The mystery of the super-ager

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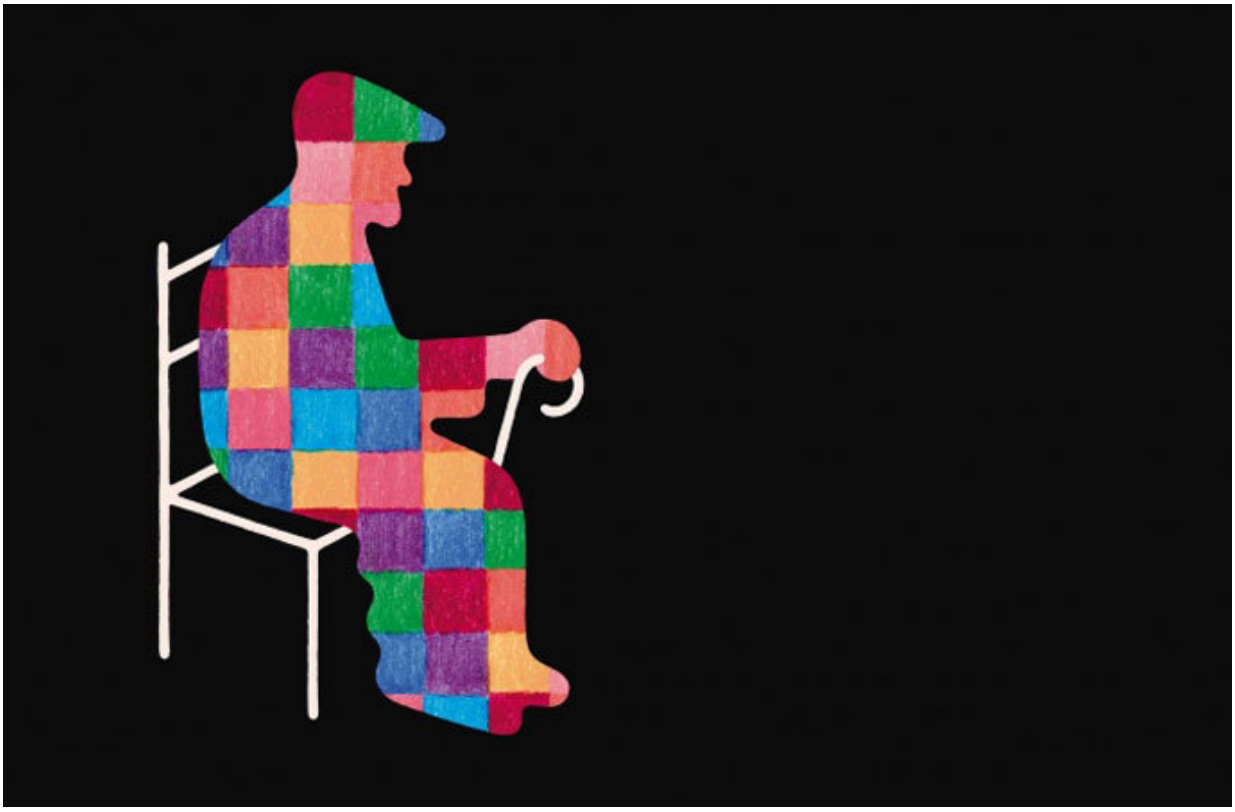


Credit: Miguel Porlan

It was the kind of case no traditional medical textbook could explain.

The subject—let's call him Peter Green—was a white male in his late 80s, enrolled in longitudinal studies of the elderly at the UCSF Memory and Aging Center. Green's brain scans "were not pretty," recalls Joel

Kramer, Psy.D., who directs the center's neuropsychology program. His brain had begun to atrophy, and its white matter—composed of long bundles of nerve cells that carry signals from one area to another—were shot through with dead patches, suggesting that Green had suffered the kind of ministrokes often associated with cognitive decline.

Yet by all behavioral measures, Green was thriving. His cognitive test scores were impeccable and his ability to function in the world remained high.

"If you look at his cognition and level of functioning, it not only remains high—it hasn't changed at all in years," Kramer says. What was it about Green, Kramer wondered, that set him apart from his peers with similar brain scans, who seemed to have been waylaid by the ravages of time?

