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More GABA in one brain region linked to better working memory, scientist says

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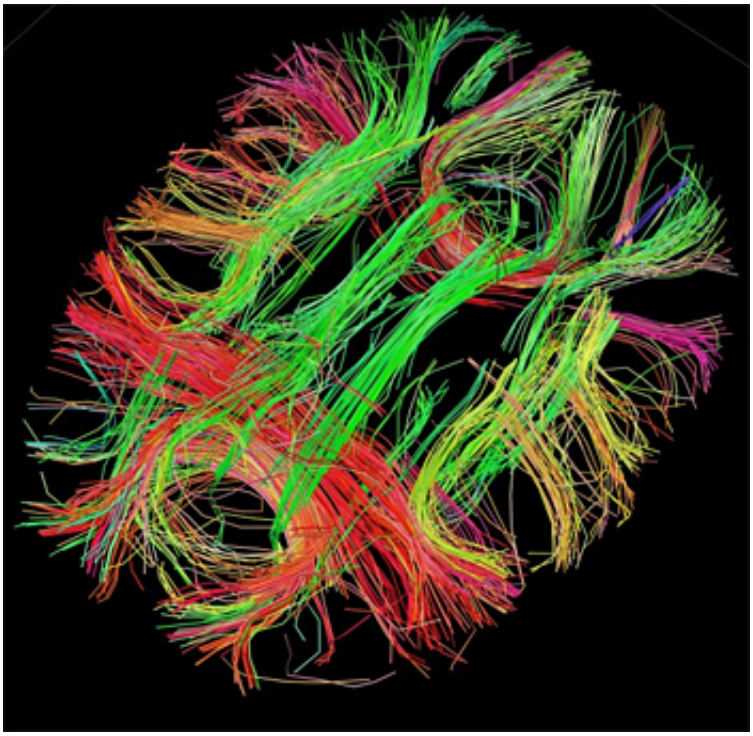

White matter fiber architecture of the brain. Credit: Human Connectome Project.

The amount of a particular chemical in a particular part of your brain predicts your ability to simultaneously hang onto several bits of information in your working memory, a Stanford University School of Medicine scientist and his University of California-Davis collaborators have learned.

The discovery helps to clarify at least one aspect of the brain's mysterious ways, and could someday help guide therapies for those whose working memory could stand improvement.

And whose couldn't?

Working memory is the brain function that lets you carry on a phone conversation while adding three numbers in your head and remembering that you need to steer the car onto the freeway exit in about two minutes—all this time not forgetting who you're talking to. Like a computer's RAM, working memory serves as a buffer where information, derived from the senses or retrieved from long-term memory, can be temporarily placed so the conscious brain can process it. It's tied to assessments of cognitive capacity such as IQ, and to real-world outcomes such as academic performance.

Load, maintenance, distraction resistance

As most people eventually find out, working memory declines with age.

"Deficits in working memory also characterize various neuropsychiatric conditions and are particularly evident in schizophrenia," said Jong Yoon, MD, an assistant professor of psychiatry and behavioral sciences at Stanford and a psychiatrist at the Palo Alto Veterans Affairs Health Care System who sees numerous patients with this disorder.

Yoon is the lead author of a study that will be published Nov. 16 in the *Journal of Neuroscience*. The study teases apart three key components of working memory and shows that one component, but not the other two, is tied to the amount of a chemical called GABA in a brain area known as the dorsolateral prefrontal cortex, or DLPFC. Richard Maddock, MD, a professor of psychiatry at UCD, is senior author of the study.

This component, referred to as load, is a measure of the number of separate bits of information a person's working memory can store at the same time. A second component, maintenance, denotes how long information can be stored in working memory before it's lost. A third, distraction resistance, gauges how well an individual's working memory holds onto information in the face of interfering stimuli.

The DLPFC, a broad swath of neural tissue on the forebrain surface, has been shown in animal studies and in observations of brain-damaged patients to be integral to high-level executive functions in the brain, such as planning, prioritizing and avoiding distractions. It has likewise been strongly implicated in working memory. The DLPFC orchestrates activity in numerous distant centers throughout the brain, including the visual cortex, which is located near the brain's surface but in the hindbrain.

GABA tied to working-memory capacity

"No previous study has ever pinpointed GABA's link with working memory in humans," said Yoon. "Working memory is a complex process, requiring coordinated activity in centers throughout the brain. Yet, remarkably, the amount of this one chemical in a single part of the brain accounts for close to one-third of the variance in individuals' load capacity."

In the study, 23 healthy participants ages 19-32 were subjected to batteries of tests of working memory. Yoon reasoned that different components of working memory would involve different neurotransmitter inputs. So he devised working-memory tests that separated the measurement of load, maintenance and distraction resistance.

Participants repeated several related tasks. In the simplest, they were

shown a drawing of a face and then, after a two-second delay, shown a second face and asked whether it was the same as or different from the first one. Variations of this task—initially presenting two faces instead of just one; lengthening the intervening delay; or displaying a different, irrelevant face between the initial and final displays—tested load, maintenance and distraction resistance, respectively. The investigators compared individuals' error rates on the simple version of the task with outcomes on tasks taxing one or another working-memory component more heavily. The smaller the deterioration in performance on a test of a particular working-memory component, the greater the individual's capacity regarding that component was judged to be.

Stop and go signals

Using an advanced imaging method, the scientists measured GABA levels in the DLPFC and, for comparison, in the visual cortex. GABA, secreted by nerve cells, is an inhibitory neurotransmitter: Its uptake by other nerve cells inhibits their firing.

Yoon and his associates also measured levels of an excitatory neurotransmitter, glutamate. By far the two most abundant neurotransmitters in the brain, GABA and glutamate are considered to be that organ's stop and go signals.

Individuals with higher levels of GABA in their DLPFC performed better on tests of their load capacity—the ability to juggle more bits of information—the researchers found. In contrast, no significant association emerged linking GABA levels in the DLPFC to maintenance or to distraction resistance, or tying participants' load capacity to GABA levels in the visual cortex. Nor did imaging reveal any connection between performance on tests of load capacity and levels of glutamate in the DLPFC.

Schizophrenic patients, Yoon said, are known to be deficient in an enzyme essential to GABA production. So, drugs that boost GABA levels or function in the brain might prove helpful in restoring their impaired working memory. He plans to test this hypothesis.

The work is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

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