposed to wear off after around six months, it's been about eight years and I have never returned to the level of pain I had before the injection. Although I still experience it most days, it's not as debilitating and I haven't needed surgery. I don't know what the surgeon would say about this, but I have my own hypothesis. The steroid injection temporarily relieved some of the 'bottom-up' pain generated by inflammation in my foot. But this temporary relief had a much longer-term effect on my pain levels, which could only have been driven by changes in my brain. This implies that while some of my pain must have originated in inflammation in my foot, what I experienced was filtered heavily by my brain. Years of pain had potentially shaped my brain pathways that had become used to pain, monitored pain, expected pain, and had begun to enhance the sensation of pain on my body.

I don't talk about my own experiences with chronic pain much, because my story is just that – a story, not data. It is most certainly not an 'easy fix' for everyone, and chances are I'll probably still need surgery eventually because a steroid injection (no matter how successful) does not stop the cartilage deterioration from osteoarthritis. But my anecdote is a demonstration that sometimes even pain with a visible, 'real', external cause is actually largely mediated by your brain. In my case, this meant the effects of a localized, short-term treatment extended far beyond their plausible actions. In other people's cases, there may even be no visible external source, yet debilitating pain driven by their brain feels just as real as an injury.

In one instance your brain might create or enhance pain – perhaps it has learned to expect it, to fear it, to detect the potential for harm even at very low non-threatening levels. In other situations, the influence of the brain on pain can have a remediative effect, which works something like a placebo (placebos get a bad reputation but they can

be brilliant – as we'll discuss in Chapter 5). In the end, chronic pain can certainly be 'all in your head', even if it feels entirely outside your head. Some scientists would even go so far as to say pain is *always* all in your head since there is no experience of pain that is unmodulated, unaffected by higher-level brain states, like attention or distraction. The real problem is the idea that something that's 'all in your head' is any less real – whether we are talking about pain or depression, something that is 'all in your head' is still *very much real* and just as physiological as an injury or infection.

Where is pleasure in the brain?

So far, I have only mentioned the ability of mild stress and skydiving to elicit pleasure. Still, I imagine you have some idea of the other, more typical sources of pleasure. I would not recommend you put yourself through mild pain just to feel good briefly. Luckily, opioid release, along with release of other pleasure-mediating neurochemicals, is not solely elicited by short-term pain or stress. Many things you would normally associate with pleasure – food, sex, exercise, social interactions and laughter – have similar effects on the brain: they all elicit release of pleasure-mediating opioids (along with other chemical changes in the brain).

Just like stress-induced analgesia, caused by chemical changes in the brain, and the cascade of signals between the brain and spinal cord that result from these small chemical changes, pleasurable things also have the rather amazing ability to reduce pain. For example, in both male and female rats, having sex can induce analgesia.[32] There are some studies showing this can be true in humans, too. There have long been anecdotal reports from people who suffer from migraines that sex can relieve the pain of a migraine. Large surveys support arguments that sex can relieve the pain in around 60 per cent of migraineurs. A word of warning, however: in people who experience cluster headache, sex is equally (if not more) likely to worsen rather than help headache pain.[33] So

if you're not certain about the cause of your headache it might not be worth the risk.

Where does pleasure come from in the brain, and why does it have this ability to reduce pain? There are many types of experiments you can do to answer this question (and related questions throughout this book). You can study animals or humans or simulate processes with a computer. You can observe how something functions or you can intervene with its natural function to see what happens. The trickiest aspect is to identify brain regions that *generate* pleasure responses – their involvement is not just incidental to pleasure. How did scientists do this?

First, you need to figure out how to measure what the brain is doing in the first place. To be able to measure the firing of brain cells you usually need to open up the skull and measure the electrical firing of brain cells using tiny electrodes. It typically wouldn't be ethical to do this in healthy humans, so to measure the precise neurobiology of pleasure, you might start by recording a rat's brain activity while it did something pleasurable and compare this to something less pleasurable. This presents you with a second problem. How do you know the rat is experiencing pleasure? You could measure factors like how much a rat is willing to exert effort – press a button, runs towards a reward and so on. But as we will discuss in Chapter 4, rats (and humans) might put effort into something that they do not necessarily get pleasure from. So how to measure if an animal *likes* something? A different approach is to measure facial expressions in an animal. As early as Darwin, scientists wrote about 'liking' facial expressions that are common across many animals, including humans, primates and rats.[34,35] You can see what a 'liking' expression looks like if you put sugar water on the tongue of a rat (or a baby). Both will start engaging in rhythmic tongue protrusions (lip-licking). As a scientist, you could quantify a rat's pleasure by, for example, counting the number of lip-licks, looking to see which electrodes in the brain correspond with lip-licks and – voila! – you have found the brain basis of pleasure in a rat.

