**SPEAKER 1:** Good afternoon, everyone. It's my pleasure to introduce today's speaker Dr. Prashanthi Vemuri. Dr. Vemuri is assistant professor at the aging and dementia imaging laboratory in the Department of Radiology here in Rochester and is an associate consultant in that department. Her educational background-- she had an undergraduate degree in engineering and a master's and PhD in electrical engineering from the University of Utah. She completed a post-doctoral fellowship with Dr. Clifford Jack here at Mayo Clinic in imaging in neurodegenerative diseases and has gone on to really have an impressive record over a relatively short period of time.

Over 69 original publications. She has been funded through a K99/R00 mechanism, one of those career transition awards to herself and is also one of the leaders of one of the projects of the Alzheimer's disease research center grant of Dr. Petersen, which is really an excellent example of the kind of multidisciplinary and collaborative research that we are trying to encourage through the Center for Clinic One Translational Sciences. So we look very much forward to hearing Dr. Vemuri's presentation on cognitive decline in the elderly and the role of cognitive reserve. Dr. Vemuri.

**PRASHANTHI VEMURI:** Thank you for the generous introduction, and thank you for this opportunity to present my work in front of all of you. I've nothing to disclose. Here that learning objectives as required by this seminar. At the end of the course, you'll be able to identify the causes of cognitive impairment in the elderly and able to discuss the role of cognitive reserve in lowering the risk of cognitive impairment.

I divided my presentation into three different sections. The first section will deal with cognitive decline in the elderly and discusses the causes underlying cognitive impairment. The second fortune deals with the role of understanding the role of cognitive reserve in preventing cognitive i impairment. And the third section will deal with understanding the mechanisms underlying cognitive reserve. I just had the last couple of slides of how we take the research we're doing and try to apply it to personalized medicine.

So coming to my first part, aging is not good news. So in this study done by Salthouse, they took about 2,000 individuals, and they measured longitudinal changes in memory, speed, reasoning, and visual spatial skills and found that all the cognitive variables that they studied declined monotonically over the period of time from 20 to 90 years of age, which means that it's bad news for all of us sitting in the room. And as you know, cognitive decline ultimately leads to dementia as it progresses.

So if you look at the fraction of people that are diagnosed with Alzheimer's disease, the fraction of people keeps going up because age is the largest risk factor of diagnosis with Alzheimer's disease. And if you look at sheer numbers, the number of subjects that are currently diagnosed are right about here. But you can see an explosion as the baby boomers age, and by 2050, we'll see a lot more number of cases in places like Mayo Clinic.

So what causes cognitive impairment? The main reason underlying cognitive impairment is brain shrinkage. Your brain shrinks. Starting at about 20 to 30 years of age, your brain does neuron death, and your brain suddenly shrinks. This is a very nice study, which studied the brain changes across the lifespan, and they tried to understand what happens regionally in every region of the brain. The answer is by 30 to 40 years of age, every single region of the brain, there is some amount of shrinkage seen throughout the lifespan.

What causes the shrinkage? It's these upstream pathological processes. There are pathological changes in the brain, which cause shrinkage, which ultimately cause cognitive decline. So they move you from a subset of subjects who are cognitively normal to cognitively impaired by the time you're 80 to 90 years of age. Just about statistics, about 50% of people who are 85 or above have pathology, which are related to dementia, so that's a pretty high percentage.

So I've taken a simplistic view of the disease. There are several pathologies that cause neural degeneration. The top two pathologies are Alzheimer's disease pathologies and cerebrovascular disease pathologies. There are other pathologies as well, which are dementia Lewy bodies, or hippocampal sclerosis, or FDLD. They cause neural degeneration or brain shrinkage, which ultimately leads to cognitive impairment. But majority of the cases are caused by the boxes shown in yellow-- Alzheimer's disease pathologies and cerebrovascular pathologies contribute a significant amount of dementia burden.

The data I'm going to discuss today is from Mayo Clinic study of aging. The PI Dr. Ron Petersen from the Department of Neurology. And it's a population-based sample of about 2000 non-demented elderly between the ages of 50 to 90 years of age sampled from the population of Olmsted County, Rochester. They have extensive longitudinal clinical and imaging follow-up.

The beauty of the study is it's free of bias because it's recruited from the population, so it's not like-- Through advertisements, you often get highly educated people who want to participate in your study, which skew your results. And generalizability is always a big issue when it comes to large observational studies.

