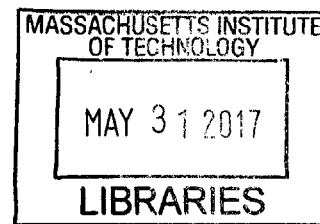


SuperAgers:  
Do Octogenarians with Exceptional Memory Hold the Key to Healthy Aging?

by

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## ABSTRACT

That older relative who stays preternaturally sharp long into their 80's or 90's may hold within their skull the secret to understanding how we lose, and keep, our memories. There are many different ways of aging successfully, but a growing group of scientists at Northwestern university and elsewhere are zeroing in on why some people keep the recall you'd expect of a middle-ager well into their 9<sup>th</sup> and 10<sup>th</sup> decades. The scientists do everything they can to get to know these the owners of these brains – their abilities, their genes, and the stories of their lives – then, when they die, dissect the brains themselves. Will the craniums of these successful "SuperAgers" give science some leverage in the battle against dementia, or even against aging itself?

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## A Crossword Without the Clues

Barb Shaeffer begins every morning with two cups of coffee and the *Chicago Tribune* crossword. To keep it interesting, the self-described “crossword freak” gives herself an extra challenge: she completes as many of the “across” answers as possible before even deigning to look at the “down” clues.

This ritual has remained nearly unchanged for the 90-year-old Shaeffer since her retirement 14 years ago. She even brings along books of *Tribune* and *New York Times* puzzles with her on her frequent travels, which range from weekend trips around the country to boating with friends around the canals of Europe. After finishing her coffee-and-crossword routine, Shaeffer might go out to meet friends for lunch or a matinee, walking through the Chicago neighborhood where she moved after outliving two husbands. “I love living downtown. I love that you can walk anywhere,” she says. She also keeps busy both taking and leading classes in theater and literature at Northwestern University’s Osher Lifelong Learning Institute (OLLI), where, the Institute’s motto states, “curiosity never retires.”

Shaeffer’s active brain may hold the solutions to more puzzles than mere crosswords. Eight years ago, Shaeffer met Dr. Emily Rogalski, a recently hired Northwestern University neurology professor, when the latter gave a talk to Shaeffer and her peers at OLLI. At the time, Rogalski was trying to solve some puzzles of her own: Why do some people’s brains age so much better than others? And is there something they can teach us about staving off dementia, or even the seemingly inevitable decline of aging?

Scientific ingenuity has eliminated smallpox, driven polio to the brink of extinction, and pushed life expectancies forward by decades across the developed world. The world’s population now reflects these advances: in 2010, there were about 2 million Americans over 90; by 2050, that number is projected to be 9 million or more. In their old age, Shaeffer and her peers encounter a host of problems driven by long-running breakdowns in the body’s own systems.

Some, like cancer or dementia, are caused directly by these declines, while others are exacerbated by the breakdown of the body's natural structures and defenses, turning otherwise survivable injuries or diseases into mortal threats. Curing these problems will not be a matter of simply fighting a foreign invader, but of carefully tinkering with the way the body itself works.

By the time Rogalski met Shaeffer at OLLI, she had already seen the neurological side of these problems first hand, both as a Ph.D. student and then as a Professor at Northwestern's Cognitive Neurology and Alzheimer's Disease Center (CNADC). But to Shaeffer and her peers, Rogalski described a new approach she and her colleagues were taking to untangle this problem. Rather than study any particular disease, or even the "normal" course of aging, they were looking to study people whose memory had largely remained intact: to qualify, participants had to be older than 80, but have a memory that would be above average for someone aged 50-65.

With criteria that daunting, Shaeffer said, she figured she had "absolutely no" chance of qualifying. "I'm one of the ones who walks into a room and forgets why I'm here," she says. But with her family history – her mother died of Alzheimer's at age 95 – Shaeffer decided she could stand to learn more about the disease, so decided to give the study a shot.

To her surprise, Shaeffer passed the tests, gaining admission into a group for which the Northwestern scientists coined a special term: "SuperAgers." For the last eight years, Shaeffer and a growing cohort of SuperAgers have given the Northwestern scientists an unprecedented view of what Rogalski calls "the sunny side of aging"—a view of the aging brain that seeks to understand not how humans grow old, but how the lucky ones stay healthy nonetheless. Like everything else in our brains, SuperAging is an interconnected tangle of genes, nerves and their networks, and more intangible ideas like wisdom and willpower. Every discovery brings more questions than answers as scientists search for clues to fill in a small part of the puzzle of aging memory.

