Memories Lost to Alzheimer’s Can Be Found

By Anne Trafton, MIT

In the early stages of Alzheimer’s disease, patients are often unable to remember recent experiences. However, a new study from MIT suggests that those memories are still stored in the brain, they just can’t be easily accessed.

The MIT neuroscientists report in *Nature* that mice in the early stages of Alzheimer’s can form new memories just as well as normal mice but cannot recall them a few days later. Furthermore, the researchers were able to artificially stimulate those memories using a technique known as optogenetics, suggesting that those memories can still be retrieved with a little help. Although optogenetics cannot currently be used in humans, the findings raise the possibility of developing future treatments that might reverse some of the memory loss seen in early-stage Alzheimer’s, the researchers say.

“The important point is, this a proof of concept. That is, even if a memory seems to be gone, it is still there. It’s a matter of how to retrieve it,” says Susumu Tonegawa, the Picower Professor of Biology and Neuroscience and director of the RIKEN-MIT Center for Neural Circuit Genetics at the Picower Institute for Learning and Memory.

Tonegawa is the senior author of the study, which appears in the March 16 online edition of *Nature*. Dheeraj Roy, an MIT graduate student, is the paper’s lead author.

Lost memories

In recent years, Tonegawa’s lab has identified cells in the brain’s hippocampus that store specific memories. The researchers have also shown that they can manipulate these memory traces, or engrams, to plant false memories, activate existing memories, or alter a memory’s emotional associations.

Last year, Tonegawa, Roy, and colleagues found that mice with retrograde amnesia, which follows traumatic injury or stress, had impaired memory recall, but could still form new memories. That led the team to wonder whether this might also be true for the memory loss seen in the early stages of Alzheimer’s disease, which occurs before characteristic amyloid plaques appear in patients’ brains.

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Lost Memories cont’d…..

To investigate that possibility, the researchers studied two different strains of mice genetically engineered to develop Alzheimer’s symptoms, plus a group of healthy mice.

All of these mice, when exposed to a chamber where they received a foot shock, showed fear when placed in the same chamber an hour later. However, when placed in the chamber again several days later, only the normal mice still showed fear. The Alzheimer’s mice did not appear to remember the foot shock.

“Short-term memory seems to be normal, on the order of hours. But for long-term memory, these early Alzheimer’s mice seem to be impaired,” Roy says.

“An access problem”

The researchers then showed that while the mice cannot recall their experiences when prompted by natural cues, those memories are still there.

To demonstrate this, they first tagged the engram cells associated with the fearful experience with a light-sensitive protein called channelrhodopsin, using a technique they developed in 2012. Whenever these tagged engram cells are activated by light, normal mice recall the memory encoded by that group of cells. Likewise, when the researchers placed the Alzheimer’s mice in a chamber they had never seen before and shined light on the engram cells encoding the fearful experience, the mice immediately showed fear.

“Directly activating the cells that we believe are holding the memory gets them to retrieve it,” Roy says. “This suggests that it is indeed an access problem to the information, not that they’re unable to learn or store this memory.”

The researchers also showed that the engram cells of Alzheimer’s mice had fewer dendritic spines, which are small buds that allow neurons to receive incoming signals from other neurons.

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Normally, when a new memory is generated, the engram cells corresponding to that memory grow new dendritic spines, but this did not happen in the Alzheimer’s mice. This suggests that the engram cells are not receiving sensory input from another part of the brain called the entorhinal cortex. The natural cue that should reactivate the memory — being in the chamber again — has no effect because the sensory information doesn’t get into the engram cells.

“If we want to recall a memory, the memory-holding cells have to be reactivated by the correct cue. If the spine density does not go up during learning process, then later, if you give a natural recall cue, it may not be able to reach the nucleus of the engram cells,” Tonegawa says.

**Long-term connection**

The researchers were also able to induce a longer-term reactivation of the “lost” memories by stimulating new connections between the entorhinal cortex and the hippocampus.

To achieve this, they used light to optogenetically stimulate entorhinal cortex cells that feed into the hippocampal engram cells encoding the fearful memory. After three hours of this treatment, the researchers waited a week and tested the mice again. This time, the mice could retrieve the memory on their own when placed in the original chamber, and they had many more dendritic spines on their engram cells.

However, this approach does not work if too large a section of the entorhinal cortex is stimulated, suggesting that any potential treatments for human patients would have to be very targeted. Optogenetics is very precise but too invasive to use in humans, and existing methods for deep brain stimulation — a form of electrical stimulation sometimes used to treat Parkinson’s and other diseases — affect too much of the brain.

