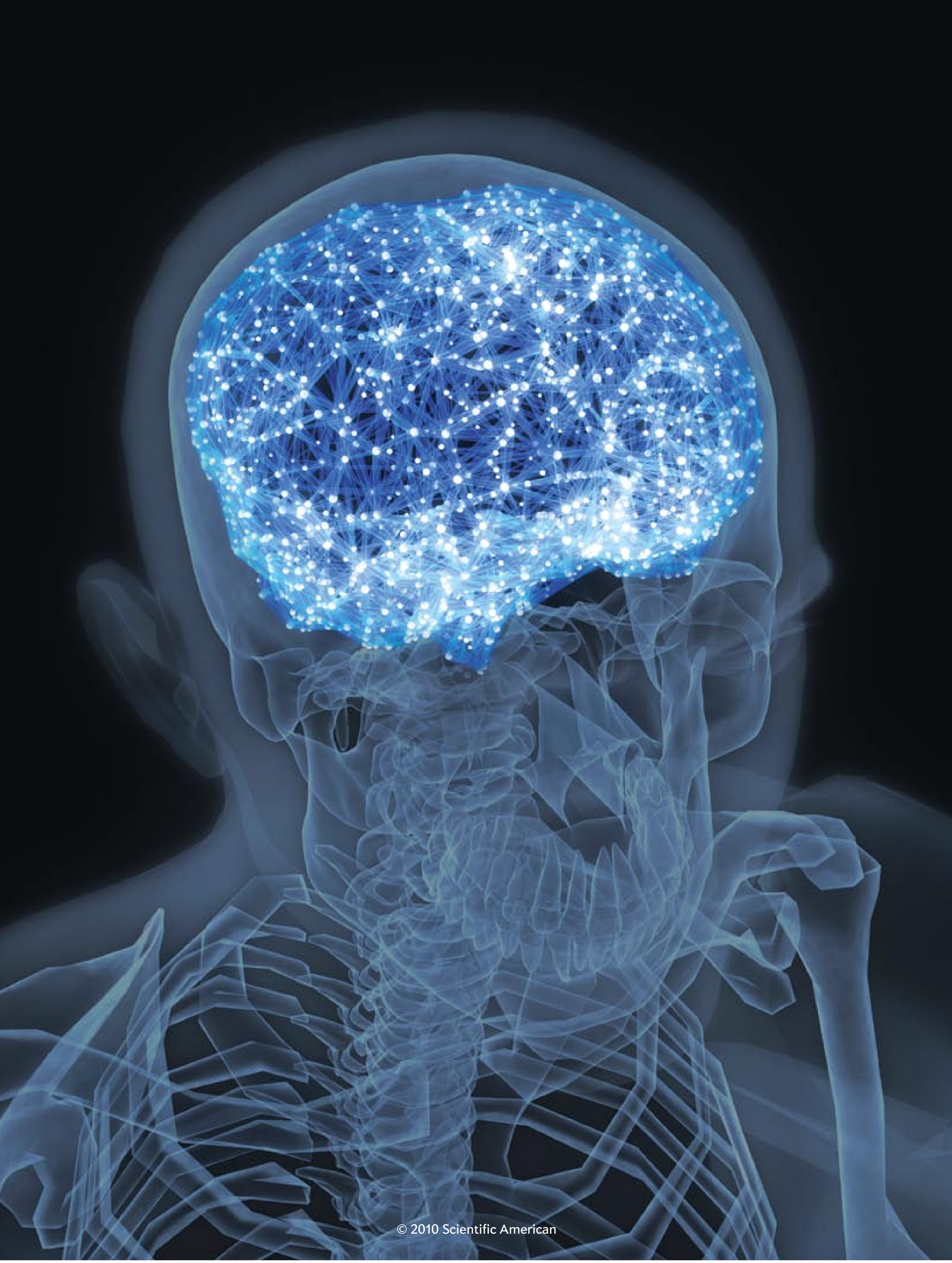

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NEUROSCIENCE

# 100 Trillion Connections

## The noise of billions of brain cells trying to communicate with one another may hold a crucial clue to understanding consciousness

