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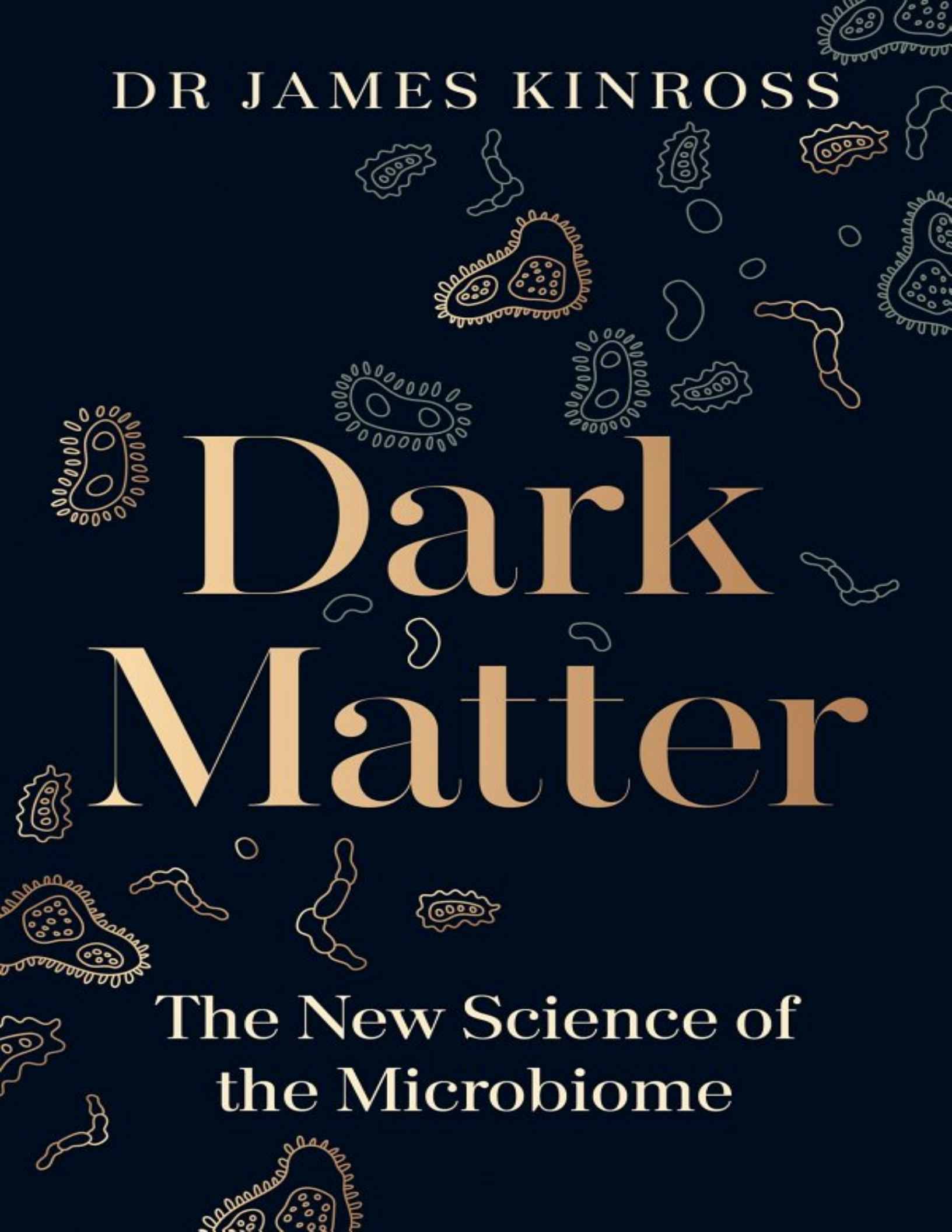

Dark Matter

The New Science of the Microbiome

7. Symbiotic Sentience

With a trembling hand I took the drill from the neurosurgeon.

‘Just don’t fuck it up,’ he said.

