ILLUSTRATIONS BY RYAN SNOOK

IDLE MINDS

Neuroscientists are trying to work out why the brain does so much when it seems to be doing nothing at all.

BY KERRI SMITH

For volunteers, a brain-scanning experiment can be pretty demanding. Researchers generally ask participants to do something — solve mathematics problems, search a scene for faces or think about their favoured political leaders — while their brains are being imaged.

But over the past few years, some researchers have been adding a bit of down time to their study protocols. While subjects are still lying in the functional magnetic resonance imaging (fMRI) scanners, the researchers ask them to try to empty their minds. The aim is to find out what happens when the brain simply idles. And the answer is: quite a lot.

Some circuits must remain active; they control automatic functions such as breathing and heart rate. But much of the rest of the brain continues to chug away as the mind naturally wanders through grocery lists, rehashes conversations and just generally daydreams. This activity has been dubbed the resting state. And neuroscientists have seen evidence that the networks it engages look a lot like those that are active during tasks.

Resting-state activity is important, if the amount of energy devoted to it is any indication. Blood flow to the brain during rest is typically just 5–10% lower than during task-based experiments[1]. And studying the brain at rest should help to show how the active brain works.

➲ NATURE.COM
Listen to the *Nature Podcast* for more on the resting brain:
go.nature.com/gww192

Research on resting-state networks is helping to map the brain's intrinsic connections by showing, for example, which areas of the brain prefer to talk to which other areas, and how those patterns might differ in disease.

But what is all this activity for? Ask neuroscientists — even those who study the resting state — and many will sigh or shrug. "We're really at the very beginning. It's mostly hypotheses," says Amir Shmuel, a brain-imaging specialist at McGill University in Montreal, Canada. Resting activity might be keeping the brain's connections running when they are not in use. Or it could be helping to prime the brain to respond to future stimuli, or to maintain relationships between areas that often work together to perform tasks. It may even consolidate memories or information absorbed during normal activity.

"There's so much enthusiasm about the approach now, and so little basic understanding," says Michael Greicius, a neuroscientist at Stanford University in California, who started studying resting-state networks a decade ago.

ALWAYS ACTIVE

A set of experiments in the mid-1990s first suggested that the brain never really takes a break. Bharat Biswal, then a PhD student at the Medical College of Wisconsin in Milwaukee, was trying to find ways of identifying and removing background signals from fMRI scans, in the hope that it would improve interpretations of the signals from tasks. "The assumption was, it was all noise," says Biswal, who is now a biomedical engineer at the New Jersey Institute of Technology in Newark. But when he looked at scans taken when people were resting in the scanner, he saw regular, low-frequency fluctuations in the brain[2]. Biswal's experiments suggested that neuronal activity was causing these fluctuations.

In the early days of resting-state research, some people were sure that they had found something profound. "When I first started looking at these networks, I was convinced we were tapping into the stream of consciousness, and this was real-time ongoing conscious processing," says Greicius. But, he says, "I was relatively quickly disabused of that notion". The networks of activity also appeared in altered states of consciousness such as when sleeping or under anaesthesia[3,4], so they weren't necessarily linked to conscious processing.

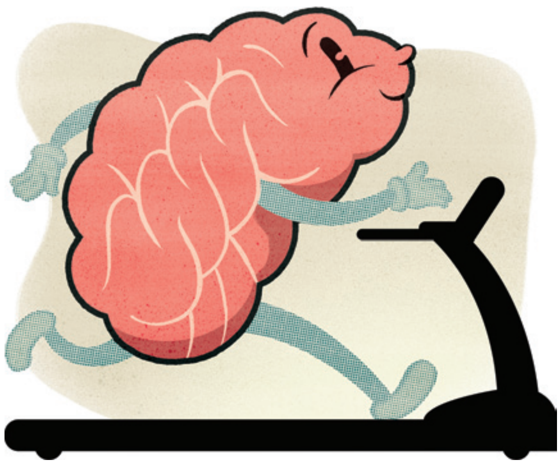
But they weren't meaningless either. Several years after Biswal's discovery, studies of the resting state in its own right began to emerge. A team led by Marcus Raichle, a neuroscientist at Washington University in St. Louis, Missouri, characterized[5] activity in one such network as the brain's default mode — what they considered its baseline setting. During tasks, default-mode activity actually dropped, coming back online when the brain was no longer focusing so intensely[5].

