

## Contents

<i>Introduction</i>	ix
PART ONE: HOW THE BRAIN CONSTRUCTS YOUR MENTAL HEALTH	
1. Natural highs: pleasure, pain and the brain	3
2. The brain-body axis	33
3. Learning to expect wellbeing	61
4. Motivation, drive and ‘wanting’	79
PART TWO: ENHANCING MENTAL HEALTH VIA THE BRAIN	
5. Placebos and nocebos	101
6. How do antidepressants work?	113
7. Other drugs	131
8. How psychotherapy changes the brain	151
9. Electric feelings	173
10. Is there a mentally healthy lifestyle?	192
11. The changing nature of mental health and disorder	216
<i>Acknowledgements</i>	229
<i>References</i>	231
<i>Index</i>	261

## *Introduction*

*Joy is such a human madness.*

Zadie Smith

*When was the last time you felt absolute joy?*

I got married in the middle of a small wood outside of Cambridge during the summer of 2019, when I was 29. It was remarkably timed. One year later – when engagements among my 30-year-old friends had peaked – pandemic weddings were cancelled, postponed, attended by only the witnesses. But the night before my wedding, on an objectively smaller scale of disaster, it started to pour with rain. At two o'clock in the morning, the rain sounded like a biblical tempest. I moved myself into the spare bedroom and spent the night awake, sick to my stomach with anxiety, imagining the tables, chairs, hay bales and sofas we had set out in the woods that day getting soaked through, and my family and in-laws covered in mud, and rather unforgiving of our reckless choice to have our wedding outside in a British summer.

But in the woods at noon the next day, there was no sign of the storm. Sunlight floated through the leaves and landed on the heads of family members I thought for years might never attend my wedding. I looked over at my wife, and then for the next ten hours felt total consummate joy up until the moment I went to sleep (deep, unadulterated – I have no idea if it rained that night).

Joy feels ephemeral, impossibly to quantify. It is by its very nature rare and unexpected – out of the ordinary, leaps and bounds better

## Introduction

than what we would predict from our day-to-day life. Many days do not consist of the singular experiences that bring joy. Most days have good elements and bad, predictable and unpredictable: a surprising success, an unforeseen loss. *The Balanced Brain* is about how our brain builds each person's sense of their mental health by learning to predict the complex, changing information in the world around us.

Something more quotidian than joy is pleasure. We experience pleasure on average at least once per day.<sup>1</sup> Some researchers think pleasure is a concrete way to think about our sense of 'wellbeing', a term that is usually defined in two basic categories: the first, feeling good at one moment in time; the second, feeling good about your life in general. These two components are often assigned Aristotle's terms: Aristotle called the first category of feeling *hedonia* – feeling happy, a pleasurable feeling. This is the category psychologists tend to measure in their experiments, and also relates to two famous definitions of happiness: the 'possession of pleasures with the absence of pains' (Jeremy Bentham's definition);<sup>2</sup> and our record of moment-by-moment pleasure and pain across time (Daniel Kahneman's definition).<sup>3</sup> But social scientists who want to know how happy one country is versus another are more likely to measure the second category, *eudaimonia*: life satisfaction, and the realization of one's potential. Their work can answer questions like: are richer people more satisfied with their lives? (The answer is: up to a point.<sup>4</sup> See Chapter 10.)

Personally, I think these two traditional categories of wellbeing have more in common than not. Studies have found that people who experience more pleasure in everyday life also report better life satisfaction – the experience of *eudaimonia* is interwoven with *hedonia*.<sup>5</sup> Perhaps unsurprisingly, because the two categories are so closely related within individuals, it may be impossible to measure them separately from one another. When measuring *hedonia* and *eudaimonia* using separate questionnaires on people from around the world, they were almost entirely correlated (0.96), casting doubt on whether they can be truly differentiated.<sup>6</sup> Moreover, people's

## *Introduction*

responses to separate *eudaimonia* and *hedonia* questions were mathematically better accounted for by a *single* wellbeing measure than two separable wellbeing constructs,<sup>6</sup> meaning perhaps pleasure and life satisfaction, while conceptually different, operationally reflect the same overarching wellbeing construct.

Improving mental wellbeing has been a quest for decades, centuries, millennia – but society and science are still urgently grappling with it today. In this book, we will explore what neuroscience reveals about what it means to feel better, momentarily or durably. This means diving into where someone’s feelings of mental wellbeing come from: what makes one person experience *hedonia* from a small, everyday pleasure of life? How do our own experiences of positive and negative events help us construct a general sense of our life as negative or positive? How can small shifts in the mechanics supporting these processes cause worse mental health, and how are the same processes adjusted by things we do to improve our mental health, such as drugs, exercise or psychotherapy?

## *What is mental health?*

In my lab at the MRC Cognition and Brain Sciences Unit, a department at the University of Cambridge surrounded by rivers and cow fields, we run experiments to understand the brain processes that cause better and worse mental health, particularly in people with psychiatric disorders. Eventually, decoding these processes could help us invent or improve treatments. But mental health can mean very different things to different people. Neuroscientists have not agreed on a universal definition of ‘mental health’. Nor have psychologists, or philosophers or any other group that one might turn to for a definitive stance on the matter. You would think this would be problematic for scientists like me who study mental health. Actually, most neuroscientists do not let a philosophical quandary stand in the way of doing interesting experiments. Sometimes, better mental health is taken to mean lower scores on a clinical index

## *Introduction*

(which itself might be measuring depression, anxiety, stress or any number of other factors). Other times, positive scores on wellbeing indices are used: life satisfaction, for example. Still other times, particular chemicals in the brain, behaviours performed by animals or humans, or regions of brain activity might be inferred to represent some aspect of mental health (pleasure, reward and so on). A full picture on mental health must incorporate all these aspects, from the experiential to the biological, and map the routes in-between.

