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# Memory: Forgetting Is the New Normal

By Sue Halpern

Memory researcher Dr. Scott Small would like to reassure you that you're not losing your wits. Visit him in his lab at Columbia University's Medical Center, tell him how the last time you went to a party, you couldn't put names to faces, how telephone numbers slip your mind, and he'll walk to his blackboard, pick up a piece of chalk and draw two lines. One, he will tell you, represents age. The other is memory. "As age goes up, memory goes down," he says. "Memory decline occurs in everyone."

Anecdotally, that's no surprise. Approach middle age, and it's hard not to notice that your recall is flickering. This, we're reassured, is perfectly normal--all your friends are complaining about the same thing, aren't they?--and yet it doesn't feel normal. You don't just have your mind, after all; you are your mind, and nothing threatens your well-being so much as the feeling that it's at risk. What's more, while most memory loss is normal, at least some people must be part of the unlucky minority that develops Alzheimer's disease or other forms of dementia. Why not you?

Alzheimer's is expected to strike 34 million people globally by 2025 and 14 million in the U.S. alone over the next 40 years. Half of all people who reach age 85 will exhibit symptoms of the disease. That, however, means that the other half won't. And since average U.S. life expectancy currently tops out at 80.4 for women and only 75.2 for men, by the time your 85th birthday rolls around, you're not likely to be troubled by Alzheimer's disease--or anything else.

Still, that doesn't make it any easier when you forget to pick up the dry cleaning or fumble to recall familiar addresses. The good news is, science is as interested in what's going on as you are. With better scanning equipment and knowledge of brain structure and chemistry, investigators are steadily improving their understanding of how memory works, what makes it fail, how the problems can be fixed--and when they can't.

For most people, all this will mean reassurance as worrisome symptoms turn out to be nothing at all. "Normal is the new frontier," says Mony de Leon, director of the Center for Brain Health at New York University Tisch Hospital. And for those who do drift beyond that frontier, the same research may offer new hope for treatments and even cures.

Consider, for a moment, how memory is supposed to operate. Consider, that is, the hippocampus. A cashew-shaped node of tissue, the hippocampus sits deep in the temporal lobe of the brain, near the amygdala, which is the seat of emotions. If the brain has a gatekeeper of sensory information, the hippocampus is it. The aroma and sizzle of bacon frying, the smooth finish of polished granite, a phone number you need to call--all must pass through the hippocampus. Only if information gets in can it be moved along to the prefrontal cortex, where it will be held briefly in what is called working--or short-term--memory. When you look up the phone number, dial it and promptly forget it, that's your prefrontal cortex working in tandem with your hippocampus.

But let's say you hang on to the number 10 minutes or even 10 months later. Why? Because that bit of information has gone through a chemical process called long-term potentiation (LTP) that strengthens the synapses. You need LTP to form long-term memories. And LTP takes place in the hippocampus.

The hippocampus begins to malfunction early in Alzheimer's disease. Imaging studies have shown that people with Alzheimer's typically have smaller than average hippocampi. Meanwhile, as the hippocampus is shrinking, the pathway between it and the prefrontal cortex also begins to degrade. Signals peter out and fade away, and questions take their place: Do I know you? Who am I? But it's not just with Alzheimer's: the hippocampus also goes at least somewhat awry in normal memory loss. "It's relatively stable in volume till about 60," Harvard neuroscientist Randy Buckner explains, "and then begins to change. People with Alzheimer's disease, though--they slide off the cliff."

Small and his colleagues have been trying to understand this difference. Small's hunch--now proven--was that a node of the hippocampus different from the one affected in Alzheimer's was breaking down in normal memory loss. "In humans, monkeys and rats," he says, "normal aging targets a node called the dentate gyrus, while a different node--the entorhinal cortex--is relatively spared. But in Alzheimer's disease, it's almost exactly reversed." Small has gone deeper, pinpointing a protein molecule known as RbAp48 that is lower in the brains of people suffering ordinary age-related memory loss. He and his colleagues are now testing the effect of that molecule in a knockout mouse--one engineered not to express RbAp48. They are also looking at interventions that might amplify the molecule and presumably boost memory.

But even if you, like the mouse, are low in RbAp48, don't pin all the blame for your memory loss on your hippocampus. As people get older, their attention starts to flicker, and that plays a role of its own. The prefrontal cortex, which controls planning, organization, abstraction and forethought, is the same region that allows us to concentrate, and it starts to diminish in size well before middle age. It also begins to use the brain's fuel, glucose, less efficiently and loses about half the neurotransmitter dopamine it once had. The result of all this, says Amy Arnsten, a neurobiologist at Yale Medical School, is that as we get older, we get "ADHD, but it's attention-deficit hypoactivity--not hyperactivity."

In her lab at Yale, Arnsten has roused idling monkey and rat brains with a medication called guanfacine, which appears to amplify the circuits of the prefrontal cortex. The drug has been tested

on children with ADHD as well as on people with traumatic brain injury, posttraumatic stress and schizophrenia, and in each case it seems to revitalize working memory.

This could be a boon to middle-agers whose concentration is slipping, since studies show just how vital paying attention can be to forming memories. In one study, neuroscientist Dr. Adam Gazzaley of the University of California, San Francisco, recruited two groups of subjects--one ages 19 to 30 and the other 60 to 77--and scanned their brains while they were looking at pictures of human faces, then again when they were viewing landscapes. This allowed him to map out where in the brain they were taking in these images. Then he put the volunteers back in the scanner and told them that he was going to show them four pictures simultaneously--two of faces, two of scenery--and that he wanted them to focus only on the faces. When the younger volunteers did this, they showed increased activity in the part of the brain that deals with facial recognition and decreased activity in the part that processes landscapes. Not so the older participants; they couldn't shut out the scenery and focus on just one thing. Says Gazzaley: "They are overwhelmed by interference."