*By Carl Zimmer*

A SINGLE NEURON SITS IN A PETRI DISH, CRACKLING in lonely contentment. From time to time, it spontaneously unleashes a wave of electric current that travels down its length. If you deliver pulses of electricity to one end of the cell, the neuron may respond with extra spikes of voltage. Bathe the neuron in various neurotransmitters, and you can alter the strength and timing of its electrical waves. On its own, in its dish, the neuron can't do much. But join together 302 neurons, and they become a nervous system that can keep the worm *Caenorhabditis elegans* alive—sensing the animal's surroundings, making decisions and issuing commands to the worm's body. Join together 100 billion neurons—with 100 trillion connections—and you have yourself a human brain, capable of much, much more.

How our minds emerge from our flock of neurons remains deeply mysterious. It's the kind of question that neuroscience, for all its triumphs, has been ill equipped to answer. Some neuroscientists dedicate their careers to the workings of individual neurons. Others choose a higher scale: they might, for example, look at how the hippocampus, a cluster of millions of neurons, encodes memories. Others might look at the brain at an even higher scale, observing all the regions that become active when we perform a particular task, such as reading or feeling fear. But few have tried to contemplate the brain on its many scales at once. Their reticence stems, in part, from the sheer scope of the challenge. The interactions between just a few neurons can be a confusing thicket of feedbacks. Add 100 billion more neurons to the problem, and the endeavor turns into a cosmic headache.

Yet some neuroscientists think it is time to tackle the chal-

IN BRIEF

**A single neuron** cannot do much, but string a few hundred together and a primitive nervous system emerges, one sophisticated enough to keep a worm going.

**More neurons equate** to a more complex organism. A central preoccupation of neuroscience is deducing the way billions of neurons produce the human mind.

**Neuroscientists have begun** to unravel the brain's complexity by adopting research on other elaborate systems, ranging from computer chips to the stock market.

**Understanding the workings** of the brain's intricate networks may provide clues to the underlying origins of devastating disorders, including schizophrenia and dementia.

*Illustration by Mirko Ilic*

lenge. They argue that we will never truly understand how the mind emerges from our nervous system if we break the brain down into disconnected pieces. Looking only at the parts would be like trying to figure out how water freezes by studying a single water molecule. "Ice" is a meaningless term on the scale of individual molecules. It emerges only from the interaction of a vast number of molecules, as they collectively lock into crystals.

Fortunately, neuroscientists can draw inspiration from other researchers who have been studying complexity in its many forms for decades—from stock markets to computer circuits to interacting genes and proteins in a single cell. A cell and a stock market may not seem to have much in common, but researchers have found some underlying similarities in every complex system they have studied. They have also developed mathematical tools that can be used to analyze those systems. Neuroscientists are picking up those tools and starting to use them to make sense of the brain's complexity. It's still early days, but their results so far are promising. Scientists are discovering the rules by which billions of neurons are organized into networks, which, in turn, function together as a single, coherent network we call the brain. The organization of this network, scientists are finding, is crucial to our ability to make sense of an ever changing world. And some of the most devastating mental disorders, such as schizophrenia and dementia, may be partly the result of the collapse of the brain's networks.

Interaction among just a few neurons creates a thicket of feedbacks. Billions more brain cells in the mix elicit the essence of a complex system.

Neurons form networks by extending axons that make contact with other neurons. These contacts enable a signal traveling through one nerve cell to trigger a wave of current in the other neurons. Because each neuron can join to thousands of other cells—both those nearby or on the other side of the brain—networks can take on an inconceivable number of arrangements. How your brain's particular network organizes itself has a huge effect on how it works.