In this book, I use terms like ‘mental health conditions’, ‘psychiatric disorders’ and ‘mental illness’ relatively interchangeably to refer to disorders such as major depression, schizophrenia, generalized anxiety disorder and so on. These more medical terms are used to indicate when experiences of poor mental health are severe enough to impair functioning and meet other specific diagnostic criteria. However, the way scientists refer to these conditions is constantly changing. In some cases, I use the more general phrase ‘mental health problems’ or ‘mental ill-health’ to signify that someone might experience problems without meeting the threshold for these traditional diagnostic criteria, or their problems might not fall clearly into a single diagnostic category. In any case, it is worth remembering that different people who experience poor mental health might choose to refer to their own experiences with the terms that are most meaningful for them (for example, as ‘experiences’ or ‘problems’ rather than ‘disorders’ or ‘illness’ or vice versa).

My view of mental health in the brain is that it is a sort of balance. In biology, living organisms survive by maintaining homeostasis: a relatively stable state inside the body, irrespective of changes elsewhere (the temperature outside, your blood sugar level, your hydration and so on.). To stay in balance requires change: your body sweats to decrease your temperature; you eat a doughnut to increase your blood sugar; you drink fluids after running a race. What we think of as ‘mental health’ also requires homeostasis. Like our body’s homeostasis, maintaining a ‘balanced brain’ requires flexibly responding to changes in your environment. This includes our internal environment – which might present challenges via emotional pain, or even infection – as

## *Introduction*

well as our external environment, which challenges us daily with the various stressors of life. Inherent in this balance is the ability of your mental state to help, rather than hinder, your functioning, increasing your chances of survival. For people who have experienced poor mental health at points in their life, their mental state may sometimes impinge on their ability to do daily activities, enjoy time with loved ones, or other things that are vital to living well in the world.

### *Where does mental health come from?*

Mental health is supported by many different brain processes, from those involved in pleasure and pain, to those supporting motivation and learning. Your brain's biology, and its close relationship with your physical body, creates, sustains and protects your mental state. You may already use many different techniques to support or improve your mental health, and these techniques will each have particular effects on these brain processes. But you have probably already noticed that if a friend recommends whatever technique they use ('try yoga!'), it might do absolutely nothing for you. That is because an intervention to improve mental health works or doesn't in the context of a particular person's brain (and bodily) processes. These ongoing biological processes in your brain are shaped by often-subtle differences in your genes, which affects your general propensity to particular thought, mood or behaviour patterns. Equally importantly, these processes are shaped by a whole gamut of earlier-life experiences. (I say earlier-life because often it is assumed that all formative experiences for mental health or illness happen in childhood, when risk is highest, but they can happen throughout life.) These are not independent but interactive factors, with the effect of some genetic predispositions altered by environmental experience, and (though more neglected in popular conception) exposure to specific environmental experiences affected by someone's genetic makeup. Nothing about 'biological' implies a static cause, however: these factors (and their interactions) are dynamic,

## *Introduction*

particularly crucial at certain developmental timepoints, but relevant throughout someone's life.

This is because many elements of the nervous system are plastic, changeable, moulded by their environments. By 'nervous system' I mean the brain and spinal cord, but also their extensive and bidirectional path of communication with the rest of the body. The function of the nervous system is influenced by our genetic makeup, cultural factors, economic security, stressful life experiences, the social world we live in, our diet and the physical condition of our bodies (to name but a few), all of which affect our mental health via their effects on the nervous system. It may seem impossible to measure and quantify a phenomenon originating from such a widespread set of factors. It is certainly very tricky. But each factor causes better or worse mental health by changing a physiological process in the nervous system. Experience of poor mental health can originate from vastly different causes, inside and outside the body. As you will discover in this book, mental health can also be improved or treated via just as wide a variety of things inside and outside the body. But no matter its cause, the brain is the final common pathway for mental health: the eventual target of every risk factor and every treatment.

This may surprise you. Perhaps your intuition is that mental health works a bit differently to physical health conditions affecting particular organs or organ systems, such as heart disease or diabetes. Perhaps it even seems pejorative to claim that mental health conditions are physical, given that they are undoubtedly influenced by many important societal factors (although societal influence is not unique to mental health: diseases affecting other organ systems, such as the lungs or the heart, can have social causes such as unequal pollution or access to healthy food). But just like the endpoint of these other socially caused diseases is in their effect on our biology, the experience of all mental states is also a physical process. Mental wellbeing, and our susceptibility to mental ill-health at various points in our lives, is constructed via ongoing biological processes in our brain. These biological processes shape our perception of the

## *Introduction*

world: our outside environment, and the body (our internal environment). Changes to these processes, or different calculations by the same brain processes, can cause your perceptions to become distorted, maladaptive and altogether unhelpful to life's pursuits. This causes the symptoms we associate with 'mental illness' – when your feelings, thoughts or behaviours interfere substantially with your everyday life, to the degree that you experience, for example, chronically low mood and suicidal thoughts (as in conditions such as major depression and bipolar disorder), repetitive thoughts that stop you from doing other important aspects of life (as in disorders such as generalized anxiety disorder, social anxiety and obsessive-compulsive disorder), or a disrupted sense of reality (as in psychotic disorders such as schizophrenia).

One example of a general function of the brain that supports mental health, and can precipitate mental illness, is our brain's ability to learn about and predict events in the world. This includes predictions about the outside (Is there a tiger nearby?) and internal environments (Am I hungry? Thirsty? Terrified?). What is most salient, most important, most attention-grabbing to our brain is when these predictions are incorrect, because the brain might need to update its representation of the world – it might need to learn. This process of predictions and learning is often unconscious, woven into the background experiences of every day of your life. For instance, your whole life you have learned that objects fall towards the earth, despite (likely) never having been taught this explicitly. In the context of mental health you have also learned about many other things that affect your mood, emotions and thought patterns: whether you expect you will experience positive or negative reception when you meet new people, whether you expect very much or very little pleasure from everyday activities, whether you are particularly sensitive to pain or other bodily signals (among other factors). And these expectations influence how likely you are to experience poor mental health.

