

66| SuperAging – With Dr. Emily Rogalski

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Speakers: Emily Rogalski, Ryan Van Patten, John Bellone



Intro Music 00:00



Ryan Van Patten 00:17

Welcome, everyone, to Navigating Neuropsychology: A voyage into the depths of the brain and behavior, brought to you by INS. I'm Ryan Van Patten...



John Bellone 00:25

...and I'm John Bellone. Today we have an episode on SuperAging with Dr. Emily Rogalski. Dr. Rogalski is a clinical and cognitive neuroscientist and professor at Northwestern University's Feinberg School of Medicine. She has been central to the

creation and development of this concept of SuperAging, which we're going to describe in our conversation. Standard research practice has been to study pathological aging - to figure out why a person with dementia has dementia, what might make people more likely to develop dementia, which is obviously very important work. But I really like how Dr. Rogalski and her team kind of flips that paradigm around. First, she shows that there are people who do not show normal age-related decline. And now more and more, she's trying to figure out why that might be the case. Why those individuals might not show typical age related decline. So, without further ado, we give you our conversation with Emily.



Transition Music 01:29



John Bellone 01:38

Emily, welcome to NavNeuro. We are so excited to have you.



Emily Rogalski 01:41

Thanks for having me. I'm glad to be here.

John Bellone 01:43

So, I often lecture on how lifestyle changes can reduce our risk of cognitive decline. Both of my grandfathers actually lived past age 90. They were in very good health physically and cognitively up until just a couple months before their death. So this is a topic that's pretty close to my heart. It's kind of selfish of me because I want to know how to be like that, how to age like that.



Before we get to the meat of the conversation, I wanted to ask you, kind of tee this up for you, is cognitive decline a normal and completely unavoidable aspect of getting older? Or might there be some alternative trajectory to aging that could potentially bypass the typical aging profile?

Emily Rogalski 02:31

Sure. So those words get really loaded, right? When you think about the word "normal" - so what is normal? What is abnormal? If you think of normal as what happens on average, then I would say that, on average, some cognitive decline tends to happen. If we looked at the data and looked at the averages across the lifespan, we'd see that, unfortunately, our memory and some of our cognitive abilities peak in our 20s and 30s, maybe 40s if we stretch it, and then you get some



decline that happens on average from there. But I think, to me, the exciting part of the SuperAging story, and the exciting part as a scientist, is to remember that averages don't always tell the whole story. We spend a lot of time thinking about data in our lab and understanding it in the nitty gritty. That also teaches you to look beyond the averages and say, "Well, what's happening at the individual level?" I think this has been - it's not that our group is the first to think about this, this has been taught time and time again. When we think about understanding variability, where it occurs and where it doesn't occur can be just as instructive as understanding the averages. What we see that happens over the lifespan is that there tends to be a smaller band of what is average when we're younger. So there's more similarities among our cognitive performance than differences. We see that variability increases as we age. And, excitingly, there are people who fall out of that variability range - that are on the high end. So that's what we think of as SuperAgers. People who look as if they're performing just as good, if not better, than the 50 to 60 year olds. The words "intact", "normal," and "average" sometimes get conflated all into one term. But you really have to separate out this idea that we give a pass or - you know, I'm not a golfer but to use a golfing term, we give a handicap as we age. To say, "Oh, suddenly, this is what is normal." But that doesn't necessarily mean that memory is intact or it hasn't changed.

Ryan Van Patten 04:50



Yeah. Can you follow up on what you just said - the difference between average and intact? That's something that you've written about. And I agree with you, a lot of people may not differentiate those two terms. But how do you do so?

Emily Rogalski 05:02



Sure. So when we think about the average scores across the lifespan, the average score for a 50 year old, for example, on the Rey Auditory Verbal Learning test, which is an episodic memory test that we use of retentive memory, to think about SuperAgers, the average score is a 9. And because it's average, that's also what is considered to be the normal - you're performing in the normal range if you remember 9 out of 15 words at the delay. But the average score or normal score for an 80+ year old is 5. So, somehow, just by being 30 years older now, you're allowed to have a score that is much lower and still considered normal. But, baked into that is that it's not intact in that there has been some change, presumed change, that has happened to those individuals. They were once in this range of 50 year olds, at a 9 or better, and then now it's a bit lower.



Ryan Van Patten 06:11

Right. So you mentioned that it is expected. Most people decline in terms of their cognition as they get older, but maybe not everyone. For those people that do decline, what are a few of the neurobiological mechanisms of the senescence that happens to them?

Emily Rogalski 06:30

Yeah, so [when] we think about changes associated with aging, things have gotten more complex rather than less complex, right? So you can look at it through many different lenses. When we think about the SuperAging program, our goal is to use multiple lenses. There may be this one common end goal to say, "What are the factors that contribute to outstanding memory performance and aging?" But understanding that some of those factors may be rooted in genetics, some of those factors may be rooted in other aspects of biology, some of them may be rooted in our lifestyle factors, things that are more modifiable. So we know from other research that there's this handful of modifiable factors that may stack up your protective column and decrease your factors that are associated with decline. So I think our goal here really is to think about that, right? Instead of focusing on "Gosh, here's all the things that can go wrong in aging, let's figure out how to fix those." Let's think about, "Here are people who are doing extraordinarily well. How did they get there? Did they avoid certain common things associated with aging? Or do they have really unique genetic profiles or other factors?" It's not going to be one magic bullet. There isn't going to be one recommendation of eating 12 blueberries, and, you know, exercising some perfect number of minutes per day. But I think it is going to be this amalgamation of different things because, after all, we are individuals, especially by the time we get to age 80. It's that accumulation of wear and tear and experience that makes us who we are. So the path for one person may be slightly different than another. However, if there are some common factors among the SuperAgers that might be instructive to lead to new hypotheses and paths to avoid cognitive decline and maintain functional ability as long as we can.