## BUILDING A TOY BRAIN

JUST HOW DOES ONE go about studying the brain's network of neurons? What experiment could scientists do to trace billions of network connections? One answer is to make a miniaturized model of a brain that can demonstrate what happens when neurons interact in different ways. Olaf Sporns of Indiana University and his colleagues made just such a model. They created 1,600 simulated neurons, which they arrayed around the surface of a sphere. Then they linked each neuron to other neurons. At any moment, every neuron has a tiny chance of spontaneously firing. Once a neuron fires, it has a small chance of triggering other neurons linked to it to fire as well.

Sporns and his colleagues tinkered with the connections between the neurons and watched their toy brain in action. First they connected each neuron only to its immediate neighbors. With this network, the brain produced random, small flickers of activity. When a neuron spontaneously fired, it created a wave of electricity that could not travel far. Next Sporns and his team linked every neuron to every other neuron in the entire brain, which produced a very different pattern. The entire brain began to switch on and off in regular pulses.

Finally, the scientists gave the brain an intermediate network, creating both local and long-distance links between the neurons. Now the brain became complex. As neurons began to fire, they gave rise to great glowing patches of activity that swirled across the brain. Some patches collided with one another. Some traveled around the brain in circles.

Sporns's toy brain offers an important lesson about how complexity emerges. The architecture of the network itself shapes its pattern of activity. Sporns and other researchers are taking the lessons they glean from models of the brain and looking for similar patterns in the real ones in our heads. Unfortunately, scientists cannot monitor every single neuron in a real brain. So they are using clever techniques to record the activity in relatively few neurons and drawing some big conclusions from their results.

## BRAINS IN A DISH

DIETMAR PLENZ, a neuroscientist at the National Institute of Mental Health, and his associates have been probing the brain's architecture by growing pieces of brain tissue the size of sesame seeds in petri dishes. They stick 64 electrodes into the tissue to eavesdrop on the spontaneous firing of the neurons. Their electrodes detect a rapid-fire staccato of activity, known as neuronal avalanches.

At first, it seems as if the neurons are just crackling with random noise. If that were true, then each neuronal avalanche would be equally likely to be tiny or widespread. That's not what Plenz and his colleagues found, however. Small avalanches were the most common; large avalanches were rare; even larger avalanches were rarer still. On a graph, the odds of each size form a smooth, descending curve.

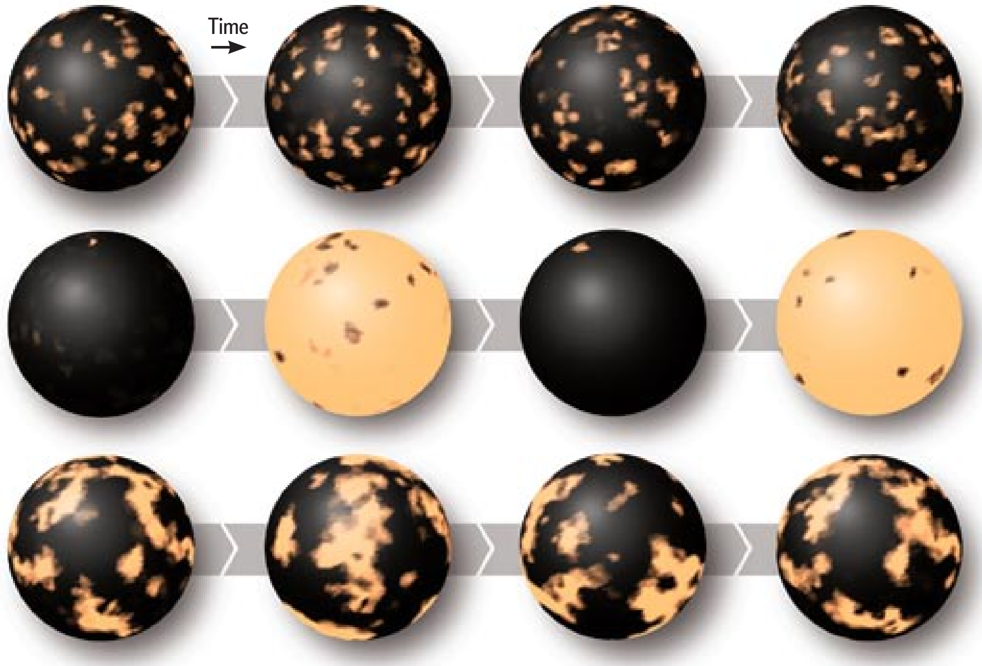
Scientists have seen this kind of curve before. Heartbeats, for example, are not all alike. Most of them are a little longer or shorter than the average. A smaller number of beats are a lot longer or shorter, and a far smaller number are even further away from average. Earthquakes follow the same pattern. The shifting continental plates produce many small earthquakes and a few large ones. During epidemics, each day may typically bring a few cases, with a burst of new cases coming from time to time. And if you plot heartbeats, earthquakes or numbers of new cases on a graph, they form an exponentially falling curve.