For instance, a common principle across feelings of wellbeing, happiness, pleasure, mirth and other positive feelings is that positive



## *Introduction*

feelings arise when an outcome is better than what your brain expected (but is still within the range of possibility for your brain's predictions). That means it is helpful to expect good things, but it might be even more helpful to expect things that are slightly less good than they turn out to be – it is this positive surprise experience that might increase momentary wellbeing (see Chapter 3). Sometimes an experience in the world is vastly better than what you might have expected: a wedding that narrowly escaped being a mudslide is an overwhelmingly positive surprise causing an outsize effect on immediate wellbeing. In most cases, though, the surprises you experience happen in a less remarkable fashion, as repeated, everyday experiences – usually mundane, sometimes disappointing, occasionally extraordinary – that build up over time, cumulatively affecting your sense of mental health. This building of expectations happens via learning processes in the brain, triggered by surprise (both positive and negative) to subtly change the way you will experience the world tomorrow compared to today. This process of expectations, surprise and learning is one of the fundamental ingredients of mental health, including the science of what makes us resilient, what puts us at risk of mental health disorders and what aspects of mental health might be key targets of various treatments and interventions.

Because your brain's representation of the world is unique to you, formed after years of experiences and your own genetic makeup, there is no one-size-fits-all recipe for mental health. Differences in the neurochemistry of your brain (among many other factors) might make some people abhor what others adore. Similarly, the individual makeup of your brain means that different ways of improving mental health tend to work only in a subgroup of people. When you encounter a popular article about X treatment or Y diet improving mental health or happiness, at best that means on average across a whole group (sometimes quite a small group). But only using the average can obscure the fact that the treatment may have worked brilliantly in some people – and terribly in others.

That is why when it comes to mental health, what works for

## *Introduction*

someone else might not work for you at all. This also means that potential roads to better mental health, whether in a medical setting, or at-home diet or exercise remedies, can come with personalized risks – they might even be harmful for you because of their effect on your particular biology. Mental health is supported by a complex mosaic of factors. Neuroscience is racing fast to find ways of measuring these factors to predict which treatment works for which patient – but in most cases, these predictions have not yet been successful on a large scale.

### *Why bother understanding mental health?*

Understanding the cause of poor mental health and how to improve it is one of the most crucial questions of our time. Mental health conditions are the world's leading cause of disease burden. The most common mental health disorder, depression, affects over 250 million people worldwide. The global economic costs of mental health disorders were estimated at US\$2.5 trillion in 2010, a number that is expected to double by 2030.<sup>7</sup> Most importantly, experiencing a mental illness can have a devastating impact on an individual's quality of life. The vast majority of people who take their own lives (about 90 per cent) suffer from a mental illness.<sup>8</sup> Our mental health crisis is also global: 77 per cent of suicides occur in low- and middle-income countries.<sup>9</sup> Suicide is also not the only, or even the largest, contributor to mortality in people with mental ill-health: people with severe mental health conditions, such as schizophrenia, bipolar disorder and depression, are estimated to lose around 25 years of life expectancy, mostly due to an increased risk of cardiovascular disease,<sup>10</sup> underlining how inextricable physical health is from mental health and vice versa. Even in rich countries with well-funded mental healthcare, our best treatments – psychological therapy and antidepressant medication – only work in around 50 per cent of people, a mystery that motivates much of neuroscientific research into mental health as we try to uncover better routes to treatment.

## *Introduction*

Mental illness is also only one aspect of mental health. For people who are lucky to never experience life-changing illness, preserving good mental health is just as relevant for their wellbeing and quality of life. Simply feeling happier is associated with a longer and healthier life, even after accounting for other sources of longevity – physical and mental health conditions, age, sex and socioeconomic status.<sup>11</sup> It is not clear why this is: it may be mediated by cardiovascular, hormonal and immune system changes associated with experiencing negative emotions.<sup>12,13</sup> In contrast, experiencing positive emotions is associated with lower rates of stroke,<sup>14</sup> heart disease<sup>15</sup> and even cold symptoms.<sup>16</sup> There is a world of difference between feeling down and having a mental illness – but there is some overlap in how these experiences affect the body and brain. Perhaps the best information we have about how the brain supports mental health comes from studying the brains of those who have experienced mental illness and examining what it tells us about the brain processes supporting wellbeing, happiness and other positive mental health phenomena.

What we know that leads to good mental health may surprise you. Things you might consider bad for your health – eating sugar, drinking beer, having a late night out – could have short- or even long-term positive effects on mental health. Each of these ‘bad for you’ things represent one of the myriad ways of tapping into your brain’s various systems supporting mental health. For instance, and I’m not exaggerating here, laughing at a television show with friends harnesses the same brain system as heroin (see Chapter 1).

This book is not going to tell you to deprive yourself of everything fun, from sugar to online games, to feel better. It’s not going to tell you that the solution is thrice-daily mindfulness practice or taking probiotics. No – it’s going to tell you what neuroscience reveals about how mental health works.

This book will take you from some of the first modern experiments on the neuroscience of pleasure to the cutting-edge trials exploring new drugs, therapies or totally different interventions that might improve mental health. Different chapters of this book explore different scientific ingredients for mental health, some obvious (the

## *Introduction*

neurobiology of pleasure) and some less obvious (the neural processes supporting motivation), though just as essential. Along the way we will find out how particular chemicals in your brain, such as dopamine, serotonin and opioids, contribute to mental health. And while the experience of mental health arises from processes in the brain, the brain itself is closely linked with the rest of the body. I will describe fascinating new work on the link between our physical body and mental health, including the role our gut and immune system play in mental health. This body-brain link may be key to understanding how positive mental states like happiness can improve our physical health – and why improving physical health by activities like exercise might alter mental health.

We will explore humans' vast quest to improve mental health, from the discovery of antidepressant drugs to modern experiments using magic mushrooms; from the effects of mindfulness on the brain, to lifestyle changes in sleep or exercise, to cutting-edge electrical treatments for depression. Across all these myriad paths we will find commonalities: common brain networks and processes that underpin mental health and support recovery from mental illness. These common pathways could be the key to new, personalized treatments for mental health disorders – the future of mental health neuroscience.