But there are some major drawbacks to this method. What if

pleasure is not the only thing that causes a rat to lick its lips? Or what if not all pleasure causes lip-licking – perhaps only food-related pleasure? The problem with interpreting its tongue protrusions as pleasure is that you cannot check with the rat to make sure they actually like the taste. In this experiment, you are engaging in something called the 'mental inference fallacy' by emotion neuroscientist Lisa Feldman Barrett. What that means is, because animals cannot tell you what they are thinking, your projection of an experience (pleasure) onto an observable metric (tongue protrusion) is by definition a total guesstimate.

So perhaps you concede that you cannot run this experiment unless you know exactly how your animal is feeling: you need to measure whether the animal is experiencing happiness, sadness, disgust, anger or pleasure. Well, in that case you would make your life a lot easier if the animal in your experiments was a human. With humans, you can ask them if they are experiencing pleasure and hope they will tell you the truth. (I myself have made this very decision in all my experiments, and my life is easier for it.)

Once you have decided to measure pleasure in humans, you will soon encounter some new obstacles. Unlike in animal experiments, neuroscience in humans cannot easily measure the firing of individual brain cells (except in very special cases, such as recordings from neurons conducted during brain surgery). Instead, we use various brain-imaging techniques to take live-action measures from the brain that measure electrical activity in the brain, or measures that can approximate brain activity.

Early brain-imaging experiments used a brain-scanning technique called positron emission tomography (PET), which among other things can measure the brain's metabolic activity, which roughly corresponds to neural activity. The way that PET works is by injecting people with radioactive tracers: when someone has been injected with a particular radioactive tracer, areas with high metabolic activity in the brain (or body) are marked by high radioactivity, which can be recorded and reconstructed as an image showing approximately where in the brain neurons were active.

Today, to measure more anatomically specific brain activity, scientists mostly use a slightly newer technique called functional magnetic resonance imaging (fMRI). You have probably seen fMRI pictures in the news: they look like coloured blobs on different bits of a magnetic resonance imaging (MRI) scan. When you read in the news (or in this book) that some region of the brain is involved in a particular function, this claim usually comes from an average across many measurements in one person (someone lying in the scanner looking at a succession of similar images, for example), again averaged across a number of people (ideally as many as possible, for statistical purposes).

fMRI approximates neural activity by measuring how oxygenated blood is throughout the brain. The images produced have better resolution than PET scans, in some cases in areas as small as one millimetre cubed. However, blood oxygenation rises and falls very slowly, on the scale of seconds, while neural firing is much, much faster. So, fMRI cannot possibly keep up with the real speed of brain activity. Instead, it approximates brain activity over both time and space. These technical challenges of fMRI (and other brain-imaging techniques) requires all neuroscientists to form very close collaborations with physicists, who have discovered how to tweak and optimize the magnetic fields generated by an MRI scanner to create the best images possible. But even after overcoming these technical challenges there are undeniable and insurmountable limitations to fMRI: it still does not measure the chemical-electrical activity of brain cells directly and does not have the resolution to get signal from a single brain cell. Even a cubic millimetre, a decent resolution for human fMRI experiments, contains about one million neurons. So the most convincing evidence is *convergent evidence*: when an experiment in humans confirms something an animal experiment also shows.

Which brings us back to your pleasure experiment – trying to find regions that cause pleasure. In the context of pleasure, to get convergent evidence you really require two experiments: one precisely measuring brain activity in rats, but with an imperfect

measure (or measures) of pleasure, and one imprecisely approximating brain activity in humans, but with a verified, subjective measure of pleasure.