## The Waiting Room

The Cognitive Neurology and Alzheimer's Disease Center fills the 11<sup>th</sup> floor of a tower on Northwestern's medical campus, halfway between Lake Michigan and Chicago's "Magnificent Mile" shopping district four blocks inland. The elevator opens into a lobby that could pass as an academic lounge or a medical waiting room. On the table, *People* and *Time* share space with scientific magazines like *Nature*, *Cell*, and *Neurology Now*. The requisite medical office ferns frame posters describing new brain imaging techniques.

Though most medical care takes place down the street in the clinical center, patients in varying states of cognitive decline are a regular sight in the lobby here, filling out questionnaires at the circular table in the corner or walking – sometimes unassisted but often with walkers, canes, or partners – for cognitive testing in the study rooms beyond. Some are taking experimental treatments for Alzheimer's disease. Others are suffering from primary progressive aphasia, another dementia, which affects the brain's capacity for language and was first described by the Center's director, M.-Marsel Mesulam, in 1982.

Another sort of experimental subject passing through the lobby doesn't walk at all. Post-mortem brains, donated by the participants of several different studies, pass through the lobby about twice a week. These are carried to a lab just behind the offices, where they are sectioned off and then frozen, sliced for microscopic examination, or preserved in a yellow fixative solution whose floating, pale brain slices give it the appearance of egg drop soup. There, technicians analyze the brains' cell structures and chemical composition, looking for signs of disease or degradation. The parts of the brains not analyzed immediately go in the "brain bank," to be sent out to researchers around the country interested in any of the diseases these donated brains may have. Even the brains of people who have shown no sign of disease in life can exhibit the seemingly universal hallmarks of aging such as dead cells or the molecular signature of Alzheimer's.

We tend to think of aging as a steady, scripted decline, with wrinkles, weakness, and greying hair serving as outward signs of the approaching twilight, while, within, our thoughts slow and our memories fade. Except, said Rogalski “while that’s true on average, everybody has an aunt or an uncle who really doesn’t fit that stereotype.” Just as some suffer from severe decline, others seem particularly successful in evading the ravages of time.

Defining success, though, is a problem in itself—Rogalski often mentions a literature review that found 29 different definitions of “successful aging” in only 28 research papers.

Rogalski and the other principle investigators for what would become the SuperAging project wanted to be able to identify more precisely about what caused success in their specific area of expertise—memory. Specific criteria meant a specific wording, said Rogalski. “We came up with this quirky term” – SuperAging – “because we have a very distinct definition,” she said.

To make sure they were getting only the subjects whose memory was truly superlative, the scientists set a high standard for inclusion in the study. Prospective participants got a list of 15 words, and were then distracted with other tasks until, 20 minutes later, they had to recall as many of the 15 as possible. With the words entirely unrelated to each other, even the average middle-aged participant can remember only nine. To be a SuperAger, you had to beat that average, with a brain aged decades further.

“We weren’t sure whether *anyone* would be able to meet this challenge,” said Rogalski. And indeed, of the hundreds of octogenarians and nonagenarians who were tested because they thought they had exceptional memory, only about 5% qualified. Still, that was enough participants for Rogalski to start asking what about their brains were different—or, first, *where* their brains are different.

## The Blue Dot

Place your clenched fists together, with thumbs side-by-side and knuckles aligned, and you have a rough approximation of your cerebrum, the wrinkled grey mass that makes up the

majority of your brain. Other, more evolutionarily ancient parts hang from the middle – things like the thalamus, hypothalamus, and brain stem. But most of your sensing and thinking takes place on the wrinkled surface of these two halves, or hemispheres, of your cerebrum.

Of course, your hands are relatively smooth and solid, while your cerebrum is made of folds, wrinkles, ridges, and fissures burrowing deep into the brain. These folds increase the surface area of your cerebrum to about 2.5 square feet – and the entire surface is covered by a millimeters-thick layer of grey matter, called the cortex. The cortex is where your thinking takes place, where your brain cells live; the rest of the cerebrum, underneath that grey cortex, houses the trillions of connections between the neurons on the surface. One way to estimate brain health in living patients is to look at the thickness of their grey matter, which can be measured with an MRI scanner.