At some point, we will all experience mental and physical pain and distress, and many of us will seek some sort of treatment. Many will be disappointed by a much-lauded pill or lifestyle intervention: one person's miracle cure is another's snake oil. But there are many things we can try to improve mental health, including lifestyle changes that might preserve or protect mental health, a renewed focus on sleep, and openness to the arsenal of effective psychiatric medications and psychological therapies for more disabling conditions.

Every time a new treatment is discovered, every time a different lifestyle factor is found to be associated with greater happiness, the best-case scenario is that it works for some people. Ideally, many people. But not everyone. To grapple with this complexity requires a paradigm shift in mental health, away from the concept that

*Introduction*

something ‘works’ or ‘doesn’t work’ for mental health, and towards an understanding of which process it affects and which people it might help. My hope is that this book will be something of a guide toward this new paradigm, showing what lessons you can take from neuroscientific research to inform your own mental health, and what lessons you can ignore.

PART ONE

*How the brain constructs  
your mental health*

© Copyright, Princeton University Press. No part of this book may be distributed, posted, or reproduced in any form by digital or mechanical means without prior written permission of the publisher.

I.

*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.<sup>17</sup> 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.<sup>18</sup> In general, the more frequently you experience pain and unpleasant experiences, the more likely you are to experience worse mental health.<sup>17</sup>

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



### *The Balanced Brain*

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

*Natural highs: pleasure, pain and the brain*

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.<sup>19</sup> 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.<sup>20</sup> 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

*The Balanced Brain*

neurons' activity and stopping the release of other brain chemicals.<sup>21</sup> 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.<sup>22</sup> 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.<sup>23</sup> 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.<sup>20</sup> Rotating rats at a certain speed has a similar effect<sup>20</sup> (do not try this with your pets, please!). Like with swim temperatures and skydiving, all these stressors have something in

*Natural highs: pleasure, pain and the brain*

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.<sup>20</sup> 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).

*The Balanced Brain*

more and more sensitive to pain. This is called *hyperalgesia* (as opposed to analgesia, the absence of pain).<sup>24</sup> 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.<sup>25</sup> 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,<sup>26</sup> the association between chronic

*Natural highs: pleasure, pain and the brain*

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.<sup>27</sup> 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<sup>28</sup> (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.<sup>29</sup> 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.<sup>30</sup> 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

*The Balanced Brain*

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.<sup>30,31</sup> 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.<sup>31</sup> For instance, interpreting pain as a potential threat can enhance pain perception.<sup>31</sup> Previous sensations associated with pain can begin to evoke pain on their own, overgeneralizing the pain response to a non-painful input.<sup>30</sup> 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

*Natural highs: pleasure, pain and the brain*

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



### *The Balanced Brain*

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.<sup>32</sup> 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.<sup>33</sup> So

*Natural highs: pleasure, pain and the brain*

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, 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.<sup>34,35</sup> 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

*The Balanced Brain*

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.

*Natural highs: pleasure, pain and the brain*

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

*The Balanced Brain*

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.

## Index

(by Paula Clarke Bain)

- addiction 21, 26, 28–9, 75, 94, 96, 98  
adolescents 49, 50, 216–17  
adrenaline 36, 37, 38, 148  
affect network 167  
alcohol 26, 131, 132–7, 138, 140, 151, 207  
Aldini, Giovanni 178  
algorithms 65–6, 125–6  
Alzheimer’s disease 222  
amphetamines 75, 90, 91, 96, 115, 137, 148  
amygdala 42, 59, 119–20, 127, 146, 157, 166–7, 185, 189  
analgesia 7, 8, 12, 20, 22, 23, 30  
anger 33–4, 35–9, 118–19, 167, 173, 174  
anhedonia 3, 28–9, 70, 95  
anorexia nervosa 211, 212, 213, 214  
anterior cingulate cortex 199  
antibiotics 50–1, 52  
antidepressants 113–30  
    chemical deficit in depression 113–17  
    efficacy 123–7  
    electrical brain stimulation 175, 178  
    gut microbiome 51  
    overview xvii, xix, 113  
    and placebos 109, 128–30  
    and psychedelics 141, 146, 149  
    and psychotherapy 156, 157, 160, 161, 168, 170  
    and recreational drugs 144  
    side-effects 130, 133, 166  
    time taken to work 117–22  
    transdiagnostic factors 224  
anxiety 8–9, 42, 49–51, 53, 61, 122, 153–5, 171, 203, 208, 216–17, 222  
apathy 95, 96, 97, 98  
apps 152  
arachnophobia 42–3, 169  
Aristotle viii, 79, 80, 97  
arthritis 161, 163, 226  
artificial intelligence (AI) 65, 152  
attention deficit hyperactivity disorder 50, 217  
autism spectrum disorder 50, 217  
autobiographical memory 169  
avoidance behaviour 155  
*Awakenings* (film) 93  
Barrett, Lisa Feldman 14, 81  
Beaumont, William 53  
behaviour 79, 80, 82, 84  
behaviourism 153–4, 155  
Bentham, Jeremy x  
Bergenholtz, Stephen 94–5  
Berridge, Kent 19, 89  
bias, emotional 118–22, 123–4, 126, 127  
binge eating disorder 96, 122, 214  
bipolar disorder xv, xvii, 76, 122, 157  
births 49–50  
bisexual people 222  
black people 137  
Blood, Anne 18  
body-to-brain axis xix, 52; *see also* brain-body axis  
booster techniques 168–72