When Kramer finally met the study subject in person, the neurologist was struck by Green's dynamism and sunny outlook on life. He told Kramer he volunteered in the community, was constantly busy with projects and organizations, and remained close to his family. He shared how grateful he was for what he had and really seemed to be enjoying his golden years.

"He talked about how his attitude toward life is one of embracing it—not getting stressed out by the little things and valuing the importance of relationships," Kramer says. "I was so impressed. It was inspiring."

Kramer has a name for people like this vigorous, dynamic octogenarian: "super-agers." In recent years, he's become increasingly fascinated by their qualities and has set out to solve the mystery of their success.

"There are some suggestions that people who are more optimistic age better than people who aren't," Kramer says, pointing to Peter Green as Exhibit A. "We're just starting to look at these personality traits and how

they influence aging." For decades, those studying the science of aging have devoted most of their time to trying to understand what goes wrong as we get older, what risk factors predispose us to disease, and how we might better diagnose and treat it. But in recent years, a growing number of researchers at UCSF and elsewhere have turned their attention to a separate but related series of questions: What is it that allows some older people to thrive? What is there to learn from the most resilient and functional senior citizens among us? And how might we apply that knowledge to everyone else to promote healthy aging?

Though the approaches UCSF researchers are taking to answer these questions vary—from studying large cohorts of elderly patients, to measuring telomeres, to analyzing components in the blood of variously aged mice—many of them have begun to converge on an optimistic conclusion.

"As we get older, when we see declines in memory and other skills, people tend to think that's part of normal aging," Kramer says. "It's not. It doesn't have to be that way."

Stress can make us older

Elissa Epel, Ph.D., a professor of psychology who co-directs the UCSF Aging, Metabolism, and Emotions Center, believes one's chronological age and biological age do not always align. She is trying to understand what makes some of us more resilient than others, and one of the answers seems to be stress.

"The biology of aging and the biology of stress are intimate friends, and they talk to each other and influence each other," she says. "The greater the feelings of chronic stress, the greater the signs of aging in cells."

Epel is studying participants under almost constant stress: family

members who are caring for a child with a chronic condition or a spouse with dementia. As one proxy for biological age, Epel monitors the length of individuals' telomeres, or caps on the ends of chromosomes, which shorten as we get older.

When our telomeres get too short, our cells are no longer able to divide. It becomes harder for our bodies to replenish tissues, and our chances of developing chronic diseases increase, Epel explains. Short telomeres in midlife predict an early onset of cardiovascular disease, diabetes, dementia, some cancers, and many other diseases often associated with aging.

Chronic stress, she and others have found, can lead to a buildup of proinflammatory factors called cytokines, which mobilize our immune system to release a series of chemicals that, though important in fighting infection, can over time harm the body's own cells. Chronic stress can impair mitochondria, the energy centers of our cells, accelerate the epigenetic clock (a measure of cellular age based on the methylation patterns of genes), and prematurely shorten our chromosomes' telomeres.

But Epel has found that there are things we can do to counteract the toxic effects of stress and slow down the aging process.