Ryan Van Patten 08:46

Right. Sometimes in neuropsychology I think we might hyperfocus on pathology of various kinds. It's refreshing that you take this approach. John and I are both excited to really get into it. So, you coined the term SuperAging, and you define it as people aged 80 or older with episodic memory performances that were as good or better than people 20 to 30 years younger than them and whose performances in other cognitive domains were average or better compared to their own age cohort.



I'm wondering why you selected this particular definition or way of operationalizing SuperAging? Walk us through your thought process.

Emily Rogalski 09:25

Sure. So it's probably important when we think about the definition of SuperAging, there's no one corrected definition. But I'll tell you why we use a special term, SuperAging and why we avoided using the term successful aging. Let me walk through a few of our thought processes. In part it has to do with the lens with which my expertise lies in our center. So maybe I'll start there. I'm a neuroscientist by training. But I'm situated in a center, the Mesulam Center for Cognitive Neurology and Alzheimer's disease, which is a mouthful, but it means we do aging and dementia research. But our focus is on the brain and our focus is on older adults and quality of life. We have a deep focus on Alzheimer's disease and related dementias. So through that lens, when we're thinking about brain health and cognition, that is why our focus is on the cognitive aspects and a greater focus on the neuroscience of it than the cardiac side or some other organ.



But then when we think about "Why age 80?" Okay. So what's the biggest complaint of older adults as they age? It's their memory. They don't complain about their language unless they have a language-based dementia. But they forget where they put their keys, they can't remember. They're not quite as sharp as they used to be. We also know that, in addition to being the biggest complaint as individuals age, we know that age alone is the biggest risk factor for Alzheimer's dementia and Alzheimer's disease. So if we take individuals at age 80, they represent individuals who are at the greatest risk for memory loss, just by being older, and the greatest risk for Alzheimer's dementia caused by Alzheimer's disease. So those two factors together say, "Okay, if they are at this greatest risk, but they've somehow been able to maintain this outstanding memory performance and they're at the far right tail of the curve, that seems to be unique." Whereas if you took people who were a bit younger, maybe in their 50s and 60s, there's more noise there. Their trajectory hasn't been as differentiated in a way. People could certainly look at superior aspects of other cognitive functions, but for us memory was important for these very practical reasons. And because we're a place that is interested in forming theories about Alzheimer's disease, and we firmly believe that what we can learn from SuperAgers can have relevance to Alzheimer's disease and Alzheimer's dementia and look through a different lens.

Then when we think about successful aging, we owe a great debt of gratitude to Rowe and Kahn for bringing out this term successful aging, which typically what was happening is we're tending to focus on the things that go wrong with aging. I

think we should celebrate the idea that there can be something theoretically constraint called successful aging. But the important thing to remember is that successful aging is not one single definition, it's this concept and it's been lived out in many different ways. So there was a review that was done several years ago that looked at 28 different studies, and they found 29 different definitions for successful aging. Then they looked at how many people were successful agers within those studies and the report was 0.4% of the cohort that they looked at to 95% of the cohort that they looked at. So virtually nobody to virtually everyone. The definitions of successful aging could range in general from people who are 65 and free of dementia to people who live to age 100. So definitions based on longevity versus those who need to have at least normal cognitive health and physical health by a certain age. So now you have all these different definitions, which in and of themselves are not problematic, but it can be challenging to say, "Oh, the key factor in the study of longevity was this and that didn't show up in the 65 year old, so it must not be important." Well, they're two different questions. So I think it's really important in the synthesis of all of this information that successful aging isn't defined then by each of these factors.

But you need to know the conditions under which successful aging occurs. So these are some of the reasons that we focused on this idea of SuperAging. We thought that these individuals represented people who not only live long, but are living well. If we think about the medical community right now, we've gotten good at extending our lifespan but it hasn't necessarily kept up with our health span. So the SuperAgers represent what I think many of us, or at least I know I would, like to be when I grow older - living long and living well, especially at those later years of my life.

John Bellone 14:50



Yeah, I think quality of life matters more than longevity to most of us, if not all of us. I like that there's so many different factors here to this definition. I think where you put the threshold makes sense at every level. I'm wondering, especially comparing an 80 year old to a 60 year old, you had mentioned variability increases as we age. So that's another reason maybe to look at older [adults] like 80 or 90 year olds. I'm wondering how we might expand the concept of SuperAging to older adults in their 50s and 60s, is that possible? To separate them at that age? I guess in other words, I'm wondering what the 85 year old SuperAger looks like as a 65 year old or a 50 year old, let's say? Do we have an idea of that?

Emily Rogalski 15:42



You know, I think that's a fascinating question. Once we start to identify factors associated with SuperAging, of course, the first question is, "Well, how did that happen?" So for the SuperAgers, when we look at the thickness of the cortex, we see that there's no significant thinning relative to the 50 year olds. So we said, "Well, is that because they had some particularly robustly thick cortex early on? Or are they avoiding changes in cortical thickness over time? Are they avoiding atrophy?" Then the other thing we see is that the anterior cingulate is thicker and that there's an abundance of Von Economo Neurons. And so we say, "Oh, gosh, well, were they always there? Did they accumulate them based on some past experience?" It does become tricky to answer some of those questions. So when we think about the SuperAging study, if you think of them as a pool to learn about factors that may be important, then I think it opens a door for saying, "Okay, now how can we look backwards and set up studies to investigate this?" So the SuperAging study isn't the one [study] necessarily to find that Fountain of Youth or that one factor, but it is meant to open the door to things that, if we solely looked at the negative aspects of aging, wouldn't be as visible.