*Index*

- brain  
  brain basis of placebos 107–10  
  defining mental health x–xii  
  how psychotherapy changes the  
    brain 151–72  
  pleasure, pain and the brain 3–32  
  roads to pleasure in the brain 19–24  
  where mental health comes from  
    xiii–xvi  
  where pleasure is in the brain 12–19  
  why understand mental health  
    xviii–xix  
  *see also* brain-body axis
- brain-body axis 33–60  
  gut, immune system and  
    microbiome 40–52  
  heart and emotions 35–40  
  influence of brain on body 52–60  
  overview 33–4
- brain damage 16, 18, 26, 176
- brain function 54, 82, 83
- brain imaging 14–16, 17, 22, 145–6, 165,  
  168, 184, 188
- brain stimulation 173–91  
  deeper brain stimulation 185–9  
  electrical stimulation today 180–5  
  electric brain 174–80  
  motivation, drive and ‘wanting’ 81,  
    83–90, 91, 97  
  neurohackers and DIY 189–91  
  overview xix, 172, 173–4
- Brazil 218
- Brissaud, Édouard 95
- bulimia 211, 214
- Bullmore, Ed 48
- caesarean births 49–50
- caffeine 130, 131, 137, 171
- Calder, Andy 25, 26
- cancer treatment 124
- cannabidiol (CBD) 139, 140
- cannabinoids 20, 24, 31, 137, 139
- cannabis 19, 20, 87, 96, 135, 136, 137–40,  
  164
- Carhart-Harris, Robin 144–5, 147, 149,  
  158
- Carlsson, Arvid 92, 93, 94
- CBD (cannabidiol) 139, 140
- CBT *see* cognitive behavioural therapy
- chemical deficit theory of depression  
  113–17
- chemotherapy 104
- children xi, 49, 50–1, 216–17
- China 218
- chocolate 16, 17, 136
- chronic pain 3, 7–12, 40, 56, 61, 87, 122,  
  178, 193–4, 203–4, 226
- chronotherapy 205
- citalopram 116
- cocaine 96, 131, 135, 137
- codeine 5, 19, 20
- cognitive behavioural therapy (CBT)  
  152, 153, 155–7, 159–61, 163–5,  
  168–9, 183
- cognitive distancing 159
- cognitivism 153, 154–5
- coldspots 25–7
- cold water 5–7, 30, 32
- colour of drugs 104–5
- colour vision 190
- conditioning 64, 153, 155
- convergent evidence 15
- conversion therapy 87
- COVID-19 pandemic vii, 152, 198, 216,  
  225
- Cowen, Philip 120
- Critchley, Hugo 41
- crowd phobia 158–9
- culture 217, 221
- Curran, Val 139, 140

## Index

- Dalgliesh, Tim 69  
Dalmaijer, Edwin 42, 43  
Darwin, Charles 13  
Dayan, Peter 63  
deep brain stimulation 185–9  
delusional parasitosis 220, 221  
dementia 54, 176, 222–3, 225  
depression  
  anhedonia 28  
  antidepressants 113–17, 119–27, 128–9  
  brain stimulation 173–5, 177, 178,  
    181–3, 185–8  
  CBT 153, 155–7  
  changing nature of mental health  
    216–17, 222, 224, 225, 226  
  chemical deficit theory 113–17  
  emotions versus mood 69–74, 76–7  
  exercise 196–7, 199–201  
  food and diet 17, 207–9, 211  
  gut microbiome 50, 51  
  immune system and inflammation  
    44–6, 48  
  influence of brain on body 54, 56  
  lifestyle factors 45–7, 196–7, 199–205,  
    207–9  
  and memory 177  
  and pain 3, 8, 9  
  placebo effect 111  
  and psychedelics 142, 145, 146, 147, 149  
  psychotherapy 153, 155–8, 160, 165,  
    168, 171  
  sleep 202–5  
  why understand mental health xiv,  
    xvii  
Dercon, Quentin 159  
diet *see* food and diet  
discrimination 222  
disgust 26, 35, 42, 43–4  
dissociation 167, 171  
distal and proximal causes 223–4  
Dolan, Ray 158  
domperidone 43  
dopamine  
  and antidepressants 114–16, 120  
  deep brain stimulation 185  
  and depression 76–7, 114–16  
  emotions versus mood 72–6  
  impulse control disorders 95–7  
  motivation, drive and ‘wanting’ 91,  
    92–7  
  Parkinson’s disease 93–5, 185  
  placebos 108  
  predicting mental wellbeing 67–8  
  prediction errors 63–6  
  and psychotherapy 170  
dorsal striatum 212  
dorsolateral prefrontal cortex 181, 182,  
  184  
drive 79–81, 88–91, 95, 97–8  
drop attacks 162  
drugs *see* recreational drugs  
duloxetine 116n  
eating disorders 28, 122, 155, 198,  
  211–14, 217  
Eccles, Jessica 59  
ecstasy 135, 136, 147  
electrical brain stimulation *see* brain  
  stimulation  
electricity 81, 174, 175, 178–80, 188  
electroconvulsive therapy (ECT) 115,  
  175–7, 178, 211  
emotional bias 118–22, 123–4, 126, 127  
emotions  
  brain-body axis 33–42, 59  
  emotions versus mood 69–78  
  heart and emotions 35–40  
  and laughter 23  
  prediction errors 66  
  psychotherapy 157, 167



*Index*

- endocannabinoids 20, 24, 137  
endogenous (natural) opioids 5–6,  
    21–2, 24–5, 31, 63, 199  
endorphins 5, 6  
epilepsy 54, 58, 219  
escitalopram 116, 145  
ethics 86, 88, 176  
ethnic minority groups 222  
eudaimonia (life satisfaction) x–xii, 24,  
    27–8, 79, 97, 144  
euphoria 75  
excitatory currents 76  
exercise xvii, 30, 45–6, 171, 193–5,  
    196–201, 210, 214–15  
expectations 62, 64, 67, 72, 102, 106–9,  
    111–12, 121  
exposure therapy 42–3, 44, 155, 170  
exteroception 41, 41n  
eye gaze 42, 43  
eye movement desensitization and  
    reprocessing (EMDR) 169  
  
facial expressions 13, 32, 41, 118–19  
faecal transplants 193  
falls 162  
fibromyalgia 204  
fluoxetine (Prozac) 116  
flu shots 47  
fMRI *see* functional magnetic  
    resonance imaging  
food and diet  
    gut and microbiome 45–6, 51–2  
    and hunger 32, 33  
    lifestyle changes 193–5, 206–10  
    pleasure and matters of taste 24–6, 27  
    pleasure in the brain 16, 17  
    side-effects of ‘healthy’ lifestyles  
        210–15  
frankincense 115  
Franklin, Benjamin 179  
  
