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Alimentary thinking

Your brain isn't the only organ that influences your mood and behaviour, discovers **Emma Young**

IT'S been a tough morning. You were late for work, missed a crucial meeting and now your boss is mad at you. Come lunchtime you walk straight past the salad bar and head for the stodge. You can't help yourself – at times of stress the brain encourages us to seek out comfort foods. That much is well known. What you probably don't know, though, is that the real culprit may not be the brain in your skull but your other brain.

Yes, that's right, your other brain. Your body contains a separate nervous system that is so complex it has been dubbed the second brain. It comprises an estimated 500 million neurons – about five times as many as in the brain of a rat – and is around 9 metres long, stretching from your oesophagus to your anus. It is this brain that could be responsible for your craving under stress for crisps, chocolate and cookies.

Embedded in the wall of the gut, the enteric nervous system (ENS) has long been known to control digestion. Now it seems it also plays an important role in our physical and mental well-being. It can work both independently of and in conjunction with the brain in your head and, although you are not conscious of your gut "thinking", the ENS helps you sense environmental threats, and then influences your response. "A lot of the information that the gut sends to the brain affects well-being, and doesn't even come to consciousness," says Michael Gershon at Columbia-Presbyterian Medical Center, New York.

If you look inside the human body, you can't fail to notice the brain and its offshoots of nerve cells running along the spinal cord. The ENS, a widely distributed network of neurons spread throughout two layers of gut tissue, is far less obvious (see diagram, p 40), which is why it wasn't discovered until the mid-19th century. It is part of the autonomic nervous system, the network of peripheral nerves that control visceral functions. It is also the original nervous system, emerging in the first vertebrates over 500 million years ago and becoming more complex as vertebrates evolved – possibly even giving rise to the brain itself.

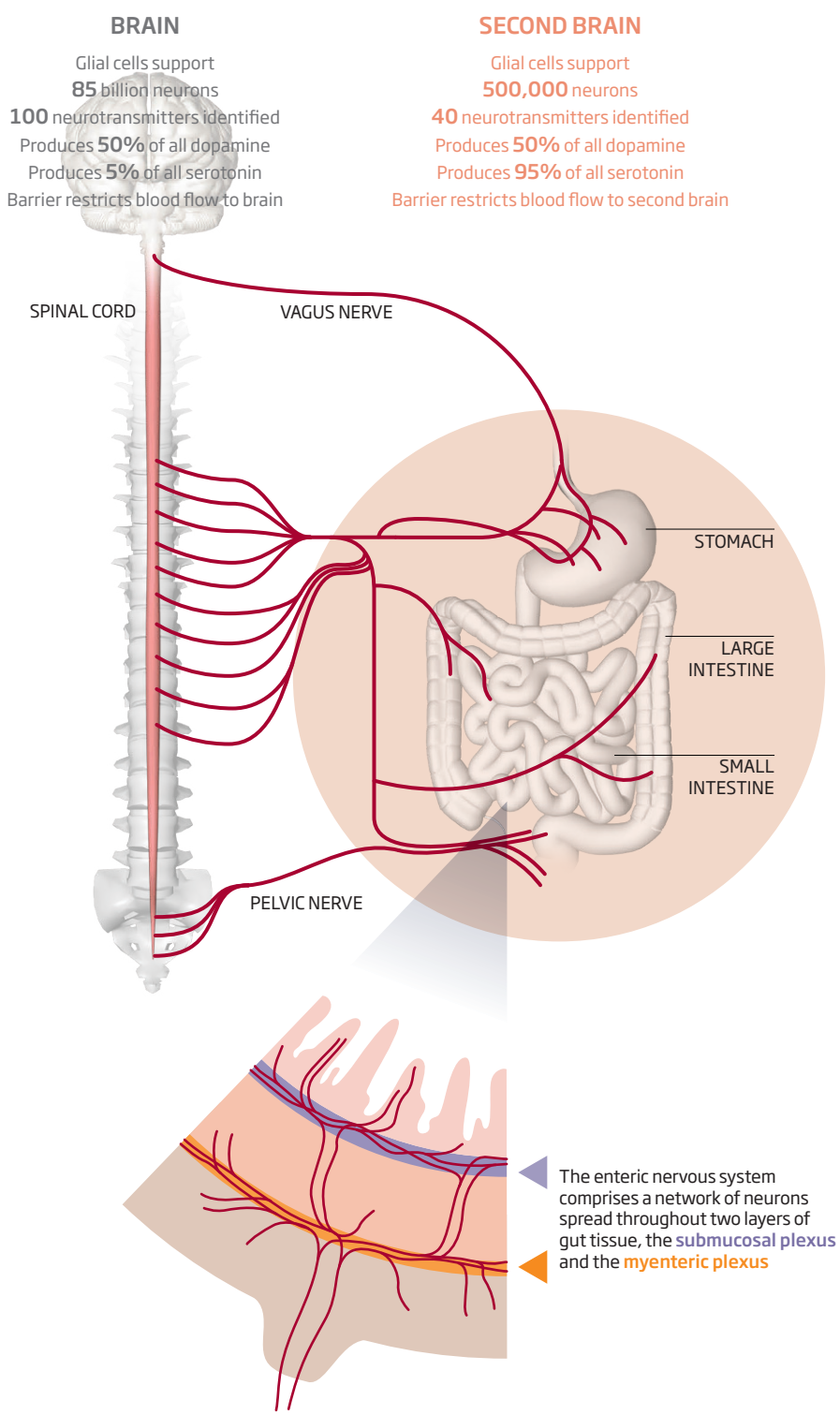
Digestion is a complicated business, so it makes sense to have a dedicated network of nerves to oversee it. As well as controlling the mechanical mixing of food in the stomach and coordinating muscle contractions to move it through the gut, the ENS also maintains the biochemical environment within different sections of the gut, keeping them at the correct pH and chemical composition needed for digestive enzymes to do their job.

