Core Concept: Resting-state connectivity

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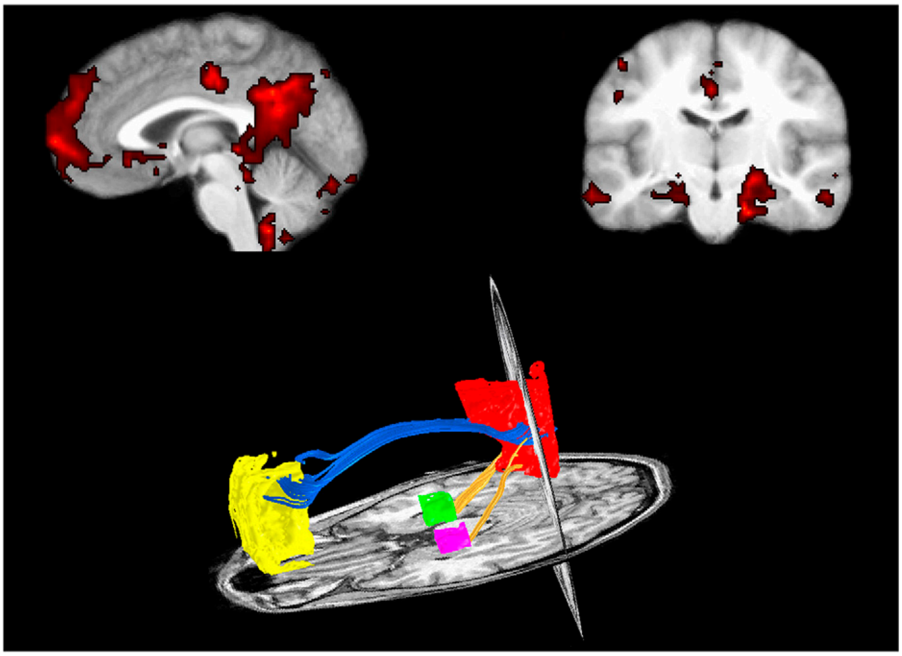
In the early days of functional magnetic resonance imaging (fMRI), researchers mostly analyzed how brain areas responded to a stimulus, whether a light, a noise, or some sort of cognitive task. But as a graduate student at the Medical College of Wisconsin in Milwaukee, Bharat Biswal had an unusual request of his fMRI test subjects: climb into the scanner and do, well, nothing.

Biswal expected that the spontaneous neuronal chatter at rest would be more or less random and unstructured. Instead, he saw structure, organization, correlations among groups of brain regions that were known to function together. Different regions of the brain's sensorimotor system fluctuated slowly and synchronously in the absence of any explicit task. It was the first step toward the study of "resting-state connectivity," an approach that promises to help researchers study the functional organization of both the healthy and abnormal brain, particularly in children and others who cannot complete challenging cognitive tasks. (See Perspective page 14105.)

Biswal's 1995 paper, which is now recognized as a seminal resting-state fMRI study, received little attention at first (1). But in 2001, neuroscientist Marcus Raichle and his colleagues at Washington University in St. Louis sparked widespread interest in the approach when they described a previously unknown brain network that appeared to play a key role in a baseline, or default, mode of the brain (2). Unlike the sensorimotor and several other brain networks, which were initially identified by their activation during tasks, this mystery network displayed high baseline activity that actually decreased when subjects engaged in a variety of cognitive tasks.



The default mode network, shown here in resting-state fMRI scans (*Upper*), includes the posterior cingulate cortex, hippocampus, and the medial prefrontal cortex. (*Lower*) Diffusion tensor imaging, an MRI technique that highlights the brain's white matter, reveals nerve fibers connecting these brain regions (posterior cingulate cortex in red; medial prefrontal cortex in yellow; hippocampus in green and pink). Adapted from ref. 5, with permission from Oxford University Press.

"It said something important about the ongoing activity of the brain, and the fact that it is not just sitting there waiting for someone in a white coat to come along and tell you what to do," says Raichle.

Intrigued by what the brain might be doing during supposedly inactive periods, Raichle and others began to explore this so-called "default mode network," which seemed to be involved in high-level cognitive processes, such as self-awareness and memory. Michael Greicius, a behavioral neuroscientist at Stanford University in California, soon followed on Raichle's work by demonstrating that at rest, the individual components of the brain's default mode network show correlated oscillations, just as Biswal had seen for the sensorimotor network (3).

"That series of papers really increased the profile of the research," says Biswal, now a professor at the New Jersey Institute of Technology in Newark. The findings suggested that networks of brain regions that activate or deactivate together during tasks maintain signatures of their connectivity that can be detected and studied even at rest. Potentially, it meant that neuroscientists would be able to map the brain's basic wiring diagram without the use of specially designed tasks.