This curve, known as a power law, is a hallmark of a complex network that encompasses both short- and long-distance links. A tremor in one spot on the earth may, in some cases, spread across only a limited area. In rare cases, the motion may be able to extend across a much wider domain. Neurons work in the same way. Sometimes they excite only their immediate neighbors, but other times they can unleash a widespread wave of activity.

The shape of a power-law curve can give scientists clues about the network that produced it. Plenz and his co-workers tested out a number of possible networks of neurons to see which ones would produce neuronal avalanches in the same way real neurons do. They got the closest fit with a network of 60 clusters of neurons. The clusters were linked, on average, to 10 other ones. These links were not scattered randomly among the clusters. Some clusters had lots of connections, although many had just a few. As a result, the number of links from any given cluster to any other one was very few. Scientists call this kind of arrangement a small-world network.

## Anatomy of a Toy Brain

A brain simulation crafted by Olaf Sporns and his colleagues at Indiana University gives rise to three different patterns of connections among 1,600 virtual neurons arrayed around a sphere. The simulation—in which some neurons activate spontaneously (*yellow areas*) while the rest remain dormant—helps researchers deduce how different types of networks produce complex interactions, some of which replicate activity that occurs throughout actual brain circuits.




OLAF SPORNS *Indiana University*

It turns out that this kind of network may make our brains exquisitely sensitive to incoming signals, in much the same way a powerful microphone can amplify a wide range of sounds. Plenz and his team applied electrical shocks of different strengths and measured how the neurons responded. They found that faint shocks produced responses from a limited number of neurons. Strong shocks triggered a strong response from a wider range of cells.

To see how the network structure affected this response, Plenz and his colleagues added a drug to the neurons that weakened the connections between the neurons. Now the cells failed to respond to faint signals. The scientists got a different result when they injected a drug that made neurons more likely to fire in response to signals from their neighbors. Now the neurons responded intensely to weak signals—so intensely that their response to weak signals was no different than it was to strong ones. These experiments revealed how finely tuned neural networks can be and how that fine-tuning lets them relay signals accurately. If the neurons were organized in a different network, they would produce meaningless, incoherent responses instead.

Neuroscientists ultimately wish to know how activity in a lab dish relates to everyday mental processes. Looking across the entire brain, experimenters discover patterns of spontaneous activity that mirror the kind Plenz finds in his small bits of brain tissue. Marcus E. Raichle of Washington University in St. Louis and his collaborators have found that waves of electricity can travel across the entire brain in complex patterns when we are just resting, thinking of nothing in particular. Recent experiments suggest this spontaneous activity may play a vital part in our mental life. It may allow the resting mind to reflect on its inner workings, reviewing memories and making plans for the future.

### NEURAL CARTOGRAPHERS

TO UNDERSTAND HOW these waves behave, neuroscientists are trying to map the connections between neurons across the entire brain. Given how hard it is for scientists such as Plenz to figure out what is going on in a bit-size piece of tissue, this is no small challenge. Sporns has been leading one of the most ambitious of these mapping projects. Teaming up with Patric Hagmann of the University of Lausanne in Switzerland and his neuroimaging group, he analyzed data acquired from five volunteers' brains, using a method known as diffusion spectrum imaging, or DSI. DSI readily captures images of axons that are covered by a thin layer of fat, the long fibers linking the different regions of the cortex, known as white matter. The scientists selected almost 1,000 regions of the cortex and mapped the white matter links from each one to the others.