So this focus on this definition - and I should mention, one of the reasons that we focus purely on memory rather than bringing in other cognitive domains or bringing in physical health, is it gives us an opportunity to look at those as factors. So if we require superior memory performance plus good physical health, then it eliminates a cohort of people that may otherwise have maintained their good memory performance but would be booted out because they didn't maintain that physical health. By keeping the definition simpler then all of those other things become fair game to explore and examine.

Ryan Van Patten 17:55



I do like how you have operationalized SuperAging in comparison to successful aging, which, like you said, there's nothing wrong inherently with successful aging. But when you have a concept that's so hard to pin down and heterogeneous, then we don't really know what someone else means when they say "successful aging". We don't know what definition they're using. But when you say SuperAging, going by your strict definition, I know what you mean.

Related to something you had alluded to earlier, intraindividual variability in cognitive performance is higher in older adults than in younger adults. Why might this be and how is it very directly relevant to SuperAging?

Emily Rogalski 18:37



When we think about inter or intraindividual variability in aging, I think that, in part, some of the variability that we see in aging is that we're aging at different paces. Some people are on different paths or different trajectories. There's also a lot of accumulated experience and also wear and tear that occurs as we age in our ability to respond to that consistently. And maybe over time, we can be more influenced by that that's less likely to be observed when we're in our 30s, where maybe we're a bit more resilient to a bad night's sleep or something like that. I think another way to think about it - sometimes I conceptualize this when I think about Alzheimer's dementia individuals with a neurodegenerative dementia - when you hear family say, "Well, today, my loved one really seemed to recognize me, but two hours earlier, they didn't." This is a hard analogy these days because we don't really use TV antennas anymore, but if you can remember way back when there were TV antennas and you would have the TV on one day and the antennas were in the same place and the picture came in fine. And then you turn the TV on the next day and the antennas were in the same place, but it was fuzzy. And so you had to adjust things a bit. So I think some days, as we get older, those connections are a little bit fuzzy and they're not able to be as maintained. Scientifically, we can then decode this and understand, well, what are the factors that are leading to this fuzziness?

John Bellone 20:22



I'm curious, roughly - and I'm sure our audience is thinking, "Well, how many people are SuperAgers?" Do we have a sense of the percentage of older adults who super age?

Emily Rogalski 20:34



This is a question that I get really often, especially when I talk to the media. They want to know, "Well, what percentage of individuals are SuperAgers?" And I think, "Gosh, you know, I really can't say because that's not the type of study we're doing." Unfortunately, especially in the US, we don't keep that type of data. We don't have access to information on all 80+ year olds to know what that percentage would be. And we have not cast a far enough net to say. It's not as if we've even blanketed the whole city of Chicago to say, "Oh, can we get access to records of all 80+ year olds in Chicago, and then one by one vet them to see how many people fit into this category or not?" What I can say anecdotally is that we know that the risk of Alzheimer's dementia or memory loss is quite high at age 80. Even some reports from the Alzheimer's Association and others would say that up to 50% of individuals over age 80 are likely to have Alzheimer's dementia. So there's one number. I can

say that the people that come to us, we've been fortunate enough to get some good press and media times - so we get people through word of mouth, we get through TV, radio, other venues, which has been lovely. I'll do community lectures and various other outreach. But they understand that we're looking for individuals who think that they have outstanding memory. Even so, we've screened well over 1000 individuals and we find that the percentage of individuals who have superior memory performance is relatively low. I would say less than 10% of this biased sample. So it's really tough to say the exact number of individuals. This is a good thing from a scientific standpoint, that the number of individuals is low. But I'll say the goal would be to have more people be there. But, scientifically, that means, if this is a unique cohort, then when they do share something in common, it's more likely that it's scientifically meaningful or worth pursuing further.

Ryan Van Patten 22:58



What does your screening battery look like for these 1000 people when you're testing for whether or not they're superAgers? Obviously they have AVLT. What else?

Emily Rogalski 23:06



They do a brief phone screen that gives us a sense - that includes some cognitive measures over the phone. Of course, a brief hearing check - if they're not able to hear us over the phone then we make some accommodations. So that gives us a pretty good guess of how they'll do in person. Then we would bring them in for that in-person testing. Their final disposition in the study is decided based on that in-person testing, not on that phone screening.

Ryan Van Patten 23:36



Which is the AVLT, and how long is the cognitive battery?

Emily Rogalski 23:41



The cognitive in-person battery takes us a couple of days to get through, so we have people coming back quite a few times, which can be challenging. So the supervisors are busy. [laughs] Sometimes one of the most challenging things is making sure they're willing to come back over the course of a couple visits. We have them participate in MR imaging sessions. They're donating blood so that we can look at genetic and other factors. We asked them to donate their brain at the time of death.

They do a series of cognitive tests, including the WAIS so that we can get a measure of IQ. It's very important to us that in our control group and our SuperAging group that there's able to be similar levels of IQ so that the results can't be solely explained by all of the SuperAgers having a really high IQ and the controls do not. So that's the major factor.