Freeman, Tom 139, 140  
Freud, Sigmund 217  
Friston, Karl 149, 158  
frontal cortex 22  
functional magnetic resonance  
    imaging (fMRI) 15, 18, 66, 73, 146,  
    188  
functional neurological disorders 54–8,  
    162, 164, 179, 219  
  
Galen 195, 198  
gambling 96, 98  
Garfinkel, Sarah 41  
gay people 87, 222  
generalized anxiety disorder xii,  
    xiv, 222  
genetics xiii, 24–5, 168, 213  
grooming, social 23  
gut xix, 17, 41, 48–53, 208, 209  
  
habenula 72–4  
habituation 42, 43–4  
Halahakoon, Chamith 183  
hallucinations 139, 202, 204  
hallucinogens 141, 143  
‘hangry’ phenomenon 33–4, 38, 59, 205  
happiness  
    definitions x  
    electrical brain stimulation 81–2  
    and exercise 197, 198, 200  
    mentally healthy lifestyle 192  
    motivation, drive and ‘wanting’ 79,  
        80, 81–2  
    predicting mental wellbeing xiv, xix,  
        67–8  
Harmer, Catherine 118  
Harris, Wilfred 180  
headaches 12–13  
health 195; *see also* mental health;  
    physical health

## Index

- healthy eating 207, 211  
heartbeat 35, 36, 37, 39, 41, 42, 132  
Heath, Robert Galbraith 86–7, 88–9  
Hebb, Donald 82, 83  
hedonia x–xi, 27, 30, 79, 97, 199  
hedonic adaptation 192  
hedonic hotspots and coldspots 18–20,  
    25–7, 31  
hedonics 7, 27–9  
hepatitis 47  
heroin xvi, 19, 21, 96, 131, 135  
hippocampus 108, 176, 199  
Hippocrates 193  
Hitchcock, Caitlin 155, 156, 159–60, 163,  
    165, 169  
homeopathy 101–2, 103, 104, 105, 106  
homeostasis xii, 32, 69, 76, 194, 228  
homosexuality 87, 222  
'hot and cold bath' experiments 5,  
    6, 30  
hotspots 18–20, 25–7, 31  
hunger 32, 33–4, 38, 39, 59, 212, 213  
hyperalgesia 8  
hypermobility 59  
hypersexuality 96, 98  
hypersomnia and hyposomnia 203  
hysteria 217–19  
  
IBS *see* irritable bowel syndrome  
immune system xvii, 41, 44, 45, 47, 48,  
    49, 58, 193  
impulse control disorders 95–6, 97  
income level 192, 197  
India 218  
inflammation 9, 11, 33, 44–8, 52, 58, 200,  
    208  
insomnia 201, 202, 203, 204  
insula 47  
interleukins 225  
interoception 40–1, 47, 52, 59, 213  
  
iproniazid 114–15, 123  
irritable bowel syndrome (IBS) 102,  
    105, 122, 226  
  
Jauhar, Sameer 176  
joy ix–x, 228  
  
Kahneman, Daniel x  
Kringelbach, Morten 19, 90  
  
lamotrigine 76  
laughter xvi, 19, 20, 22–3, 24, 27–8, 109  
Lavan, Nadine 23  
Lawson, Rebecca 73, 74n  
L-DOPA 93–4, 95–6, 97, 108, 185  
learning to expect wellbeing 61–78  
    emotions versus mood 69–78  
    overview xiv, 29, 60, 61–2, 91  
    predicting mental wellbeing 67–8  
    prediction errors 62–6  
legal highs 137  
Leitao, Mary 219  
life expectancy xvii, xviii  
life satisfaction (eudaimonia) x–xii, 24,  
    27–8, 79, 97, 144  
lifestyle factors 192–215  
    exercise 195–201  
    food and diet 52, 206–10  
    inflammation 45–6  
    overview xix, 192–4  
    side-effects of 'healthy' lifestyles  
        210–15  
    sleep 201–6  
liking responses 13–14, 18, 24–6, 89  
lip-licking 13–14, 18  
London Homeopathic Hospital 101  
long COVID 225  
low mood 28, 44, 46–7, 70, 71, 75  
LSD 135, 136, 147, 149  
Lynall, Mary-Ellen 48

*Index*

- MAAS (Mindful Attention Awareness Scale) 166n
- magic mushrooms xvii, 135, 136, 141, 148
- magnetic resonance imaging (MRI) 11, 15, 16
- major depression xiii, 182, 204–5, 222
- Manninen, Sandra 22
- marital satisfaction 24
- Mayberg, Helen 185, 186
- MBCT *see* mindfulness-based cognitive therapy
- MCAT (mephedrone) 90, 91, 96, 137
- McGettigan, Carolyn 23
- McLoughlin, Declan 176
- MDMA 136, 170–1
- medial prefrontal cortex 108, 157, 167
- medication
- brain-body axis 53
  - and placebos 103–5, 109, 110, 128
  - and psychotherapy 160–1, 170
  - side-effects 127, 166, 210
- meditation 151, 152, 153
- Mediterranean diet 207
- Mehrhof, Sara 159
- memory 168, 169, 176, 177, 181, 199, 202, 203
- mental health
- brain-body axis 33–60
  - changing nature of mental health and disorder 216–28
  - defining xi–xiii
  - electrical brain stimulation 173–91
  - how antidepressants work 113–30
  - how psychotherapy changes the brain 151–72
  - learning to expect wellbeing 61–78
  - mentally healthy lifestyle 192–215
  - motivation, drive and ‘wanting’ 79–98
  - and physical health xvii, 225–6, 227
  - placebos and nocebos 101–12
  - pleasure, pain and the brain 3–32
  - recreational drugs 131–50
  - where mental health comes from xiii–xvii
  - why understand mental health xvii–xx
- mental health conditions (overview) xii, xiv–xix
- ‘mental health crisis’ 216
- mental ill-health (overview) xii, xiv, xvii, 3, 29, 59, 74, 98, 130, 140, 221, 223–4
- mental illness (overview) xii, xiv–xix
- mental immunity 193, 194
- mental inference fallacy 14, 19, 81, 88–9
- mephedrone (MCAT, ‘meow meow’) 90, 91, 96, 137
- metabolism 14, 213
- methamphetamine 135
- methylphenidate (Ritalin) 144
- microbiome 17, 41, 48–52, 208, 209
- migraines 12, 178
- Milner, Peter 83, 85, 90, 94
- Mindful Attention Awareness Scale (MAAS) 166n
- mindfulness xix, 152, 159, 164–8
- mindfulness-based cognitive therapy (MBCT) 152, 165
- minority groups 221–2
- monoamine deficiency hypothesis 115–16, 117
- Montague, Read 63, 66
- mood 67, 69–78, 114–17, 120–1, 157, 199, 202
- low mood 28, 44, 46–7, 70, 71, 75
- Morgellons 219–21
- morphine 5, 19, 32
- motivation xix, 29, 79, 80, 89, 91, 94, 95, 124