The scientists then created a simulated version of these 1,000 regions and experimented with it to see what kind of patterns it would produce. Each region generated signals that could travel to linked regions, causing neurons there to send out similar signals as well. When the scientists powered up this virtual brain, it began to produce slowly shifting waves of activity. Remarkably, these waves resemble the real ones, seen by Raichle and others, in resting brains.

The network that Sporns and his colleagues have mapped across the brain is organized very much like the smaller one Plenz found in his small pieces of tissue—it is a small-world network, with a few well-connected hubs. This large-scale architecture may help our brains save resources and work faster. It takes a lot of resources for us to grow and maintain white matter. With a few well-connected hubs, our brains require much less white matter than they would with other kinds of networks. And because it takes few links to get from one part of the brain to the other, information gets processed faster.

Neuroscientists are going to be able to make much better maps of the brain's networks in years to come, thanks to a $30-million project launched last year by the NIH. Known as the Human Connectome Project, it will survey every connection between neurons in an adult brain. But even this map will not, on its own, capture the brain's full complexity. That is because neurons use only a subset of the brain's connections to communicate with other neurons. From moment to moment, this network can change shape as neurons switch from some connections to others. Creating models of the brain that can capture these dynamic networks will demand all the tricks of the trade that complexity theory can offer.

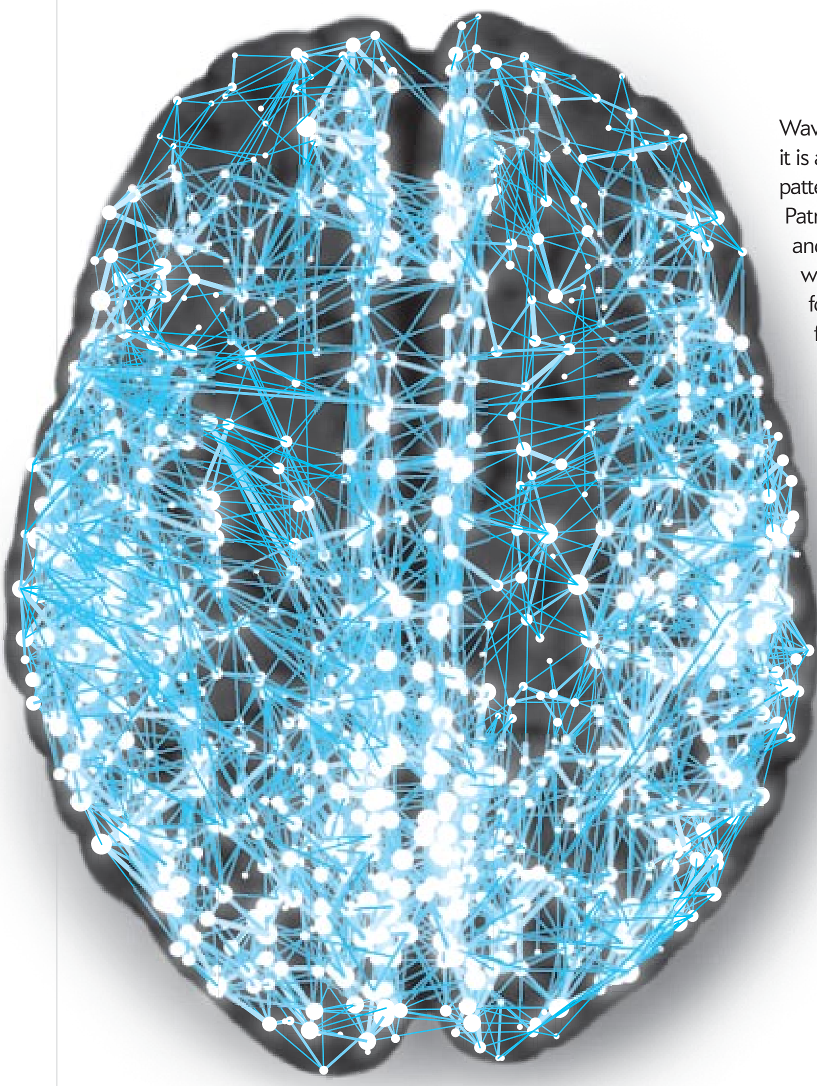
### THE WALL STREET NEURON

TWO MATHEMATICIANS at Dartmouth College, Daniel N. Rockmore and Scott D. Pauls, are attempting to parse this complexity by treating the brain like the stock market. Both the brain and the stock market consist of lots of small units—traders, neurons—that are organized into a large-scale network. Traders can influence one another in how they buy and sell, and that influence can rise up to affect the entire network, making the stock market rise

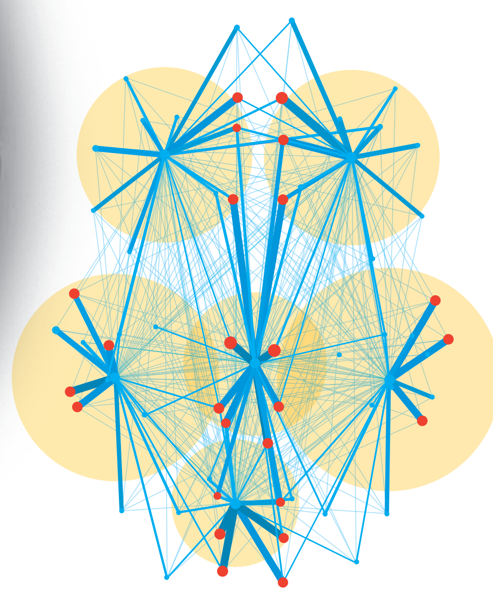
HACKING THE BRAIN

