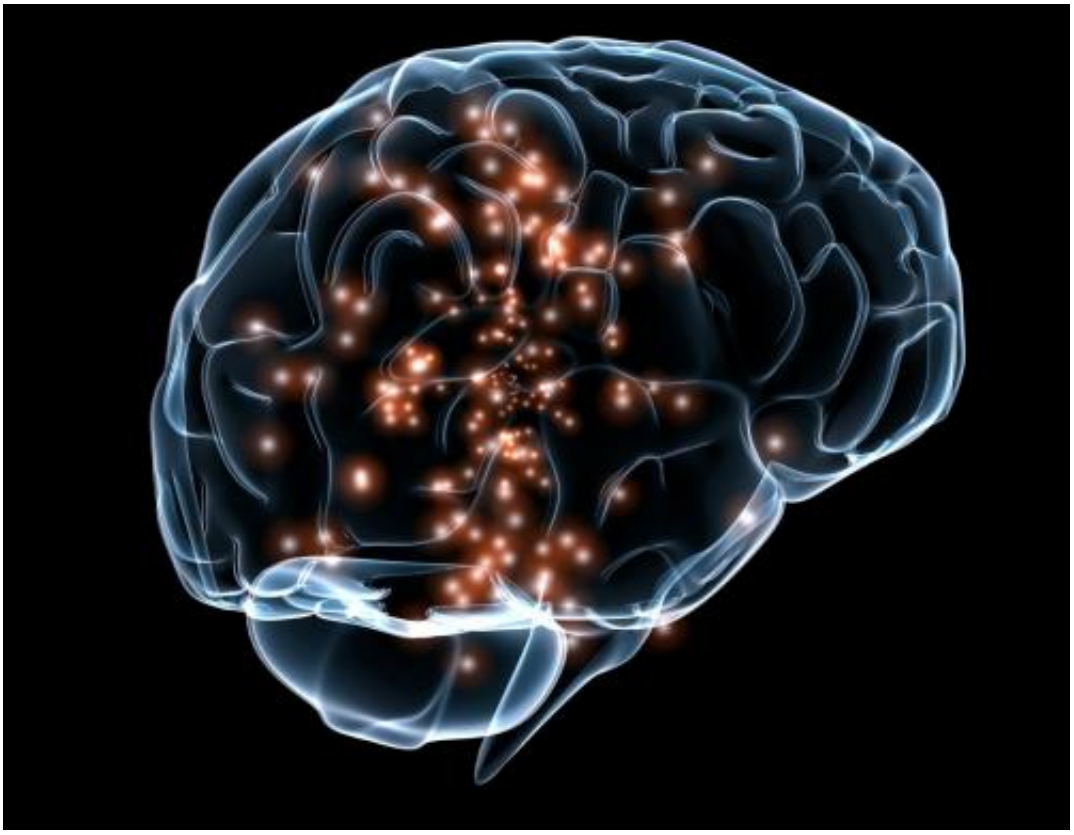
Team follows zinc to uncover pathway that fine-tunes brain signaling

May 4 2015, by Anita Srikameswaran



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A study team led by researchers at the University of Pittsburgh School of Medicine who used specially developed technologies to "follow the zinc" have uncovered a previously unknown pathway the brain uses to fine-tune neural signaling—and that may play a role in Alzheimer's and other

diseases. Their findings appear online this week in the *Proceedings of the National Academy of Sciences.*

Scientists have long observed the presence of bubble-like vesicles that contain the neurotransmitter glutamate and zinc at the synapses, specialized contacts among neurons where neurotransmitters are released to propagate electrical signals through the brain. Glutamate is the major excitatory neurotransmitter in the brain, but the need for synaptic zinc, an essential element that acts as a co-factor for many enzyme and regulatory proteins, has not been understood, said Thanos Tzounopoulos, Ph.D., associate professor in the Auditory Research Group, Department of Otolaryngology, Pitt School of Medicine.

"Until now, we haven't had the ability to quantify or follow zinc when it is released into the synaptic cleft," he said. "In this study, we employed new tools to do that and found a pathway that could be important for conditions such as Huntington's disease and Alzheimer's."

Co-investigator Stephen Lippard, Ph.D., and his team at the Massachusetts Institute of Technology (MIT) developed an agent that fluoresces when it binds zinc, making it possible for the first time to measure zinc levels accurately and track the element's movements. They also created an agent that blocks zinc activity, thus allowing them to disrupt the metal's actions to determine its function.

The researchers learned that, indeed, zinc was released from vesicles and diffused from the release site. Surprisingly, it could bind to so-called extrasynaptic glutamate NMDA-type receptors, just like the neurotransmitter glutamate. Whereas glutamate activates these receptors, zinc inhibits them.

"Glutamate acts like an accelerator of neuronal activity, while zinc behaves like a brake that fine tunes that signal," Dr. Tzounopoulos said.

"The receptors that zinc influences are thought to play a role in neurodegenerative diseases, so these findings could open new research avenues in the field."

More information: Modulation of extrasynaptic NMDA receptors by synaptic and tonic zinc, www.pnas.org/cgi/doi/10.1073/pnas.1503348112

Provided by University of Pittsburgh Schools of the Health Sciences