Sweating, I pressed the drill bit against the skull, right above the temple where the hair had been shaved and the skin had been peeled back. Luckily for the patient – a twenty-three-year-old woman we’ll call Betty – and for me, modern orthopaedic drills used for cutting into skulls are extremely clever, and a clutch safely cuts the power to the drill as soon as it reaches softer tissues that lie beneath the skull.

The objective of the operation was to release a large volume of gelatinous, clotted blood that was pressing on the brain. Betty had sustained a head injury after being knocked from her motorbike, tearing blood vessels in the lining of the brain. There was a finite amount of time before permanent brain damage would be caused by the pressure of the expanding clot, which would ultimately force her brainstem through the base of her skull. As I stood under the operating lights, overheating in my gown, I thought about how bland the brain appeared. A lifetime of experience, love and learning lost in grey-and-red blancmange.

The only way we’ve been able to map the dense network of eighty-six billion neurones that make up the original biological supercomputer is, ironically, by using artificial intelligence. But even the insights into the brain’s ‘interactome’ aren’t enough to completely break the software code for the brain’s operating system. The collision of neuroscience and the microbiome is, however, providing startling new insights that are redefining our understanding of how the brain develops, how it degenerates, how it thinks and even how it responds to injury. This has led to an existential question: if our brain is in conversation with our gut microbiome, what role do microbes play in human sentience? Could we be experiencing a collective symbiotic consciousness? To answer this, let’s start by

considering how our nervous system works and how it’s connected to the gut.

The blood–brain barrier

The brain is physically separated from the rest of the body by a microscopic anatomical and physiological wall. Blood vessels and capillaries that carry oxygen and fuel to the nerve cells of the brain are guarded by tight junctions designed to prevent unwanted invaders from getting in, because pathogens that infect the brain are a threat to life. Most commonly it’s viruses and bacteria that cause the damage, but not always. In 2012, doctors from Sichuan University in China reported a case of a fifteen-year-old girl who had, for a year, been complaining of numbness in the right side of her face and upper limbs.[1] She then started having seizures, which led to an MRI that revealed an irregular lesion on the left side of her brain. On further questioning, the young woman confessed to eating inadequately cooked frogs, from which she contracted a tapeworm. The larvae had travelled to her brain and there they grew up to 12 cm in length, ultimately requiring surgical removal. This condition is called neurocysticercosis and is more commonly caused by ingesting a pork tapeworm (*Taenia solium*), but the lesson here has to be: don’t eat raw frogs.

Fortunately, stories like these are rare because, as a general rule, the brain is extremely good at keeping out pathogens, all the while bathing itself in a constant supply of the finest metabolites known to humanity. It’s so good at its job that until recently it was assumed that the microbiome couldn’t penetrate the blood–brain barrier. The gut microbiome, however, has co-evolved with the brain over millions of years, which means it has a multitude of tools at its disposal for hacking this security feature.

How the brain and gut talk to each other

The peripheral nervous system describes the nerves outside the brain and spinal cord (known as the central nervous system). Its job is to regulate the physiological processes that happen in our bodies involuntarily which keep us alive – such as our heart rate, blood pressure, breathing and digestion –

and it is also responsible for sexual arousal. It's made up of three parts, called the *sympathetic*, *parasympathetic* and *enteric* nervous systems.

The sympathetic nervous system is responsible for initiating our 'fight or flight' response; in the wake of her motorbike accident, Betty's sympathetic nervous system was literally fighting for her life.

Meanwhile the parasympathetic nervous system manages the 'rest and digest' reflexes; it's dominated by the vagus nerve, which controls 70 per cent of the parasympathetic nervous system and manages our heart rate, our digestive system and our mood. It even has an immune function. The vagus nerve takes a long and tortuous course through the body. While part of its job is to send signals 'down' the network, almost 90 per cent of all fibres are used to send signals 'up' to the brain from various parts of the body for processing.

