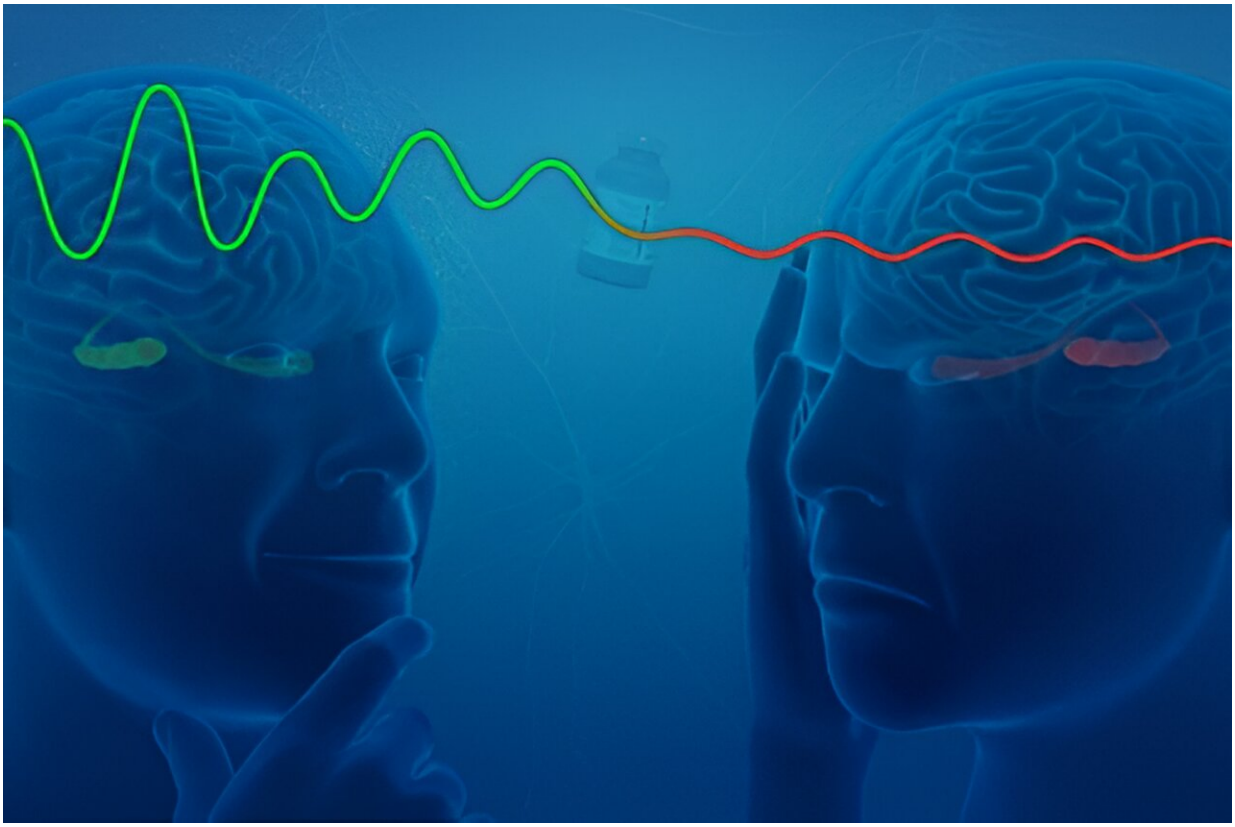
Study maps brain wave disruptions affecting memory recall

October 5 2023



Theta oscillations—brain waves associated with encoding memories—lessen in intensity with administration of a drug called scopolamine, according to a study by UT Southwestern researchers. The findings suggest an area of focus for new therapies for Alzheimer's disease. Credit: UT Southwestern

The brain circuitry that is disrupted in Alzheimer's disease appears to

influence memory through a type of brain wave known as theta oscillation, a team led by UT Southwestern Medical Center researchers report. The findings, published in *Nature Communications*, could help researchers design and evaluate new treatments for Alzheimer's, a condition that affects millions of people around the globe and has no cure.

"We hope to use this data to refine neuromodulation strategies so that they could have a greater ability to treat Alzheimer's disease and other degenerative brain diseases," said study leader Bradley Lega, M.D., Associate Professor of Neurological Surgery, Neurology, and Psychiatry and an Investigator in the Peter O'Donnell Jr. Brain Institute at UT Southwestern.

Cholinergic circuits in the brain—networks of cells that communicate with each other using the neurotransmitter acetylcholine—play a critical role in memory. These circuits heavily populate the hippocampus, a region that serves as the brain's memory headquarters.

Disruptions in this circuitry are a hallmark of Alzheimer's disease and related dementias. Cholinesterase inhibitors, one of only two classes of drugs approved to treat the symptoms of Alzheimer's disease, work by stimulating cholinergic pathways. However, the mechanisms behind how cholinergic circuits support human memory are unknown, Dr. Lega explained.

To help answer this question, he and colleagues at the Texas Computational Memory Lab at UT Southwestern and Columbia University worked with 12 patients at UTSW's Epilepsy Monitoring Unit who were being evaluated before surgery to remove the damaged parts of their brains that spark seizures. Electrodes implanted in their brains not only help surgeons precisely identify the seizure foci, Dr. Lega said, but they also provide valuable information on the brain's inner workings.

As the electrodes recorded brain activity, the patients performed memory tasks in which they tried to memorize lists of words and then recall as many as they could. In separate sessions, these volunteers received either a small amount of intravenously delivered scopolamine—a drug typically used for motion sickness that is also known to affect memory by acting on cholinergic circuits—or saline, which has no discernible effect. Between different recall tests in the same session, the volunteers performed math problems as a distraction to clear their minds.

Not surprisingly, scopolamine significantly affected the volunteers' ability to remember words. Although they could recall about 31% of the word lists on average when given saline, that dropped to about 10% when given scopolamine.

When the researchers analyzed the brain recordings, they saw that scopolamine appeared to disrupt theta oscillations, which are associated with encoding memories. As patients were given this drug, their theta oscillations decreased significantly in intensity. Additional characteristics of these affected oscillations suggested that the hippocampus couldn't communicate as well internally and with the rest of the brain. These disruptions were most pronounced in the volunteers with the worst recall after scopolamine, supporting the link between cholinergic circuits and theta oscillations.

Together, Dr. Lega said, these findings suggest that one of the principal ways that cholinergic circuits affect memory is through theta oscillations. Thus, improving the quality of theta oscillations could be a focus for developing new Alzheimer's disease therapies. Theta oscillations could also serve as a biomarker to determine whether experimental therapies are effective in clinical trials.

Other UTSW researchers who contributed to this study include David

McDonagh, M.D., Professor of Anesthesiology & Pain Management, Neurological Surgery, and Neurology; Ryan Joseph Tan, B.S., Clinical Data Specialist; and Haley Moore, B.S., Graduate Student Researcher.

More information: Tamara Gedankien et al, Acetylcholine modulates the temporal dynamics of human theta oscillations during memory, *Nature Communications* (2023). DOI: 10.1038/s41467-023-41025-y

Provided by UT Southwestern Medical Center