On a blustery January day, the amorphous clouds outside the window of the Center’s conference room seem to mimic the grey shape of a brain on Emily Rogalski’s laptop screen. She’s showing me what she discovered when she and her team compared the thickness of SuperAgers’ grey matter to that of elderly patients without exceptional memory and of middle-aged people between the ages of 50-65.

On her laptop screen, Rogalski pulls up a rotating model of a brain’s left hemisphere. Splotches of yellow and red cover most of the grey surface—each representing an area where the normal elderly brains had thinner grey matter than the middle-aged brains. “This is nothing new,” she says: As we age and cells in our grey matter die, it grows slightly thinner. Over time, the result is a slight reduction in our cognitive function.

The next image Rogalski shows me is a comparison of the middle-aged brains with the SuperAgers. The smears of red and yellow have vanished. “We thought this was a mistake the first time we saw it,” she says. To their surprise, Rogalski and her team found no measurable difference between the middle-aged brains and those of the SuperAgers—except one, which was even more unexpected.

As Rogalski rotated the image on the screen, a small spot of blue appeared on the inside of the left hemisphere. It was a small region known to be involved in decision-making and impulse control, called the left anterior cingulate, where the SuperAgers' grey matter was significantly *thicker* than the middle-aged subjects who were decades younger. Was there a part of SuperAgers' brains that was even healthier than the average middle-ager?

The thickness of the grey matter is only one way of measuring health, and doesn't give much information about why the brains are healthier. One part of the puzzle may be that they're less susceptible to dementias like Alzheimer's. But an official diagnosis of Alzheimer's disease can only come after the patient dies, when pathologists can search the brain for the tangles of proteins within brain cells, and the plaques just outside the cells, that characterize the disease. To help unlock these and other secrets unavailable from a living brain, SuperAgers are encouraged to donate their brains to the study after dying—and 90% have agreed to do so. But, said Rogalski, "One thing that has limited our pathology studies is that our SuperAgers aren't dying!"

In the meantime, evidence taken from still-living SuperAgers did show that Alzheimer's disease, which affects 10 percent of the population over the age of 65, might be part of the puzzle. Though your brain can't be examined under the microscope until you die, it only takes a blood sample to check for one of the largest genetic risk factors for Alzheimer's, the gene *APOE*. Everyone has two copies of the *APOE* gene, one from each parent. If one copy is a variant form known as *ApoE4*, then your odds of developing Alzheimer's are approximately tripled; if both copies are *ApoE4*, then those odds are increased 15-fold.

So if avoiding Alzheimer's was part of the SuperAging puzzle, that variant form ought to be less common among SuperAgers – and sure enough, when the Center's scientists sequenced the SuperAgers' DNA, only 8% of them had a copy of *ApoE4*, compared to 27% of the general population.



That fact provides two potential clues about SuperAgers. First, not surprisingly, to be a SuperAger, it helps not to be at risk for Alzheimer's. But the second is more profound: since some SuperAgers achieved their status *despite* being at increased risk for Alzheimer's, was it possible there was something about these SuperAgers was staving off the disease?

Your genes are not your fate: even a high genetic risk of Alzheimer's doesn't make it inevitable. And remember, the only foolproof way to diagnose Alzheimer's is post-mortem, by looking for plaques and tangles within the brain. So to find the whole story, the Center's scientists needed to open up their participants' brains and look inside.

## The Quick and the Dead

The microscope room at Northwestern's Cognitive Neurology and Alzheimer's Disease Center is a dim, cramped space, with trays full of glass slides stacked high on every surface. The room seems far too small for the enormity of what it contains – thousands of brain slices mounted carefully on the slides over the years, each dyed with some combination of stains to illustrate some aspect of how its owner's mind worked.

But for neurologist Tamar Gefen, sitting in the claustrophobic dark space is calming. Gefen spends part of her time studying the dissected brains and the rest meeting with patients at another Northwestern clinic down the road. It is a hectic schedule and, with many of the patients she meets with suffering from some form of dementia, an emotionally taxing one as well. "The clinic," she says, "can depress me." Staring through a microscope to count the number of Alzheimer's tangles in a slice of human brain isn't just an escape from the clinic – it's real work towards a hopeful future.