Now you must decide what would reliably give volunteers pleasure. One popular option is a chocolate milkshake shot directly into their mouth, having made sure all your volunteers like chocolate (this is also a method of alcohol consumption at some parties, but those are not good environments for scientific experiments). Delivering a liquid directly to a volunteer's mouth also has an advantage unique to the MRI environment: it does not require chewing or other movement. Keeping still is essential to get a clear, good-quality MRI image (in contrast, you would not want to scan someone's brain while they are eating a doughnut: you would get very blurry MRI images).

Once you've decided what counts as pleasure for your experiment, the next thing you need to do is look at what is happening in the brain while volunteers experience pleasure. After popping your volunteers in the scanner one by one, you analyse their brain images (this takes ages and does not happen during the scan itself, despite what is often depicted on the telly). Ah ha! you think when you see the same brain regions become more active in all your volunteers while they drink the milkshake. Those must be the pleasure regions of the brain.

But soon afterwards you mention your cool pleasure-region discovery over a pint with a scientist friend. It turns out that by coincidence, this friend has been running experiments on a group of stroke patients who have specific brain damage in one of the regions that you identified in your chocolate pleasure network. According to your results, this brain damage should mean that they do not experience pleasure. You ask your friend to test this in their experiments. The patients show a perfectly normal experience of pleasure, on every measure. The brain region you found, while clearly correlated with the experience of chocolate-milkshake drinking in your first experiment, was not responsible for *generating* pleasure: losing it did not eliminate the experience of pleasure.

This is because of a classic statistical error. Many people with an affinity for statistics who are familiar with this error like to shout at you whenever they detect it: 'correlation is not causation!' (Perhaps they have less of an affinity for social interaction.) What this means is: just because two things occur together does not mean there is a causal link between them. It is important to remember that any time you read about brain regions or brain chemicals 'causing' an experience or behaviour, that is not necessarily true unless the experiment manipulated the region or chemical to evoke the experience – for example, using a drug, brain stimulation or other method that changes the region and causes a particular outcome, not just brain imaging. It is always important to consider multiple experiments, including animals (where causal methods are easier) as well as humans (where knowing what someone is experiencing is much easier), to be more certain about what brain regions or chemicals can cause pleasure, pain or other experiences. Of course, this is not a problem unique to brain imaging. Throughout the book you will hear about strong, believable correlations in humans, or convincing causal evidence in animals (or both in the case of the gut microbiome) that are not necessarily causal when it comes to human mental health.

So if one day you read an article in the news that claims (for example) eating chocolate treats depression by changing the brain, you should try to figure out: is there truly a causal relationship between eating chocolate and lower depression? Or do happier people just eat more chocolate? Even if it is causal, is this specific to chocolate or would it work for any sweet? And what in chocolate could be the cause – the taste or a key ingredient?

Many scientists have run something like your hypothetical chocolate milkshake experiment. They have found that there are many brain regions associated with tasting something pleasurable. For instance, neurons in the orbitofrontal cortex (situated behind your eyes) carefully track how pleasant you find a particular food. The activity of these neurons is tightly coupled (correlated) with pleasure. This pleasure-activity coupling is not just the case for pleasurable food. Many will have

experienced the divine pleasure that particular segments of music can evoke. Two decades ago, Anne Blood and Robert Zatorre used PET to measure brain activity while people listened to music. Because music that makes you swoon is highly personal, the scientists let volunteers choose their own music. (With the same piece of music, one person's swoon might be another person's nausea, messing up the whole experiment.) They measured volunteers' heart rate, breathing, brain activity and subjective report of feeling 'chills' during the music. As the volunteers' 'chills' increased, so did the activity of orbitofrontal cortex, as well as other brain regions active during food, sex, drugs and other pleasurable things.[36] These brain regions were tracking participants' subjective musical pleasure.

But, as you discovered, just because the orbitofrontal cortex is tightly correlated with the experience of pleasure does not mean it is causing pleasure. Unlike what you would expect if the orbitofrontal cortex was causing pleasure, patients who have damage to the orbitofrontal cortex are still able to experience pleasure, although related decisions and expressions of emotion are changed.[37, 38] That means the orbitofrontal cortex is involved, but not causing the experience of pleasure.