The enteric nervous system (ENS) is embedded in the wall of the bowel and is sometimes referred to as our 'second brain'. It's made up of more than 100 million neurones and contains more nerves than the sum of all other peripheral nerves in the human body combined. Because it's responsible for managing so much of the gut's operating system, there's a huge diversity of nerves within it – twenty different subtypes of nerve use more than thirty different types of neurotransmitters – and it is connected to both the parasympathetic and sympathetic systems. These in turn work against each other and, by doing so, create an equilibrium. Every day our body's nervous system performs a balancing act with one foot on the accelerator (sympathetic) and one foot on the brake (parasympathetic). In this analogy, the microbiome in the gut serves as the clutch, regulating how much power is transferred from the engine to the wheels.

We're now starting to understand quite how deep some of the wiring from the brain to the gut runs. The vagal and spinal nerves that carry signals from the brain reach all the way to the lining of the intestine, called the mucosa. These nerves directly control the gut's secretions and absorption of food and fluid, and even blood flow to the gut, which in turn influences the type and number of microbiota living in our bowels. For example, pain receptors in the gut can sense the bacterial pathogen *Salmonella*, which is very good at picking the lock of important immune cells that live there, called M cells. The enteric nervous system works like a burglar alarm: when it detects the *Salmonella* bacteria it fires a message to the brain to warn it that there's trouble.[2] But it also reduces the number of M cells to

stop more bacteria from getting in, and closes the gate to the castle. Even more cleverly, it promotes the growth of defensive filamentous bacteria that line and guard the gut against the invaders. So the enteric nervous system also has immunological functions and is a critical component of our defence against pathogens.

Your brain relies on far more than just five senses to understand the world. Because it is so intimately connected to the microbiome, it has trillions of sensing microbial organisms that monitor and interact with your environment. But the connection goes even deeper: because the gut microbiome plays a part in regulating all three components of the nervous system, it also has a say in your flight-or-fight response, your rest-and-digest response and the day-to-day function of your immune system. This means that the microbiome influences how you experience stress, and how tired, horny or angry you are. Cracking this microbial code is becoming increasingly urgent, as it's this cross-talk that also defines our risk of both acute and chronic neurological disease.

Brain attack

Each year thirteen million people will have a stroke – or brain attack – and around 5.5 million will die from this event.[3] A stroke occurs when the blood supply to part of the brain is interrupted, leading to the death of irreplaceable neurones within it. We've recently discovered that clots retrieved from arteries in the brains of patients during a stroke have a diverse microbiome of their own.[4] This is peculiar, because they should in theory be completely sterile, and no one is quite sure how these microbes got there or what they are doing.

Stroke usually occurs in older people who have an ageing microbiome and less resilience to any injury in general, and multiple studies suggest that the severity of a stroke is greater in people who have a less diverse gut microbiome. For example, patients with stroke have increased abundances of *Streptococcus*, *Lactobacillus* and *Escherichia* and lower abundances of *Eubacterium* and *Roseburia* taxa in their gut, and these changes also correlate with the severity of a stroke. Many of these associations relate to how our lifestyle and our diet modify stroke risk. For example, fibre in our diet protects against stroke risk because it is metabolized by bacteria such

as the *Eubacterium* and *Roseburia* taxa into anti-inflammatory molecules that protect the brain.[5] If you are not eating enough fibre, the relative abundances of these bacteria fall and your stroke risk rises.

A brain attack also causes reciprocal changes in the gut microbiome, because when the brain suffers an injury, blood flow to the gut is reduced, leading to the release of unstable atoms that damage cells, known as free radicals.[6] This also allows bacteria that like a low-oxygen state to bloom in the gut, changing its diversity and in turn the systemic levels of inflammatory molecules. Stroke damages the gut barrier and, for this reason, many bacteria that cause chest infections in stroke patients originate in the gut.[7] It also means that the gut microbiome disrupts the integrity of the blood–brain barrier and alters the severity of the brain injury.[8] So it follows that, in mouse models at least, antibiotics reduce the severity of stroke and, amazingly, this neuroprotective effect can be transferred through faecal transplantation.[9]

Because of this close link between the gut and the brain, scientists are now starting to identify biomarkers that measure the activity of the microbiome to predict stroke severity. For example, the gut microbiome breaks down animal proteins and nutrients (such as choline) in our diet, to produce inflammatory metabolites such as Trimethylamine *N*-oxide. High levels of this compound in the blood are associated with increased stroke risk. Maybe it's time to look deeper at how the gut microbiome communicates with the brain – and how it influences brain development.