In a related study, psychologist Susan De Santi of NYU's Center for Brain Health studied subjects who had been diagnosed with mild cognitive impairment (MCI), a condition that can be transitory but one that also often segues to Alzheimer's. Two years later, some did develop the disease, but in others the symptoms faded. What De Santi found was that younger subjects who had no trouble paying attention saw their conditions improve.

"MCI is memory problems combined with problems in some other cognitive domain, like verbal fluency or spatial reasoning," De Santi says. "Seventy-one percent of those who had memory problems plus some other problem ended up getting sick with Alzheimer's, but only 8% of people who had only memory problems got sick."

Something else is going on as we get older that also impairs memory: our brains are making fewer neurons. Until a decade ago, the common assumption was that we were born with a fixed number of brain cells that die off as we age, making us, well, dimmer. That, however, is not the case. It is now known that the brain continues to produce neurons throughout the life cycle, but only in two places: the olfactory bulb and the hippocampus. And not just anywhere in the hippocampus but in the dentate gyrus, the very node that Small has identified as the site of impairment in normal memory loss. So why should memory fade at all? The answer may come from the gym.

A decade ago, when neuroscientist Fred Gage of the Salk Institute made the discovery that the adult brain continues to regenerate, the brains in question belonged to mice. Some of the mice had been sedentary, others had been exercising, and the ones that logged the most miles on their wheels produced many more new neurons than did the sedentary ones.

Now it turns out that the same appears to be true for humans. In a paper published last spring, a team led by Gage, Small and Richard Sloan, a psychologist at Columbia University, revealed that after pounding the treadmill four times a week for an hour for 12 weeks, a group of previously inactive men and women, ages 21 to 45, showed substantial increases in cerebral blood volume

(CBV)--a proxy for neurogenesis because where there are more cells, there are more blood vessels.

Not only did the CBV profile of the human exercisers mirror that of the mice, but the people who exercised more did better on a slew of memory tests. Other evidence backs this up. In a study of "previously sedentary" older subjects by psychologist Arthur Kramer at the University of Illinois and others at Israel's Bar-Ilan University, investigators found that those who engaged in aerobic exercise did better cognitively than those who stretched and toned but never got their heart rates pumping. What's more, subsequent imaging showed that aerobic exercise "increased brain volume in regions associated with age-related decline in both structure and cognition."

Meanwhile, researchers from the Karolinska Institute in Stockholm who have been following over 1,500 people for more than 35 years found a significantly lower rate of dementia, including Alzheimer's, in those who exercised. Another study, this one of 2,000 elderly men living in Hawaii, showed that those who walked two miles or more a day were half as likely to develop dementia as those who walked a quarter-mile or less.

Cerebral blood volume is not the only thing responsible for this brain-boosting. Also at work is the fact that exercise increases what's known as brain-derived neurotrophic factor (BDNF), a protein that stimulates the birth of new brain cells and then helps them differentiate and connect. BDNF also enhances neural plasticity, the process by which the brain changes in response to learning. In diseases like Alzheimer's, depression, Parkinson's and dementia, BDNF levels are low. In people who exercise, BDNF levels rise.

But physical activity isn't all there is to improving your memory. There's also what you eat. Take blueberries. According to Jim Joseph, a neuroscientist with the U.S. Department of Agriculture in Boston, blueberries seem to have nearly magical powers: they zap free radicals (highly reactive atoms that can damage tissue), reverse aging, enhance cognition and--and this is the kicker--cause new neurons to grow. If you're a rat.

In one of his animal studies, Joseph and his associates developed a series of motor-skills tests that they called the Rat Olympics. Rats had to walk balance beams and stay upright during a log-rolling task. Those raised on special blueberry rat chow did significantly better than those that were not, leading Joseph to conclude that "blueberries were actually able to reverse motor deficits in these aging animals." More remarkably, when mice that had been genetically altered to express Alzheimer's were put on the blueberry diet, they did not experience memory loss. Joseph's research has shown some similar benefits from walnuts, which contain alpha-linolenic acid, an essential omega-3 fatty acid.

No matter what you eat, if you want to keep your memory sharp, you should strive for a diet that keeps your belly fat down. A study of more than 6,500 people published in the March 26 edition of the journal *Neurology* showed that people who were overweight and had a large belly were 2.3 times as likely to develop dementia as those with normal weight and belly size, while those who were obese and had a large belly were 3.6 times as likely. As scientists have long known, as belly fat--which

disrupts body chemistry more than less reactive fat elsewhere on the body--increases, blood glucose rises along with it. Some of Small's most recent animal studies show that rising glucose levels in turn disrupt the function of the dentate gyrus. That doesn't draw a straight and conclusive line between waistline and memory, but it does suggest one. "It's possible," Small says, "that blood glucose, which tends to drift upward as we get older, is one of the main contributors to age-related memory decline in all of us."

None of these insights, of course, make your sputtering memory less frustrating. When you've misplaced your keys for the third time this month, it does you little good to be reminded that it all may be just too much glucose and too few blueberries. And nothing entirely removes the specter of true dementia and the horrors it implies. Still, figuring out how memory works is the most important step in figuring out how it can be fixed. When you can make some of the fixes yourself, the news is even better. If you needed one more reason to get your exercise and watch your diet, the memory scientists are providing you with one--even if you have to write it down.

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