Some regions in the brain do directly generate pleasure. Our brains possess a number of tiny, distributed regions called 'hedonic hotspots'. Hedonic hotspot activity directly causes pleasure. Their name comes from geology: hotspots are regions distributed across the Earth where the magma is hottest, and volcanoes can emerge. Hedonic hotspots are where pleasure can emerge, and are dotted across almost the entire brain.[39]

The first discovery of regions that cause pleasure (hedonic hotspots) measured pleasure-like responses in rodents (lip-licking and so on) after scientists directly injected drugs into highly specific brain regions. This gave them a map of 'objective and precise plots of hedonic hotspots in the brain'. These hotspots then can be (and in some cases have been)[40] tested in human studies using fMRI and other techniques.

Although hedonic hotspots are both small and distributed, they

also function together as a pleasure network. Hotspots are 'analogous to scattered islands that form a single archipelago,' wrote acclaimed pleasure neuroscientists Morten Kringelbach and Kent Berridge. In fact, it may be advantageous that they are distributed, scattered islands. Falling within various different regions enables sources of pleasure to play different roles in different brain processes by interacting with distinct bits of the brain. When directly stimulated (e.g. in animals, or with a drug), hotspots have the capacity to enhance liking of a sensory pleasure: they can directly cause pleasure. Although hedonic hotspots in the brain can be stimulated by drugs (such as morphine or cannabis), most of the time they are naturally stimulated by particular experiences, such as laughter, sex or music. These hedonic hotspots are your brain's map of pleasure, and their biology gives us a route into understanding the role of pleasure in mental health.

The dangerous and not-so-dangerous roads to pleasure in the brain

One lesson from hedonic hotspots is that there are many roads to pleasure in the brain – pleasure involves a large network of brain areas. Take one tiny hotspot, a one cubic millimetre-sized region of the nucleus accumbens in rats (about one cubic centimetre in humans). In rats, when this region is injected with a drug that stimulates opioid receptors, animals display four times as many pleasure responses (tongue protrusions) to sugar water as before.[39] If we were to engage in the mental inference fallacy this could be interpreted as this region causing pleasure – but there is converging evidence because drugs that stimulate these same receptors, such as opium, heroin and codeine, also reliably evoke some degree of pleasure in humans*.

* Not all scientists agree that typical opioid drugs cause pleasure in healthy humans: pain relief is often pleasurable, of course, but most opioids also have distinctly less-pleasurable effects such as nausea and dizziness.

Opioids are not the only chemical route to pleasure in this hotspot. Another class of brain chemicals called endocannabinoids activate the very same hotspot. As the name implies, endocannabinoids are natural substances related to plant cannabinoids, one of which is the chief ingredient of the drug cannabis. Injections of an endocannabinoid into this hedonic hotspot also cause a dramatic increase in animals' pleasure-like responses to sweet tastes,[39] not unlike the human pleasure many people get from cannabis. So two very different classes of chemicals can evoke similar pleasure via the same brain region.*

Perhaps this all seems a bit like science fiction when it comes to real, human happiness. Surely I'm not suggesting opioids or cannabis are the secret to happiness? Not for most, anyway. But what this tells us is that our brain has multiple routes to similar pleasure outcomes. And there are things in everyday life that, just like drugs, stimulate opioid or cannabinoid release, among other brain chemicals (such as social laughter, as we discuss later in this chapter). This knowledge could be useful when it comes to pain relief, as well as when it comes to understanding our pleasure system.

In medicine, the role of the brain's opioid system in pain relief has long been exploited for analgesia. Most people who have taken an opioid drug, including codeine, Vicodin, oxycodone and so on, can attest that their threshold for pain increases while under the influence of the drug, and many also report that it evokes a subjectively pleasurable feeling (arguably this may work by relieving unpleasant, dysphoric feelings). This is a highly useful property clinically. But as we are now aware, even medically prescribed opioid drugs have profound dangers in some cases, including dependence and overdose.

In 2021, 80,816 people died of opioid overdoses in the US,[41] where prescription of opioid drugs is common. And 80 per cent of people

* Incidentally, endocannabinoid injections to this hotspot also double the amount of food consumed by rats, an effect not totally foreign to those humans familiar with the plant version who have experienced 'munchies'.

who misuse heroin first misused a prescribed opioid. This is complex because prescription opioids are vital in pain management, and for most people they're safe when their use is monitored carefully. (Note opioid overdose also occurs in the UK, but overdose from prescription opioids is less common than in the US. American readers will be surprised to learn that British patients are typically only offered over-the-counter painkillers for surgeries like wisdom tooth removal, while in the US many patients would be prescribed a fairly large quantity of Vicodin for the same procedure.)