The gut–brain axis

Our gut, microbes and brain have three different ways of talking to each other. They can do so through the manufacture of neurotransmitters (like serotonin); through the hormones in our endocrine system; and through the immune system. The microbiome can work across all three of these at the same time, and we are now slowly unravelling some of the detail of how this works.

Neurotransmitters produced by the microbiome don't cross the blood–brain barrier under conditions of health, but they can act directly on the enteric and peripheral nervous system, which in turn sends signals back to

the brain. Microbes can also create metabolic precursors of neurotransmitters that can cross the blood–brain barrier, and the amino acid tryptophan is increasingly recognized as a ‘master switch’ for this process because it can be made into multiple different types of neurotransmitters.[10] The vagus nerve hooks the brain into a hormonal ‘endocrine’ network that makes steroid hormones that influence our body’s stress response. However, the gut also contains its own endocrine cells that produce hormones and bacteria that live along the lining of the gut and are able to interfere with this system, influencing everything from our appetite to our mood. Very sub-specialized ‘neuropod’ cells plug these endocrine cells directly into the enteric nervous system, which means that bacteria can communicate directly with the nervous system.[11] The immune system influences the function of all organs in our body, and our nervous system is no different. Microglial cells, for example, are the resident cells of the innate immune system, and these make up to 15 per cent of all cells found in the brain. Microbes are able to interact directly and indirectly with these cells to modify brain health and our behaviours. Collectively, all these pathways can be manipulated by the microbiome to influence our state of mind.

The psychobiome

When we’re ill we tend to display what doctors call ‘sickness behaviour’: a suite of systemic responses, including social withdrawal and loss of appetite. There’s an evolutionary benefit to this, because isolation prevents us from spreading infection. Losing our appetite when we’re ill might also promote metabolic changes in our bodies that keep us healthy – for example, by limiting the nutrients available for pathogens that wish us harm. But some bacteria have learned to subvert this process for their own benefit, and they do it through the vagus nerve. *Salmonella enterica* is responsible for a quarter of all cases of diarrhoea, causing more than ninety-four million gastrointestinal infections each year. In mouse models, *Salmonella* blocks the attempts made by the vagus nerve to detect inflammation in the brain and prevents normal sickness responses from developing. More specifically, it inhibits the loss of appetite response – so

the mouse carries on eating as it would if it were healthy.[12] In other words, these bacteria alter our higher brain function for their own survival benefit.

We don't need to be ill for the microbiome to influence our moods, and more complex behaviours, via these same pathways. Across Europe, it's been noted that people suffering from depression have distinct changes in their gut bacteria.[13] After correcting for the confounding effects of antidepressants, an analysis of the microbiomes of 2,124 people determined that levels of *Coprococcus* and *Dialister* spp. – bacteria that produce the pleasure chemical dopamine – were depleted in depression. At the same time, higher abundances of bacteria such as *Faecalibacterium* and *Coprococcus* spp. were consistently associated with higher quality-of-life indicators.

Because dopamine controls our most important reward pathways in the brain, food and drug studies have started to explore the connection between the microbiome and our vulnerability to addiction. For example, mice given prolonged courses of antibiotics show a higher susceptibility to cocaine addiction.[14] It's unlikely, however, that it was the antibiotics that made Tony Montana quite so psychotic.

We've made similar observations about the microbiome's role in regulating our anxiety. Bacteria such as *Bacteroides ovatus* produce metabolites that break down dietary sources of tyrosine – which is found in foods such as soy, chicken, avocados, bananas and milk products. This metabolite interferes with a cell responsible for wrapping the axons of nerves in a type of fat. The fat allows the nerve cell to send its electrical signal along its arm-like axons, which connect with other nerve cells via a synapse to send signals.[15] Mice that don't have enough *B. ovatus* are unable to lay down this fat effectively, and this prevents their brain from developing normally, producing anxiety-like behaviours.