## Index

- motor cortex 181  
Moutoussis, Michael 158  
movement 92, 93, 94, 95, 185, 195  
MRI *see* magnetic resonance imaging  
multiple sclerosis 58, 163  
mushrooms, magic xix, 135, 136, 141, 148  
music 18, 19
- natural (endogenous) opioids 5–6, 21–2,  
24–5, 31, 63, 199  
‘natural high’ of pain 4–7  
negative bias 119, 121–2, 123, 126, 127, 128  
negative prediction errors 62, 63, 65,  
67–9, 72, 159  
nervous system xiv, 57, 178, 224, 228  
neurogenesis 176, 199, 200  
neurohackers 172, 189, 190  
neurological disorders 53–7, 222  
neuroplasticity 82, 180  
neuropsychopharmacology 92  
neuroscience xi, xvii–xviii, 81–3, 87,  
142–3, 154, 176, 178, 181  
nocebo effect 108, 110, 190  
nociceptors 9, 10, 61  
non-epileptic seizures 217, 218, 219  
noradrenaline 92, 93, 97, 115, 116, 120  
nucleus accumbens 19  
Nummenmaa, Lauri 22, 23  
Nutt, David 134, 135–6, 137, 140, 145
- obesity 127, 214  
obsessive-compulsive disorder (OCD)  
xv, 155, 157, 178, 186, 198  
Olds, James 83, 84, 85, 90, 94  
*One Flew Over the Cuckoo’s Nest* (film)  
176  
opioids  
focusing on pleasure 22, 30–1, 32  
food and taste 24, 25  
laughter 27, 28  
natural/endogenous opioids 21–2,  
24–5, 31, 63, 199  
‘natural high’ of pain 5–7  
overdoses 20–1  
placebos 106, 108, 109, 128  
roads to pleasure in the brain xix,  
12, 19, 20–2, 23  
opium 5, 19  
orbitofrontal cortex 17, 18, 22  
orthorexia 211  
Osmond, Humphry 141
- pain  
and alcohol 132  
brain stimulation 87–8, 178  
chronic pain 3, 7–12, 40, 56, 61, 87,  
122, 178, 193–4, 203–4, 226  
and depression 3, 8, 9  
emotions 40  
exercise 199  
focusing on pleasure 31, 32  
functional disorders 56  
and laughter 22–3  
learning mechanisms 61, 63  
lifestyle factors 193–4, 199, 203–4  
‘natural high’ of pain 4–7  
negative bias 122  
opioid system 20–3, 32  
physical and mental health  
treatments 226  
placebos 102, 106, 108  
pleasure, pain and the brain 3–4  
recreational drugs 131, 132  
sleep disturbance 201, 203–4  
pandemic (COVID-19) ix, 152, 198, 216,  
225  
panic disorder 42, 59, 162, 163, 219, 222  
paralysis 179, 180  
paranoia 202, 204  
parasitosis, delusional 220, 221

*Index*

- parkinsonism 92, 93, 94
- Parkinson's disease 93–5, 96, 97, 108, 114, 185
- paroxetine 116
- Pavlovian conditioning 64
- perigenual anterior cingulate cortex 168
- personalized medicine ix, 124, 188
- PET *see* positron emission tomography
- phobias 42–3, 102, 158–9
- physical health xiv, xvii–xix, 44–5, 53–4, 59, 111, 161–4, 195, 225–7
- placebo effect 102–11, 128, 148–9, 153, 179, 190, 215
- placebos 101–12
  - additive effects with antidepressants 128–30
  - brain basis of 107–10
  - brain stimulation 179–80, 183, 184
  - chronic pain 11
  - disgust response 43
  - harnessing for mental health treatment 110–12
  - lifestyle changes 215
  - 'natural high' of pain 6
  - overview 98, 101–3
  - psychedelics 147–9
  - psychotherapy and physical health 161
  - why placebos work 103–7
- placebo surgery 105, 161
- pleasure
  - anhedonia 70
  - and dopamine 63
  - focusing on pleasure 30–2
  - hedonia x
  - hedonics of mental health 27–9
  - motivation, drive and 'wanting' 79, 88, 89, 90, 97
  - pleasure and matters of taste 24–7
  - pleasure in the brain 3–4, 7, 12–19
  - why understand mental health xviii, xix
- polysomnography 203
- positive bias 127
- positive prediction errors 62, 63, 64, 65, 67, 68
- positron emission tomography (PET) 14, 15, 18, 22, 145, 146
- post-traumatic stress disorder (PTSD) 40, 157, 168, 170–1, 202, 203
- prebiotics 51, 52
- prediction errors xiv–xvi, 62–8, 69–71, 73, 77, 156–9
- prefrontal cortex 165, 166, 183, 184, 199
- probiotics 51, 52, 208–10, 215
- proprioception 151
- proximal and distal causes 223–4
- Prozac (fluoxetine) 116
- psilocybin 141–2, 143–6, 147–50, 170
- psychedelics
  - altered beliefs 112
  - boosting therapy 170
  - downsides and side-effects 147–50, 211
  - illegality 137
  - neuroscience of 140–6, 158
- psychiatric disorders xii, xiv–xix, 53–4, 178, 221–4
- psychoactive substances 136–7
- psychobiotics 52
- psychoeducation 110, 153
- psychosis 28, 50, 54, 138–40, 202–5, 222, 224
- psychotherapy (psychological therapies) 151–72
  - boosting treatments 168–72
  - downsides of psychedelics 150
  - harnessing placebos 110–11
  - how therapy works 155–61
  - how to change your mind 152–5

