



The *life* *&* *death* OF MEMORIES

Our memories are integral to our personal identity, but we cannot take for granted that they will always be with us.

By Susan Green



Robert Santulli, a Geisel professor of psychiatry, works not only to understand Alzheimer's disease but to help patients overcome the stigma associated with the disease. Here, he leads a session of a Memory Café with Kimberly Betts, a Geisel medical student.

or nerve cells, that are constantly zinging electrical pulses to each other across synapses. In a complex and still somewhat mysterious interplay of chemical and electrical activity, trillions of synapses allow signals to flash through the brain's neural networks, creating the cellular basis of memory.

Bombarded by vast amounts of information gathered from our senses throughout the day, our brain is constantly making decisions about what to remember and what to toss out. Our experiences and our priorities influence the formation of our memories, including what we remember and which extraneous details can be discarded, such as a colleague's cough, a casual lunch conversation, how much coffee we drank.

We might expect our memories to be stored whole in one convenient location ready to be recalled at a moment's notice, but that is not the case. They are stored as bits and pieces of encoded neural connections scattered throughout the brain's three memory systems—working memory (temporary), declarative memory (what we know), and procedural memory (what we know how to do).

A memory's split-second birth begins with perception. If what we perceive is important, it is temporarily stored in the prefrontal cortex as working memory. The ephemeral nature of working memory allows us to hang onto this information briefly, remembering a phone number long enough to make a call. On average, we can hold up to seven bits of information for nearly 30 seconds before it is gone forever—unless we make an effort to retain it.

Turning this fleeting information into long-term memory requires the conscious effort of assigning it meaning (Ted's new cell phone number), and repeating it (277-2772, 277-2772) in order to engrave the information along a neural pathway that can be followed later. We have all done this with varying degrees of success.

forward: information is taken in and it's either stored or forgotten. But the brain functions that allow us to revisit the glorious, frightening, and embarrassing moments of our past are far from simple. Memory is an intricate, elusive, and awe-inspiring system involving many areas of the brain. And for many people, that system will, at some point, start to falter.

The Alzheimer's Association estimates that more than five million people in the United States are living with memory loss as a result of dementia. People with the illness may clearly remember what happened decades ago but not what happened a few minutes ago. In its early stage, this loss of short-term memory is frightening to those with Alzheimer's disease—they're aware that who they are is disappearing.

Researchers at the Geisel School of Medicine and Dartmouth College are studying every aspect of memory, from the initial

ur memories shape us both as individuals and as a culture. Without the ability to store and recall information, we would not be able to learn new skills, to plan for the future, or to manage our day-to-day lives.

On the surface, memory is straightforward: information is taken in and it's either stored or forgotten. But the brain functions that allow us to revisit the glorious, frightening, and embarrassing moments of our past are far from simple. Memory is an intricate, elusive, and awe-inspiring system involving many areas of the brain. And for many people, that system will, at some point, start to falter.

storage of ideas, facts, and feelings to the loss of that ability due to Alzheimer's or other diseases. They are part of a long tradition. More than 2,000 years ago, Aristotle postulated that memory is imprinted on the mind like writing on a blank slate. Today, neuroscientists are still trying to understand memory and how it affects our sense of self.

ANATOMY OF A MEMORY

Weighing in at nearly three pounds, our brain contains tens of billions of neurons,

Facts, figures, faces, events, and personal experiences that can be consciously recalled are the provenance of declarative memory. Once encoded, electrical signals in the hippocampus send the bits of information to the temporal cortex and elsewhere for storage, where the stimuli patiently await recall.

Emotional memories require far less effort. Tucked into the curve of the hippocampus, the almond-shaped amygdala is the seat of emotion. An interwoven interaction between the two encodes emotional aspects of memory and guarantees that we will remember those experiences, whether individual—who among us has forgotten their first kiss—or collective.

“Emotion has a strong modulating affect on memory,” says David Bucci, PhD, a professor of psychological and brain sciences at Dartmouth. “For instance, nearly everyone can say where they were on September 11, 2001, but can they say where they were a few days earlier? Probably not.”

The emotional charge of that day was encoded with visual information, creating an inextricable link and carving the experience into our collective memory. Whenever that memory is recalled, the emotions are relived.

Procedural memory is encoded by the cerebellum and areas of the brain associated with fine motor skills. Deeply embedded, it operates independent of the hippocampus. The longer and more frequently we follow certain routines, the more familiar they become, and the more likely we are to perform them unconsciously. This is what allows us to talk, walk, play the violin, and ride a bicycle.

WHILE WE'RE SLEEPING

Memory depends on a good night's sleep.

“When you learn something for the first time,” says Jeffrey Taube, PhD, “neurons change how things are connected in your brain and sleep consolidates these new connections.”

During sleep the hippocampus industriously reviews the day's experiences and sorts through relevant and important new information to see how it connects to what's already stored in memory. Prior knowledge is revised and updated giving us a more

accurate representation of our environment—essentially creating new memories.