People with inflammatory bowel disease and other chronic gut diseases have higher rates of mental-health problems like depression and anxiety than the general population. Irritable bowel sufferers also experience this, and commonly endure high rates of hypervigilance, pain anticipation or emotional hypersensitivity. And there's increasing evidence that says the gut–brain axis plays an important part in causing these symptoms. For now, though, it's not clear which comes first: the gut or the brain. My view is that

they should not be considered separately and that these things occur in parallel.

The gut microbiome grows a brain

As a dyslexic person, I have personal experience of the obstacles that many neurodiverse people face in getting through school or holding down a job. My head constantly fizzes with unconventional ideas (like the microbiome), and in my academic career I have had to retrain my brain to perform the simple tasks that most people take for granted, like spelling. In time, I have come to realize that my dyslexia is a superpower, and now I would not choose to be without it.

In 1999, the sociologist Judy Singer coined the term ‘neurodiversity’ to de-stigmatize neurodevelopmental conditions such as dyslexia, Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD). Until that point, these conditions were typically labelled disabilities or pathologies; Singer’s goal was to celebrate difference and acknowledge that as well as presenting challenges, these conditions create extraordinary potential. A huge amount of work is now being performed to explain how these conditions occur, and scientists are asking whether the microbiome contributes to their development.

New nerves – created during foetal development – slowly migrate into position as the baby gestates. These must also make new chemical connections between each other, called synapses, and it’s this pattern of connections that creates memories, thoughts and our higher brain functions. Synaptic pruning happens when connections that are incorrect or no longer useful are destroyed and it is an important method for regulating this process. One hypothesis is that the development of our neurones is co-dependent on the gut microbiome, which undergoes parallel changes in its diversity and structure with the developing brain. Or to put it another way, the microbiome modifies the structure and function of emerging neural circuits, creating neurodiversity – and my dyslexia. The race is now on to define the precise mechanism through which this occurs.

By the age of two the brain is 75 per cent of its adult size. At ten years, a child’s brain represents 5–10 per cent of body mass, and it consumes twice

the glucose and one and a half times the oxygen per gram of tissue compared to an adult's brain. This is hungry work, and it accounts for up to 50 per cent of the body's metabolic output. The gut produces much of the energy for this massive and rapid brain growth, and it's hard to sustain a healthy growing brain with the wrong gut bugs.

So the timing and the quality of the assembly of the microbiome are important. As previously described, the altered behaviour of germ-free mice can be reversed by colonization with normal bacteria into their gut. However, this intervention is age-dependent. Post-weaning recolonization, for example, is more effective at restoring anxiety-related behavioural deficits than recolonization later in life.[16] These behaviours are particularly influenced by the neurotransmitter serotonin, whose functions cannot be restored by recolonization of the gut after weaning. The implication is that the greatest time for microbial influence over our behaviour and psychological well-being occurs in the earliest parts of our lives and, when this is over, it may be over for good.

For now, the role of the microbiome in brain development remains contentious, and the greatest controversy is saved for ASD. This refers to a condition manifested by a range of symptoms characterized by some degree of impaired social behaviour, communication and language, and by a narrow range of interests and activities that are both unique to the individual and carried out repetitively. There is a huge amount of work across multiple scientific fields attempting to define why children develop autism, and the microbiome is merely one avenue of investigation. Regardless of the cause, the rates of ASD in the developed world are climbing. It now affects around one in fifty-seven children (1.76 per cent) in the UK, with the highest rates in pupils of Black ethnicity (2.1 per cent) and the lowest in Roma/Irish Travellers (0.85 per cent).[17] The significant differences in autism prevalence across ethnic groups and geographical location implies that the exposome – and, by definition, the microbiome – is likely to have an important role.