Also, there's similar levels of education whenever we have our comparison groups. And there's a range, right, so that range is 12 to 20. So a decent amount of education for the group, but it's not entirely doctors and lawyers, it's not just highly over-educated individuals. I think that is important.

About 10% of our cohort is from underrepresented groups. This is a space that we're really focusing on now in outreach efforts, specifically in underrepresented communities to increase. So I'm excited for this next phase so that we can start to better understand how these factors may change depending on race and ethnicity. Also, as we find more SuperAgers, we can answer more questions about sex and how might they differ from men versus women.



John Bellone 25:30

You answered so many of our follow up questions. [laughs]



Ryan Van Patten 25:32

[laughs]



John Bellone 25:35

I don't know where to go next. There's so many avenues. [laughs] Just to go back to what you said earlier about the - and I know it's so difficult. Your study is not designed to find out the percentage of people who are SuperAgers. But to clarify, it sounds like probably less than 10%. Unless there's something different about Chicago compared to the rest of the world.



Emily Rogalski 25:58

I would say far less than 10%. Because it's 10% of the people who come to us and say, "I have a great memory." I should note that these are not individuals, though, like the HSAMs that are studied, where they have that autobiographical memory. Where you can give them a date, you know, 1974, June 4, and they say, "Oh, well, I lived in Atlanta at that time, and it was 70 degrees that day, and I was wearing a red dress with polka dots, and a hat, and blah, blah, blah." That's not the type of memory they report. For the most part, the SuperAgers don't report having been

particularly strong in memory in childhood or in grade school. For some individuals, their families are surprised that they're doing so well. They don't question how they're doing in everyday life, but it's not as if memory performance was a special gift throughout their life.

John Bellone 26:58



I'm glad you explained that because one question would be "Well, are these people just memory savants?" And, you know, they're terrible at everything else. But that makes it much clearer.

Emily Rogalski 27:08



So when I think about them, they're "everyday folks" so to speak, who have aged very well and are very active. They do take a lot of pride in being SuperAgers. One of my favorite stories is [when] a former SuperAger told his friends that he was in the study, and they bought him a cape.

Ryan Van Patten 27:32



[laughs]

John Bellone 27:32



[laughs] That's awesome.

Emily Rogalski 27:34



There are funny stories like that. And that brings a lot of joy to this kind of research. I think [it] highlights another thing that's really important to me. There's so much stigma associated with aging and, in part, because the Alzheimer's crisis is real. And it's real emotionally and it's real economically. So we are right to focus on it a lot. But it consumes headlines in a way that can also erode our perception of what is possible in aging. So the first time you forget where your keys are, you just say, "Well, I must be just that old now." And you accept it. And then your expectation is set at a bar that is much lower than what you're able to achieve. So the more that we can get a story out there that there are other trajectories to be had, then that can be achieved. If we set our expectations a little bit higher, we might be able to achieve something different because the psychology or the believing aspect of it is important, individually but also culturally.

John Bellone 28:46



I 100% agree. The expectation can actually affect the cognitive trajectory. There's really good research coming out of Dr. Levy's lab at Yale in particular on how negative beliefs about aging, both as an individual and as a society, can impact the trajectory. I know part of your criteria was to ensure that no other cognitive domains other than memory were below average with respect to their age cohort. And that makes sense given everything you've laid out about memory changes and Alzheimer's disease. I wonder if you considered defining [or] having another definition based on processing speed performance rather than memory? I guess conceptually you could divide it however you wanted to and you can look at other types of SuperAging from a cognitive perspective.

Emily Rogalski 29:35



I think it's certainly possible. Depending on your scientific question, it may make good sense to look with a different lens. For us, it's the salient aspect of memory as the thing that people complain about. And then memory, because our lens as an aging and Alzheimer's and related dementia center and the focus on neuroscience really has us focused in this space. Certainly we can explore processing speed and what effects that may have, and we do give those tests. The salient aspect at the end of the day that can compromise functional ability and activities of daily living is that memory performance. The contributors to that from other cognitive domains may be varied. But memory is that core space that, with that single definition, allows us to pursue that lens. If you start to add in more definitions for how you can be a SuperAger within a single study, it gets very complex very fast. Because it's like, "Well, they did great on one domain but not the other two. So what do I do with that?" So how do you build a cohort that's cohesive? And I think you get a little bit into the space of the successful aging span, where there's all these different definitions to this theoretical construct which in and of themselves are not problematic, but then trying to glean important things. I'm a rule-bound person...



Ryan Van Patten 31:15

[laughs]



Emily Rogalski 31:15

...and see what we can learn from this lane. But, certainly, it is more than reasonable for others to pursue other lanes.



John Bellone 31:23

Sure. Or once you get enough of a sample size, then you can start maybe cutting it. You can look at people who did very well on executive functioning measures. That just depends on the end to some degree.



Emily Rogalski 31:36

Yeah, exactly. Sorry to speak over you. One way we can do that is to say, "Okay, well, we've got these people with superior memory performance. How can their neuropsychological profiles, how does their performance in other cognitive domains help us to understand how they were able to maintain this memory performance?" So we can do that statistically. This is a project that we have in revision right now that hopefully will be published soon. Where we can say, "Well, where else do SuperAgers... What other cognitive functions might be contributing?" And there we see that working memory and executive function are contributors. We can understand, "Well, how much does performance on these measures explain their memory performance?" And we can see that about 21% of the variance of episodic memory performance is explained by attention and executive function performance. And interestingly, in our cohort, the processing speed wasn't different between SuperAgers and average agers. So that didn't seem to be a space where SuperAgers were above and beyond that of their 80+ year old average peers. So we can ask those questions statistically and contribute to them.