## Index

- mindful brain 164–8  
overview 78, 151–2, 171–2  
psychological therapy and physical health 161–4, 227  
why understand mental health xvii, xix
- psychotic disorders xiv, 202  
psychotic experiences 138–40, 201–2  
PTSD *see* post-traumatic stress disorder  
punishments 47, 61, 71–4, 213
- quality of life xvii, xviii, 24, 51  
quantifying behaviour 79, 80  
questionnaires x, 28, 36, 79, 80, 125, 166n
- rapid eye movement (REM) 32  
recreational drugs 131–50  
  addiction 21, 26, 28–9, 75, 94, 96, 98  
  classification 223  
  and dopamine 96  
  downsides of psychedelics 147–50  
  hedonics of 29  
  hotspots 19  
  motivation, drive and ‘wanting’ 80, 98  
  neuroscience of psychedelics 140–6  
  overview 131–3  
  possession and punishment 137  
  regulating psychoactive substances 133–40  
  risks and benefits 133–6  
reinforcement learning 65–6, 85  
relationships 23  
REM (rapid eye movement) 32  
resilience xvi, 74–5, 76, 193, 194, 200–2, 204  
rewards 47, 61, 63–4, 66–8, 70–4, 77, 80, 94, 153  
rheumatoid arthritis 102  
Ritalin (methylphenidate) 144  
Roiser, Jon 73, 183  
Royal London Hospital for Integrated Medicine 101  
Rutledge, Robb 67, 68  
Sacks, Oliver 93  
satiety 25, 32, 212, 213  
satisfaction 79; *see also* life satisfaction (eudaimonia)  
schizophrenia xii, xiv, xvii, 28, 122, 138, 202, 222  
Schultz, Wolfram 63  
Scott, Sophie 23  
Scribonius Largus 178–9  
seizures 58, 175, 179, 217, 218, 219  
Sejnowski, Terry 63  
selective serotonin reuptake inhibitors (SSRIs) 113, 141, 145, 149  
self-compassion 165  
self-efficacy and self-esteem 200  
self-report scales 79, 80  
septal area 84, 86, 87, 88, 89  
serotonin xix, 92, 97, 113–17, 120, 128, 129, 141  
sertraline (Zoloft) 116, 123  
sex 12, 19, 29, 87, 96, 133  
sexism 218  
shell shock 218, 219  
Sherrington, Charles 95  
side-effects  
  antidepressants 130, 133, 166  
  brain stimulation 173, 174, 177, 187, 190, 210  
  ‘healthy’ lifestyles 194, 200, 210–15  
  medication 127, 166, 210  
  mindfulness therapy 166, 167  
  psychedelics 147–50, 211  
  psychotherapy 171–2  
sleep xix, 32, 194, 201–5, 214  
Smith, Zadie ix

*Index*

- smoking 45, 46, 223  
social anxiety xv, 157, 170  
social cohesion 23  
social defeat stress 75–6  
social factors, in mental health 221–5  
social harm 132, 135  
social laughter 20, 22–4, 27  
social media 206, 216  
Society for Neuroscience 82  
spider phobia 42–3, 169  
spinal cord xiv, 6, 9  
SSRIs *see* selective serotonin reuptake inhibitors  
St. Martin, Alexis 53  
stress 5, 6, 7, 23–4, 32–4, 132, 206  
stress-induced analgesia 4–5, 6, 7  
strokes xviii, 16, 26, 163, 176, 178, 179  
subgenual anterior cingulate cortex 186  
substantia nigra 93  
suicide xvii, 152, 222  
supplements 51–2, 207, 208, 209  
surgical deep brain stimulation 185, 186  
surprise xvi, 62, 64, 65  
survival response 4, 23, 61, 66, 67, 91  
swimming 5–7, 32  
  
tai chi 197  
thalamus 87  
thalidomide 143  
THC ( $\Delta^9$ -tetrahydrocannabinol) 139, 140  
tobacco 135, 136  
Tourette's syndrome 186  
Tower of London game 71  
Tracey, Irene 106, 108  
transcranial electrical stimulation 175, 180–2, 187  
transcranial magnetic stimulation 175, 178, 181, 182  
transdiagnostic factors 203  
trauma 170–1, 193, 202, 221  
tuberculosis 114  
tumour necrosis factor 225  
  
US Centers for Disease Control and Prevention (CDC) 219–20  
  
vaccines 46–7  
venlafaxine 116n  
ventral pallidum 25, 26  
ventral striatum 47, 167  
vestibular system 41  
Vicodin 20, 21  
  
wanting 89–90, 91, 94, 96, 97  
wellbeing  
  alcohol 132–3  
  definitions x–xii  
  hedonics of mental health 27–8  
  learning to expect wellbeing 61–78  
  lifestyle changes 192–4  
  motivation, drive and 'wanting' 79–81, 91  
  predicting mental wellbeing xv–xvi, xviii, 67–8  
  recreational drugs 131–3, 144  
women 205, 216, 217–18, 222  
World Health Organization 8  
  
yoga 151, 152, 153, 164, 197  
young people 49, 216–17  
  
Zatorre, Robert 18  
Zolofit (sertraline) 116, 123