The mean age of diagnosis of ASD is five years old,[18] just after the microbiome has finished assembling, and multiple studies have found differences in the faecal microbiome compared to children without ASD. In 1943, when the Austrian-American psychiatrist and physician Leo Kanner published the first description of eleven children with autism,[19] he reported

on a thirty-three-page letter from the father of a child called Donald T. In this extraordinarily detailed and moving description of his son, the father noted: ‘he has never shown a normal appetite’. It’s now recognized that many children with ASD also suffer from gastrointestinal symptoms ranging from constipation to diarrhoea, and that these might be under-reported.[20] Gut dysfunction and autism appear to be linked, but like all things gut–brain, it’s not clear which comes first.

A Chinese study of more than 773 children with ASD and 429 neurotypical children suggests that this might be more than mere coincidence. The researchers studied the dynamics of the gut microbiota across different ages,[21] and found that the gut microbiome of children with ASD evolves in a way that is indeed influenced by diet and gut function. But this evolution is strikingly different from that of neurotypical children. Children with ASD have an immature gut microbiome, with less diversity, and the most important changes take place before the age of three. These observations on the microbiome closely associate with the severity of behaviour change, sleep patterns and altered bowel function in the ASD group. Researchers were able to identify the children with ASD through the detection of the bacteria *Veillonella* and Enterobacteriaceae, along with just seventeen microbial co-metabolites found in their stool, which differentiated them from the neurotypical children.

The severity of ASD also appeared to be significantly linked to the function of the microbiome and bacterial pathways for tryptophan metabolism, which is relevant because it is used to make neurotransmitters. There’s more evidence that other metabolites created by gut bacteria influence brain development. For example, bacteria in the gut putrefy proteins and one of the by-products of this process is a metabolite called p-Cresol. When this is given to mice, it selectively causes ASD behavioural symptoms and social behavioural deficits.[22]

However, it also changes the composition of the gut microbiome, and when faeces from p-Cresol-fed mice is transplanted into control mice, they not only produce more p-Cresol, but also develop the same behavioural symptoms. Most interestingly of all, when faeces from healthy control mice is transplanted back into p-Cresol-fed mice, their behaviour changes back to that of healthy mice.

So it should not be a surprise that transplanting faeces and the microbiome from human donors with ASD into germ-free mice also

prompts autistic behaviours in the mice.[23] This is likely to be an 'orchestral' effect.

These clever experiments don't, though, explain the role of the parental microbiome in the development of conditions of neurodiversity. This needs to be understood, because it appears that a misdirected maternal immune system is important in the development of ASD. In one Swedish analysis of more than 1.8 million people, children of mothers who were hospitalized for any infection during pregnancy had a 79 per cent higher risk of being diagnosed with ASD.[24] Intriguingly, this observation can be replicated in mouse models, and certain types of bacteria known as 'segmented filamentous bacteria' seem to be particularly important in changing the behaviour of the immune system in pregnant mice. These bacteria take the brake off the adaptive immune systems and induce the production of a particular type of lymphocyte (T helper 17 cells), causing abnormal behaviours in their offspring.[25] Interestingly, these bacteria do not behave the same way in non-pregnant mice, but it is not clear precisely why.

We don't know the exact source of the infection of those women included in the Swedish study, but where there are pathobionts, there is inflammation, and this is one of the major methods through which the microbiome influences behaviour. The problem is that there could have been too many pathogens driving inflammation or not enough symbionts preventing it. It is also possible there is a confounding factor (such as a medicine) or something in the way these infections were treated that explains this observation. We don't know yet if COVID-19 is going to serve as a driver of maternal inflammation, but it's possible. If you're a woman thinking about having a baby, it's another very good reason to get vaccinated.

As we come to understand that the microbes in our gut are an important cog in the ASD and neurodiversity engine, we're also faced with an important question: what do we want to do about it? Just as diversity determines the health of our environmental and internal ecosystems, so neurodiversity is an important measure of the resilience of our society, our schools and our workplaces. Despite humans' genetic similarity, the brain exhibits a wonderful variance: we don't all think the same, and our species relies on this to survive. As we start to unravel the mysteries of how the microbiome influences our neurocognitive development, we can hold on to the fact that it offers a new therapeutic avenue where few exist. This is

incredibly important for those people and their families who have been adversely affected by conditions of our developing brain, which can certainly be disabling, as Donald T's father so eloquently described.

