

The Brain's (Dark Energy)

Brain regions active when our minds wander may hold a key to understanding neurological disorders and even consciousness itself

By Marcus E. Raichle

KEY CONCEPTS

- Neuroscientists have long thought that the brain's circuits are turned off when a person is at rest.
- Imaging experiments, however, have shown that there is a persistent level of background activity.
- This default mode, as it is called, may be critical in planning future actions.
- Miswiring of brain regions involved in the default mode may lead to disorders ranging from Alzheimer's to schizophrenia.

—The Editors

Imagine you are almost dozing in a lounge chair outside, with a magazine on your lap. Suddenly, a fly lands on your arm. You grab the magazine and swat at the insect. What was going on in your brain after the fly landed? And what was going on just before? Many neuroscientists have long assumed that much of the neural activity inside your head when at rest matches your subdued, somnolent mood. In this view, the activity in the resting brain represents nothing more than random noise, akin to the snowy pattern on the television screen when a station is not broadcasting. Then, when the fly alights on your forearm, the brain focuses on the conscious task of squashing the bug. But recent analysis produced by neuroimaging technologies has revealed something quite remarkable: a great deal of meaningful activity is occurring in the brain when a person is sitting back and doing nothing at all.

It turns out that when your mind is at rest—when you are daydreaming quietly in a chair,

say, asleep in a bed or anesthetized for surgery—dispersed brain areas are chattering away to one another. And the energy consumed by this ever active messaging, known as the brain's default mode, is about 20 times that used by the brain when it responds consciously to a pesky fly or another outside stimulus. Indeed, most things we do consciously, be it sitting down to eat dinner or making a speech, mark a departure from the baseline activity of the brain default mode.

Key to an understanding of the brain's default mode has been the discovery of a heretofore unrecognized brain system that has been dubbed the brain's default mode network (DMN). The exact role of the DMN in organizing neural activity is still under study, but it may orchestrate the way the brain organizes memories and various systems that need preparation for future events: the brain's motor system has to be revved and ready when you feel the tickle of a fly on your arm. The DMN may play a critical role in



synchronizing all parts of the brain so that, like racers in a track competition, they are all in the proper “set” mode when the starting gun goes off. If the DMN does prepare the brain for conscious activity, investigations of its behavior may provide clues to the nature of conscious experience. Neuroscientists have reason to suspect, moreover, that disruptions to the DMN may underlie simple mental errors as well as a range of complex brain disorders, from Alzheimer’s disease to depression.

Probing Dark Energy

The idea that the brain could be constantly busy is not new. An early proponent of that notion was Hans Berger, inventor of the familiar electroencephalogram, which records electrical activity in the brain with a set of wavy lines on a graph. In seminal papers on his findings, pub-

lished in 1929, Berger deduced from the ceaseless electrical oscillations detected by the device that “we have to assume that the central nervous system is always, and not only during wakefulness, in a state of considerable activity.”

But his ideas about how the brain functions were largely ignored, even after noninvasive imaging methods became a fixture in neuroscience laboratories. First, in the late 1970s, came positron-emission tomography (PET), which measures glucose metabolism, blood flow and oxygen uptake as a proxy for the extent of neuronal activity, followed in 1992 by functional magnetic resonance imaging (fMRI), which gauges brain oxygenation for the same purpose. These technologies are more than capable of assaying brain activity, whether focused or not, but the design of most studies inadvertently led to the impression that most brain areas stay pretty quiet until called on to carry out some specific task.

Typically neuroscientists who run imaging experiments are trying to pinpoint the brain regions that give rise to a given perception or behavior. The best study designs for defining such regions simply compare brain activity during two related conditions. If researchers wanted to see which brain areas are important during reading words aloud (the “test” condition) as opposed to viewing the same words silently (the “control” condition), for instance, they would look for differences in images of those two conditions. And to see those differences clearly, they would essentially subtract the pixels in the passive-reading images from those in the vocal image; activity of neurons in the areas that remain “lit up” would be assumed to be the ones necessary for reading aloud. Any of what is called intrinsic activity, the constant background activity, would be left on the cutting-room floor. Representing data in this way makes it easy to envision areas of the brain being “turned on,” during a given behavior, as if they were inactive until needed by a particular task.

Over the years, however, our group, and others, became curious about what was happening when someone was simply resting and just letting the mind wander. This interest arose from a set of hints from various studies that suggested the extent of this behind-the-scenes activity.