According to Taube, a professor of psychological and brain sciences at Dartmouth, hippocampal sharp waves during sleep are thought to play a critical role in this reviewing process, consolidating memory traces within the hippocampus and transferring memories to the prefrontal cortex and other brain areas. Lasting less than one-tenth of a second, sharp waves are also considered to be part of the process that allows us to filter out unnecessary information.

A fragmented or inadequate sleep pattern negatively affects memory because all aspects of learning, from studying to performance, require sleep in order for us to retain and remember what we need to know—although learning and memory are closely linked, they utilize separate systems. Lack of sleep not only affects memory, it also impairs fine motor skills, our ability to pay attention, and our ability to make decisions.

“If you really need to remember something, go over it the night before,” Taube says. “There's something to be said for ‘sleeping on it.’”

A TRIP DOWN MEMORY LANE

Memory is a complex construction of relationships between our experiences, rather than details of the actual experiences, that reside in specific brain cells in different parts of the brain.

Through mechanisms that are still poorly understood, we are able to pick out a specific memory and relive it, Bucci explains. “Groups of cells interacting together and continuing to act together over time build a memory trace,” he adds. And like pieces of a jigsaw puzzle, all we need to do is bring them together.

Sensory cues activating a tiny fraction of those cells seamlessly bring an entire memory into consciousness with astounding speed—hearing a few notes of a favorite song takes us back to our youth, the scent of freshly baked chocolate chip cookies reminds us of our grandmother, one bite of a hotdog and we relive a bout with food poisoning.

Given this instant recall, it's tempting to think that memory is an accurate ongoing

record of our life. But it's quite the opposite—every time we recall a memory it's vulnerable to change.

With each recall, the hippocampus and cortex collaborate to reconstruct the memory, but the process is affected by our biases, by what we want to believe, by what is retained from the past, and by our current situation. It's a complex dance between the past and present—some aspects of the memory are reinforced while others fade.

“We now know that the very same cellular and molecular changes that happen when we're consolidating a memory are playing the same role once we've retrieved it,” Bucci says. “At this point our brain is seeing if there is anything new we need to know about that stimulus. If not, the memory remains intact.” Memories without strong emotions are more susceptible to change, he notes.

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Unconscious memory adaptations are beneficial, because they help us create coherent narratives about our lives, contribute to our sense of self, and tap into our survival instincts. They also help us reduce complexity to something more understandable.

"As time goes on and things change, a particular stimulus may not have the same meaning as it used to," Bucci further explains. "We do need a mechanism to introduce new factors into the memory trace in order to have an adaptive advantage. But the downside is that you can introduce such a variety of inaccurate changes and adaptations that the memory may become distorted over time."

WHY WE FORGET

Frederich Nietzsche famously said, "The advantage of a bad memory is that one enjoys several times the same good things for the very first time."

We tend to forget more information than we remember. Our brain has evolved to allow us to get rid of useless stimuli to avoid information overload, but the constant editing process that protects us is vulnerable. Stress and multitasking are the chief culprits of forgetfulness—these distractions prevent

long-term memories from being brought to consciousness. And when our memories are continually suppressed, they begin to fade and eventually disappear.

Lack of motivation is equally problematic. If we aren't motivated to remember something, we won't. Forgetting, for instance, to start an unpleasant household chore, to run an irksome errand, or to make a commitment we have no intention of honoring is no accident. Our lack of interest results in a failure to encode and store the information, meaning we'll never remember it.

Not remembering the name of someone you just met is as normal as forgetting where you left your car keys or sunglasses. We dismiss this kind of forgetfulness when we're young, but as we age we become more cognizant of our occasional memory lapses and we dread what our forgetfulness may represent.

For most people, forgetting where you left your sunglasses is simply an irritation—when you forget what sunglasses are, you have a problem.

Alzheimer's disease, the most common form of dementia, is more than simple forgetfulness, even though that's an early sign of the illness. It's a progressive neurological disease that's the result of dying brain cells. This cell death causes

deterioration in memory, behavior, and the ability to think clearly.

In healthy cells, electrical charges travel freely to other cells releasing neurotransmitters, but Alzheimer's disease disrupts both the way charges travel within cells and the activity of neurotransmitters. The cause of this is still largely unknown, but proteins present in plaques and tangles appear to play a role. Plaques contain peptide fragments produced by the amyloid precursor protein, and tangles contain Tau protein.

"Amyloid peptide fragments tend to self-assemble—it is believed that small assemblies of amyloid peptide fragments are very toxic to neurons," says Ta-Yuan Chang, PhD, a professor of biochemistry at Geisel.

Small clusters of amyloid peptide build up inside and between nerve cells and may block cell-to-cell signaling. The Tau protein, produced mainly in neurons, interacts with amyloid peptide fragments to cause neurotoxicity. In addition, deformed Tau proteins may destroy the transport system in neurons.

"Mutant forms of enzymes involved in producing the amyloid peptide fragments can cause early onset Alzheimer's disease," Chang explains. "This occurs between ages 30 and 60, but these are very rare cases." A genetic variant of the protein apoE is a major risk factor for late

Geisel student Kimberly Betts helped create the Memory Café when she was a Dartmouth undergraduate and she has remained involved as a medical student.