The default-mode network has been joined by dozens of other flavours of resting-state network — some of which resemble the circuitry that contributes to attention, vision, hearing or movement. They seem very similar across study participants but are also dynamic, changing over time. "The fact that it's always present but modifiable tells you that it's got its importance," says Michael Milham, director of the Center for the Developing Brain at the Child Mind Institute in New York.

Still, some researchers have questioned whether these resting patterns represent anything real. After all, fMRI does not measure brain electrical activity directly: it monitors blood flow. The low-level idling activity could be an artefact. "People suspected it was lousy scanners or respiratory noise," says Andreas Kleinschmidt, director of research at the French National Institute of Health and Medical Research's Cognitive Neuroimaging Unit in Gif-sur-Yvette. But using fMRI and electroencephalography (EEG) recordings, Kleinschmidt and his team confirmed[6] that various resting-state networks are correlated with real neural activity.

Shmuel and David Leopold, a neurophysiologist at the US National Institute of Mental Health in Bethesda, Maryland, did much the same[7], imaging resting states in monkeys while recording the animals' electrical brain activity using probes implanted deep in the visual cortex. They found correlations between resting-state networks and electrical activity in a band of frequencies around 40 hertz. Such 'γ activity' is associated with communication between distant brain areas, and seeing it convinced Shmuel that resting-state networks represent actual brain activity. "I strongly believe that there is a neurophysiological mechanism that underlies the entire thing that we call resting-state networks," he says.

RESTING-STATE ACTIVITY IS IMPORTANT, IF THE AMOUNT OF ENERGY DEVOTED TO IT IS ANY INDICATION.



DISORDERED THINKING

It is a mechanism that may go awry in brain disorders. People with early signs of Alzheimer's disease, for example, have unusual resting-state signatures that can be detected even at very mild levels of dementia and which vary as the disease progresses[8]. In children with autism spectrum disorder, resting-state networks can be 'hyperconnected', displaying more links than for kids without the condition[9]. The reasons for these differences are not clear, and they may not matter to clinicians, who are interested in finding disease markers. "From a clinical perspective, you're not always going to understand why a biomarker is serving as that biomarker," says Milham. But some neuroscientists are deeply curious as to what these fluctuations do. "It keeps me up at night," says Timothy Ellmore at the University of Texas Health Science Center in Houston, who is studying resting brain activity in people with Parkinson's disease.

Some researchers now think that resting-state networks may prime the brain to respond to stimuli. "The system is not sitting there doing nothing and waiting," says Kleinschmidt. Cycling activity in these networks may be helping the brain to use past experiences to inform its decisions. "It's incredibly computationally demanding to calculate everything on the fly," says Maurizio Corbetta at Washington University School of Medicine in St. Louis. He has been studying resting state using magnetoencephalography, a technique that measures magnetic fields associated with the electrical activity of neurons. "If I have ongoing patterns that are guessing what's going to happen next in my life, then I don't have to compute everything." He likens the activity to the idling of a vehicle. "If your car is ready to go, you can leave faster than if you have to turn on the engine."

"IF YOUR CAR IS READY TO GO, YOU CAN LEAVE FASTER THAN IF YOU HAVE TO TURN ON THE ENGINE."

But idling networks might not just save time. They may also influence perceptions — albeit unconsciously. To study how spontaneous resting activity affects perception, Kleinschmidt and his colleagues scanned[10] the brains of people who were looking at a picture that can be perceived as a face or as a vase. Study participants who reported seeing a face had more spontaneous activity in the fusiform face area — a brain region that processes faces — before they were shown the picture. Kleinschmidt suspects that the brain is running several models of the world in the background, ready for one of them to turn into reality. "Ideally, you're always prepared for what happens next," he says.

Corbetta has discovered evidence in people with brain damage that resting activity can change behaviour. In unpublished work, he has found hints that lesions in frontal brain regions — caused by stroke, for example — can give rise to changes in spontaneous brain activity in distant areas. What is more, the changes to the resting activity are linked to the behavioural deficit. "This is clear evidence that resting-state impairments are affecting the way the network is recruited during a task," he says.