Ryan Van Patten 32:54

Well, I think we now have a solid grasp on the definition of SuperAging. Thanks for walking through that. You've touched on what I'm getting ready to ask - I'd like you to summarize the main findings of the SuperAging literature with respect to cognitive trajectories over time. You've mentioned cortical thickness, you mentioned cingulate cortex size. Also there's been a little bit of work in the hippocampal size, not surprisingly, functional connectivity and the default mode and salience networks, AD neuropathology, and any other relevant neurobiological outcomes that you've looked at in these people.



Emily Rogalski 33:28

I should say that our approach has been multidisciplinary or transdisciplinary or interdisciplinary even, rather than focusing on just one aspect of SuperAgers. So we're not just interested in how they perform in other cognitive domains. We should note that I just mentioned that we can explain about 21% of memory performance through other cognitive tests. However, individually, again, I think it's important to go back and say, "How reliable is this across the individuals?" And there we do see

some variability. For some SuperAgers, it's that memory performance is their primary domain where they have strengths and others they're average at. Where other individuals, seemingly whatever neuropsychological tests we throw at them, they're in the superior range. So that's a space when we were talking about looking at different groups later on as we get larger numbers. This is an interesting space to look at, to say, "Okay, there are likely to be different paths to SuperAging. Let's see the individuals who have this phenotype versus that phenotype." So you can do that cognitively.

The study is longitudinal and we ask people to come back over time. And so we can also look from the lens of they seem at base, at a single visit, to have avoided atrophy relative to their 50 to 60 year old peers and to have a thicker anterior cingulate cortex. So what happens to their atrophy rates over time? We see that the atrophy rate in average agers is more than two times that of super agers suggesting that they're on a slower trajectory of aging. More recently we've looked at "Well what's the atrophy rate in 50 to 60 year olds?" And we see that the SuperAgers' atrophy rate is not different than the 50 to 60 year olds suggesting that they have been able to shift their chronologic clock somehow in a way to be more in pace with that of a 50 to 60 year old. Because of the anterior cingulate finding we focused on the anterior cingulate in our early work neuropathologically for the first few SuperAgers who came to autopsy. And that's where Dr. Changiz Geula, Marsel Mesulam, and at the time, Tamar Gefen, who is now Dr. Tamar Gefen, she was a graduate student at the time. Her dissertation work focused on looking at the density of these von Economo neurons and found that there was four to five times the number of von Economo neurons in SuperAgers relative to the average agers. That study was also followed up to show that, across the lifespan, SuperAgers have a greater density of von Economo neurons than even younger individuals, and the young sample had individuals as young as in their 20s. So this starts to suggest something about the origin of where the von Economo neurons story is going. As we move forward, we're focused in this area in better understanding von Economo neurons and the molecular factors that are driving them.

And of course, SuperAgers being age 80, Alzheimer's comes into question - Alzheimer's pathology. So we know Alzheimer's pathology is, of course, plaques and tangles. We know that individuals with a diagnosis of Alzheimer's dementia and [that] have Alzheimer's disease pathology have an abundance of plaques and tangles. But individuals who are average agers also can have some plaques and tangles sometimes in a greater abundance than one would think. So the question was, "Do SuperAgers also have plaques and tangles? Or are they able to avoid them?" And we see that, for some SuperAgers, they are able to avoid the

accumulation of plaques but others have an abundance. The tangle story seems to be that there's more likely to be fewer tangles in the SuperAgers than in average agers. We've started some initial genetic studies, a varying in effect 2K3 has come up. This needs further validation and follow up. So we're working on that with our colleague Matt Huentelman in Arizona - so more to come there. In addition, now that we are accumulating higher numbers of SuperAgers, we can ask different genetic questions than we were able to earlier.

We also started a study with our colleagues at UCSD where they had a polygenic hazard score for Alzheimer's risk. And I said "Well, wouldn't it be interesting to know if the SuperAgers are just merely low at-risk individuals?" When we look at that, we see that the SuperAgers and the average ages have low AD risk, but the SuperAgers do not have unusually low AD risk. So they were not different from their cognitively average 80+ year old peers. So SuperAgers does not equal extremely low risk for AD. We couldn't merely identify them by their AD risk and distinguish them from average agers.

We also looked at APOE. So APOE comes in three flavors, 2, 3, and 4. And everybody has a pair - 2/3, 3/3, or 4/4, etc. If you have at least one copy of the 4 allele, it increases your risk for Alzheimer's disease. And E2 is thought to be protective. When we look at the SuperAgers, it seems like E4 is a little bit less common than in the average ages, but not profoundly so. There doesn't seem to be an over representation of E2. So those two factors alone don't seem to be the driving impetus there.

Lifestyle factors and exercise are variable in the group. The majority of SuperAgers are reporting that they have active lifestyles, but this is all subjective report right now. This is a space that we are hoping to move into more quantifiable and objective data, perhaps with the use of ambient and digital biomarkers, sensors and the like. We see that the family history of SuperAgers is variable. So some with longevity in their family and others with a family history of dementia.

John Bellone 40:18



So much there. So they are different in a number of ways, it sounds like. Just to clarify something about the von Economo neurons, maybe some of our listeners haven't heard of those. My understanding is that they're relatively large neurons in the anterior cingulate and other areas of the frontal cortex. Anything else you want to say about them?