Psychobiotics

The emerging data on the microbiome raise the intriguing possibility that we can now selectively engineer specific strains of bacteria to deliver the healthy metabolites we need in order to improve our higher brain functions. To date, trials in humans of probiotics, which are sometimes referred to as psychobiotics, are lacking, and the evidence base for their wider use comes largely from animal studies. However, these are rather extraordinary pieces of research.

Both *Bacteroides fragilis* and *Lactobacillus reuteri* have been observed to reverse some of the behavioural and gastrointestinal changes reported in animal models of Autism Spectrum Disorder, but these bacteria work in discretely different ways. For example, in a mouse model of ASD, *L. reuteri* rescues social behavioural deficits by working through the vagus nerve to increase the amount of a pro-social hormone called oxytocin in the reward pathways of the brain. It also changes behaviour by creating a metabolite called tetrahydrobiopterin, which is a co-factor involved in the production of several neurotransmitters such as dopamine, serotonin and nitric oxide. It is also true that psychobiotics don't simply work on any ASD-associated behaviours. For instance, they did not have any impact on hyperactivity behaviours because these are almost exclusively controlled by the host genetics of the animal.

To date, many of the studies in this very early field have focused on the ability of probiotic strains to produce neurotransmitters. For example, the probiotic *Bacteroides uniformis* CECT 7771 cured binge-eating in rats and reduced their anxiety-like behaviour, at least in part, because of changes in the circulating levels of dopamine, serotonin and noradrenaline produced by the bacteria.[26]

It is important to add that we don't have any evidence that these probiotic strategies are effective in humans. The best way to improve our brain health may be to prevent conditions from forming in the first place. And the best way to do this may simply be to get a good night's sleep.

Sleep tight and don't let the bedbugs bite

Our bacteria and their functions are closely associated with our sleep cycle, and our gut microbiome's activity subtly fluctuates over a twenty-four-hour period. The brain controls circadian rhythm by means of a neurological 'master clock' called the suprachiasmatic nucleus. However, our sleep cycles are also influenced by diurnal variations in the function of the microbiome and daily oscillations in its metabolite production and epigenetic programming of the gut. Similar circadian rhythms exist in fungi and cyanobacteria. If this microbiome 'rhythmicity' is interrupted, it perturbs the regular work of organs like the liver, and it causes low levels of inflammation in the brain.[27] This goes some way to explaining why those who can't sleep are at greater risk of metabolic syndrome and heart disease.

If, like me, you're a shift-worker and you work nights, then your microbiome is also being influenced by your work pattern. Scientists can tell if you're a day-worker or night-worker just by looking at your microbiome: an analysis of male security guards found that the *Faecalibacterium* genus abundance in the gut is a biomarker of day-shift work, and *Dorea longicatena* and *D. formicigenerans* were significantly more abundant in individuals working the night-shift.[28] *F. prausnitzii* is one of the most abundant and important commensal bacteria of the human gut microbiota and is strongly associated with gut health.

So how do bacteria know what time of day it is? Some bacteria, such as *Bacteroides ovatus*, possess their own internal clocks that do not rely on light. Instead their populations 'oscillate', based on environmental cues that come from our diet and lifestyles. Diets that are generally thought to be healthy, such as plant-based low-fat diets, promote their growth, while unhealthy low-fibre, high-sugar, high-fat diets inhibit their growth. These bacteria influence our own circadian rhythm or our metabolism, and this is another reason why eating junk food when you are working nights will not help you sleep.

In fact if you want to repair your nerves or your brain, eating less might also help: we've recently learned that intermittent fasting promotes nerve regrowth. This process relies on a metabolite called indole-3-propionic acid (IPA),[29] which is produced by a specific bacteria called *Clostridium sporogenes.* In a mouse model, IPA administered after an injury to the sciatic nerve significantly sped up the recovery of sensory function because

IPA helps coordinate the immune-dependent regeneration of the axon. It is amazing to me that the gut microbiome may yet be a target for devastating nerve injuries. But let's look now at what you do if your injuries are in the mind.

