GUT THINKING

There are strange forces at work behind our food desires. Chloe Lambert reports

YOU'VE just had a hearty lunch, but the doughnuts next to your desk are winking at you. You can't shake the hought of what the glazed, soft dough would aste like – and know that you won't be able o get on with your day until you have it.

On a basic level our relationship with food s simple – signals between the gut and the rain tell us when we're hungry, and when ve are full. But experience shows us that he drive to eat is much more tangled and rrational. Some of that is down to the eward hit – the feeling of pleasure, mediated y the brain's reward centre – that we get rom eating calorie-dense food like that listening doughnut. Indeed, the effect of uch foods has led some to liken our desire or them to drug addiction.

But we now know the gut itself, and also he microbes inside it, manipulate what we rave, painting a much more complex picture f the forces that determine the way we see ood. Cravings could even be contagious – iterally. When it comes to food, we're not as n control as we might think.

"People think we have much more onscious control over our eating behaviour han we do. There's a lot going on behind the cenes and it makes it very difficult to exert ontrol on it," says Tony Goldstone, an ndocrinologist at Imperial College London.

Even so, knowing about the forces that nanipulate the way we think about food pens up new ways to regain control – for nstance by retraining the brain or altering our gut flora. Fresh approaches would be nore sensible than just expecting people o eat better, says Goldstone: "We don't just ell asthmatic people to breathe more."

What, when and how much we eat has ypically been explained by two systems, ne based on hunger and one on reward. The hunger system is mediated by hormones rom the gut and from fat cells, which send nformation to the brain via the gut's own nervous system about when we last ate and ow hungry we should feel. "We can eat very ittle one day, and a great deal the next, but his system works to ensure that body weight s relatively stable across the years," says John Menzies, a neurobiologist at the University of Edinburgh, UK.

The reward system is more concerned with what type of food we eat. At its heart is the dopamine pathway, which seems to respond most strongly to foods that are high in fat and sugar. This is natural and necessary – it evolved to prompt us to seek out such food, helping us survive. "If we see a high-energy food, it pays to get it while it's available - a famine may be round the corner," says Menzies. "However, in our modern environment where food is abundant and cheap, the reward system may work against us, pushing us towards eating sweet and fatty foods even though we already have plentiful energy stores."

The brain even has its own calorie counter that drives our choices without us knowing, according to a recent study. Participants were shown pictures of 50 foods and asked how many calories they thought each contained, and then invited to bid in an auction for a chance to eat the foods. Regardless of their calorie estimations, which were often inaccurate, the individuals were more likely to bid for the foods that were truly the most calorific. MRI scans showed that activity in reward regions of the brain correlated with the true calorific content of foods – the more calories, the greater the reward.

Although these hunger and reward systems sound very different, there's a growing awareness of how interconnected they are. Some clues come from genetics. A gene called *FTO* is strongly linked to weight gain, and one variant of it raises a person's risk of becoming obese by 70 per cent. A recent study showed that such people have higher than normal levels of the hormone ghrelin, which is released by the gut, telling them they are still hungry after eating, but their reward system works differently too. MRI studies showed that this group's brains responded differently when they were shown pictures of food: the most pronounced differences being in the reward regions. The reward pathways in the brains of obese people have also been shown to respond less strongly to food – which could be driving them to seek out even more each time.

More evidence of the link comes from people who have had gastric bypass surgery – which reduces the capacity of the stomach and makes food pass more quickly into the small ›

ꞮUNNING HIGH

hey're hungry and exhausted – ɔ why do runners often get a feeling f euphoria? It could be to do with the ɜtiety hormone, leptin, or a lack of it. ɘptin is synthesised in proportion to ɘvels of fat in the body and after a meal sends signals to the brain to say we are ıll, curbing appetite. But it is also an nportant regulator of dopamine in the rain, which triggers feelings of pleasure nd reward (see main story).