The addictiveness of opioid drugs also shows the close link between pain and mental health. This is because opioids do not just numb pain from outside sources: if you ask people who have taken opioids, many report that the drugs also dull internal pain, softening or muting people's despair. But as everyone now knows, killing pain with opioids – whether physical or psychological – can have terrible long-term consequences. To add to this, experiencing difficult life events or having an existing mental health vulnerability might make the relief provided by opioid drugs even more salient, and even more dangerous. It is understandably very, very hard to resist an escape from emotional pain.

This means that alternative pain treatments are absolutely critical. This includes developing new drugs with painkiller properties but without the potential for addiction or overdose, many of which are already available. But as we will discuss later in the book, this also includes various psychological therapies, changing your thoughts or behaviours regarding pain. This approach works in some people because it can alter high-level brain processes that contribute to pain perception, including your expectations and learning. Even short-term pain treatments like steroid injections could be tweaked to have larger effects on pain suppression brain systems.

Natural opioids also have the ability to suppress pain. Natural opioids are involved in such trivially pleasurable activities that one might be inclined to think they are not important. This would be a mistake. One example of the simple things that evoke natural opioid release is laughing with friends. This was illustrated in a

lovely experiment by Finnish neuroscientist Lauri Nummenmaa and his then-PhD student Sandra Manninen, who used PET brain imaging to measure levels of natural opioid release in healthy human volunteers.[42] Before the scan, volunteers hung out with their close friends while watching comedy clips. After only thirty minutes of hanging out with friends watching comedy videos, the volunteers' brains showed natural opioid release in various regions, and the volunteers themselves reported feeling calmer and happier.[42] Most compellingly, the number of times a volunteer laughed in a given minute was associated with their potential for opioid-derived pleasure: the more opioid receptors someone had in the frontal cortex (including the orbitofrontal cortex), the more they laughed. The biology of your brain is directly related to your experience of pleasure, and social laughter harnesses the very same system as opioid drugs. Opioid drugs are merely piggybacking on a system designed to support laughter and other routes to natural opioid release.

Also, like opioid drugs, laughing with friends has analgesic properties: relieving pain. The same experiment found that watching comedy clips with friends increased the amount of time volunteers could spend doing uncomfortable 'wall sits' (leaning against the wall with legs at right angles until your legs become too painful to hold you up – if this doesn't sound painful, try it). By releasing endogenous opioids, social laughter gives you a higher pain threshold, making you more resilient to discomfort. (And unlike opioid drugs, as far as I am aware, there is no significant risk from watching television comedies with your friends.) But be warned: not all television, even when social, has this magical analgesic ability. Wall sits were still more painful after watching drama clips than after the comedy clips. Of course, this is a smaller effect on pain than if the scientists had given volunteers opioid drugs but it's a beautiful demonstration of how social laughter also evokes opioid release and pain relief.

This is a rather extraordinary ability of something so quotidian. What is the purpose of the brain's pleasure system being so

sensitive to social laughter, to the degree that social laughter can suppress something as salient as pain? Nummenmaa interprets their results to mean that opioid activity is a safety signal, calming and relaxing people to facilitate social cohesion. This relates to an evolutionary theory of the purpose of social laughter: that it facilitates mass group bonding and cohesion, essential for species survival, and therefore underpinned by this powerful pleasure system. Group cohesion is highly evolutionarily advantageous: in other species, social grooming is thought to promote group cohesion. Social grooming is also underpinned by the opioid system: drugs that alter opioid levels change monkeys' social grooming behaviour.[43] According to this evolutionary theory, social laughter might function as an extension of grooming, promoting social cohesion by releasing opioids, causing pleasure and analgesia. Unlike grooming, laughter has the advantage that it does not necessitate one-to-one physical contact. That means it can be spread across much larger groups than grooming. Laughter is also so contagious that sometimes just hearing someone laugh can make you laugh. Laughter may use contagiousness to facilitate social cohesion by triggering mass opioid release on a scale much larger than one-on-one grooming.