## Small Worlds from Large Networks

Waves of electrical activity sweep across the brain, even when it is at rest. A number of studies now try to map these neural patterns because they may play a critical role in mental life. Patric Hagmann of the University of Lausanne in Switzerland and Olaf Sporns of Indiana University have charted the brain with a technique called diffusion tensor imaging. They found that the dense network of connections (*left*) has a few well-connected hubs (*red dots*) through which many links pass (*below*). Such "small-world" networks of hubs may help our brains process information more rapidly and allow the organ to maintain its structural integrity efficiently.



Large network



Small-world network

SOURCE: "MAPPING THE STRUCTURAL CORE OF HUMAN CEREBRAL CORTEX," BY P. HAGMANN ET AL., IN *PLOS BIOLOGY*, VOL. 6, NO. 7; 2008



*Illustration by Jen Christiansen*

or fall. In turn, the entire network can influence the lowest levels. When the stock market begins to rise, for example, individual traders may want to jump on a rally, driving the market even higher.

Rockmore and Pauls and their colleagues developed a set of mathematical tools to uncover the structure of the network underlying the New York Stock Exchange. They downloaded the daily close prices of 2,547 equities over 1,251 days and searched for similarities in the changing prices of different equities—a tendency to rise and fall around the same time, for example.

This search revealed 49 clusters of equities. When the scientists turned back to their financial information, they found that the clusters mostly corresponded either to particular sectors of the economy, such as software or restaurants, or to particular places, such as Latin America or India.

That they had found these categories simply by analyzing the data gave the scientists some confidence in their methods. It makes sense, after all, that the stocks of companies that provide Internet access would tend to rise and fall in tandem. A dangerous Internet worm could spell trouble for the entire group.

Rockmore and Pauls also found that these 49 clusters were actually organized into seven superclusters. In many cases, these superclusters corresponded to industries that depend on one another. The strip-mall business and the construction business move hand in hand. The two researchers found that these superclusters were linked in a giant loop. That loop was likely the result of a common practice of investment managers called sector rotation. Over the course of several years these managers move their money from one part of the economy to another.