But there is another reason the ENS needs so many neurons: eating is fraught with danger. Like the skin, the gut must stop potentially dangerous invaders, such as bacteria and viruses, from getting inside the body. If a pathogen should cross the gut lining, immune cells in the gut wall secrete inflammatory substances including histamine, which are detected by neurons in the ENS. The gut brain then either triggers diarrhoea or alerts the brain in the head, which may decide to initiate vomiting, or both.

You needn't be a gastroenterologist to be aware of these gut reactions – or indeed the more subtle feelings in your stomach that accompany emotions such as excitement, ›

Two brains in one body

The enteric nervous system in the gut, or "second brain", shares many features with the brain in your head. It can act autonomously and even influences behaviour by sending messages up the vagus nerve to the brain



fear and stress. For hundreds of years, people have believed that the gut interacts with the brain to influence health and disease. Yet this connection has only been studied over the last century. Two pioneers in this field were American physician Byron Robinson, who in 1907 published *The Abdominal and Pelvic Brain*, and his contemporary, British physiologist Johannis Langley, who coined the term "enteric nervous system". Around this time, it also became clear that the ENS can act autonomously, with the discovery that if the main connection with the brain – the vagus nerve – is severed the ENS remains capable of coordinating digestion. Despite these discoveries, interest in the gut brain fell until the 1990s when the field of neurogastroenterology was born.

We now know that the ENS is not just capable of autonomy but also influences the brain. In fact, about 90 per cent of the signals passing along the vagus nerve come not from above, but from the ENS (*American Journal of Physiology – Gastrointestinal and Liver Physiology*, vol 283, p G1217).

The feel-good factor

The second brain also shares many features with the first. It is made up of various types of neuron, with glial support cells. It has its own version of a blood-brain barrier to keep its physiological environment stable. And it produces a wide range of hormones and around 40 neurotransmitters of the same classes as those found in the brain. In fact, neurons in the gut are thought to generate as much dopamine as those in the head. Intriguingly, about 95 per cent of the serotonin present in the body at any time is in the ENS.