To test its effects, Stephanie Fulton at ıe University of Montreal, Canada, and ɔlleagues used genetically engineered ıice that lacked a leptin-sensitive ɛceptor and so had more dopamine. ıe mice lacking leptin ran almost twice ; far and as fast as normal mice over the ɔurse of a day. Fulton believes that, ɹring a run, falling levels of leptin send signal to the brain to create feelings of easure and motivation. This echanism may have evolved to keep us ɘarching for food during periods of arvation, she says. "In the evolutionary ɜst we had to move to get food – it asn't immediately available so we had chase it down. Leptin inhibits not just ıe consummatory part of feeding, but so the behaviour that's important to ɜt access to food, including running."

Leaner people such as marathon ınners, who have lower levels of rculating leptin, may be more ısceptible to the rewarding effects exercise, says Fulton. It could also help ɛplain why people with low leptin as a sult of anorexia are often restless and ʏperactive.

testine. After surgery, not only do people ant to eat less, they experience a profound ıange in what they want to eat, finding they e drawn to much less calorie-dense foods. nd brain scans of people before and after ıstric bypass surgery showed altered activity their reward centres. That contrasts with ɘople who have a gastric band inserted. One ɛplanation for these effects is that after a ıstric bypass, food reaches the bowel much ore quickly, so there's a faster hormone sponse, whereas a gastric band has no effect ı hormone levels.

"These hormones are normally released ter a meal to make us feel full, but as we're scovering, they also have effects on the ɜy the brain works, to regulate the hedonic sponses, the pleasure from food," says ɔldstone. "The bypass patient will say, 'I'm not ıngry, and I also don't want or like the food'. ıe band patient will say: 'I'm not hungry, but ould murder the chocolate cake'."

What if you could recreate these effects without the surgery? Susan Roberts, at Tufts University in Medford, Massachusetts, has designed a diet in which foods look like the kinds of calorie-dense treats people have learned to crave, but with a twist. "We basically confused people's reward system by giving them foods that had the flavour and appearance of high-calorie foods that are easily digested, but in fact they were lower calorie, slowly digested versions," she says. For instance, her diet includes a lower-calorie, slowly digested pizza, made with added fibre.

In a small trial, she scanned the brains of a group of overweight people before and after putting them on a six-month diet based on these foods. At the end of the study, the scans showed an increase in activity of reward pathways when the participants looked at pictures of healthy, low-calorie foods, compared with a group not eating the diet.

IMAGE SOURCE/PLAINPICTURE

Risky rewards

"We were effectively retraining their brains," says Roberts. "You can think of pizza and you start craving pizza because you anticipate that rush of calories. If you eat the food and you fail to get the rush of calories, over time the reward circuitry adapts so it's no longer expecting a great zoom of carbohydrate coming in," she says.

The added fibre helped recondition cravings by making people feel full, but Roberts says it's also important that the participants only ate when they were truly hungry, to strengthen the reward they got from the food. And if dieters cheat and tuck into old favourites, it would strengthen the old reward pathways. Roberts is now beginning two larger clinical trials, and has commercialised the diet plan.

So we can retrain our brains to desire different foods. But we are also starting to better understand how the brain influences people who are driven to avoid food, such as those with anorexia. It used to be thought of as a mainly psychological disorder but it now seems that there might be profound changes in the brains of people with the condition. "These are biologically driven disorders," says Cynthia Bulik, a psychiatrist specialising in eating disorders at the University of North Carolina.

Many studies into anorexia and the brain hint that the same forces that cause some people to overeat might be at play in anorexia too, but having the opposite effect. For instance, recent research has found that the same genes that confer a high risk of obesity also seem to be involved in anorexia.

The exact mechanisms at work are still being investigated, but it could be that while those who overeat may have a dampened dopamine response, those with anorexia have a heightened, more sensitive one. "That may make all reward stimuli, especially those associated with food, overwhelming to them, and so their response is to pull away and not eat," says Caitlin O'Hara, who researches eating disorders at King's College London.

Another idea is that this group feel reward from things that most of us find unpleasant – like being hungry. "People with anorexia feel terrible when they're full," says Bulik. "Starvation actually calms their biology."