For her PhD, which she completed in 2015, Gefen studied both living and dead SuperAgers, hoping to draw connections between what she saw meeting with the participants and what she saw in their brains after they died. "We formed some pretty tight relationships," she says. "You end up knowing them; you follow them every 18 months. Then I would go in the

wet lab and open up the brains and sit with the microscope trying to figure out what makes them so special.”

Even with the small sample of dead SuperAgers available, Gefen was able to corroborate what the genetic testing said about SuperAging and Alzheimer’s. In 2015, she published a paper reporting that, after looking at the brains of five SuperAgers, five normal elderly, and five middle-aged, the SuperAgers had far less of the Alzheimer’s plaques than did the normal elderly.

That doesn’t mean that SuperAgers are immune to plaques and tangles, nor that these symptoms prevent SuperAging. In fact, these symptoms show up in brains of all ages – even in people who seem healthy. “One thing that working here has taught me is that everybody gets Alzheimer’s,” says Zach Parton, a lab technician in the center, referring to plaques he’s seen in seemingly healthy brains, and in brains of those as young as 25.

To supplement the few brains of dead SuperAgers, Gefen worked with pathologist Changiz Geula, another of the professors leading the study, to examine brain tissue donated by participants in another study, at the University of California-Irvine. They looked at eight brains that had passed similar qualifications to the SuperAgers in life; of those, two had a severe build-up of plaques and tangles. “If a pathologist looked at these brains they would classify them as having Alzheimer’s disease,” said Geula.

Because the brains only came to Northwestern after death, Geula has no way of knowing for sure if they would have exactly met the qualifications of SuperAgers. And because it was only two brains, of a sample size of only eight, the experiment is far too small to reach any broad conclusions. Still, combined with the results from the genes and the brains of SuperAgers, these exceptions were enough to show that the story about memory loss here wasn’t just about Alzheimer’s disease. So the SuperAging project found itself facing the same obstacles of any study of aging – the sheer complicated multitude of ways the aging body falls apart.

## Running Out of Time

The aging of your brain is a natural process, which means that even if it seems to follow a script, there isn't an intentional purpose behind the story that evolution and genetics have written. The mere existence of SuperAgers shows us that that script runs slower for some people, but it's also important to understand that the story is a sprawling one, with a cast of millions of cells, each dying for its own reason. One cell detects a potentially cancerous mutation in its DNA and initiates the molecular cascade that leads to its shutting down. Another finds itself unable to maintain its structure in the face of a tangle of proteins and does the same. Others may shut down after physical damage, or loss of oxygen.

Each of these tiny dramas occurs at a different time, triggered by different combinations of blood and the environment. So even as the cell deaths continue, their causes change as we continue to age. "What applies to younger elderly doesn't apply to the oldest old," said Maria Corrada, a professor of Neurology at the University of California-Irvine. Corrada cited an example from one of her own studies, of people 90 years old and older: while high blood pressure seems to increase the risk of dementia in general, it actually decreases for those over 90. The effects of high blood pressure, and the causes of dementia, change from year to year and person-to-person – underscoring that aging isn't a single, inexorable decline.

But even with no script, this process does follow certain rules, formalized in a 1966 paper by English biologist W. D. Hamilton. Hamilton's model is based on the idea that evolution is a series of trade-offs: if natural selection is weighing two versions of a gene against each other, it will favor the version that benefits young, reproducing members of the species against one which benefits older members who may well die before it matters. Only, now that we've extended our life expectancies well beyond the few decades evolution had to work with for eons beforehand, the tradeoffs are catching up with us; our DNA has become a minefield of small

problems that crop up late in life, and which, combined, age us. This decline is especially severe in our brain where, outside a few specific regions, we stop creating new cells in adulthood.

These tradeoffs include genes like the *APOE* variant that confers a significantly higher risk of Alzheimer's: One reason this variant is so common could be that it helps produce the essential compound Vitamin D. Looking for other places those where evolution might have made such trade-offs is the goal of the genetic sequencing, said Geula. Though the *APOE* results are intriguing, "we are actually more interested in genes that nobody knows about."

This is the promise and the pain of the project, and aging research in general. So many factors play into aging and cellular breakdown that any single study can't help but find new factors – but they also can't hope to find a panacea, says Rogalski.