One clue came from mere visual inspections of the images. The pictures showed that areas in many regions of the brain were quite busy in both the test and the control conditions. In part because of this shared background “noise,” differentiating a task from the control state by look-

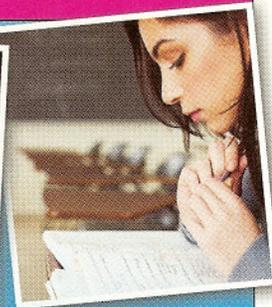
[COMPETING THEORIES]

BRAINS AT REST

Noninvasive methods, such as positron-emission tomography and functional magnetic resonance imaging, did not initially capture signs of background activity in the brain when a subject was doing nothing and so provided an inaccurate picture of neural activity.



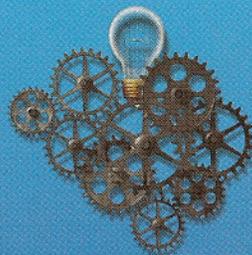
No activity, such as daydreaming



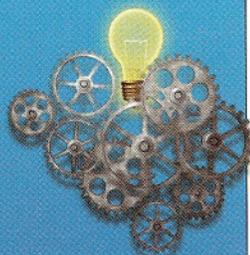
Focused activity, such as reading

OLD VIEW ▶

Brain scans originally seemed to suggest that most neurons were quiet until needed for some activity, such as reading, at which point the brain fired up and expended energy on the signaling needed for the task.



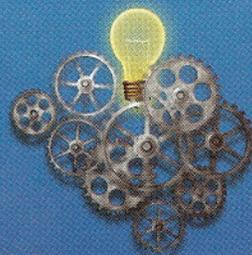
No activity in brain



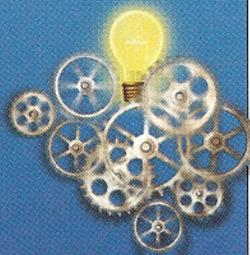
High activity in brain

NEW VIEW ▶

In recent years additional neuroimaging experiments have shown that the brain maintains a high level of activity even when nominally “at rest.” In fact, reading or other routine tasks require minimal additional energy, no more than a 5 percent increment, over what is already being consumed when in this highly active baseline state.



High activity in brain



Higher activity in brain

ing at the separate raw images is difficult if not impossible and can be achieved only by applying sophisticated computerized image analysis.

Further analyses indicated that performing a particular task increases the brain's energy consumption by less than 5 percent of the underlying baseline activity. A large fraction of the overall activity—from 60 to 80 percent of all energy used by the brain—occurs in circuits unrelated to any external event. With a nod to our astronomer colleagues, our group came to call this intrinsic activity the brain's dark energy, a reference to the unseen energy that also represents the mass of most of the universe.

The question of the existence of neural dark energy also arose when observing just how little information from the senses actually reaches the brain's internal processing areas. Visual information, for instance, degrades significantly as it passes from the eye to the visual cortex.

Of the virtually unlimited information available in the world around us, the equivalent of 10 billion bits per second arrives on the retina at the back of the eye. Because the optic nerve attached to the retina has only a million output connections, just six million bits per second can leave the retina, and only 10,000 bits per second make it to the visual cortex.

After further processing, visual information feeds into the brain regions responsible for forming our conscious perception. Surprisingly, the amount of information constituting that conscious perception is less than 100 bits per second. Such a thin stream of data probably could not produce a perception if that were all the brain took into account; the intrinsic activity must play a role.

Yet another indication of the brain's intrinsic processing power comes from counting the number of synapses, the contact points between neurons. In the visual cortex, the number of synapses devoted to incoming visual information is less than 10 percent of those present. Thus, the vast majority must represent internal connections among neurons in that brain region.

Discovering the Default Mode

These hints of the brain's inner life were well established. But some understanding was needed of the physiology of the brain's intrinsic activity—and how it might influence perception and behavior. Happily, a chance and puzzling observation made during PET studies, later corroborated with fMRI, set us on a path to discovering the DMN.

