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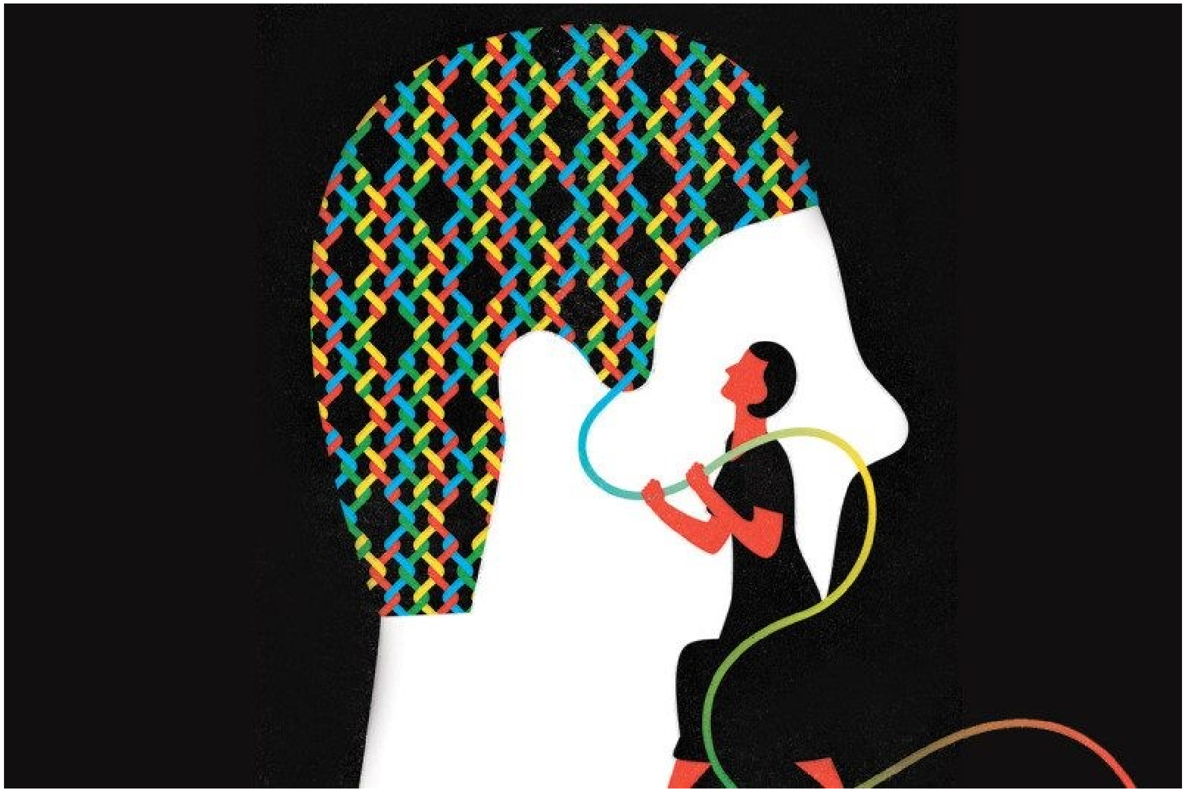
# Mind the gaps: The holes in your brain that make you smart

A map of the brain's wiring reveals the spaces may be just as important as the connections – and you have the holes to thank for your most impressive mental feats



Andre da Loba

By **Caroline Williams**

IT HAS been described as a "monstrous, beautiful mess", a "tangled web" and a "dense canopy of tropical branches". But in reality, it is nothing of the sort. The human brain is a highly organised, efficient machine, no circuit laid without good reason. If it appears tangled, that is only because we haven't managed to unravel its 100 billion wires and 100 trillion connections well enough to explain how it works.

The reward for that feat wouldn't just be a map of the most complex object in the known universe. Understanding the brain's connections would begin to teach us how its flashes of electricity add up to a fully conscious experience, one in which our senses, intuition, reasoning and memory interact to give a coherent view of the world.

That understanding has long eluded us. But a new approach is providing fresh clues by focusing not on the neural cables but the spaces between them. By applying a curious branch of mathematics more usually applied to exotic states of matter, neuroscientists are revealing a hidden dimension of the brain. It turns out that the wiring between your ears is full of holes – and you might have them to thank for your most impressive mental feats.

In the early 1900s, the Spanish anatomist Santiago Ramon y Cajal was the first to draw the neurons that make up the basic scaffolding of the brain. His sketches made it obvious that the cells form a connected network. The cell bodies make up what is known as grey matter, brain areas where particular types of processing happen. The cells also have long protrusions, called axons, which not only connect to nearby neurons but also make up white matter, the tissues containing long-range links that allow electrical signals to flow to distant areas of the brain.