"People always want to know 'what if I take this one pill that I saw online?' or 'what if I eat this one food?' or 'I ate a lot of blueberries, why did I get Alzheimer's?,'" says Rogalski. "But there's no magic blueberry."

So rather than searching for one answer, aging studies often find themselves searching for the right questions – the clues to the crossword puzzle. For Corrada and her 90+ study, one of those questions is why the risk factors for dementia change so dramatically over time. For Rogalski and the SuperAging study, the most intriguing questions have to do with the anterior cingulate, that small blue area of surprisingly healthy cortex that Rogalski found on the brains of SuperAgers. Perhaps the biggest mystery of all was this: why did a part of the brain that was supposed to be involved in decision-making and impulse control seem to be the key to the SuperAgers' memories?

## A Cellular Difference

In the early 2000's, neuroscientists led by Caltech professor John Altman were studying a special kind of nerve cells called von Economo neurons: long, skinny neurons named after the Austrian psychiatrist who discovered them in 1929. Altman found that the von Economo

neurons were found in the brains of humans and our great ape relatives, but not in other primates. Because of this, and because damaging them seemed to damage our social aptitude, *New Scientist* billed the von Economo neuron as “the cell that makes us human.” Later, however, they were found sprinkled throughout the brains of many other mammals, from wales and dolphins to giraffes and hippos.

But there’s still something unique about the von Economo neurons in the brains of great apes like us: they’re clustered in just a few areas: our old friend the anterior cingulate and a nearby section called the anterior insula. The two regions work together to motivate us, said Bill Seeley, a neurologist at the University of California-San Francisco who studies von Economo neurons. “If I’m thirsty, I feel the thirst in my anterior insula,” he said, while the motivation to get a drink comes from the anterior cingulate.

Scientists don’t traditionally think of memory as among the anterior cingulate’s roles, but when it showed up as that blue spot of healthier grey matter in Rogalski’s MRI’s, the Northwestern team knew they needed a closer look.

Tamar Gefen is fascinated by the microscopic structure of that impossibly thin coating of grey matter on the surface of our brains. Stacked in six layers, each with its own purpose, the cortex carries out a fantastic number of calculations every second, just to keep us thinking. “That six-layer cake is our everything,” said Gefen. So when Gefen examined the SuperAgers brains for disease, she was also looking at how the neurons were arranged, whether they were larger or more dense, and whether there was any connection between the rare von Economo neurons and the mystery of the healthier grey matter.

The neurons in SuperAgers’ anterior cingulate cortex didn’t seem to be any bigger, or any closer-packed. But when it came to von Economo neurons, there was a striking difference – Gefen counted four times as many von Economo neurons in the SuperAgers brains than in either group of normal brains.

Because von Economo neurons and the regions of the brain where they are found hadn't previously been linked to memory, Seeley wonders if there is some underlying cause of SuperAging that isn't directly linked to memory. If so, it could be helping SuperAgers in other ways.

"What else are they good at?" he says. "It could certainly be that people who are identified as SuperAgers because of their memory are also superior on other functions."

One way these brains stay healthy could be related to a well-known advantage of age: experience. Our brains can make up for some cognitive decline, says Seeley, by using continued life experience to re-wire themselves. This can be especially true for some of the abilities related to the anterior cingulate, like impulse control or decision-making. "Those functions tend to hang around, and in some ways, they improve," says Seeley. "And that is what we call wisdom." Measuring something like wisdom, then, might better explain SuperAgers' superior memories and thicker grey matter.

There are any number of ways that a more nebulous trait, like motivation or wisdom, might help SuperAgers qualify for the study. Gefen thinks an ability to set and complete goals could keep people more engaged with the world around them, keeping their memory and other functions active and strong. Or perhaps this focus and will to overcome difficulty, what Rogalski calls "resilience," could help the SuperAgers complete the difficult laboratory tests in a stressful environment, scoring higher on any number of tests, including the memory tests.

Rogalski has more reason than just the brain scans to wonder whether resilience or a more memory-specific effect, is what helps SuperAgers. "One thing you assume is that many of these SuperAgers must be really well educated, be very wealthy, have amazing lives, but the first couple that I met really had awful lives. We had someone who was in the holocaust and lost her whole family except for her sister." Others had lost children, or grown up poor. "It seemed in a

qualitative, anecdotal way that the people we were finding did not have life handed to them on a silver platter.”