Emily Rogalski 40:40



Von economo neurons. Yes, you're exactly right. They're large neurons. When we think of neurons, pyramidal cells normally pop into our head as being large neurons. But von economo neurons are bigger than pyramidal neurons. The other unique features about them are that they've only been described in two regions of the human brain, the anterior cingulate and the frontal insular cortex. They've also only been described in higher order species, like whales, for example, or elephants. The loss or abnormal development of von economo neurons have been noted in schizophrenia, bipolar disorder, frontotemporal dementia, and attention deficit, individuals with ADHD. So there's some thought that they play a role in social behavior. But much, much more is to be learned in this space.

John Bellone 41:40



Okay. Yeah, that's interesting. I'm also glad you ran through some of the genetic predispositions that SuperAgers may or may not have. My understanding is that there are no E4 homozygous individuals - no one with two copies of E4 allele. Is that right?

Emily Rogalski 41:57



That is correct. We don't have anyone who is E4/E4.

John Bellone 42:02



But there are some heterozygous E4s?

Emily Rogalski 42:05



Yes.

John Bellone 42:06



Yeah. Okay. Because other people [might] ask, "Well, are these people just genetically pristine from an APOE standpoint, maybe from other genetic predispositions?"

Emily Rogalski 42:17



Correct. So it's not as if there are no E4s, and they're all E3 or E2. So about 20-some percent of them have an E4. Though, in our cohort of healthy controls, only looked at a few years ago, which is on par with what's reported by other groups, our cognitively average controls [are] about 27%. And this is, individuals really aged 65 and above have an E4. Whereas the SuperAgers when we looked at

them a bit ago, they were at 23%. So, again, slightly lower, but within the margin of error a bit.

Ryan Van Patten 43:02



You mentioned von Economo neurons and social cognition. Some people may not be aware that older adults in general have higher levels of emotional well being and lower rates of mental illness than younger adults. But today, we're talking about SuperAgers. I know you've examined psychological well being and social relationships in SuperAgers. How do they compare along this dimension to typically aging older adults?

Emily Rogalski 43:27



Great question. I think this is a really important part to understand, and the fun part about being able to conduct a study from so many different vantage points. What it also means is we don't have robust batteries in each of these domains. And so some of them are like feeler topics. So psychological well being, I think of it like, we've got the surface level information but now we need to dig. We gave them a questionnaire. So what we have right now is questionnaire answers from the PWB-42, which is the Psychological Well Being measure that has 42 questions. It looks at different aspects of psychological well being, including positive relations with others, purpose in life, self acceptance, autonomy, environmental mastery, and personal growth. This is work that was done by my graduate student at the time Amanda Cook and we found that the SuperAgers tend to endorse positive relations with others to a greater degree than their cognitively average peers. So this is in line with the idea that there are negative consequences - loneliness and social isolation - and that there are positive consequences to staying socially connected. So whether you are cognitively healthy or if you have a diagnosis of Alzheimer's dementia, one thing that we talk about is maintaining that social connectedness and how it may influence or help avoid more rapid decline by maintaining this connectedness.

We don't have quantitative information of why the SuperAgers perceive this. We have anecdotal information that they're quite busy and that they're active, either by volunteering [or] many of them are still working or employed. Some of them still have their primary occupation. We got an individual whose first career was as a lawyer, he tried to retire, got bored, and went back and got certified to do taxes seasonally. So then he just works when it's the season of the year to do taxes, and found that that was intellectually stimulating for him. So there's a whole variety of different ways that we see the SuperAger staying connected. We don't know, other

than anecdotally, whether this is that they are social, they have large social circles, or they have one or two close friends. I want to make sure it's clear that having positive relations with others doesn't dictate the size of your social circle, but the quality for that person is likely to be the important thing to them. This is yet another area that we think we can follow up with and think of creative ways to get good quantitative data in this space.

Ryan Van Patten 46:24



Gotcha. Yeah, in the broader aging literature, there is quite a bit of work on social engagement, cognitive intellectual enrichment engagement, and it seems as though your preliminary work suggests that that might be part of the story behind SuperAgers.

John Bellone 46:42



Exactly. So we really benefit from the literature that's out there, that robust literature that's out there, and we're just saying, "Hey, and us, too." [laughs] We see that that's in line. And it's possible it wasn't that way. Right?

Ryan Van Patten 46:56



Yeah. You've alluded to the role that cognitive reserve might play in SuperAgers. So just briefly, you know, the idea that some older adults have a high pathological burden, but still maintain at least average performance cognitively. It sounds like based on what you said that [for] some SuperAgers, it's not so much cognitive reserve that we would use to describe what's going on because they have lower neuropathological burden as well. But for others, they do have a high neuropathological burden and maintain good, objective cognitive performance. So is it variable in terms of the role of cognitive reserve in SuperAgers?

Emily Rogalski 47:40



Well, I think the term "cognitive reserve" is another tricky one, right? Because it's one of those conceptual ideas that at least I have difficulty seeing. What is it tangibly? Because sometimes cognitive reserve is described as, "Well, what can be accounted for?" High education is helping people, cognitive reserve this concept. So we tend to use terms like "resilience" and "resistance", which also are problematic and controversial. [laughs] But we can say, for example, "Are SuperAgers able to resist the changes that are associated with aging? Or are they resilient to them?" So is it that they were able to avoid having plaques and tangles appear in their brain altogether? Or do they have them and they don't seem to have the deleterious effects that we perceive to be associated with them? And both

lenses are important, right? The how and why you get there. So how are you able to avoid them, if nearly everybody is getting them? And then how are you able to avoid the effects of plaques and tangles if that is the case? So both paths are interesting and possible to study. So we can then dig down and say, "Gosh, what could be the factors that allow you to have plaques and tangles?" And really this is a space where it improves our understanding of what Alzheimer's disease is, which is defined by plaques and tangles. So what other factors contribute to whether someone is going to have memory loss or not when these plaques and tangles emerge? It can improve our biologic understanding of Alzheimer's disease as well.