Three of my friends are experts on laughter (a wonderful thing to be an expert in). London neuroscientists Sophie Scott, Carolyn McGettigan and Nadine Lavan have worked together on a number of experiments measuring laughter in the brain and figuring out what makes humans laugh. Their theory is that the function of laughter is actually broader than just promoting social bonding: it also regulates negative emotional experiences.[44] This means laughter could have both immediate positive consequences on emotional state and long-term positive consequences for social relationships. Laughter itself could sustain healthy, long-lasting relationships. Consider, for example, a couple having an argument, a source of great physiological and mental stress for most people. Usually, when couples have an argument, as you might imagine, each person's physiological signs of stress spike – a faster heart rate, sweating, a rise in blood pressure and so on. But one study showed that the

physiological signs of stress do not spike to the same degree in every arguing couple. While discussing an area of marital conflict, some couples did not show the same degree of physiological stress. These lucky pairs were the couples who laughed the most during their discussions.[45] Their lower levels of stress were not confined to the stressful discussion: the more a couple used positive emotional expressions like laughter during their discussion, the higher they rated their level of marital satisfaction. This ability of laughter to dampen down marital stress could be crucial to general wellbeing in people with long-term partners, because marital satisfaction is a close corollary of life satisfaction.[46] Social laughter seems to fulfil multiple pleasure-related functions, from momentarily feeling good, to relieving pain, to facilitating greater social bonding – perhaps even improving one's overall quality of life.

De gustibus non est disputandum

Although there are some near-universal likes and dislikes (laughter, sex, etc.), the specific constellation of what elicits pleasure in each person is relatively unique. Or perhaps the way to think about it is that everyone enjoys fulfilment of the same basic needs – relief of cold or hunger, reproduction, social connection – but we fulfil them in different ways. This is underpinned by the fact that we do not all have the exact same brain responses: differences in our likes and dislikes are mirrored by differences in our brain's release of natural opioids, endocannabinoids and other chemicals.

Take food, a common source of pleasure. From animal studies, it seems that how much you like a particular food is driven by whether that food evokes natural opioid release in your brain.[47] But do not be mistaken that just because something is biologically based it is innate (that is, present from birth). As with all brain physiology, the amount of opioid release you experience from (say) a slice of cake is influenced by *both* your genetic makeup and your previous experience with cake (and other experiences, too). The environment and

everything you have experienced in it shapes your brain's biological response to every situation, interacting with inborn genetic predispositions. Pretty much everyone likes cake because food high in fats and sugar provide quick, accessible energy and also cause endogenous opioid release. Opioid release from fat and sugar can even counteract natural drives like satiety.[48] This explains why you might feel that you cannot eat another bite of your dinner but upon being presented with a delicious-looking cake, if you are someone who likes cake, your appetite miraculously recovers. If opioid release is blocked, this effect goes away. In one experiment, rats with full bellies were no longer interested in their dessert (cream) after scientists blocked release of their natural opioids.[48] So you have a personal brain mapping of your food likes and dislikes, co-written by your genes and your previous experiences, and edited and re-written whenever you have new experiences with food.

A similar personal mapping exists for your dislikes. Just like the hotspots we discussed at the beginning of the chapter, elsewhere in the brain lie hedonic 'coldspots' – regions that, when activated, directly suppress pleasure. Coldspots are often located very close to hotspots (for example, one is a direct neighbour of the opioid and endocannabinoid hotspot I mentioned). In these coldspot regions an opioid injection in rats does the exact opposite of its actions in hotspot regions: it suppresses so-called liking responses.

In everyday life, how much you like or dislike something is associated with the degree to which your hotspots and coldspots in your brain are activated. Cambridge neuroscientist Andy Calder was working in my department a couple decades ago when he discovered a 'hotspot' region of the ventral pallidum found in rats was also activated in humans in brain scanners when the volunteers were looking at pictures of chocolate cake, ice-cream sundaes and other delicious foods, compared with bland foods*. Most compellingly, the more

* Sadly, I never met him because he passed away before I joined, but I always felt like I did because he had been my wife's PhD supervisor and had said several particularly incisive one-liners about scientists that we still repeat to this day.

each person said they liked chocolate or sundaes and so on, the more active the hotspot region was when they were shown a picture of that particular dessert. The activity of this region was related to that person's subjective pleasure – the degree they found that food rewarding.[49] But just like in rat brains, in the human volunteers' brains this hotspot had a coldspot neighbour right next door to it. When volunteers were looking at pictures of disgusting, rotten food, a spot just in front of the ventral pallidum hotspot was activated. This was also associated with subjective displeasure: the more someone was disgusted by the rotten food, the more activation there was in this coldspot region.[40] Your personal enjoyment of a sundae or your personal disgust of a rotten vegetable directly relates to activity in these hotspot and coldspot regions of the brain.