It's not yet clear whether this altered reward response is a cause, or a consequence of eating disorders. But finding that the condition could at least in part be down to brain changes opens new avenues for treatment. For example, a recent study at Kings College London on five people with severe, treatment-resistant

"Gut hormones modify not only consumption of food but also any drug of abuse"

Is your gut bacteria making you want to tuck in to cake instead of salad?

MICROBIAL MIND CONTROL

Your gut bacteria weigh more than your brain, and this mass of microbes could affect your mind. We know that transplanting the microbiota of anxious and normal mice switches their personalities, for example. Kathy Magnusson at Oregon State University has shown that feeding animals a high-sugar diet causes changes in gut bacteria that impair their cognitive flexibility – the ability to adjust to changing situations.

John Cryan at University College Cork in Ireland found that rodents fed a broth containing *Lactobacillus rhamnosus* showed reduced signs of stress and anxiety. This particular bacterium is known to release the anti-anxiety neurotransmitter GABA, and last month, Cryan's team presented work at the Society for Neuroscience meeting in Chicago that replicated this study in 22 men. They took the probiotic for four weeks and found similar results with regards to stress and anxiety.

In 2013, another study showed that healthy women who drank a probiotic milk product for four weeks showed changes in brain areas that process emotions. The team says this paves the way for work using probiotics to treat depression and other mood disorders.

orexia suggests that stimulating a
ain region involved in appetite and
otion regulation can help. Experimental
atments involving implants deep in the
ain that stimulate the reward pathway
en a person eats have also been successful
very severe cases.

While the brain clearly has a huge influence
er what we eat, the influence of gut bacteria
ght be surprisingly large, too, and they can
en affect our minds (see "Microbial mind
ntrol", above). Bulik's team has found stark
ferences in gut bacteria when people are in
acute stages of anorexia compared to
en they have gained some weight. She
nks that during starvation, microbes that
survive on minimal calories flourish.

Gut microbes could have more pervasive
ects too. Last year, Joe Alcock at the
iversity of New Mexico in Albuquerque and
colleagues published a review of research
the microbiome and came to an intriguing conclusion – gut microbes don't just flourish on certain diets, they may also control our food cravings and preferences to serve their own purposes.

There are several ways they could do this. Animals' gut flora has been shown to affect their taste receptors, which changes their food preferences. And many gut microbes can produce proteins that mimic gut hormones. Alcock's team even thinks that changes in food preferences that people experience after bariatric surgery might be down to changes in gut microbes, not hormones.

That means interventions like probiotics, which help to change the composition of the microbiome, might be useful tools in regulating food cravings. And it suggests a varied diet would make it harder for any one type to flourish and exert control.

Because the faecal and oral microbiomes of families under the same roof are more similar than people who don't live together, the idea that food cravings are influenced by gut bacteria also raises the intriguing possibility that through the spread of these microbes, cravings could even be contagious. Of course, this similarity could be because the members of a household have the same diet. But it might also be that gut bacteria are spread person to person. We already know people are much more likely to become obese if they have a friend who is obese, leading some to speculate that the effect is not down to social contagion, but the spread of microbes.

More needs to be done to work out how strong all these effects are, but this new appreciation for the hidden forces influencing our perception of food has wide-reaching implications. Goldstone even wonders whether tapping into the connection between the hunger and reward pathways could alter appetites of a different kind. Animal studies have already shown that ghrelin increases intake of alcohol, nicotine and other drugs, while "fullness" hormones reduce intake.

He suspects the same is true for humans. "We've shown that your nutritional state modifies the way the brain responds not just to food but also to winning money, and to stress," he says. "That's because the same reward circuitry is involved. There's evidence that gut hormones modify not only reward and consumption of food but also any drug of abuse – such as nicotine, cocaine, alcohol," he says. They are now beginning a large study.

At the very least, all this suggests that expecting people to rely purely on willpower to control what they eat, especially if they are obese, is misguided. "There's a cabal of obesity researchers that have turned up their hands and said the only thing you can do is rely on willpower," says Roberts, "I don't think it's worked for the last 30 years and it's not going to work next year either. Which is why we're trying to do it in a different way." ■

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