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New imaging method identifies specific mental states

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New clues to the mystery of brain function, obtained through research by scientists at the Stanford University School of Medicine, suggest that distinct mental states can be distinguished based on unique patterns of activity in coordinated "networks" within the brain. These networks consist of brain regions that are synchronously communicating with one another. The Stanford team is using this network approach to develop diagnostic tests in Alzheimer's disease and other brain disorders in which network function is disrupted.

In a novel set of experiments, a team of researchers led by Michael Greicius, MD, assistant professor of neurology and neurological sciences, was able to determine from brain-imaging data whether experimental subjects were recalling events of the day, singing silently to themselves, performing mental arithmetic or merely relaxing. In the study, subjects engaged in these mental activities at their own natural pace, rather than in a controlled, precisely timed fashion as is typically required in experiments involving the brain-imaging technique called functional magnetic resonance imaging. This suggests that the new method — a variation on the fMRI procedure — could help scientists learn more about what the brain is doing during the free-flowing mental states through which individuals move, minute-to-minute, in the real world.

FMRI can pinpoint active brain regions in which nerve cells are firing rapidly. In standard fMRI studies, subjects perform assigned mental tasks on cue in a highly controlled environment. The researcher typically divides the scan into task periods and non-task periods with strict start and stop points for each. Researchers can detect brain regions activated by the task by subtracting signals obtained during non-task periods from those obtained during the task. To identify which part of the brain is involved in, for example, a memory task, traditional fMRI studies require experimenters to control the timing of each recalled event.

"With standard fMRI, you need to know just when your subjects start focusing on a mental task and just when they stop," said Greicius. "But that isn't how real people in the day-to-day world think."

In their analysis, the Stanford team broke free of this scripted approach by looking not for brain regions that showed heightened activity during one mental state versus another, but for coordinated activity between brain regions, defining distinct brain states. This let subjects think in a self-paced manner more closely resembling the way they think in the world outside the MRI scanner. Instead of breaking up a cognitive state into short blocks of task and non-task, Greicius and his team used uninterrupted scan periods ranging from 30 seconds to 10 minutes in length, allowing subjects to follow their own thought cues at their own pace. The scientists were able to accurately capture subjects' mental states even when the duration of the scans was reduced to as little as one minute or less — all the more reflective of real-world cognition.

Greicius is senior author of the new study, to be published online May 26 in *Cerebral Cortex*. His team obtained images from a group of 14 young men and women who underwent four 10-minute fMRI scans apiece. Importantly, during each of the four scans, the investigators didn't tell subjects exactly when to start doing something — recall events, sing to themselves silently, count back from 5,000 by threes, or just rest — or when to switch to something else, as is typical with standard fMRI research. "We just told them to go at their own pace," Greicius said.

Greicius's team assembled images from each separate scan. Instead of comparing "on-task" images with "off-task" images to see which regions were active during a distinct brain state compared with when the brain wasn't in that state, the researchers focused on which collections, or networks, of brain regions were active in concert with one another throughout a given state.

Greicius and his colleagues have previously shown that the brain operates, at least to some extent, as a composite of separate networks composed a number of distinct but simultaneously active brain regions. They have identified approximately 15 such networks. Different networks are associated with vision, hearing, language, memory, decision-making, emotion and so forth.

>From the scans of those 14 healthy volunteers, the Stanford investigators were able to construct maps of coordinated activity in the brain during each of the four mental activities. In particular, they looked at 90 brain regions distributed across multiple networks, accounting for most of the brain's gray matter.

In their analysis, the Stanford team identified groups of regions throughout the brain whose activity was correlated to form functional networks. The new fMRI method let them view such networks within a single scan, without having to compare it to another scan via subtraction. In the scanning images, different thought processes showed up as different networks or regions communicating with one another. For example, subjects' recollection of the day's events was characterized by synchronous firing of two brain regions called the retrosplenial cortex, or RSC, and medial temporal lobe, or MTL. Standard fMRI, in which the brain's activity during a recall exercise was compared to its activity in the resting state, has already shown that the RSC and MTL are each active during memory-related tasks. But the new study showed that coordinated activity between these two regions indicates that subjects were engaged in recall.

Once they had completed their mapping of the four mental states to specific patterns of connectivity across the 90 brain regions, Greicius and his colleagues tested their ability to determine which state a subject was in by asking a second group of 10 subjects to undergo scanning during the same four mental activities. By comparing the pattern of a subject's image to the patterns assigned to each of the four states from the 14-subject data set, the researchers' analytical tools were, with 85 percent accuracy, able to correctly determine which mental state a particular scanning image corresponded to. The team's ability to correctly determine which of those four mental tasks a subject was performing remained at the 80 percent accuracy level even when scanning sessions were reduced to one minute apiece — a length of time more reflective of real-life mental behavior than the customary 10-minute scanning time.

As an additional test, Greicius's team asked the second participant group to engage in a fifth cognitive activity, spatial navigation, in which subjects were asked to imagine walking through the rooms of their home. The team's analytical tools readily rejected the connectivity pattern reflecting this mental activity as not indicative of one of the four states in question.

The ability to use fMRI in a more casual, true-to-life manner for capturing the mental states of normal volunteers bodes well for assessing patients with cognitive disorders, such as people with Alzheimer's disease or other dementias, who are often unable to follow the precise instructions and timing demands required in traditional fMRI.

In fact, the technique has already begun proving its value in diagnosing brain disorders. In a 2009 study in *Neuron*, Greicius and his associates showed that different cognitive disorders show up in fMRI scans as having deficiencies specific to different networks. In Alzheimer's disease, for example, the network associated with memory is functionally impaired so that its component brain regions are no longer firing in a coordinated fashion. This network approach to brain function and dysfunction is now being widely applied to the study of numerous neurological and psychiatric conditions.

Provided by Stanford University Medical Center

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