So the imaging studies in Mayo Clinic study of aging are done at Aging and Dementia Imaging Research Lab. The PI is Dr. Clifford Jack. And we involve in the acquisition, quantification, and the mechanistic interpretation of several images, not only the one shown here, but the primary ones are amyloid imaging, cerebrovascular disease imaging, structural MRI, diffusion tensor imaging, glucose metabolism measurement, and task-free resting state of MRI.

For the sake of the talk, I'll focus on the two imaging modalities that are shown in red. So what is amyloid imaging. B-amyloid is the primary protein in Alzheimer's disease. So if you find the B-amyloid in subject's brain, it's more likely that they are on Alzheimer's disease pathway and ultimately will end up with dementia. So the image amyloid in the brain in the elderly subjects. We also image's flair fMRI images, which measure the set of cerebrovascular disease. Basically, the small vessel disease changes to the brain due to vascular disease is measured using the flare MRI.

So just to show you how amyloid imaging looks, I've taken about 670 population based individuals on the 80s spectrum from Mayo Clinic study of aging. And there's a radioactive tracer called Pittsburgh Compound B or PIB PET, which measures the amount of brain amyloid in people's brain. And you can really appreciate that, in people who have nothing, you see literally nonspecific white matter uptake and no cortical uptake.

The next slide clearly shows you what happens. This is almost Alzheimer's disease or extensive amount of amyloid pathologies. And you can see that there's a significant amount of cortical uptick in subjects who have a PIB uptake of 2.5 or more. So if you contrast a normal subject to an Alzheimer's disease subject, visually you can really make a distinction of what is happening.

The cutoff for amyloid levels is about 1.5. So at 1.5, scans are going to be abnormal. So it's just about in between 1.35 and 1.6, the scan would like to look like that. This data is from Australian imaging and biomarker flagship study, or the able study, where they tracked several hundred people over a long period of time. Some of them have about five years of follow-up. The left last panel shows cognitively normal individuals. And as you can see majority of the people are below 1.5. But about 30% of cognitively normal individuals have amyloid levels. So they have positive amyloid scans, and they have deposition as they go forward.

The middle panel shows mild cognitively impaired subjects. And these subjects are the middle stage between cognitively normal to dementia. So these subjects have subtle cognitive impairment but not insufficient to call them demented. So these individuals, about 60% of them, have an abnormal amyloid scan. And about 30% to 40% of them have a normal amyloid scan. And in Alzheimer's disease patients, typically, they have a positive amyloid scan, and the one thing that this plot drives forward is that amyloid deposition is a slow and protracted process likely to extend for more than two decades.

This is the study done by Dr. Clifford Jack from our group, which shows that amyloid deposition is a slow process, and it reached reaches a plateau quite awhile later. So if you estimate the time from the point where a scan is slightly abnormal, about 1.5, to the time when an average Alzheimer's disease the subject, the time period is about 15 years, which is a very long window if you want it on secondary prevention trials. And very promising because there is hope that there is a time period before which you could have drugs that could work.

The second imaging modality I wanted to talk about was cerebrovascular imaging where you could see brain changes due to vascular disease. As you can see by these red arrows, you could see cortical or subcortical infarcts are shown by these bright spots on flare MRI images. You could see white matter hyper intensities, which are due to leukoaraiosis or small vessel disease.

So the first study I wanted to discuss as part of the first topic was that we studied vascular and amyloid pathologies and how they affect longitudinal cognitive decline in the Mayo Clinic study of aging subjects. We identified about 393 controls who had vascular grading available as well as amyloid pathology assessment available and a complete psych assessment and clinical follow-up. And we tried to tried to divide people based on amyloid disease as well as vascular disease.

So we call a scan positive if they had a global cortical uptake of 1.5 or greater. I showed you examples of where you can see positivity of an amyloid scan, so typically 1.5 was used as cut off. And because someone as being on vascular pathway, if they had a brain infarct or they had a white matter hyper intensity to TIV ratio of about 1.11%, which is our recent published criteria. This is the amount of white matter hyper intensity load a subject has to be redeemed as having vascular disease in the brain. The

First thing we did was try to see how many people were in each subgroup. In the total population that we looked at, we found that about 45% of people did not have vascular or amyloid disease. About 23% were in the vascular pathway. About 21% were on the amyloid pathway. And 11% had both pathologies.

You can appreciate what happens to the brain over the age range. You start out with 75% of people not having amyloid or vascular disease to begin with at 70 years of age, which drops to about 25% by the time you reach age 90. And if you sum up the total number of people who have vascular disease at the end of age 90, it's about 65% to 70%, which is a pretty high percentage of people.