What are these neurotransmitters doing in the gut? In the brain, dopamine is a signalling molecule associated with pleasure and the reward system. It acts as a signalling molecule in the gut too, transmitting messages between neurons that coordinate the contraction of muscles in the colon, for example. Also transmitting signals in the ENS is serotonin – best known as the "feel-good" molecule involved in preventing depression and regulating sleep, appetite and body temperature. But its influence stretches far beyond that. Serotonin produced in the gut gets into the blood, where it is involved in repairing damaged cells in the liver and lungs. It is also important for normal development of the heart, as well as regulating bone density by inhibiting bone formation (*Cell*, vol 135, p 825).

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But what about mood? Obviously the gut brain doesn't have emotions, but can it influence those that arise in your head? The general consensus is that neurotransmitters produced in the gut cannot get into the brain – although, theoretically, they could enter small regions that lack a blood-brain barrier, including the hypothalamus. Nevertheless, nerve signals sent from the gut to the brain do appear to affect mood. Indeed, research published in 2006 indicates that stimulation of the vagus nerve can be an effective treatment for chronic depression that has failed to respond to other treatments (*The British Journal of Psychiatry*, vol 189, p 282).

Such gut to brain signals may also explain why fatty foods make us feel good. When ingested, fatty acids are detected by cell receptors in the lining of the gut, which send nerve signals to the brain. This may not be simply to keep it informed of what you have eaten. Brain scans of volunteers given a dose of fatty acids directly into the gut show they had a lower response to pictures and music designed to make them feel sad than those given saline. They also reported feeling only about half as sad as the other group (*The Journal of Clinical Investigation*, vol 121, p 3094).

There is further evidence of links between the two brains in our response to stress. The feeling of "butterflies" in your stomach is the result of blood being diverted away from it to your muscles as part of the fight or flight response instigated by the brain. However, stress also leads the gut to increase its production of ghrelin, a hormone that, as well as making you feel more hungry, reduces anxiety and depression. Ghrelin stimulates the release of dopamine in the brain both directly, by triggering neurons involved in pleasure and reward pathways, and indirectly by signals transmitted via the vagus nerve.

In our evolutionary past, the stress-busting effect of ghrelin may have been useful, as we would have needed to be calm when we ventured out in search of food, says Jeffrey Zigman at UT Southwestern Medical Center in Dallas, Texas. In 2011, his team reported that mice exposed to chronic stress sought out fatty food, but those that were genetically engineered to be unable to respond to ghrelin did not (*The Journal of Clinical Investigation*, vol 121, p 2684). Zigman notes that in our modern world, with freely available high-fat food, the result of chronic stress or depression can be chronically elevated ghrelin – and obesity.

Gershon suggests that strong links between our gut and our mental state evolved because a lot of information about our environment comes from our gut. "Remember the inside of your gut is really the outside of your body," he says. So we can see danger with our eyes, hear it with our ears and detect it in our gut. Pankaj Pasricha, director of the Johns Hopkins Center for Neurogastroenterology in

"A better understanding of the second brain could pay huge dividends in efforts to control all sorts of conditions from obesity to Alzheimer's"

MENTAL ILLNESSES OF THE GUT

A growing realisation that the nervous system in our gut is not just responsible for digestion (see main story) is partly fuelled by discoveries that this "second brain" is implicated in a wide variety of brain disorders. In Parkinson's disease, for example, the problems with movement and muscle control are caused by a loss of dopamine-producing cells in the brain. However, Heiko Braak at the University of Frankfurt, Germany, has found that the protein clumps that do the damage, called Lewy bodies, also show up in dopamine-producing neurons in the gut. In fact, judging by the distribution of Lewy bodies in people who died of Parkinson's, Braak thinks it actually starts in the gut, as the result of an environmental trigger such as a virus, and then spreads to the brain via the vagus nerve.

Likewise, the characteristic plaques or tangles found in the brains of people with Alzheimer's are present in neurons in their guts too. And people with autism are prone to gastrointestinal problems, which are thought to be caused by the same genetic mutation that affects neurons in the brain.