A mathematical model that simulates the interactions underlying buying and selling in the stock market can also represent the networks underlying brain activity.

Now Rockmore and Pauls are using the same mathematical methods to build a model of the brain. Instead of financial information moving from one part of the market to another, they now look at information moving from one region of the brain to another. And just as financial markets have mutable networks, the brain can reorganize its network from one moment to the next.

To test out their model, Rockmore and Pauls recently analyzed functional MRI images that Raichle and his colleagues recorded of a subject's resting brain. They noted the rising and falling activity in each voxel, the peppercorn-size chunk of brain that is as small as fMRI can measure. They then searched for close relations in the patterns. Just as the two found clusters of equities in the stock market, they now discovered that the voxels could be grouped into 23 clusters. And these clusters, in turn, belonged to four larger clusters. Remarkably, these four larger clusters carry out a neurological version of the sector cycling Rockmore and Pauls found in the stock market. They are joined together in a loop, and waves of activity sweep through them in a cycle.

Now that Rockmore and Pauls can reconstruct the network in a resting brain, they are turning their attention to the thinking brain. To understand how the brain changes its organization, they are analyzing fMRI data from people who are shown a series of objects. If their model works, Rockmore and Pauls may be able to predict what kind of results a neuroscientist would get from a scan of someone seeing a particular kind of stimulus, such as the face of an old friend. Such an achievement would push neuroscience toward a truly predictive science.

Studies like these won't let scientists completely decipher the human brain's complexity for a very long time. The nematode worm *C. elegans* offers a cautionary tale. More than 20 years ago researchers finished mapping every connection bridging all its 302 neurons. But investigators still do not know how that simple network gives rise to a working nervous system.

## NETWORK NEUROLOGY

SCIENTISTS MAY NOT HAVE TO DRAW a complete diagram of the brain's wiring before they can learn some important practical lessons. A number of studies suggest that some brain disorders are not the result of any particular part of the brain malfunctioning. Instead the network itself may go awry. Sporns and his colleagues wondered how the small-world network they identified might change if they turned off different nodes. If they shut down a region of the brain with only a few connections to its neighbors, the network as a whole continued to behave much as it had before. But if they shut down a single hub, the patterns of activity across the entire network changed dramatically. This finding may explain the puzzling unpredictability of brain damage. A tumor or a stroke can sometimes cause devastating harm by knocking out a tiny patch of neurons. But other times they may wipe out a lot of neurological real estate without causing any noticeable change to the workings of a brain.

A number of diseases of the brain may also turn out to be network disorders. Ed Bullmore, a neuroscientist at the University of Cambridge, and his colleagues have been investigating the possible link between the brain's networks and schizophrenia. In a recent study the scientists took fMRI scans of 40 people with schizophrenia and 40 healthy people lying quietly with their eyes open. Bullmore and his team then mapped the network of regions still active in their resting brains. The scientists found that some regions of this resting-state network were more in sync in the brains of schizophrenics than in normal brains.

Scientists do not yet know how schizophrenia and these changes to the brain's network are related. At the very least, it may be possible to use this understanding to develop sensitive tests for schizophrenia, as well as a range of other disorders such as autism and ADHD, which show signs of being diseases of the brain's networks. Doctors might also be able to track the progress of their patients by observing whether their brains' networks have returned to a healthy state. That would be a welcome advance, even if we had to wait still longer for neuroscientists to decipher the brain's full complexity. SA

### MORE TO EXPLORE


**Theoretical Neuroanatomy: Relating Anatomical and Functional Connectivity in Graphs and Cortical Connection Matrices.** O. Sporns, G. Tononi and G. M. Edelman in *Cerebral Cortex,* Vol. 10, No. 2, pages 127–141; February 2000.

**Mapping the Structural Core of Human Cerebral Cortex.** Olaf Sporns et al. in *PLoS Biology,* Vol. 6, No. 7, e159; July 2008.

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**Networks of the Brain.** Olaf Sporns. MIT Press, 2010.


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