I just wanted to show you three things from the demographics table. One is that age is the largest risk factor. So if you are higher in your age, the more likely you are to be on one of the pathways, either amyloid pathway or vascular pathway. As you can see, people in

As you can see, people in both vascular and amyloid pathway, were 82 years of age, compared to people who are in the normal aging pathway, who are much younger.

The other two things I wanted to show you were the number of E4 carriers. So APOE4 indicates the genetic risk of having Alzheimer's disease. If you have an E4 allele, that indicates that you have 67% more chance of getting Alzheimer's disease if you do not-- compared to when you do not. So as you can see, if you have an E4 allele, you're more likely to end up in the amyloid pathway. About 50% of people on the amyloid pathway are E4 carriers.

And the third thing from this slide is that the baseline performance in a neutral is dramatically affected by which pathway they are on. So if you had both vascular disease as well as amyloid, then your performance is much lower than you did not have either.

Moving on to the results, the only thing I wanted to show from this slide was, if you're trying to say that you're trying to predict cognitive decline in the elderly and say what pathologies drive your cognitive decline, if you look at the bottom portion of this table, you'll see that age-- indicates that age is the biggest driver of cognitive decline. So there is an age association with your cognitive decline. Higher your age, faster is your cognitive decline, which you can understand from the first slide that I showed you. The other two things are that, if you are on the amyloid pathway or vascular disease pathway, you decline much more faster.

So this is a graph summarizing all the data. If you are neither on amyloid or vascular disease pathway, your cognition is defined by this blue line here. If you are on the vascular pathway, it's indicated by the red line here. If you're on the amyloid pathway, it's indicated by the green line here. And if you have-- both biomarkers are positive, your cognitive decline is indicated by a black line here.

On the y-axis-- on the x-axis is time from baseline. And these are the values for a typical 79-year-old in our study. 79 is the average age in our study. So these numbers are indicative of what happens to an average individual in our study.

Take home points from the first part of my presentation are amyloid and vascular diseases are the major drivers of cognitive decline in the elderly and both appear to have an independent effect on cognition and both affect cognition adversely. I drew this curve just to indicate what happens if you have both cardiovascular disease as well as Alzheimer's disease. Then your likelihood or time to detection of dementia is much more shorter, compared to having one or none.

So coming to the second part of my talk, I'll talk about role of cognitive reserve. So to understand cognitive reserve, two completely different individuals can have scans shown as here, one with very little amyloid in their brain, the second with significant amount of amyloid in their brain, 2.5 or so. But they both seem to perform very similar, in terms of cognition. Why is that? The common term that's used to explain this phenomenon or the disconnect between imaging and how they're performing is called cognitive reserve.

What is cognitive reserve? People have better IQ, higher education, better occupations, and they engage in high amounts of physical and cognitive activities, which helps them perform better. But the term that is used to explain this disconnect is called cognitive reserve. The reserve term in dementia started in 1988, where Robert Katzman observed that there are certain people, when they come to autopsy, have heavier brains. So the weight of the brain is much heavier, and they're able to withstand a lot more amount of pathology than subjects with smaller brains. So he used the term brain reserve. So people with larger brains have more brain reserve, so they can defend against ongoing pathological processes.

The second observation was that about 30% of cognitively normal individuals have significant amount of pathology when they go to autopsy. Why? How is that possible? So Yaakov Stern has grouped all the data in the field and come up with the theory of cognitive reserve, and this particular publication summarizes the whole theory really well. But he indicated that there are two components of reserve. One is passive reserve, which indicates that someone has greater capacity, for example, someone has a bigger brain, or they have more efficient networks, because they're using them more.

The second part of reserve is active reserves. Somehow, you're able to compensate for what's going on in your brain. So you have the pathological processes happening in your brain, but you're better equipped to be able to compensate or recruit other regions of the brain in the face of pathology.

So we have been doing work in the last few years on cognitive reserve, and the central framework for all the work we take is as follows-- we know, one, age is bad. Age is good in terms of wisdom, but age is generally bad for cognitive decline. So age is bad. Having a genetic risk is bad. Having pathologies is bad. We already saw that having Alzheimer's disease pathology and cerebrovascular disease is bad. The only good thing that could happen for us is cognitive reserve. So that should contribute to improving your cognition and how does it do it?

The motivation behind this is that, if we can figure out how much cognitive reserve can help, it will have a huge public health impact. This is from the Alzheimer's Association trajectory report. The solid line here, shows the number of people over decades of number of cases being diagnosed by Alzheimer's disease. But if we are able to delay the onset by at least five years, let's say, just look at the number of people being diagnosed by Alzheimer's disease. It's going to have a huge public health impact. So that's the main motivation, to understand how can cognitive reserve help.