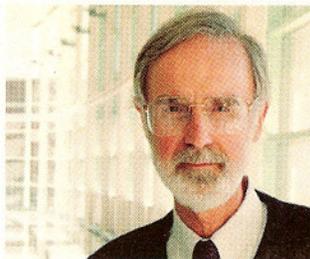


A CLUE TO THE NEW VIEW

Researchers have known for some time that only a trickle of information from the virtually infinite flood in the surrounding environment reaches the brain's processing centers. Although six million bits are transmitted through the optic nerve, for instance, only 10,000 bits make it to the brain's visual-processing area, and only a few hundred are involved in formulating a conscious perception—too little to generate a meaningful perception on their own. The finding suggested that the brain probably makes constant predictions about the outside environment in anticipation of paltry sensory inputs reaching it from the outside world.

[THE AUTHOR]

Marcus E. Raichle is professor of radiology and neurology at the Washington University School of Medicine in St. Louis. For many years Raichle has led a team that investigates human brain function using positron-emission tomography and functional magnetic resonance imaging. He was elected to the Institute of Medicine in 1992 and to the National Academy of Sciences in 1996.



In the mid-1990s we noticed quite by accident that, surprisingly, certain brain regions experienced a *decreased* level of activity from the baseline resting state when subjects carried out some task. These areas—in particular, a section of the medial parietal cortex (a region near the middle of the brain involved with remembering personal events in one's life, among other things)—registered this drop when other areas were engaged in carrying out a defined task such as reading aloud. Befuddled, we labeled the area showing the most depression MMPA, for “medial mystery parietal area.”

A series of PET experiments then confirmed that the brain is far from idling when not engaged in a conscious activity. In fact, the MMPA as well as most other areas remains constantly active until the brain focuses on some novel task, at which time some areas of intrinsic activity decrease. At first, our studies met with some skepticism. In 1998 we even had a paper on such findings rejected because one referee suggested that the reported decrease in activity was an error in our data. The circuits, the reviewer asserted, were actually being switched on at rest and switched off during the task. Other researchers, however, reproduced our results for both the medial parietal cortex—and the medial prefrontal cortex (involved with imagining what other people are thinking as well as aspects of our emotional state). Both areas are now considered major hubs of the DMN.

The discovery of the DMN provided us with a new way of considering the brain's intrinsic activity. Until these publications, neurophysiologists had never thought of these regions as a system in the way we think of the visual or motor system—as a set of discrete areas that communicate with one another to get a job done. The idea that the brain might exhibit such internal activity across multiple regions while at rest had escaped the neuroimaging establishment. Did the DMN alone exhibit this property, or did it exist more generally throughout the brain? A surprising finding in the way we understand and analyze fMRI provided the opening we needed to answer such questions.

The fMRI signal is usually referred to as the blood oxygen level-dependent, or BOLD, signal because the imaging method relies on changes in the level of oxygen in the human brain induced by alterations in blood flow. The BOLD signal from any area of the brain, when observed in a state of quiet repose, fluctuates slowly with cycles occurring roughly every 10 seconds. Fluctua-

tions this slow were considered to be mere noise, and so the data detected by the scanner were simply eliminated to better resolve the brain activity for the particular task being imaged.

The wisdom of discarding the low-frequency signals came into question in 1995, when Bharat Biswal and his colleagues at the Medical College of Wisconsin observed that even while a subject remained motionless, the “noise” in the area of the brain that controls right-hand movement fluctuated in unison with similar activity in the area on the opposite side of the brain associated with left-hand movement. In the early 2000s Michael Greicius and his co-workers at Stanford University found the same synchronized fluctuations in the DMN in a resting subject.

Because of the rapidly accelerating interest in the DMN’s role in brain function, the finding by the Greicius group stimulated a flurry of activity

in laboratories worldwide, including ours, in which *all* of the noise, the intrinsic activity of the major brain systems, was mapped. These remarkable patterns of activity appeared even under general anesthesia and during light sleep, a suggestion that they were a fundamental facet of brain functioning and not merely noise.

It became clear from this work that the DMN is responsible for only a part, albeit a critical part, of the overall intrinsic activity—and the notion of a default mode of brain function extends to all brain systems. In our lab, discovery of a generalized default mode came from first examining research on brain electrical activity known as slow cortical potentials (SCPs), in which groups of neurons fire every 10 seconds or so. Our research determined that the spontaneous fluctuations observed in the BOLD images were identical to SCPs: the same activity detected with different sensing methods.

We then went on to examine the purpose of SCPs as they relate to other neural electrical signals. As Berger first showed and countless others have since confirmed, brain signaling consists of a broad spectrum of frequencies, ranging from the low-frequency SCPs through activity in excess of 100 cycles per second. One of the great challenges in neuroscience is to understand how the different frequency signals interact.