John Bellone 49:33



You talked before about how it's really tough at this current moment to parse out whether there are sex differences or differences based on race or SES. I wanted to circle back around and make sure I heard you correctly there.

Emily Rogalski 49:46

So let's talk about different factors that may influence SuperAgers. When we think about sex, if I showed you my demographic slide, you would see that there's more SuperAger women than men. And I always tried to stop when I talk about them and say, let me preemptively answer this question, "Is it that SuperAgers are more likely to be women than men?" And I'll say I think it's premature to answer that question for a couple of reasons. So one influence could be that women tend to live a little bit longer, so we've got a sampling bias there maybe. But I think the more important factor or bias is that women tend to volunteer for research more. So we got to work a little bit harder to find our male SuperAgers and enroll them. Once we get sufficient numbers, we can start to ask some of those questions of what's the influence of sex.



When it comes to race, we haven't, again, had robust enough numbers to divide things out and look statistically to understand how factors may differ. But this is a space that we're actively - we just had an R01 [grant] that was recently refunded. And so one area of focus is in enrollment of underrepresented groups. We also submitted an application that is under review at the moment that, if funded, would create new SuperAging sites across the US and Canada. In that application, there is a large focus on recruitment of underrepresented groups. So that would also change the generalizability by having more regional variability across the United States and Canada, but also be able to explore differences by race.

Then SES is complex. This is another space that, especially if we get the grant, would allow us to go multi-site. We plan to incorporate - so Amy Kind has done a lot of work in developing these neighborhood maps that can give us measures at a very fine grained level about the way that the advantages that some have can influence our health outcomes. This is a way for us to start thinking about this quantitatively, rather than just thinking about it theoretically, and to drill down and look through different lenses. So that's the space that we hope to get into.

From an IQ standpoint, we do make sure that the SuperAgers have, when we do group comparisons, we're either accounting for that or by and large there's been similar levels of IQ between the two groups.



John Bellone 52:35

And the [level of] education is also controlled?



Emily Rogalski 52:38

Correct. Yes. The education ranges have always been similar between the two groups. The range and education is from 12 to 20 in our group.



John Bellone 52:48

Sure. Well, that grant sounds really exciting. I really hope that pulls through.



Emily Rogalski 52:53

We were excited about it, too. It was a little tricky to put together during the pandemic.



John Bellone 52:58

I bet. I know we're unfortunately approaching the end of our time with you. So we'll have to be picky here about the questions we ask. I'm wondering quickly how stable the SuperAger status is? Do they remain SuperAgers until they die? Or do they show rapid decline later on?



Emily Rogalski 53:16

Right. So stability is a really important question because you could easily say, "That's great. You found people who had a lucky memory day, and they did really well today. But if you tested them tomorrow, would they do the same? And [what] if you tested them a year from now?" I think that the longitudinal component is really important to the study. It then takes a long time to accumulate this data. Because

we've been enrolling people for more than 10 years, we have some people who've got 10 or more years of data depending on whether they were pre-followed or not, and then others who enrolled last week. So we've got variable amounts of longitudinal data. But an early study we did back in 2014, I believe, showed that the majority of SuperAgers are able to maintain that memory performance at least over an 18 month period. That's not a particularly long period, but it's something that suggests, at least, that they didn't have just a lucky memory day when they came into our center the first time. We have other individuals documented where they have been able to maintain that cognitive performance over a long period of time. But this will be one of the things that - there's lots of sub-studies going on - but this is one of the things that we monitor really closely of the SuperAgers. And, of course, there are some that decline. We don't have a robust enough group yet to talk about which percentage of the group show some decline and the rates, and we've got to account for the different amount of time that they've been followed as well.

John Bellone 54:45

In terms of lifestyle, you touched upon this already. I'm sure our listeners are thinking "Well, what are these people doing right? What can we do right?" And I said earlier, that's kind of my selfish reason for talking with you more or less. This is also just an exciting area. You mentioned how it's a little bit variable - some exercise, nutrition, we talked about social engagement.



I'm also curious how this concept relates to the concept of Blue Zones. So locations in the world where people live longer; they have higher concentrations of centenarians. Greece, an area of Japan, Loma Linda, California, Sardinia - these are places where people live substantially longer. Do we know if Blue Zones have more SuperAgers? I know it's maybe early days to answer this, but is your hunch that the lifestyle factors are really driving some of this?

Emily Rogalski 55:40



Well, especially, right now, where I think we've all been living in our houses and not traveling anywhere, I'd like to write a grant that allows me to go live in a Blue Zone for a while.



Ryan Van Patten 55:50

[laughs]

Emily Rogalski 55:51

That's my selfish request there. [laughs] I think the Blue Zones are fascinating. My guess would be that, yes, there would be SuperAgers there. It would be fascinating to have the opportunity to talk to some of those individuals. Anecdotally, sometimes when certain publications have gotten picked up and distributed worldwide, I've gotten postcards from individuals in Costa Rica and across the globe inviting us to come and, boy, that would be great. [laughs] It's really something fascinating. We have been talking to colleagues across the world and in different countries in doing some preliminary work to see if we can set up these cohorts and ask some of these questions in spaces that are outside of the Chicagoland area and outside of the US. I think there's room to grow and think about questions from that vantage point.