The first study I'm going to discuss in this subtopic is that we try to understand how lifestyle can help cognitive decline. The study goals were really simple. Can intellectual enrichment help baseline, and can it help rate of cognitive decline? If so, how many years can it help? Can we come up with concrete numbers that can indicate the amount of help that high intellectual activity can help us?

For this, we grouped lifetime intellectual enrichment into two major components. The first is early and mid-life non-leisure activities. Some of you might argue here that work is also leisure, because research is so much fun. But education, occupation would fall under early and mid-life non-leisure activities. And the second is mid-life and current leisure cognitive activities. So we give questionnaires to the participants and ask them what they did during their mid-life and what they did in the last 12 months. So what kind of activities did they engage in? Did they read newspapers, magazines, books? What did they do on a weekly basis? How many times did they do it? Two or three times, five or six times, or they did it daily, and so on.

In this study, because we did not limit the number of imaging scans, we had many more number of subjects who had baseline-- were baseline non-demented subjects had complete neuropsych assessments, and they had follow-up available.

And the first things we found was that males perform slightly worse than women. That's what our data shows, as well as data outside shows. And education/occupation has a significant impact on baseline cognitive performance. So if you have a higher education, you perform way better on cognitive tests.

If you're engaged in mid/late-life cognitive activity, you really do, but the coefficients are about half as education and occupation. If you're an E4 carrier, because you have a genetic risk, you perform worse than a non-E4 carrier. And what drives cognitive decline? Age, as we saw earlier, drives cognitive decline. Mid/late-life cognitive activity seems to help a little. Not too much, but it did help a little bit in improving your rate of decline. If you're an E4 carrier, you decline faster, which is understood.

What was surprising was the last component. There was an interaction between education, occupation, and mid/late-life cognitive activity, which basically indicates that if you have low education and occupation, mid- and late-life cognitive activity can really help.

So we divided subjects by, as men, women, E4 carriers versus non-E4 carriers. And from the curves, you can see that E4 carriers generally decline much faster. Women seem to start out a little higher than men. But the curves here shown in dotted blue line are subjects who have high education/occupation, as well as had high mid/late-life cognitive activity. And subjects shown on the red solid line, were low on education/occupation, as well as low on mid/late life cognitive activity. So if you had low education but you still engaged in leisure activities later in life which are cognitively stimulating, you could really bump up your trajectories to this red dotted line.

So summarizing the model, both better education and occupation and mid/late-life cognitive activity contributes towards better cognitive performance. And one thing to consider is that who does higher mid/late-life cognitive activity really help? It helps subjects with lower education. So this has a significant meaning, in terms of what public policies should be in place.

And if you look at time to dementia, time to cognitive impairment in an 80-year old E4 carrier in our subjects-- so you take an 80-year-old subject, who's at genetic risk of helping Alzheimer's disease in our study, and you say, do you have low education? OK. You're 80 years old. About 82 years of age is when approximately you would be developing cognitive impairment. But if you engaged in high mid/late-life cognitive activities, you're about 3.5 years away from that. So 3.5 plus 2, which is 5.5 years away from the time you would develop cognitive impairment.

And if you have high education and occupation and if you are-- the solid lines indicate males-- you're about seven years away from developing cognitive impairment, but higher cognitive activity can move it out by about 3.2 years, which is pretty significant. So this study was particularly very promising.

Going back to our first study, we asked the question, OK, we know that high education/occupation bumps up our cognitive performance. So you are performing right here if you have low education/occupation, but if you have high education, you're bumped up onto this trajectory.

What happens to an average individual who's on a vascular disease pathway? So you have vascular disease as well as you have high education/occupation. You're indicated by the dashed red line here. You're better off than a subject who has low education/occupation but have no pathologies. So it can really help you in the face of pathologies. Similarly for amyloid disease, you're helped by about five years. So if you have high education and occupation, you are indicated by this line, but you have amyloid disease, which is a bad thing, but you're still five years better off than someone who has low education and occupation, that's significant amount of help. And similarly, if you have both but you have none, you can be helped by about two years with higher education and occupation.

Conclusions from the second part of my talk are that lifetime intellectual enrichment may help delay the onset of cognitive impairment. And we need to look at providing better education and jobs and intellectual enrichment to mid/late-life individuals.

Coming to the final part of my talk, I'll talk about mechanisms underlying cognitive reserve. So I think this is one of the most debated field in the area I work in, because every couple of months or so, there's a paper out, and everybody comes up with a different hypothesis of how cognitive reserve is helping. So our initial understanding was that there's an independent effect on cognition, and there are studies, not only the one indicated here, but the last couple of studies, one said that it prevents neuro degeneration. The other said it helps with glucose metabolism. One more said that it lowers amyloid deposition, but it doesn't affect the others. So there's so much literature in this area, but none of them agree with each other. No two studies are alike, so far, I've seen.