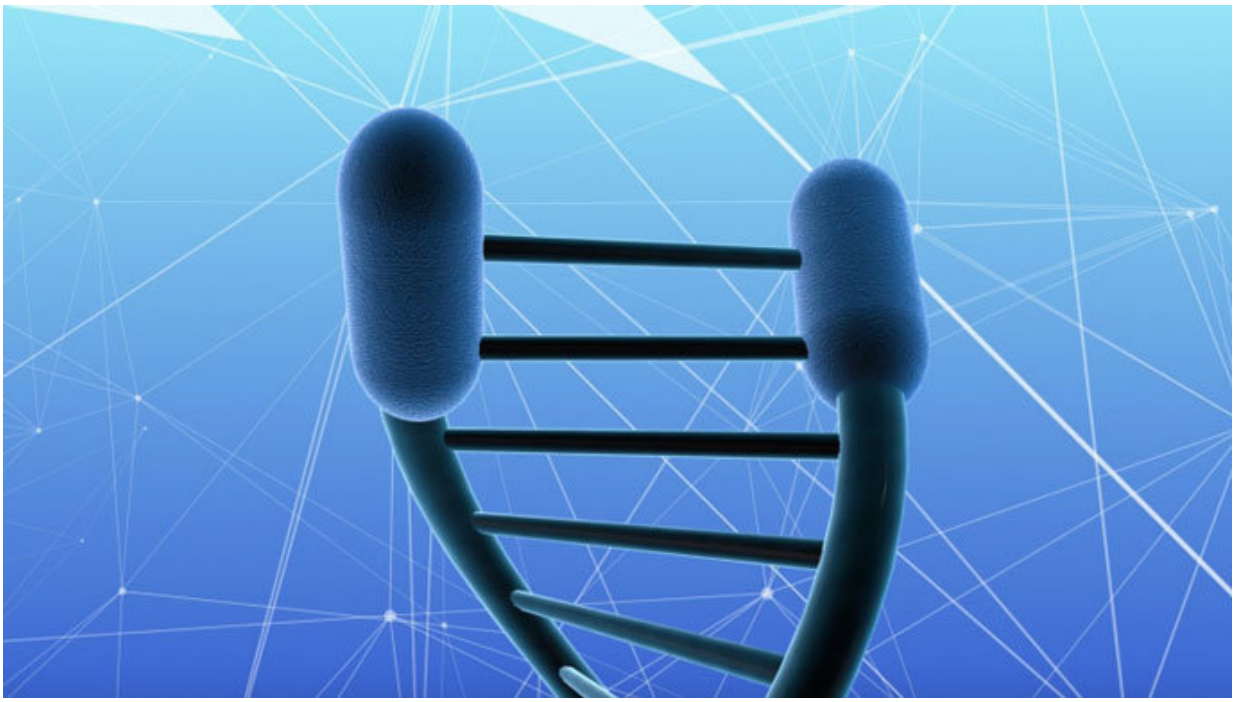
"The big story is that there are so many differences among caregivers in the way that they're responding to their life situation," Epel says. "What's emerged is how much our mental filter—how we see the world—determines our reality and how much we will suffer when we find ourselves in difficult situations in life."

It's possible to modify that filter through consciously cultivating gratitude and a mindful response to stress, Epel says. This sounds much like the mindset of the "super-ager" that Kramer has observed. Social

support is one of the largest factors protecting us from stress. Caregivers who have a greater number of positive emotional connections appear to be protected from much of the damage caused by stress. In addition, meditation, exercise, and an anti-inflammatory diet can reduce and possibly reverse some effects of aging.

"While extreme biohacks are super interesting, most of them are probably not feasible and not healthy in the long run," she says. "But lifestyle interventions are a form of biohacking that is feasible, safe, and reliable. Our biological aging is more under our control than we think. If we can make small changes and maintain them over years and years, our cells will be listening and maintaining their resiliency and health."

She adds that context also plays a role. Culture and environment—at home, work, and in neighborhoods—are important components in the ability of individuals to maintain lifestyle interventions over the long run. She notes that while extended health span is feasible and already unfolding for many of those with higher education, so far there are very slim gains in health span for minorities and those with strained socioeconomic resources.



UCSF researcher Elissa Epel, Ph.D., monitors the length of telomeres (illustrated) as one proxy for biological age. Credit: UCSF

Aging—and youth—are literally in our blood

While Epel is zooming out to explore how the mind-body connection might promote healthy aging, UC San Francisco's Saul Villeda, Ph.D., is zooming in, examining how microscopic, cellular messages that travel through our bloodstream might impact geriatric health.

Villeda, an assistant professor of anatomy, oversees a group of 12 researchers looking into mechanisms of brain aging and rejuvenation. His experiments sound a little like science fiction. In 2014, Villeda published a study in *Nature Medicine* showing that infusing the blood of young mice into older mice could significantly reverse signs of age-related cognitive decline—that is, geriatric mice infused with young

mouse plasma were better able to both recall the way through a maze and find a specific location. Conversely, younger mice injected with older blood experienced accelerated symptoms of aging.

What is it about young blood that can have such a profound effect? Using a method known as parabiosis, connecting the circulatory systems between older and young mice, Villeda found that the young blood caused the number of stem cells in the brains of older mice to increase and the number of neural connections to spike by 20 percent.