Puppets on microbial strings

If the microbiota within us are able to influence our feelings of satiety, anxiety, sexual arousal and pleasure, we may well start to question how much free choice any of us really have. What if we're simply serving our microscopic overlords? Nature shows us several horrifying precedents for this behaviour. Take the *Ophiocordyceps unilateralis* fungus, for example, which infects ants in tropical forests. Through a combination of brute force and enzymes, its spores eat their way through the ant's exoskeleton. Once on board, the fungus enters the ant's brain, where it takes control of the ant's higher brain functions by releasing neurotransmitters and metabolites.[30] In doing so, it creates a 'zombie ant', which it then directs to leave the safety of its colony. Sometimes it will induce a seizure to encourage it to fall, but it will also alter the ant's climbing behaviour to send it marching down to the cool, damp forest floor, which is better suited for the fungus. Once there, the ant is instructed to dig its jaws into the vein of a large leaf and it dies. The fungus then feasts and slowly grows out of the ant's skull in a long spear-like stroma, before dispersing its young into the forest, where they will repeat the cycle. The ant's body is left looking as if it has been killed by a javelin to the back of the head.

This gruesome host-manipulation could be taking place in you and me right now and it's feasible that we're all just existing in a microbial matrix. After all, there is theoretical evolutionary benefit for microbes that are able to reproduce and disperse by exerting their control over our behaviours. You'll be relieved to hear, however, that this is very unlikely. It's far more probable that microbes influence our behaviour through a process of symbiosis. For instance, our gut symbionts are selected to be there by our genome and our exposome, and in turn they are naturally selected to influence the local gut environment. The impact they have on our behaviour is a side-effect of this relationship; for example, it changes how we regulate the environment of the gut. Similarly, if a person's behaviour changes when

they’re missing a particular type of bacteria, that’s more likely to be because the physiology of the gut has changed than because that individual has had their mind changed. In other words, we exist in a finely balanced state of evolved co-dependence with our microbes.

Unfortunately, this careful balance has been dramatically disrupted by the discovery of antiseptics, antibiotics and urban living. And this is exacerbating the explosion of mental-health conditions that we’re seeing among young people. The frail human symbiont brain has been unable to adapt to these insults to our internal ecology, causing a fundamental disruption to its development and a pandemic of neurological and psychological disease.

It’s hard to speak in more concrete terms because we’re overwhelmed by a confounding range of causative factors. Digital addictions are distorting our dopamine sensitivity and serotonin-feedback loops; while relationships, trauma, social isolation, education, socioeconomics, drugs, antibiotics, alcohol and culture all modify the mental-health exposome. The psychobiome is doing its best to survive in the exposome we have created, but it isn’t happy: between 2017 and 2018, 7.3 million adults in England – 17 per cent of the entire adult population – took an antidepressant.[31] And this has only climbed since, given that just under one in three adults reported a clinically significant level of psychological stress during the pandemic lockdowns of 2020 and 2021.[32]

Unless, as a society, we choose to invest in social-care systems to prevent, detect and manage mental-health problems or cognitive decline, we will continue to fail the most vulnerable members of our society. These systems must now also prioritize the health of the gut as an enabler of a healthy mind. This solution doesn’t require expensive microbial biotech, but it needs to make use of the knowledge we already have when it comes to optimizing the maternal microbiome and gut–brain development in early life and preventing the neurological diseases of old age.

I want to tell you that Betty did well after the operation, but her injuries were too great, and she died in the intensive care unit forty-eight hours after her surgery. The treatment of all neurological disease has been revolutionized by better diagnostic technologies, therapeutic drugs and personalized surgical techniques, which means that outcomes for people like Betty are improving. I am sure that in the future the manipulation of the microbiome will be part of this therapeutic arsenal.

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