“It’s possible that in the future some technology will be developed to activate or inactivate cells deep inside the brain, like the hippocampus or entorhinal cortex, with more precision,” Tonegawa says. “Basic research as conducted in this study provides information on cell populations to be targeted, which is critical for future treatments and technologies.”

*Original research*: “Memory retrieval by activating engram cells in mouse models of early Alzheimer’s disease” by Dheeraj S. Roy, Autumn Arons, Teryn I. Mitchell, Michele Pignatelli, Tomás J. Ryan and Susumu Tonegawa in Nature. Published online March 16 2016 doi:10.1038/nature17172
Women May Keep Verbal Memory Skills Longer than Men in the Early Stages of Alzheimer’s

Women may have a better memory for words than men despite evidence of similar levels of shrinkage in areas of the brain that show the earliest signs of Alzheimer’s disease, according to a study published in the March 16, 2016 online issue of Neurology®, the medical journal of the American Academy of Neurology.

According to study author Erin E. Sundermann, PhD, of the Albert Einstein College of Medicine in Bronx, NY, “One way to interpret the results is that because women have better verbal memory skills than men throughout life, women have a buffer of protection against loss of verbal memory before the effects of Alzheimer’s disease kick in. Because verbal memory tests are used to diagnose people with Alzheimer’s disease and its precursor, mild cognitive impairment, these tests may fail to detect mild cognitive impairment and Alzheimer’s disease in women until they are further along in the disease.”

The study included participants from the Alzheimer’s Disease Neuroimaging Initiative: 235 people with Alzheimer’s disease, 694 people with mild cognitive impairment that included memory problems, and 379 people with no memory or thinking problems. The groups’ performance on a test of verbal memory was compared to the size of the hippocampal area of the brain, which is responsible for verbal memory and affected in the early stages of Alzheimer’s disease.

Women performed better than men on the tests of both immediate recall and delayed recall among those showing evidence of minimal to moderate amounts of hippocampal shrinkage. At the high level of hippocampal shrinkage, there was no difference in the scores of men and women. At the score that indicates the start of verbal memory impairment, or 37 on a scale of zero to 75 for immediate recall, women showed greater evidence of hippocampal shrinkage (ratio of hippocampal volume to total brain volume multiplied by 103 was 5 compared to 6 for men).

Mary Sano, PhD, of Icahn School of Medicine at Mount Sinai in New York, NY, and a member of the American Academy of Neurology, said in a corresponding editorial, “At a public policy level, the potential health care cost for under-detection or delayed diagnosis of women with Alzheimer’s disease or its early stages is staggering and should motivate funding in this area.”

“If these results are confirmed, then we may need to adjust memory tests to account for the difference between men and women in order to improve our accuracy in diagnosis,” said Sundermann.

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Tau accumulates in the brain in Alzheimer’s disease, but also during normal aging. Can PET scans tell the difference? Two recent papers say yes, and propose schemes for imaging-based staging that until now was possible only at autopsy. As reported in the March 2 Neuron, scientists led by Bill Jagust at the University of California, Berkeley, used the tau PET ligand AV1451 to reveal an age-related accumulation of tau in the medial temporal lobe in healthy older adults that tracks with weakening episodic memory. When amyloid enters the picture, however, things ramp up. Tau binding extends beyond the medial lobe and higher up into the cerebral cortex in AD, while cognition declines more broadly. Imaging enabled the scientists to stage disease severity in vivo, closely matching the stages predicted by neuropathology. A second group of scientists also reported that they have recapitulated disease staging with tau imaging in vivo. Led by Adam Schwarz at Eli Lilly and Company, Indianapolis, and Mark Mintun at Avid Pharmaceuticals, Philadelphia, that paper appeared in the March 2 issue of Brain.

“Imaging studies will help clarify the contribution of amyloid and tau pathology to cognition, normal aging, and Alzheimer’s dementia,” said Karen Duff, Columbia University, New York, who was not involved in the work. “I am happy to see how useful tau PET imaging is going to be in staging and monitoring of disease, which will contribute greatly to diagnosis and drug development.”