Was there a connection, Rogalski wondered, between how SuperAgers navigated life crises and how well they pushed through the memory tests? Rogalski, with her specialties in mapping brains and testing mental function, was hardly in a position to start measuring people’s pasts. Fortunately, she knew another professor who’d devoted her life to doing just that.

## The Study of Lives

Laughter escapes the conference room as Rogalski finishes telling some droll tale to her friend Gina Logan. The two women have an easy back-and-forth, each occasionally stopping mid-sentence and gesturing for the other to continue. Logan introduces herself as a developmental psychologist, but she is quick to say that she doesn’t study childhood development. Instead, she and her colleagues at Northwestern’s Foley Center for the Study of Lives study how psychological development continues into adulthood.

To tackle the “Study of Lives,” Logan uses something called narrative psychology. Rather than rigid questionnaires, she sits down with her study subjects for hours-long interviews about the full course of their life. Only the general outlines of the interview are pre-set – the interviewer will ask a question about a time the subject thought they showed wisdom, or overcame adversity, and will record the resulting story or discussion for ten or even twenty minutes.

From these long-form responses, Logan and her colleagues try to answer some profound questions, from what sorts of internal conflicts the subjects are undergoing at a given point in their life to how they find a sense of meaning and purpose.

It is not, as you might gather, an exact science, but the analysis of the interviews is intended to be as redundant as possible, with two different students comparing the answers with

rules in a manual often dozens of pages long, and rating at each point to what extent the subject showed wisdom, or maturity, or any number of other traits, each with its own manual.

“It’s very akin to literary analysis,” she said.

When Rogalski heard about Logan’s way of quantifying people’s life stories, she was intrigued. Could Logan’s narrative analysis turn anecdotes of SuperAgers’ resilience into hard data about their lives? Thirty-one SuperAgers agreed to be interviewed, spinning the stories of their lives into data for Logan and Rogalski’s students to quantify and measure.

Rogalski and Logan have yet to run the numbers from the life story interviews, comparing the ratings of resilience and other traits with data like the brain scans. Since this portion of the project isn’t funded by the grants that pay for students’ time, it hasn’t been a priority. But they expect a treasure trove that will keep yielding new insights – and new questions – even after SuperAgers die. “Eventually when we have these individuals brains we have those narratives along with it,” says Rogalski. Will higher wisdom or resilience correlate with higher numbers of von Economo neurons? Only time – and death – will tell.

## Emotional networks

Dr. Alexandra Touroutoglou was born and raised in Greece. She started her career studying behavioral psychology but soon became frustrated by how the electrical signals behind the behaviors she studied were a mystery. So she leaped at the chance to work at Massachusetts General Hospital, where she shifted her focus to neurology and used functional MRI machines to watch the wiring of people’s brains in real time. The building that houses Touroutoglou’s lab, a stone’s throw from Bunker Hill, has more fMRI machines than the entire country of Greece.

Functional MRIs, or fMRIs, differs from regular MRIs in that they track the movement of oxygen-rich blood in the brain, showing which regions are full of active neurons at a particular period in time. This is the technology used to show which regions of the brain ‘light



up' when we're doing or thinking various things – but the information from the images is much richer than simply labeling the static function of one region of the brain or another.

Rather than studying the brain as a collection of isolated regions with separate purposes, Touroutoglou studies “connectivity,” trying to determine which distant regions of grey matter are wired together by connections stretching across the white matter in between. These connections are another part of the brain's structure that are impossible to track accurately in living brains, but if patches of grey matter light up together, chances are they have a fairly strong neural connection.

By watching how different brain areas lit up together in the brains of people were at rest – or as “at rest” as one can be in a noisy, cramped fMRI machine – Touroutoglou and other practitioners of fMRI have found that there are six “intrinsic” networks in the brain – clusters of dispersed patches of grey matter which tend to fire together at rest, so probably have many nerve fibers stretching through the white matter between them, and which also probably work together to perform various functions.

Armed with the knowledge of these networks, Touroutoglou and her Boston-area colleagues, including Lisa Barrett of Northeastern University and Brad Dickerson of Harvard and MGH, decided to scan the brains of elderly with exceptional memory to see if the protected parts of their grey matter clustered within any of these networks.