ZEN AND THE ART OF NETWORK MAINTENANCE

Raichle favours the idea that activity in the resting state helps the brain to stay organized. The connections between neurons are continually shifting as people age and learn, but humans maintain a sense of self throughout the upheaval. Spontaneous activity might play a part in maintaining that continuity. "Connections between neurons turn over in minutes, hours, days and weeks," says Raichle. "The structure of the brain will be different tomorrow but we will still remember who we are."

Or perhaps the activity is part of the reshaping process, tweaking connections while we idle. Several teams have reported changes in resting connectivity after language and memory tasks and motor learning. Chris Miall, a behavioural brain scientist at the University of Birmingham, UK, and his colleagues have shown that spontaneous activity at rest can be perturbed by what has just happened[11]. The team scanned volunteers at rest, and then asked them to learn a task involving using a joystick to track a moving target. When the participants were scanned at rest again, the team could see the effects of motor learning in the resting networks. That study, and subsequent work along the same lines, suggests that "the brain is not only thinking about supper coming up, but it's also processing the recent past and converting some of that into long-term memories", says Miall. The network changes are specific to the tasks performed.

Work on memory consolidation in animals backs that conclusion. It used to be assumed that memories from the day were strengthened during a night's sleep. Working with rats, however, Loren Frank and Mattias Karlsson, neuroscientists at the University of California, San Francisco, have found[12] that the brain replays and consolidates new memories at any chance it gets — even when awake. "These events happen when it doesn't look like the animal is doing very much," says Frank.

He speculates that resting activity could be doing the same thing in human brains — reactivating patterns that correspond to past experiences. At the same time, activity in the networks could have a normalizing, housekeeping function too. "How do you keep the brain flexible?" Frank asks. "If you have random patterns of activity washing through your network, those can help reduce the strength of the pathways associated with what you've just learned." That would stop the brain from reinforcing the same pathways too often. "Perhaps down-time periods are also important for that," he says.

Shmuel says that it is still not possible to rule out the idea that this activity is just a by-product of the brain being alive. Current may flow through these circuits "simply because there is current — the brain is not dead — and there are anatomical connections that give this current a non-random structure". But, he admits, "I hope this is not the case. Then it's extremely uninteresting."

Narrowing down the range of interesting possibilities may take time, given that the very nature of resting-state science makes it difficult to test hypotheses. When a researcher slides someone into a scanner and instructs them to think about nothing in particular, there is no task to do and no hypothesis to address. So researchers have to generate reams of data and line up hypotheses as they go along. "Resting state opens up discovery science," says Milham enthusiastically, before admitting that, because he trained as a hypothesis-driven cognitive neuroscientist, "it's like heresy that I've got into this".

Whatever resting activity is doing, its existence certainly proves one thing. Miall puts it bluntly: "The brain only rests when you're dead." ■

Kerri Smith *is podcast editor for* Nature *in London.*

1. Raichle, M. E. & Mintun, M. A. *Annu. Rev. Neurosci.* **29,** 449–476 (2006).
2. Biswal, B., Yetkin, F. Z., Haughton, V. M. & Hyde, J. S. *Magn. Reson. Med.* **34,** 537–541 (1995).
3. Greicius, M. D. *et al. Hum. Brain Mapp.* **29,** 839–847 (2008).
4. Boly, M. *et al. Ann. NY Acad. Sci.* **1129,** 119–129 (2008).
5. Raichle, M. E. *et al. Proc. Natl Acad. Sci. USA* **98,** 676–682 (2001).
6. Laufs, H. *et al. Proc. Natl Acad. Sci. USA* **100,** 11053–11058 (2003).
7. Shmuel, A. & Leopold D. A. *Hum. Brain Mapp.* **29,** 751–761 (2008).
8. Brier, M. R. *et al. J. Neurosci.* **32,** 8890–8899 (2012).
9. Di Martino, A. *et al. Biol. Psychiatry* **69,** 847–856 (2011).
10. Hesselmann, G., Kell, C. A., Eger, E. & Kleinschmidt, A. *Proc. Natl Acad. Sci. USA* **105,** 10984–10989 (2008).
11. Albert, N. B., Robertson, E. M. & Miall, R. C. *Curr. Biol.* **19,** 1023–1027 (2009).
12. Karlsson, M. P. & Frank, L. M. *Nature Neurosci.* **12,** 913–918 (2009).