The idea generated intense interest, but also a healthy dose of skepticism from many neuroscientists. "It just seemed too good to be true, and too easy," says Greicius. "People started to wonder if it could really be neural."

Many researchers initially questioned whether the rhythmic, synchronized fluctuations observed during the resting-state could be artifacts of other bodily functions, such as breathing or heartbeats. But those doubts gradually faded as more studies replicated and expanded on the early findings. Research showed that the correlated activity ran along structural networks of nerve fibers in the brain, and that surgically severing connections between areas could disrupt resting-state network activity, all suggesting that the correlations reflected a genuine and fundamental aspect of neuronal communication (4–6). The precise function of the default mode network remains a matter of debate, but its component brain regions are involved in such processes as self-referential thinking, emotional processing, and recalling memories.

Besides the sensorimotor and default mode networks, many other brain networks have now been observed at rest, including those involved in vision, hearing, and memory (7). In each of these cases, the same regions that fire together during tasks seem to hum along together at rest, maintaining a signature of their functional organization. The slow, synchronized oscillations within each network—which are independent of each other—are also remarkably robust, persisting even during sleep and under anesthesia (8, 9).

In recent years, acceptance of the approach has taken off. And in 2010, when the NIH launched the Human Connectome Project—a large-scale, five-year effort to map the brain networks of more than 1,000 people—the agency selected resting-state fMRI as one of the core techniques for the project. "That was a big signal from the field at large that resting-state connectivity is ready for prime time," says Greicius.

With resting-state fMRI, neuroscientists can study brain activity in young children or patients who would otherwise be unable to complete long experiments or perform complex cognitive tasks. And unlike task-based imaging, which typically highlights a single brain network associated with any given task, resting-state fMRI allows researchers to observe many networks at once. The simplicity of the procedure and its relatively short duration (often taking about 5–10 min compared with 30 min or more for many task-based studies), has also made it easier for researchers to replicate each other's experiments and compare results.

Neuroscientist Wei Gao, at Cedars-Sinai Medical Center in Los Angeles, is one of several investigators using resting-state fMRI in sleeping infants to study how brain networks form and evolve during development. Whereas some circuits, such as the sensorimotor network and the auditory network, appear fairly well-established at birth, Gao has found that other networks, such as the default mode network, are much slower to develop (10).

"At two weeks of age, there's not a default mode network per se, just isolated brain regions," he says. Gao's results show that core regions of the network gradually sync up over the first year, with additional refinements continuing at least until age two (10, 11). The function of these changes is still unclear; but Gao's findings align with psychological data showing that babies typically initiate self-admiring and embarrassed behaviors between 14 and 20 months, and learn to recognize their own reflections between 20 and 24 months of age (12).

Resting-state imaging may also provide new insights into how brain connectivity goes awry. Disruption of the default mode network, for example, has been associated with Alzheimer's disease, depression, autism, and schizophrenia (13). In the case of autism, both task-based and some resting-state studies have also revealed abnormal patterns of connectivity in several other networks, including those involved in working memory, language, emotion processing, and social cognition (14).

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—Lucina Uddin

"We're still in the early phases of discovery," says cognitive neuroscientist Lucina Uddin, who studies autism in children at the University of Miami in Florida. With task-based imaging having dominated the field for decades, a shortage of data exists from children and people with severe autism symptoms, who often cannot complete a standard psychological experiment in the scanner. "Being able to use resting-state to scan young kids and people with a range of abilities is a great thing for the field clinically," says Uddin.

So far, fMRI biomarkers for diagnosing individuals with autism or neurodegenerative diseases have proven difficult to develop. But scientists do hope to use resting-state connectivity to help improve treatments for neuropsychiatric patients who have already been diagnosed by other means.

At Harvard Medical School in Boston, Massachusetts, neurologist Michael Fox is investigating the networks involved in therapeutic brain stimulation, a set of techniques used to treat Parkinson's disease, depression, and other conditions. Researchers still have only a vague understanding of how these techniques alleviate neurological symptoms, and why certain stimulation sites are most effective.

"If you want to try to understand how brain stimulation propagates and affects a network, you've got to understand what that network looks like," says Fox. A recent resting-state connectivity study by his group suggests that different stimulation sites that work for the same disorder often belong to the same brain network, whereas ineffective sites appear not to be connected (15). The finding, says Fox, suggests that in the future, resting-state connectivity maps could be used to predict whether certain sites will be effective in an individual patient, or to locate new candidate sites for stimulation.

Applications for resting-state connectivity continue to expand. "I don't think I had anticipated that later on there would be so much interest in this work," says Biswal.

Raichle and others credit the technique's simplicity and versatility. "You can study newborn children and watch them develop, and you can jump to the other end of the spectrum and study people that are aging and not performing well," he says. "It's really opened the door to studying the functional organization of the brain."

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