Even in Cajal's day, it was easy enough to see the white matter; so called because when you slice up a brain the colour shows up obviously. These days, instruments such as MRI scanners can reveal the white matter without the need for any incisions. But we have never had a full picture of how the electrical impulses move within the wires or how these create our seamless experience of the world. It's a bit like an old-school road atlas: we can see the available routes, but not the ever-changing traffic conditions.

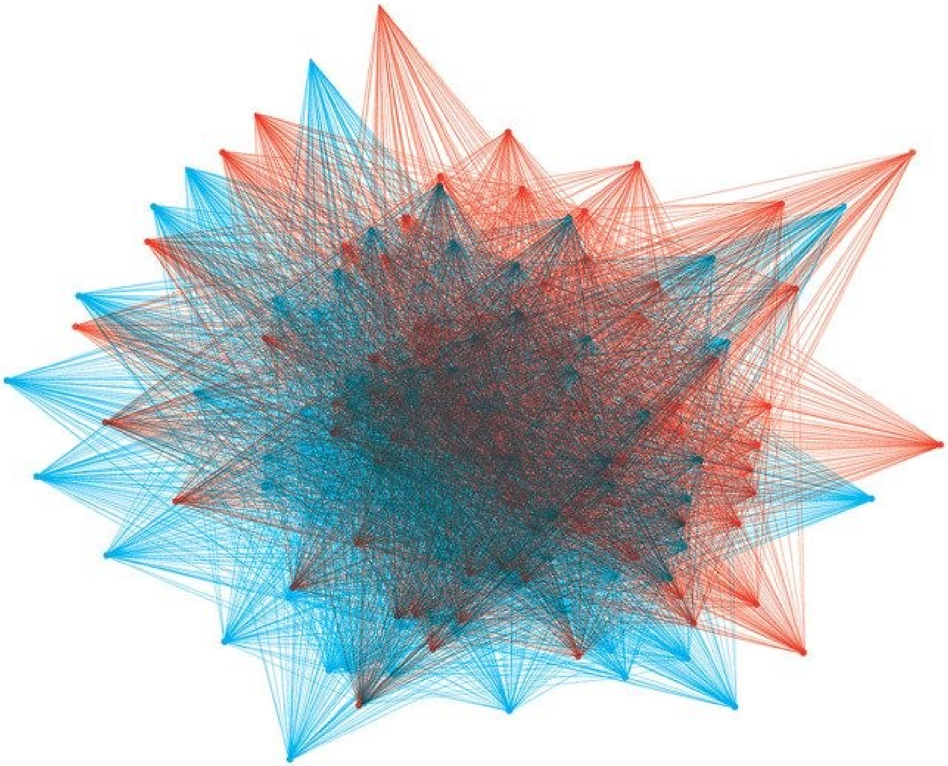
Except, until recently, we didn't even have a decent map. That only began to change after 2005, when cognitive neuroscientist Olaf Sporns of Indiana University in Bloomington called for a concerted effort to map every connection in living brains, to produce what he called the "connectome".

Sporns got his wish. In 2009, the US National Institutes of Health launched the Human Connectome Project, which has since received almost $40 million in funding. It carried out brain scans on thousands of volunteers and stored the resulting maps in a databank that researchers can use to test ideas about how brain structure relates to function. Last year the data helped identify 180 brain areas, 97 of which were previously unknown.

Studies of the connectome almost all have one thing in common: they use a mathematical approach called graph theory to describe the brain's wiring. This breaks networks down into a series of dots and lines – or "nodes" and "edges" in graph theory parlance. In the case of the brain, the nodes are grey matter and the edges white matter.

Graph theory was a reasonable choice. After all, it had already yielded insights into other complex networks, clarifying how ideas propagate via social media and how infectious diseases spread. Applied to the brain, it revealed that the connectome is what mathematicians call a "small world network". That means that each brain area has dense internal connections, with only a few links to other nodes that act as hubs, relaying signals between areas.

All this is now established neuroscience, so much so that we have moved on to comparing people's connectomes to see what the differences might tell us. For instance, Martijn van den Heuvel, who directs the



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Dutch Connectome Lab at Utrecht University in the Netherlands, has found suggestions that the shorter the connections between hubs, the higher the person will score in an IQ test. The explanation could be that shorter connections make it easier for the brain to integrate information. “The brain is a network, and we can examine it with network tools as we do the internet and social networks and so on,” says van den Heuvel.