Earlier this year, he published a study demonstrating that infusing the young blood also caused a spike in an enzyme called TET2 in areas of the brain associated with learning and memory. The research team, led by one of Villeda's postdocs, Geraldine Gontier, Ph.D., demonstrated not only that TET2 levels decline with age but that restoring the enzyme to youthful levels improved memory in healthy adult mice.

The stimulatory effect of young blood, Villeda says, likely results from a handful of factors acting together. (He also points to another factor that seems to play a role in the magical properties of young blood—a protein called metalloproteinase that is involved in remodeling the structural components that hold our cells together and give them their shape.)

Meanwhile, Villeda has also isolated factors in old blood that accelerate aging. Blood from mice who are the equivalent of 65 human years contains cellular signaling agents that he says promote inflammation. These agents play what he calls a "huge role" not just in cognitive declines but also in muscle and immune-related deterioration—results that are consistent with those found by Epel.

By continuing to decode these cellular components, Villeda believes we may someday be able to harness what he and others are learning in order to create new medicines that rather than target single diseases, target

some of the underlying factors that cause diseases of aging in general.

This idea, of making therapies that treat aging in the same way we treat other diseases, says Villeda, is becoming "more mainstream."

"We don't think of aging as final anymore. We're basically maintaining a youthful state for longer." Even 15 years ago, Villeda continues, "if you told someone, 'I can keep you healthy until you're 85 and you won't get cardiovascular disease or Alzheimer's, and all you have to do is take this pill,' people would probably have been looking at you a little strange."

But attitudes have begun to change. "If you tell them, 'We understand the molecular mechanisms that are driving certain aspects of aging, and we can target them,'" he says, "it becomes much more understandable to people."

There is still more to learn

Joel Kramer has been following some of his "super-agers" for more than a decade. They now number in the dozens and are part of a far larger cohort of subjects ranging in age from 60 to 95.

At least every two years, each subject comes in to answer questions about their lifestyle and to undergo a battery of tests—of their cognitive function, blood composition, brain volume, and a wide array of other factors associated with aging and their ability to function in the world.

The study continues to produce reams of data, much of which Kramer and his colleagues have barely begun to analyze.

But a complicated picture has started to emerge, one highlighting multiple factors that interact to affect our ability to function. In March 2017, Kramer and his colleagues published the first of many planned

studies exploring some of the characteristics that seem to be associated with cognitive and functional performance. They compared 17 "resilient agers," who exhibited fast cognitive processing speeds, to 56 "average agers" and 47 "sub-agers," whose cognitive processing speeds appeared to be slowing down.

Just as Epel and Villeda predicted, the resilient agers had lower levels of proinflammatory cytokines than the sub-agers. Anatomical differences may have also played a role in the differences among the cohorts. For example, the starting size of the brain's corpus callosum, a thick band of nerve fibers connecting the two sides of the brain, was larger in resilient agers than in sub-agers.

The lower levels of inflammation might be attributable in part to lifestyle choices—especially since this group self-reported higher levels of exercise.

In a study currently under review for publication, Kramer and his team found that the brains of those who ate a healthy Mediterranean-style diet were less likely to contain large amounts of a protein associated with Alzheimer's. One of his colleagues has found evidence that higher levels of mental activity are correlated with a growth in the connections between brain cells and with better cognitive processing speeds. Others suggest that sleep plays a crucial role in healthy aging.

"There's definitely a genetic component, which is very big," notes Kramer. "But these are all little hints that there are things we can do to improve our chances of better brain aging."

The paradigm shifts emerging from the new science are already beginning to have an impact in the clinic.

Credit: Miguel Porlan

Bruce Miller, M.D., the Clausen Distinguished Professor of Neurology and director of UCSF's Memory and Aging Center, is collaborating with Kramer on the healthy aging study. Miller, Kramer, Epel, and Villeda are all members of the UCSF Weill Institute for Neurosciences as well. Miller notes that when he first arrived at UCSF in 1998, the field in general was "very nihilistic." Age-associated decline was seen as inevitable. Since then, however, that assumption has changed.

"I think imaging in particular has advanced in a way to allow us to do these sorts of studies that we never could have done before—and say, 'Wow, we now have these really clear biological markers in elderly populations, so we can now think about whether they're changing when we intervene.'"

