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Researchers find protein essential for cognition, mental health

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The ability to maintain mental representations of ourselves and the world—the fundamental building block of human cognition—arises from the firing of highly evolved neuronal circuits, a process that is weakened in schizophrenia. In a new study, researchers at Yale University School of Medicine pinpoint key molecular actions of proteins that allow the creation of mental representations necessary for higher cognition that are genetically altered in schizophrenia. The study was released July 1 in the *Proceedings of the National Academy of Sciences*.

Working memory, the mind's mental sketch pad, depends upon the proper functioning of a network of pyramid-shaped brain cells in the prefrontal cortex, the seat of higher order thinking in humans. To keep information in the conscious mind, these pyramidal cells must stimulate each other through a special group of receptors. The Yale team discovered this stimulation requires the neurotransmitter acetylcholine to activate a specific protein in the nicotinic family of receptors—the alpha-7 nicotinic receptor.

Acetycholine is released when we are awake—but not in deep sleep. These receptors allow prefrontal circuits to come "online" when we awaken, allowing us to perform complex mental tasks. This process is enhanced by caffeine in coffee, which increases acetylcholine release. As their name suggests, nicotinic alpha-7 receptors are also activated by nicotine, which may may help to explain why smoking can focus attention and calm behavior, functions of the prefrontal cortex.

The results also intrigued researchers because alpha-7 nicotinic receptors are genetically altered in schizophrenia, a disease marked by disorganized thinking. "Prefrontal networks allow us to form and hold coherent thoughts, a process that is impaired in schizophrenia," said Amy Arnsten, professor of neurobiology, investigator for Kavli Institute, and one of the senior authors of the paper. "A great majority of schizophrenics smoke, which makes sense because stimulation of the nicotinic alpha7 receptors would strengthen mental representations and lessen thought disorder."

Arnsten said that new medications that stimulate alpha-7 nicotinic receptors may hold promise for treating cognitive disorders.

Publication of the *PNAS* paper comes on the eve of the 10th anniversary of the death of Yale neurobiologist Patricia Goldman-Rakic, who was hit by a car in Hamden Ct. on July 31, 2003. Goldman-Rakic first identified the central role of prefrontal cortical circuits in working memory.

"Patricia's work has provided the neural foundation for current studies of molecular influences on cognition and their disruption in cognitive disorders," said Arnsten. "Our ability to apply a scientific approach to perplexing disorders such as schizophrenia is due to her groundbreaking research."

Yang Yang and Min Wang of Yale are lead author and co-senior authors, respectively. Constantinos D. Paspalas, Lu E Jin and Marina R. Picciotto are other Yale authors.

More information: Nicotinic α7 receptors enhance NMDA cognitive circuits in dorsolateral prefrontal cortex, www.pnas.org/cgi/doi/10.1073/pnas.1307849110

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