Although we are only just beginning to understand the interactions between the two brains, already the gut offers a window into the pathology of the brain, says Pankaj Pasricha at Johns Hopkins University in Baltimore, Maryland. "We can theoretically use gut biopsies to make early diagnoses, as well as to monitor response to treatments."

Cells in the second brain could even be used as a treatment themselves. One experimental intervention for neurodegenerative diseases involves transplanting neural stem cells into the brain to replenish lost neurons. Harvesting these cells from the brain or spinal cord is not easy, but now neural stem cells have been found in the gut of human adults (*Cell Tissue Research*, vol 344, p 217). These could, in theory, be harvested using a simple endoscopic gut biopsy, providing a ready source of neural stem cells. Indeed, Pasricha's team is now planning to use them to treat diseases including Parkinson's.

Baltimore, Maryland, points out that without the gut there would be no energy to sustain life. "Its vitality and healthy functioning is so critical that the brain needs to have a direct and intimate connection with the gut," he says.

But how far can comparisons between the two brains be taken? Most researchers draw the line at memory – Gershon is not one of them. He tells the story of a US army hospital nurse who administered enemas to the paraplegic patients on his ward at 10 o'clock every morning. When he left, his replacement dropped the practice. Nevertheless, at 10 the next morning, everyone on the ward had a bowel movement. This anecdote dates from the 1960s and while Gershon admits that there have been no other reports of gut memory since, he says he remains open to the idea.

Gut instincts

Then there's decision-making. The concept of a "gut instinct" or "gut reaction" is well established, but in fact those fluttery sensations start with signals coming from the brain – the fight or flight response again. The resulting feeling of anxiety or excitement may affect your decision about whether to do that bungee jump or arrange a second date, but the idea that your second brain has directed the choice is not warranted. The subconscious "gut instinct" does involve the ENS but it is the brain in your head that actually perceives the threat. And as for conscious, logical reasoning, even Gershon accepts that the second brain doesn't do that. "Religion, poetry, philosophy, politics – that's all the business of the brain in the head," he says.

Still, it is becoming apparent that without a healthy, well-developed ENS we face problems far wider than mere indigestion. Pasricha has found that newborn rats whose stomachs are exposed to a mild chemical irritant are more depressed and anxious than other rats, with the symptoms continuing long after the physical damage has healed. This doesn't happen after other sorts of damage, like skin irritation, he says.

It has also emerged that various constituents of breast milk, including oxytocin, support the development of neurons in the gut (*Molecular Nutrition and Food Research*, vol 55, p 1592). This might explain why premature babies who are not breastfed are at higher risk of developing diarrhoea and necrotising enterocolitis, in which portions of the bowel become inflamed and die.

Serotonin is also crucial for the proper development of the ENS where, among its many roles, it acts as a growth factor. Serotonin-producing cells develop early on in the ENS, and if this development is affected, the second brain cannot form properly, as Gershon has shown in mutated mice. He believes that a gut infection or extreme stress in a child's earliest years may have the same effect, and that later in life this could lead to irritable bowel syndrome, a condition characterised by chronic abdominal pain with frequent diarrhoea or constipation that is often accompanied by depression. The idea that irritable bowel syndrome can be caused by the degeneration of neurons in the ENS is lent weight by recent research revealing that 87 out of 100 people with the condition had antibodies in their circulation that were attacking and killing neurons in the gut (*Journal of Neurogastroenterology and Motility*, vol 18, p 78).

If nothing else, the discovery that problems with the ENS are implicated in all sorts of conditions means the second brain deserves a lot more recognition than it has had in the past. "Its aberrations are responsible for a lot of suffering," says Pasricha. He believes that a better understanding of the second brain could pay huge dividends in our efforts to control all sorts of conditions, from obesity and diabetes to problems normally associated with the brain such as Alzheimer's and Parkinson's (see "Mental illnesses of the gut", above). Yet the number of researchers investigating the second brain remains small. "Given its potential, it's astonishing how little attention has been paid to it," says Pasricha. ■

Emma Young is a writer based in Sheffield, UK