Graph theory can only take us so far, however. While it has been incredibly useful for describing processing in densely connected brain regions that are also close in space, or are working on a similar problem, it doesn’t explain what happens next.

Imagine, for instance, that your dog’s leash breaks while you’re out walking. Thinking up a solution requires you to conjure up a mental image of a substitute – something long, thin, flexible and strong – while combing your memory for what might fit the bill. An ivy stem, maybe? Or how about a belt? We know that circuits in the frontal lobe, the seat of logical, goal-directed thinking, assess the ideas in turn to see which will work. But graph theory is silent on how the brain shifts between processes like recalling memories, planning and visualisation. That’s why, says van den Heuvel, the entire connectomics field is trying to expand its understanding of the brain as a network, to see how far it can take us.

**“The connectome has helped reveal 97 previously unknown brain areas”**

Danielle Bassett, a neuroscientist at the University of Pennsylvania in Philadelphia, began to think we could make progress by switching to another kind of maths. The field that caught her eye was topology, a branch of maths that offers something a little different from graph theory.

We are used to thinking of shapes in terms of geometry, categorising them using the angles of their corners and lengths of their sides. But to a topologist, the distances between points in a shape are unimportant; what matters is that they remain connected in the same order. So, topologically speaking, a bagel is the same shape as a coffee cup. If the cup is made of a squishy material, allowing you to pull its handle and squash its body, you would be able to form a bagel without breaking the outline or making any new joins. In effect, topology emphasises gaps in connections; the cup handle and the centre of the bagel are the important bits, so to speak. Start with these gaps, and you can quickly see the ring-like shapes that encircle them.

Topology has long been used to explain exotic states of matter, which do things like conducting electricity with no resistance. But Bassett noticed that her colleague at the University of Pennsylvania, mathematician Robert Ghrist, had recently begun to use topology in new ways; to map dead zones in mobile phone signal coverage, for example. She wondered if it could prove rewarding to look at the connectome’s dead zones, too. “If we’re not looking at the holes,” she says, “are we missing something important about how this thing works?”

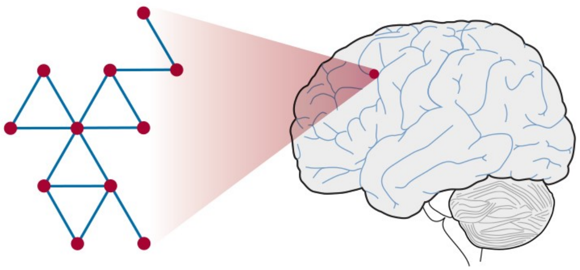
With her colleague Ann Sizemore and others, she designed an experiment to find out. First the team scanned the brains of eight healthy adults and identified the same 83 brain areas in all of them, including sensory regions such as the visual cortex and areas deeper in the brain that are involved in memory and emotional processing. Then, they mapped the white matter pathways that linked them and analysed the network using the rules of topology.

The first things they found were those familiar, highly connected brain areas. Then they reanalysed them so that areas that were densely connected to each other were considered as single processing units: cliques, in the language of topology.

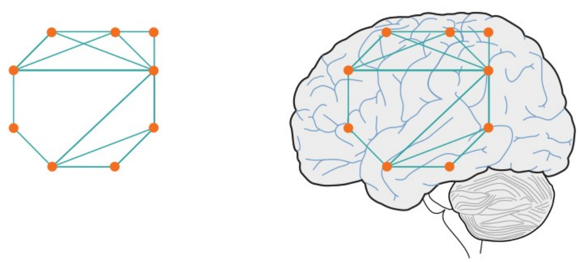
So far, so unremarkable. But when they turned their attention to the gaps that topology highlights, they saw something totally new: holes in the connectome that serve to separate cliques from each other. These “cycles” are encircled by loops of connections of assorted shapes and sizes.

## Unpicking the brain

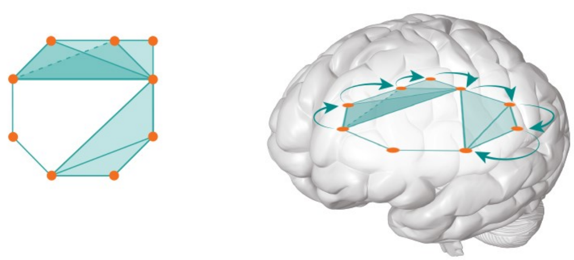
Mathematical techniques are giving us remarkable insights into how the brain is wired up



**Graph theory** has revealed **dense short-range connections** within brain areas, but not the way one area is linked to another



Now studies using **topology** have identified those long-range connections. They form loops with "holes" at the centre



That means **signals must travel around a hole's periphery** – no shortcuts across the gap. This might explain how the brain combines inputs from multiple senses without getting confused

Bassett's team identified four of these loops that join deeper parts of the brain to the outer cortex, and one that loops around the outer cortex. Some were simple loops, while others are complex three-dimensional shapes that take in many different brain regions.