Anecdotally, again, when we think about the SuperAgers in their report of their lifestyle factors, the word "curiosity" comes up a lot when we interview them or when they're interviewed by others. They tend to be curious. They are inquisitive, they're active. But "active" can mean different things. Active can mean volunteering, active can mean still working, active can mean just helping out their friend or their family. Adapting, I think, is another word. One of my favorite interviews that I'll often show is of a SuperAger who talks about that, by choice, he lives with his daughter and his grandkids. He doesn't have to live with them. But you have to remember as you get into your 80s, 90s, and our oldest living SuperAger right now celebrated her 106 birthday this summer. I'll come back to her in a second. But for this person in the SuperAging study, he says, "You know, I have to learn how to adapt, because my grandkids don't know much about Frank Sinatra."



Ryan Van Patten 58:04

[laughs]

Emily Rogalski 58:04

"So, instead, I have to ask them, you know, is Taylor Swift or Chance the Rapper coming into town this week?" This ability to say, "How do I find joy? How do I relate with people who are decades younger than me?" And being willing to be open to that, I think is remarkable, and something that we see.



They also want to meet each other. So early on, years ago when we started this, it didn't take long for me to get a lot of requests. "When are we having a SuperAging party? I want to meet the other SuperAgers." And there were a variety of requests in there, including people who wanted to find new spouses because their [spouse] passed away and they thought another SuperAger would be a good fit. [laughs]



John Bellone 58:05

A Super Couple. [laughs]



Ryan Van Patten 58:29

There should be a SuperAger dating app. [laughs]



John Bellone 58:56

[laughs]



Emily Rogalski 58:59

I momentarily had panic that I was, like, "Oh gosh, I do not want to become match.com or something." [laughs]



Ryan Van Patten 59:05

[laughs]



Emily Rogalski 59:07

To date, we've had three SuperAging cocktail hours or get-togethers with music. And they really enjoy meeting each other and having this opportunity to spend more time with us, which sounds a little bit unusual. You don't often see people who are involved in scientific study saying "Yes, let me race back and spend more time at your center." So I think their curiosity, their adaptability, their resilience. The SuperAgers, I should mention, are not individuals who have necessarily had easy lives. There are some who encountered poverty at a young age and throughout their childhood or longer or who have encountered traumatic events in their life from losing children at a young age. We've had individuals who were in the Holocaust and they themselves survived, but their families were lost. So these are heavy things, and they've been able to bounce back or find a way to move on despite these challenges.



John Bellone 1:00:18

It's a good place to maybe transition to the bonus questions.



Ryan Van Patten 1:00:22

Yeah, this has been a great conversation, Emily. Thanks for taking the time. We just have two quick bonus questions before we let you go. And these are about the field of neuropsychology more broadly. Of course, they could pertain to SuperAging, but

they need not necessarily. The first one is: if you could improve one thing about neuropsychology, what would it be?

Emily Rogalski 1:00:44



Oh, that's a tough one. I think that's a big question. [laughs] I don't know that I have an answer about one thing. I think it's exciting. There's a lot of new methodologies coming out, whether we're assessing cognition in more real time through apps or through sensors. But I think one challenge will be how do we put this information in context with the traditional methods and not to abandon some of the gold standards too early but also not to be averse to change. So the idea of being like the SuperAgers. Can you adapt? Can you adapt and evolve, but responsibly, right? So not to rush. I think there's great value in not just moving on too quickly. And so, some of them, they maybe seem boring, but the studies that replicate and are able to do those crosswalks from more traditional methods to newer methods and really show the different values or different lenses, I think is what would help the field grow.



John Bellone 1:02:00

I fully agree.



Ryan Van Patten 1:02:01

Yeah, we can have a Super Neuropsychology ultimately. [laughs]



John Bellone 1:02:07

And then there's the last question for you. What's one bit of advice that you wish someone had told you when you were training, or maybe they did tell you that really made a difference? Just an actionable step trainees can take.



Emily Rogalski 1:02:18

Find lots of mentors. I think sometimes when you think of graduate school, you think of "Oh, I got to pick the perfect mentor or the perfect lab." But there will never be one mentor. It should be a whole team. It's too heavy of a job for one person to bear the weight of being everything to that mentee. So finding people who can provide advice. And don't be afraid to ask. Scientists and neuropsychologists, we all tend to be friendly people. So send that email. Walk up to that person that you've never met and introduce yourself. It sounds scary and terrible, but it tends to work out okay.



Ryan Van Patten 1:03:01

Good advice.



John Bellone 1:03:02

Excellent advice. Well, Emily, thanks so much. I very much look forward to seeing more data from you and your group and learning more about this cohort of individuals. I'm so glad that you're studying them. It's really impressive what you've done.



Emily Rogalski 1:03:18

Well, thank you so much. It was really fun, and I appreciate the opportunity.



Ryan Van Patten 1:03:22

Thanks. Take care.



Transition Music 1:03:23



Ryan Van Patten 1:03:27

Well, that does it for our conversation with Emily. For all of you who are in need of CE credits, we have a number of our episodes that are available through our partners at INS. You can go to naveuro.com/ins to see a list of episodes that are available for CEs. And, as always, thanks for listening, and join us next time as we continue to navigate the brain and behavior.



Exit Music 1:03:52



John Bellone 1:04:15

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Ryan Van Patten 1:04:27

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