Because hotspots and coldspots are causally linked to pleasure, not just associated with it, there are even cases of dramatic differences in liking after brain damage to one of them. In one lesion study, a 34-year-old patient suffered a stroke that damaged the ventral pallidal hotspot found in Andy Calder's experiment. The stroke left this patient with a complete loss of pleasure from many different sources in his life and a severe depression. Coupled with this, there was a surprising upside: prior to the stroke this patient had experienced alcoholism and other drug addiction, and following his stroke his cravings for drugs and alcohol stopped completely. He reported, amazingly, that he 'no longer experienced pleasure from drinking alcohol'.[50]

Differences in our brain's biology (moulded by experience as well as genetics) can cause drastic differences in our likes and dislikes. The next time you like something no one else does, or dislike something that everyone else adores, you might think about your unique patterns of hotspot and coldspot activity. Personally, I despise mayonnaise – although my wife (and many other people) love it. Although I have not tested this inside a scanner, you could imagine that when I eat mayonnaise my brain would show coldspot activation – such as in my ventral pallidum – while the millions of others who enjoy it would not. In fact, they might even show hotspot activation to the very same taste. Your

hot- and coldspot activation to different foods is a map for your unique tastes. What you have in common with everyone is that pleasure and displeasure – from whatever unique source you experience it – is ultimately a very useful experience, both to society (as in social laughter) but also to you as an individual. Perhaps the most important way pleasure is useful is in supporting and maintaining mental health. This is akin to how acute pain is useful both as a short-term aid to survival and to indicate what to avoid in life generally. Pleasure tells us in the short-term what feels nice but it can also have long-lasting broad effects on life satisfaction.

The hedonics of mental health

The ability to seek out and experience pleasure is key to mental health. Not because we should be experiencing pleasure all the time – full-time hedonia is not desirable (nor, I imagine, truly possible) for the brain – but there are advantages of being just a little bit of a hedonist. Motivation to pursue pleasure in the short term sometimes has long-term positive consequences for your mental health because regular experience of pleasure is strongly associated with better mental wellbeing. For people who experience very little pleasure day-to-day, overall ratings of life satisfaction tend to be low. The more pleasure someone experiences in their quotidian life, the higher they tend to rate their wellbeing.[6]

Hang on! I hear the sceptics say. Aren't you falling for that very same correlation-is-not-causation issue? Well, yes. This association could very well just mean the rather trite observation that people with higher wellbeing also enjoy things more, not that enjoyment causes higher wellbeing. But there is convergent evidence for the latter explanation as well. Things that *cause* pleasure, like social laughter, also seem to make people generally happier in their lives. In the case of laughter, this could plausibly occur because of its physiological effects: its analgesic effects via the opioid system, which result in decreased stress responses. Of course the relationship between

wellbeing and laughter clearly runs in the other direction – happier people presumably also laugh more. The most likely possibility is that wellbeing and pleasure both cause one another in some sort of self-perpetuating spiral of pleasure and wellbeing that sounds very nice if you are lucky to find yourself in the middle of it, and very unfortunate if you do not.