The evidence is convincing that cardiovascular health, exercise, and low-fat diets can all make a positive difference, he says.

Kramer notes there's still more work to be done, however. "We clearly just started doing this," he says—but then adds that the study is already having an impact on at least one person: himself. "Having contact with so many of our older subjects who have maintained good brain health has really inspired me," Kramer says. "Even just the simple fact that they exist is inspiring. It's an exciting time."

Four strategies for aging well

1. Embrace aging

Many of us experience a better balance between positive and negative emotions as we age, notes Elissa Epel, Ph.D., co-director of the UCSF Aging, Metabolism, and Emotions Center.

"When we're older, we seek positive situations in our life much more and cut out things we don't like. We take more control of our environment," she says.

What's more, the wisdom that often comes with age may be related to structural changes in older brains. Bruce Miller, M.D., director of UCSF's Memory and Aging Center, points to recent work showing that brain circuits involved in altruism, wisdom, and thinking about other people are shaped based on the cumulative experiences of our lives. One's ability to consciously control emotions improves as this circuitry increases. This is why so many people can think of an older person who has had a profound influence on them, says Miller. "It's because of the brains of elders. We are more pro-social. We are more likely to give to people in need than younger people. This is not a huge surprise ... but we're now able to think of the biology of this. We really need our

elders."

2. Quit the negativity

Negativity and fear associated with aging often overshadow the positive aspects of growing older. Ironically, this fact can have its own damaging consequences.

"We hold these tremendously negative stereotypes about aging, and these start from when we're really young," Epel explains. "By the time we're older, these are actually having a negative effect on our health."

When we believe that aging means we're "going to be suffering and frail and dependent," Epel says, "we don't heal as quickly when we break a hip. We're more likely to get dementia, regardless of whether we have the gene associated with Alzheimer's. And we don't live as long."

The most obvious explanation is that it's a self-fulfilling prophecy: When we harbor the belief that we can't control our rate of aging, we develop a fatalistic attitude and engage in fewer healthy behaviors. But there may be something even more insidious at work. Studies show that negative attitudes about aging can actually cause us to become more stress reactive and less stress resilient—triggering biochemical cascades that may actually accelerate aging.

3. Move more

The positive effects of physical activity on cognitive functioning in older adults are well documented. Exercise leads to the production of more brain cells, increases cardiovascular health, and promotes a sense of well-being. It also appears to be highly correlated with cognitive processing speed, says Joel Kramer, Psy.D., a professor of neuropsychology who

has spent more than a decade studying the super-agers among us. In a 2017 study, Kramer and his team showed that exercise may even exert a protective effect against cognitive decline in those carrying genes that place them at a greater risk for Alzheimer's.

Meanwhile, in a 2018 study, a team led by Eli Puterman, Ph.D., examined a cohort of 68 elderly individuals who were caring for family members with dementia. These caregivers were under high stress, had high levels of depressive symptoms, and had sedentary lifestyles. The study encouraged participants to exercise for 40 minutes, three to five times per week, for six months. At the end of that period, participants had lengthened their telomeres, a biomarker associated with longevity.

4. Meditate

Epel and several collaborators recruited 28 participants enrolled in a California meditation retreat to undergo extensive testing. The researchers monitored markers associated with biological age (including telomere length, gene expression, and more) and also tracked participants' anxiety, depression, and personality traits over the course of the intensive, one-month meditation retreat.

The participants meditated for extended periods under the guidance of experienced practitioners, refrained from speaking, and were encouraged to treat all daily activities as "opportunities to attend to their ongoing mental experience with open and reflexive awareness."

At the end of the retreat, the participants' telomere length had increased significantly, and participants with the highest initial levels of anxiety and depression showed the most dramatic changes over the course of the study.

What's next? Epel's team, with a $1.2 million gift from the John W.

Brick Foundation for Mental Health, will study how natural treatments—including mindfulness meditation, high-intensity interval training exercise, and different breathing techniques—impact mood, health, and biological aging. At the time of publication, they are seeking women participants who could benefit from these interventions. More information and enrollment requirements are at stressresilience.net.

More information: Saul A Villeda et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice, *Nature Medicine* (2014). DOI: 10.1038/nm.3569

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