It turns out that SCPs have an influential role. Both our own work and that of others demonstrate that electrical activity at frequencies above that of the SCPs synchronizes with the oscillations, or phases, of the SCPs. As observed recently by Matias Palva and his colleagues at the University of Helsinki, the rising phase of an SCP produces an increase in the activity of signals at other frequencies.

The symphony orchestra provides an apt metaphor, with its integrated tapestry of sound arising from multiple instruments playing to the same rhythm. The SCPs are the equivalent of the conductor’s baton. Instead of keeping time for a collection of musical instruments, these signals coordinate access that each brain system requires to the vast storehouse of memories and other information needed for survival in a complex, ever changing world. The SCPs ensure that the right computations occur in a coordinated fashion at exactly the correct moment.

But the brain is more complex than a symphony orchestra. Each specialized brain system—one that controls visual activity, another that actuates muscles—exhibits its own pattern of SCPs. Chaos is averted because all systems are

[A BRAIN CONTROLLER]

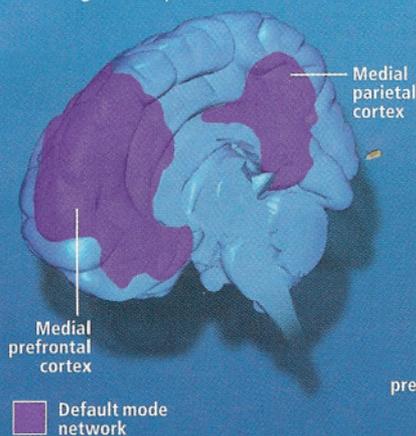
THE DEFAULT MODE NETWORK

A collaborating group of brain regions known as the default mode network (DMN) appears to account for much of the activity that occurs when the mind is unfocused and to have a key role in mental functioning.

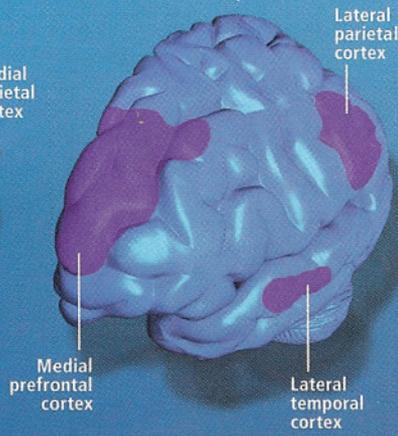
COMMAND STATION ▼

The DMN consists of several widely separated brain areas, including those depicted below.

Inside right hemisphere

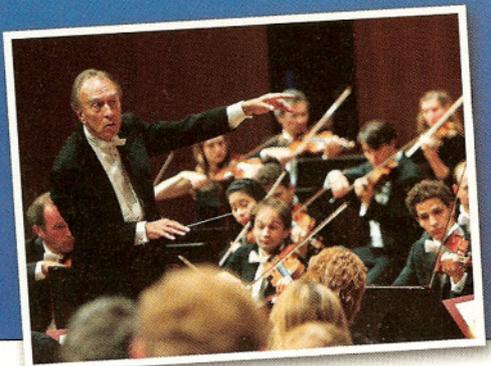


Outside left hemisphere



ORCHESTRATOR OF THE SELF ▶

The DMN is thought to behave something like an orchestra conductor, issuing timing signals, much as a conductor waves a baton, to coordinate activity among different brain regions. This cuing—among the visual and auditory parts of the cortex, for instance—probably ensures that all regions of the brain are ready to react in concert to stimuli.



not created equal. Electrical signaling from some brain areas takes precedence over others. At the top of this hierarchy resides the DMN, which acts as an über-conductor to ensure that the cacophony of competing signals from one system do not interfere with those from another. This organizational structure is not surprising, because the brain is not a free-for-all among independent systems but a federation of interdependent components.

At the same time, this intricate internal activity must sometimes give way to the demands of the outside world. To make this accommodation, SCPs in the DMN diminish when vigilance is required because of novel or unexpected sensory inputs: you suddenly realize that you promised to pick up a carton of milk on the drive home from work. The internal SCP messaging revives once the need for focused attention dwindles. The brain continuously wrestles with the need to balance planned responses and the immediate needs of the moment.