What Touroutoglou found was a scattered set of points where grey matter was thicker in her SuperAgers than in the general population at their age; many of these were within just one of six networks. Called the salience network, it includes parts of the anterior cingulate, which indicates to Touroutoglou that “resilience and the will to persevere” may play as much a role in SuperAging.

This speaks to the role of emotions and outlook in SuperAging, says Jiahe Zhang, a PhD student in Touroutoglou's lab. “No memory task can be devoid of an emotional component, especially if it's difficult, especially if you're in a lab environment that you're not familiar with,”

said Zhang. While the complexity of these networks, and of aging in general, is daunting, Zhang is excited by the role played by what she calls “grit,” and thinks it might be an early indication of a way to help others age well. “The most exciting thing would be to actually do some sort of manipulation,” she said. “If we can tell some participants to persevere more, or to exercise grit more,” it might keep their grey matter healthy.

The Boston SuperAgers are different from the Chicago ones in a number of ways. Subjects in the Boston study are between 65 and 80, which means the oldest members of that cohort wouldn’t even qualify for the Chicago study, which only includes people over 80. The Boston subjects also had to meet more stringent memory requirements: to enter the study, their memories had to be better than the average 18–32-year-old.

This might be an explanation for another difference; while Rogalski and her colleagues were happy to see even 5% of the hundreds of volunteers they tested meet the SuperAging criteria, in Boston, 17 of the 41 volunteers met the criteria, a success rate of more than 40%. But so many other factors could explain even a difference this large – the studies used different recruitment strategies, targeted at different age groups, in different cities – that it won’t be possible to know whether the Boston SuperAgers are aging as well as the Chicago group until they actually turn 80. “Our criteria were more stringent, because we compared them to young adults,” maintains Touroutoglou.

Neither the Boston nor the Chicago sample will give any firm answers on the role basic factors like sex and education play in SuperAging; they simply weren’t designed to recruit as widely and randomly as would be required. Studies that do control for this are almost prohibitively expensive, so won’t happen for years, if ever. In the meantime, scientists like Rogalski and Touroutoglou look for new questions from the data they can get. And the new questions they’ve come up with – like the role of emotion, and Von Economo Neurons – will keep them busy for years to come.

## Learning for Life

Last year, after getting several requests from different SuperAgers, Rogalski threw a party for the cohort at Northwestern. While a combo band played, SuperAgers mingled, eager to meet others with their age and experience.

By most accounts the party was a rousing success, though at least one of the subjects was disappointed by the men in the majority-female cohort. “One woman came up to me and said all the men here are boring, but is Dr. Geula single?” Gefen says.

Whether their active brains are the cause or not, it’s clear the SuperAgers are still seeking new experiences, keen to enjoy their continued vivacity. Beyond her crosswords, Barb Shaeffer has her classes, and her trips – including one to Ireland this summer. Wally Jonas, another SuperAger who also takes classes through OLLI, picked up an entirely new hobby in his retirement. After seven decades with no musical experience (besides a preternatural talent for memorizing the lyrics to songs), Jonas picked up the banjo. “I’ve probably been playing too long to be as bad as I am,” he says.

Others involved in the study are learning from the SuperAgers’ example. For Kevin Connolly, the Center’s administrator, what strikes him is the SuperAgers’ emphasis on face-to-face social engagement. “I’m eliminating technology as much as I can, focusing on being present, picking up new skills,” like playing the piano, he said.

There may be no magic blueberry that the SuperAgers have in common, but each has – though genes, lifestyle, personality, and blind luck – stumbled on a path that keeps them aging well. It’s comforting to think that our outlook on life may play a role in aging well: keep engaged, the sense is, and you’ll be able to keep doing so.

More specific treatments are a while off. If the size of the anterior cingulate cortex, or the presence of von Economo neurons is predictive, then that may provide a useful diagnostic tool

in the near future. The fact remains that locked somewhere within SuperAgers' brains is the ability to resist aging, and, in at least some, to withstand the onset of Alzheimer's.

In the meantime, though, they keep on living, keep on staying engaged. Just before her 90<sup>th</sup> birthday in March, in the midst of planning her trip to Ireland, Shaeffer went in for another round of tests, so the Center's scientists could watch how her brain continued to age. Like many of the other SuperAgers, she's concerned she didn't perform as well as she should have. "I don't think I remembered all the stuff I'm supposed to remember." For now, though, she remembers enough.