And the third argument is that there's an interaction between pathologies and cognitively-stimulating activities, which help cognition. So we have been trying to understand what exactly happens. We are not the only group, but we'd really like to understand the science of what's happening.

So we identified individuals in the Mayo Clinic Study of Aging and tried to understand the longitudinal imaging changes with respect to intellectual enrichment. And this required everybody to have two imaging visits, which dropped the number of subjects we had. And I'd like you to focus on the first panel. The first panel shows amyloid, the position, as a function of age, similar to the curves I showed earlier when I explained amyloid in the brain. And as you can see, E4 carriers have much higher rate of deposition, as well as higher baseline amyloid deposition in their brain. E4 non-carriers have lower degree of deposition. So we did not see any effect of intellectual enrichment on our models.

But then we stratified it by education. So there are these subset of people, higher educated people and engaging in high cognitive activity. And then we saw that the top panel shows you subjects with high education. You see that people who are at genetic risk of Alzheimer's disease, indicated by the blue lines here, you have a subtle effect on the degree of improvement. So you have less amyloid deposition if you have higher mid/late-life cognitive activity. So you can see the difference in the curves here.

But in lower education/occupation subjects, we did not see any dramatic effects, which indicates that there are about 10% of the population who would be really helped by high education and occupation in clearing the amount of amyloid in their brain. We don't completely understand the mechanisms through which they happen, but this is promising. And this could be the reason why there are several contradicting and conflicting results in the literature. Because the average education in the United States is about 11, depending on what group of patients you recruit, you might see different effects on the biomarkers in the brain.

So what specifically drives the difference? So we asked the question-- we recorded all this information. There are four groups of people-- high education/occupation, high mid/late-life cognitive activity, low education and occupation, high mid/late-life activity. So there are four different groups of subjects and what is the main thing that drives subjects who seem to do better? It's these four things. The top four things are reading books and magazines, computer games, and playing games and computer activities, such as checking email and doing more on the computer. So these four came out at the top.

Conclusions from the third part of my talk are, in the overall population, there seems to be a minimal effect of intellectual enrichment on amyloid deposition, but in a small segment of people, about 10% or so, subjects with high education and occupation, high mid-life cognitive activity, as well as high genetic risk of Alzheimer's disease, it seems to lower the baseline amyloid deposition, which is extremely promising.

So summarizing our cognitive reserve models, we believe that it mainly has little effect on biomarkers of pathology but what? Better lifestyles. Better physical and cognitive activities will help us, moving your cognitive decline, the downstream cognitive decline curve up or down relative to the upstream pathologies.

So I just wanted to take a short scenic detour, because we talk a lot about translational research in this forum. So I wanted to show you a couple of studies we have been doing at the Aging and Dementia Imaging Research Lab that would be useful applications of what we are currently investigating. So we have been trying to understand how atrophy changes in structural MRI scan and try to use them for differential diagnosis of individuals. So you can see an MRI can give very useful information in determining what happens in different brain structures.

As you can see, this is a 90-year-old male with AD. So it can give you a quantification, a way to quantify where the atrophy is and ultimately, help a lot with differential diagnosis of the patient. This particular application that we worked on was providing automated individual patient diagnosis based on a library of scans. And without-- just based on an image, we can do pretty well, about 90% in independent samples in separating Alzheimer's disease patients from normals. So there's significant amount of work being done at our lab to quantify and to move towards automated and neutral patient diagnosis.

The overall conclusions of my talk are, we talked about amyloid and vascular disease pathologies, and those two are the major drivers of cognitive impairment in the elderly. The second is that better intellectual lifestyle is really important. It improves baseline performance, as well as it helps you borrow time before cognitive impairment is detected. And currently, cutting-edge imaging acquisition and processing tools that are available, which not only help clinicians, in terms of understanding the disease processes, prognosis, as well as diagnosis, it helps the patients in understanding where in the disease process they are, as well as it will help us, in the future, to come up with treatment plans, which are personalized to each individual.

I'd like to thank all the collaborators that we have, especially the PIs of MCSA and the imaging portion of the grant, and the Aging and Dementia Imaging Laboratory, the Mayo Clinic ADRC, Mayo Clinic Study of Aging, and all the study participants and families, who take their time out to make such studies possible, and the generous grant support I've received in the recent past. Thank you.