For many people around the world who have experienced depression and other mental health disorders that involve reduced pleasure, it is also self-perpetuating to be inside this spiral with low wellbeing causing less laughter, less laughter producing fewer opioids and therefore lower wellbeing. The evidence that lack of pleasure causes poor mental health comes in part from the clinical symptom of anhedonia. Anhedonia was traditionally conceptualized as an inability to experience pleasure, but the definition now also includes loss of *interest* in previously pleasurable activities. Here is a typical way anhedonia is assessed as part of a mental health questionnaire:[51]

Circle the statement that most applies to you:

1. *I get as much satisfaction out of things as I used to.*
2. *I don't enjoy things the way I used to.*
3. *I don't get real satisfaction out of anything anymore.*
4. *I am dissatisfied or bored with everything.*

If you circled *1*, you are not experiencing anhedonia. But if you circled *3* or *4* this would suggest you are experiencing some anhedonia. Anhedonia is a part of several mental health disorders. It is one of the two cardinal symptoms of depression (the other is low mood). It is a core component of schizophrenia, forming part of the so-called 'negative symptoms' that make someone experiencing psychosis likely to feel fewer emotions and withdraw socially. And changes in how someone processes pleasure occur across a number of other disorders such as addiction and eating disorders. But anhedonia is not just correlated with worse mental health. Experience of anhedonia seems to precede or precipitate several different mental

health disorders, suggesting it is also a risk factor for worse mental health. In substance addiction, for example, higher levels of anhedonia are thought to drive relapse.[52] That means that if you experience a shift in pleasure experience – moving from an average amount of pleasure experience/interest towards anhedonia – you might be more at risk of developing a mental health disorder. Or in the case of substance use, risk of transition from recreational drug-taking to excessive drug-taking behaviour.[53]

Some have even suggested that anhedonia is so central as an experience of mental ill-health it transcends specific clinical diagnoses. This suggests that a loss of interest or pleasure in normally pleasurable activities could be a transdiagnostic risk factor – a component that can make someone vulnerable to poor mental health *generally* (irrespective of the specific disorder) because it makes someone less resilient to the various stressors (biological and social) that can cause mental health disorders. Our ability to anticipate, represent and learn from pleasure may be a protective factor against worse mental health, and anhedonia a warning sign that our mental health is worsening.

One route by which pleasure sustains our mental health is via its effect on learning and motivation, the processes we delve into in Chapters 3 and 4. For instance, via learning mechanisms we can learn associations between things in the environment and pleasurable experiences, a phenomenon that has profound effects on motivation: what we are willing to expend effort to achieve. In one experiment, scientists conditioned rats to associate a rodent jacket with sexual pleasure. (I picture a sort of high-vis sleeveless construction jacket, but I don't really know what it looked like.) The scientists discovered that the jacket-sex conditioning was so effective that when the rats were not wearing their jackets they (the rats, not the scientists) showed 'dramatic copulatory deficits'.[54] A rat sex jacket! There is much you can criticize scientists for, but let it never be said that scientists are dull.

Focusing on pleasure

A popular assumption is that if you want to protect and support your mental health you had better adhere to an austere, and on the surface not-particularly-pleasurable, regimen: exercise, cutting out alcohol, perhaps medication or therapy. We will explore all these avenues towards mental health in later chapters – each of them are undoubtedly useful for many people. But the centrality of pleasure to mental health means that austerity is not the only route. For some people, perhaps those vulnerable but not currently suffering from a mental health disorder, a renewed focus on valuing pleasurable experiences could be a route towards maintaining mental health. As an aside, even what seems like a punitive regimen might support mental health in part via pleasure: exercise, for example, is well known to evoke short-term hedonia (a 'runner's high') and increased pain tolerance (analgesia). This is partly, though not entirely, due to the actions of opioids. Not all exercise is equal in this regard – high-intensity short-term exercise has this effect, but not lower-intensity hour-long exertion[32] (a bit like the cold baths, which have similar Goldilocks requirements to cause analgesia). In later chapters we will examine the processes inherent in anticipating learning about, and being motivated to seek out, pleasurable experiences, which are particularly important for mental health conditions – perhaps even more so than the experience of pleasure itself. 'Just add more pleasure' is not a reasonable suggestion for most people with a chronic mental health condition who may have disruptions in these other processes supporting the acquisition of pleasant experiences. It is surely easier to keep the pleasure system going than recover it after it misfires.

Focusing on pleasure is not as trivial as it appears. Just as chronic pain shares circuitry with poor mental health, so too pleasure shares circuitry with positive mental health. Unfortunately, you cannot take a shortcut to the brain circuits supporting hedonia. Opioid drugs, for example, may allow you to feel pleasure for a bit, although you risk experiencing the decidedly anhedonic effects of opioid withdrawal

(continued...)

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(by Paula Clarke Bain)