Consciousness and Disease

The ups and downs of the DMN may provide insight into some of the brain's deepest mysteries. It has already furnished scientists with fascinating insights into the nature of attention, a fundamental component of conscious activity. In 2008 a multinational team of researchers reported that by watching the DMN, they could tell up to 30 seconds before a subject in a scanner was about to commit an error in a computer test. A mistake would occur if, at that time, the default network took over and activity in areas involved with focused concentration abated.

And in years to come, the brain's dark energy may provide clues to the nature of consciousness. As most neuroscientists acknowledge, our conscious interactions with the world are just a small part of the brain's activity. What goes on below the level of awareness—the brain's dark energy, for one—is critical in providing the context for what we experience in the small window of conscious awareness.

Beyond offering a glimpse of the behind-the-scenes events that underlie everyday experience, study of the brain's dark energy may provide new leads for understanding major neurological maladies. Mental gymnastics or intricate movements will not be required to complete the exercise. A subject need only remain still within the scanner while the DMN and other hubs of dark energy whirl silently through their paces.

Already this type of research has shed new

[MISWIRED CIRCUITS]

DISEASE AND THE NETWORK

The default mode network overlaps areas involved with major brain disorders, suggesting that damage to the network may be involved. Discerning precisely which aspects of the network are affected by Alzheimer's, depression and other disorders may lead to new diagnostics and treatments.

ALZHEIMER'S

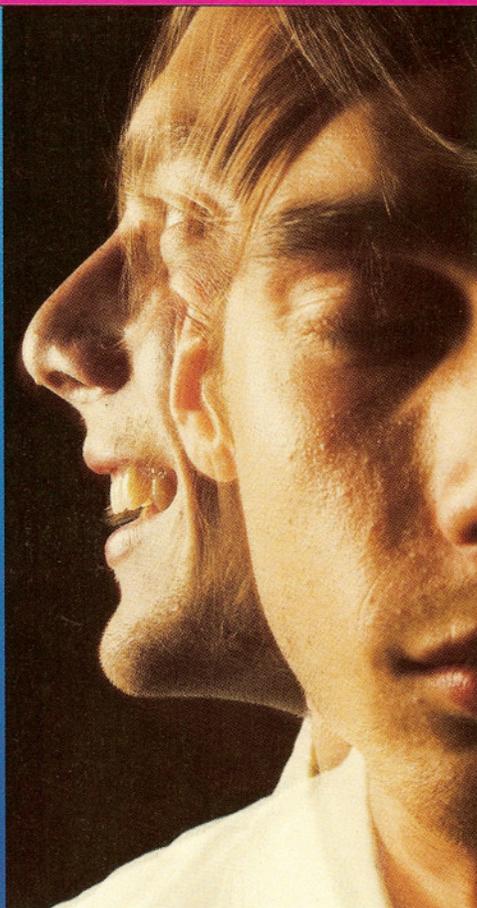
Brain areas that atrophy in Alzheimer's overlap very closely with major centers of the DMN.

DEPRESSION

Patients exhibit decreased connections between one area of the DMN and regions involved with emotion.

SCHIZOPHRENIA

Many regions of the DMN demonstrate increased levels of signaling. The importance of this finding is still being investigated.



➔ MORE TO EXPLORE

Spontaneous Fluctuations in Brain Activity Observed with Functional Magnetic Resonance Imaging.

Michael D. Fox and Marcus E. Raichle in *Nature Reviews Neuroscience*, Vol. 8, pages 700–711; September 2007.

Disease and the Brain's Dark Energy. Dongyang Zhang and Marcus E. Raichle in *Nature Reviews Neurology*, Vol. 6, pages 15–18; January 2010.

Two Views of Brain Function.

Marcus E. Raichle in *Trends in Cognitive Science* (in press).

light on disease. Brain-imaging studies have found altered connections among brain cells in the DMN regions of patients with Alzheimer's, depression, autism and even schizophrenia. Alzheimer's, in fact, may one day be characterized as a disease of the DMN. A projection of the brain regions affected by Alzheimer's fits neatly over a map of the areas that make up the DMN. Such patterns may not only serve as biological markers for diagnosis but may also provide deeper insights into causes of the disease and treatment strategies.

Looking ahead, investigators must now try to glean how coordinated activity among and within brain systems operates at the level of the individual cells and how the DMN causes chemical and electrical signals to be transmitted through brain circuits. New theories will then be needed to integrate data on cells, circuits and entire neural systems to produce a broader picture of how the brain's default mode of function serves as a master organizer of its dark energy. Over time neural dark energy may ultimately be revealed as the very essence of what makes us tick. ■