Presented at two recent conferences, Jagust’s findings corroborate histopathological and imaging data from other labs. Previous postmortem data suggested that tau collects in the medial temporal lobe (MTL) as people age, in what some call primary age-related tauopathy, or PART. Tau seems to branch outside of those areas only when amyloid enters the picture. PET now bears that out, and it does so with the great advantage of allowing scientists to view the whole brain at once, in vivo, said Aaron Schultz, Massachusetts General Hospital, Boston. Schultz was among scientists in the lab of Keith Johnson, who recently reported an age-related uptake of AV1451 in the inferior temporal lobe. Johnson’s group found that AV1451 uptake in the neocortex coincided with higher Aβ burden, and that this predicted more severe clinical impairment.

In Jagust’s lab, co-first authors Michael Schöll and Samuel Lockhart enrolled five healthy young adults between the ages of 20 and 26, another 33 cognitively healthy older adults aged 64 to 90, and 15 patients aged 53 to 77 with a diagnosis of probable AD. All participants, except the young healthy adults, underwent PET with Pittsburgh compound B (PiB-PET) to detect brain amyloid, and AV1451 to measure tau. They also took tests of episodic memory, working memory, and executive function/processing speed. Many of the healthy older adults had sat these neuropsychological tests up to six years prior to their scans.

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PET indicated that the young healthy adults had accumulated very little tau. Older people who were negative for amyloid had tau aggregates in the MTL that correlated with subtle deficits in episodic memory but not other forms. In older adults who did have brain amyloid, tau appeared in the inferior plus the lateral temporal lobe, as well as in some lateral and medial parietal regions. AD patients had tau pathology in most neocortical regions, particularly throughout temporal, parietal, and frontal lobes. Tau pathology outside the MTL correlated with a drop in global cognition, but only if amyloid was present. “It’s a pretty clear story: As you get older, there’s more tau in your medial temporal lobe, but as you get more amyloid, there’s more tau in your lateral temporal lobe and your neocortex,” Jagust told Alzforum.

Jagust said it will be difficult for imaging to determine whether amyloid causes tau to spread, or whether the spread of tau allows amyloid to deposit. Likewise, imaging will probably be unable to say whether PART and AD represent continuous or different processes, he said.

“Ultimately, by [therapeutically] targeting amyloid we may change what happens with tau,” said Schultz. “Being able to image that in vivo will be immensely useful, allowing better sensitivity and earlier assessment than would be possible with behavioral measures alone.” He noted that the current data is still cross-sectional. “One big hope is that new insights into disease will come from longitudinal data. A great many people are excited about that.”

Taking the results a step further, Schöll worked out a method for in vivo Braak staging. It defines seven stages of tau progression based on histopathology: no deposition in stage 0; the transentorhinal region in stage I; entorhinal cortex in stage II; fusiform and lingual gyri in stage III; neocortical association areas by IV. By stage V/VI, tangles have expanded widely into the outer layers of the cortex.

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Schöll adapted this staging scheme for in vivo tau PET by defining three large regions of interest that matched Braak stages I/II, III/IV, and V/VI. He then used regression models to define standard uptake value ratio thresholds for each region that indicated whether a person was positive for tau in that region. Those values classified all of the young adults and two older adults as stage 0, 25 older adults as I/II, two AD patients and six older adults as III/IV, and 13 AD patients as stage V/VI. As expected, higher Braak stage correlated with increasing, global amyloid burden.

“Tau PET is offering the possibility of staging Alzheimer’s disease in vivo,” said Schöll. Now researchers can classify living people by cognitive, amyloid, and tau profiles. This will help them predict how close a person is to progressing to AD. In turn, this will be helpful in recruiting better-characterized participants for clinical trials, and eventually for diagnosis, he said.

Schwarz, Mintun, and colleagues took a slightly different approach to staging disease in people. They used AV1451 to scan 14 young controls and 42 cognitively normal older adults who were free of amyloid (according to a florbetapir scan), as well as 87 patients with mild cognitive impairment (MCI) and 44 with a clinical diagnosis of AD, 16 of whom tested negative for amyloid. Where Schöll defined three large ROIs to tau staging, Schwarz chose six, one for each individual Braak stage. He chose cutoffs for each region that exceeded the uptake level he saw in young healthy controls.