The same cycles turned up in all the volunteers, which suggests they are there for a reason, says van den Heuvel. "Previously we simply ignored those weak connections, but if you look at multiple individuals and you find the same connections across them all, then it's very likely that it has a special role in the overall structure," he says.

Bassett speculates that the reason cliques are kept separate is to avoid crosstalk between those that are carrying out different kinds of processing. A cute example, says Bassett, is that if you had too much connectivity between the brain areas that deal with taste and vision "you could get confused and start feeling that you're seeing what you are eating".

**"Are we missing something important if we don't look at holes in the brain?"**

Crucially, information travelling between cliques has to flow neatly around the periphery of a cycle; it can't take a short cut across the gap. Bassett thinks this might allow the brain a certain amount of control over when to integrate information and how. Think back to that broken dog leash; the cycles could explain how the brain sifts through the options to make a decision without everything getting confused.

But this is about more than unfortunate dog walking incidents. Van den Heuvel reckons the discovery of cycles might open up a whole new window on how the brain works overall.

In particular, Bassett says some of the cycles seem to connect brain areas that we know are involved in executive function. This is a collection of mental processes that allow us to plan and to control impulses, attention and fear. The old view was that each brain area worked separately, without much crosstalk between them. "This work suggests that they are not necessarily segregated, but just connected by very long loops," says Bassett.

Let's say that your peripheral vision spots a snake in the grass. Messages from the visual cortex inform the amygdala, the brain's burglar alarm, that something requires immediate attention. This snaps focus to the threat, while informing the motor cortex to move your body out of the way. Meanwhile the frontal cortex, the brain's decision-maker, comes online, consults memory and spots that what you have seen is actually a stick. Finally, it's back to the amygdala, which turns off the panic button. We know all this must happen, but not how. Bassett thinks cycles might be the answer.

That's fascinating because executive function is one of the things that makes our experience so rich and humans so smart, providing us with self-control and reasoning. And this might point to a way we can test Bassett's ideas.

We know that executive function strengthens during adolescence, which would suggest that this might be when cycles start to form. To see if we can catch them in the act, Sizemore is now analysing connectome data from 2000 people aged between 8 and 22.

## Loopy minds

Similarly, if Bassett's ideas are correct, you would also expect animals lower on the evolutionary tree to have cycles that are less sophisticated. And indeed, the loops seem to link evolutionarily older and younger brain areas, says Bassett, suggesting that they might have evolved to add nuance to more basic functions like the flight response, reward seeking and learned associations. Now Bassett's team plans to train a topological lens on the few connectomes we have from other species – including fruit flies, mice and nematode worms – to check if it's possible to see cycles emerge. "Potentially, over evolution, what has changed is the length of the loops and that they are connected to the newer areas of cortex," says Bassett.

All this could have medical uses too. The existence of cycles opens up the possibility that their shape might reveal changes in connectivity that underlie problems like depressive disorders, schizophrenia and attention deficit hyperactivity disorder (ADHD). These conditions are characterised by problems in the way that the frontal areas of the brain regulate emotional processing, and it is possible that the cycles linking them are the source of the trouble. "That's an open question that we are working on," says Bassett.

Diagnosing these conditions relies on cataloguing an individual's symptoms, which can be subjective. If brain scans show that physical differences in cycles are correlated with these disorders, that might give us another mode of diagnosis, Bassett thinks. Ditto for synaesthesia, a condition in which senses are combined in unusual ways, so people might hear colours or taste sounds.

Although Bassett's work shines a powerful light on the large-scale organisation of the brain, some think topology could be revealing on smaller scales too. Experiments on mice moving through a maze have already tracked the topology of neuron firing patterns in the hippocampus, a brain region that plays a crucial role in spatial memory. Vladimir Itskov of Columbia University, New York, who led the study, found he could recreate the shape of the maze from the firing patterns alone. Some are beginning to think that whenever information is being integrated in the brain – whether on the scale of the whole brain or a few neurons – then topological rules are important.

It is still early days for this new holey view of the brain. But perhaps it is at least time we ditched our focus on pulling at its wires. If we want a better understanding of our brain, then maybe its many holes are a better place to start picking.

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