Jon Gilbert Fox

Moments of Joy at the Memory Café

FIRST-YEAR STUDENT KIMBERLY BETTS PLAYED A KEY ROLE in establishing the Upper Valley Memory Café three years ago, and she has been the driving force behind the café's success since its inception. The café, an informal monthly gathering for people with dementia and their families, addresses some of the needs not met by traditional medical care. It focuses on preserving abilities, boosting self-esteem, addressing the stigma surrounding the disease, and providing resources and support for family caregivers.

Betts's interest in working with Alzheimer's patients began when she enrolled in a Geisel School of Medicine fall elective course open to undergraduates, "Lost Minds: The Tragedies of Alzheimer's Disease," taught by Robert Santulli, MD, an associate professor of psychiatry.

"One of the things that Kim has been so wonderfully helpful with is getting undergraduate students involved in the Memory Café," Santulli says. "Each



Golgi-staining reveals the normally transparent filamentary extensions of individual neurons in the rat hippocampus.

onset Alzheimer's—after age 60—which is when the disease typically develops. "ApoE is involved in cholesterol metabolism," Chang says. "It does not cause the disease, but it increases the risk."

Chang and his research team are working on developing inhibitors for ACAT1, an enzyme involved in cellular cholesterol metabolism, to delay or reverse the disease.

Not only are people with early-stage Alzheimer's dealing with the inability to recognize what's wrong, they are struggling with the self-imposed shame of not being able to remember what day it is, or how to tell time. They are also faced with the terror of losing their sense of self. This anxiety-provoking stress can further deteriorate their short-term memory.

"People are still very ashamed about losing their memory," says Dr. Robert Santulli, a Geisel professor of psychiatry. "They will tell you in great detail about their broken bones, or their bowels, but they won't talk about their dementia."

A specialist in the diagnosis and treatment of Alzheimer's disease, Santulli says more people fear a diagnosis of Alzheimer's than of cancer—they think dementia is a personal failing rather than a biological deterioration of cognition.

Overcoming that attitude is a big challenge, Santulli says. "Dealing with those negative attitudes is one of the factors which interferes with patients coming into the office in the first place—they and their families are so frightened about it that

by the time we see them in the clinic we discover that they've had symptoms for years," he adds.

Age is still the most prevalent risk factor for Alzheimer's disease, but Santulli cautions against viewing Alzheimer's as an inevitable result of aging. It is a disease of old age, he acknowledges, but this does not imply that changes in cognitive function that are a normal part of aging lie on a continuum that ends in dementia.

We know that on nearly every level of our existence, our memory is called into action—it ties us to our past and to the present and gives us a frame of reference for the future. It is tied to how we learn, and to how we navigate through our environment. Our memory makes us who we are. And while there are still a lot of unanswered questions, our memory, with all of its complex quirks and failings, allows us to function rather well.

"How our brain works is one of the final mysteries for us to solve," Bucci says. "And who wouldn't be interested in that?"

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month, she actively works with the undergraduates, teaching them how to appropriately interact with our guests."

This intergenerational social interaction is an important aspect of their education, and it is a valuable element in beginning to break down the stigma associated with Alzheimer's disease.

"My sorority, Alpha Xi Delta, has been involved in the café from its earliest days," Betts recalls. "I invited some of my sisters to come with me to the café—everyone enjoyed the experience and they wanted to continue volunteering." Those experiences grew from a casual collection of friends into a lasting, hands-on enterprise within the sorority.

Today, Alpha Xi Delta is an official partner of the Upper Valley Memory Café, and a newly created Memory Café Chair coordinates, with Betts, the activities of the more than 80 students who volunteer.

The sorority's involvement is a defining characteristic of the café, she says. Each month the sorority sisters prepare and help serve breakfast, participate in discussions, and socialize with guests. They also bring their friends. At a café gathering in late fall, several volunteers brought male friends from Dartmouth College and Geisel—prior to that there was a noticeable dearth of male volunteers. According to Betts, the relationship between those with Alzheimer's and the student volunteers—which she likens to

the relationship between grandparents and grandchildren—makes for a pleasurable experience and a familial bond within the café community.

"Most of the volunteers are not going to medical school," Betts says. "But during their lifetime they will all come into contact with someone who has Alzheimer's, so it's important to get young people involved and at the café they get a broad perspective on the illness." She continues, "Because we focus on joy in the moment, students can take that attitude home to their own families and teach them to focus on that the next time they meet someone with dementia."

Articulate and poised, Betts speaks passionately about the need for student participation in the Memory Café. Last year, she delivered a presentation about the work of students at the café during the Alzheimer's Association International Conference in Boston, Mass.

Believing that a lack of awareness of the disease also contributes to the stigma, she and Santulli conduct workshops on keeping your mind sharp and knowing the difference between forgetfulness in normal aging and dementia's early stages.

"Alzheimer's disease is a terminal illness, but it's not the end of life—it's a lifestyle change," Betts says. "Breaking down the stigma has huge implications and we need to continue to get the word out among younger people."