Schwarz found that his in vivo staging largely matched that expected for each person’s clinical profile: worse cognitive impairment, more advanced disease stage, and amyloid positivity associated with higher stages. However, fewer cognitively normal older adults were rated stage I/II than expected based on historical histopathology data. The researchers took this to mean that tau PET imaging is less sensitive than staining methods. They also found that seven percent of their population did not show typical patterns of tau distribution—three older cognitively normal people, eight with MCI (four amyloid-positive), and one AD patient. Several retained no AV1451 in the medial and inferior temporal lobe but had strong signals in lateral temporal and/or occipital cortices, which could be related to a proposed hippocampal-sparing subtype of AD, the authors wrote. They suggested that the in-vivo staging will eventually be refined by comparing in-vivo PET imaging with postmortem neuropathology of the same study volunteers.—Gwyneth Dickey Zakaib

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To view the original article please visit: http://www.alzforum.org/news/research-news/tau-pet-aligns-spread-pathology-alzheimers-staging
A New Glimpse into Working Memory

By Anne Trafton, MIT

When you hold in mind a sentence you have just read or a phone number you’re about to dial, you’re engaging a critical brain system known as working memory.

For the past several decades, neuroscientists have believed that as information is held in working memory, brain cells associated with that information fire continuously. However, a new study from MIT has upended that theory, instead finding that as information is held in working memory, neurons fire in sporadic, coordinated bursts.

These cyclical bursts could help the brain to hold multiple items in working memory at the same time, according to the researchers.

“By having these different bursts coming at different moments in time, you can keep different items in memory separate from one another,” says Earl Miller, the Picower Professor in MIT’s Picower Institute for Learning and Memory and the Department of Brain and Cognitive Sciences.

Miller is the senior author of the study, which appears in the March 17 issue of *Neuron*. Mikael Lundqvist, a Picower Institute postdoc, and Jonas Rose, now at University of Tubingen in Germany, are the paper’s lead authors.

**Bursts of activity**

Starting in the early 1970s, experiments showed that when an item is held in working memory, a subset of neurons fires continuously. However, these and subsequent studies of working memory averaged the brain’s activity over seconds or even minutes of performing the task, Miller says.

“The problem with that is, that’s not the way the brain works,” he says. “We looked more closely at this activity, not by averaging across time, but from looking from moment to moment. That revealed that something way more complex is going on.”

Miller and his colleagues recorded neuron activity in animals as they were shown a sequence of three colored squares, each in a different location. Then, the squares were shown again, but one of them had changed color. The animals were trained to respond when they noticed the square that had changed color — a task requiring them to hold all three squares in working memory for about two seconds.

The researchers found that as items were held in working memory, ensembles of neurons in the prefrontal cortex were active in brief bursts, and these bursts only occurred in recording sites in which information about the squares was stored. The bursting was most frequent at the beginning of the task, when the information was encoded, and at the end, when the memories were read out.

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Filling in the details

The findings fit well with a model that Lundqvist had developed as an alternative to the model of sustained activity as the neural basis of working memory. According to the new model, information is stored in rapid changes in the synaptic strength of the neurons. The brief bursts serve to “imprint” information in the synapses of these neurons, and the bursts reoccur periodically to reinforce the information as long as it is needed.

The bursts create waves of coordinated activity in the gamma frequency (45 to 100 hertz), like the ones that were observed in the data. These waves occur sporadically, with gaps between them, and each ensemble of neurons, encoding a specific item, produces a different burst of gamma waves. “It’s like a fingerprint,” Lundqvist says.

When this activity is averaged over several repeated trials, it appears as a smooth curve of continuous activity, just as the older models of working memory suggested. However, the MIT team’s new way of measuring and analyzing the data suggests that the full picture is much different.

“It’s like for years you’ve been listening to music from your neighbor’s apartment and all you can hear is the thumping bass part. You’re missing all the details, but if you get close enough to it you see there’s a lot more going on,” Miller says.

The findings suggest that it would be worthwhile to look for this kind of cyclical activity in other cognitive functions such as attention, the researchers say. Oscillations like those seen in this study may help the brain to package information and keep it separate so that different pieces of information don’t interfere with each other.

“Your brain operates in a very sporadic, periodic way, with lots of gaps in between the information the brain represents,” Miller says. “The mind is papering over all the gaps and bubbly dynamics and giving us an impression that things are happening in a smooth way, when our brain is actually working in a very periodic fashion, sending packets of information around.”

Robert Knight, a professor of psychology and neuroscience at the University of California, Berkeley, says the new study “provides compelling evidence that nonlinear oscillatory dynamics underlie prefrontal dependent working memory capacity.”

“The work calls for a new view of the computational processes supporting goal-directed behavior,” adds Knight, who was not involved in the research. “The control processes supporting nonlinear dynamics are not understood, but this work provides a critical guidepost for future work aimed at understanding how the brain enables fluid cognition.”
The following studies will be enrolling in 2016. For information on these studies please visit:

http://www.adcs.org/Studies/clinicalResearchStudy.aspx