WEBVTT

NOTE duration: ”00:10:31.296”

NOTE Confidence: 0.9763176

00:00:02.720 --> 00:00:04.400 Hi. Our next speaker is

NOTE Confidence: 0.9763176

00:00:04.400 --> 00:00:05.859 doctor Carolyn Fredericks.

NOTE Confidence: 0.9791084

00:00:06.240 --> 00:00:08.180 She graduated from Brown University

NOTE Confidence: 0.9791084

00:00:08.320 --> 00:00:10.000 and completed her medical training

NOTE Confidence: 0.9791084

00:00:10.000 --> 00:00:10.740 at Stanford,

NOTE Confidence: 0.9394995

00:00:11.039 --> 00:00:12.900 Johns Hopkins Hospital, and UCSF

NOTE Confidence: 0.9394995

00:00:13.119 --> 00:00:14.420 specializing in neurology

NOTE Confidence: 0.9982934

00:00:15.005 --> 00:00:16.285 and did a fellowship in

NOTE Confidence: 0.9982934

00:00:16.285 --> 00:00:18.145 behavioral neurology at the UCSF

NOTE Confidence: 0.9738275

00:00:18.605 --> 00:00:20.605 memory and aging center. Her

NOTE Confidence: 0.9738275

00:00:20.605 --> 00:00:22.925 lab uses multimodal neuroimaging to

NOTE Confidence: 0.9738275

00:00:22.925 --> 00:00:25.085 better understand the relationship between

NOTE Confidence: 0.9738275

00:00:25.085 --> 00:00:26.064 functional circuitry,

NOTE Confidence: 0.99962676

00:00:26.605 --> 00:00:27.105 neurodegenerative

NOTE Confidence: 0.9929204

00:00:27.564 --> 00:00:30.300 pathology, and symptom trajectory in

NOTE Confidence: 0.9929204

00:00:30.300 --> 00:00:32.879 people with preclinical neurodegenerative symptoms.

NOTE Confidence: 0.9829145

00:00:33.340 --> 00:00:35.040 And, clinically, she sees individuals

NOTE Confidence: 0.9829145

00:00:35.260 --> 00:00:36.559 with a variety of cognitive

NOTE Confidence: 0.9829145

00:00:36.620 --> 00:00:38.780 and behavioral complaints, including those

NOTE Confidence: 0.9829145

00:00:38.780 --> 00:00:40.379 with less common variants of

NOTE Confidence: 0.9829145

00:00:40.379 --> 00:00:40.879 neurodegenerative

NOTE Confidence: 0.9995184

00:00:41.260 --> 00:00:41.760 disease.

NOTE Confidence: 0.9649808

00:00:48.425 --> 00:00:49.464 Thanks so much for having

NOTE Confidence: 0.9649808

00:00:49.464 --> 00:00:49.964 me.

NOTE Confidence: 0.9729028

00:00:50.585 --> 00:00:51.625 So I'm gonna talk to

NOTE Confidence: 0.9729028

00:00:51.625 --> 00:00:52.344 you a little bit about

NOTE Confidence: 0.9729028

00:00:52.344 --> 00:00:53.545 what I consider the dimension

NOTE Confidence: 0.9729028

00:00:53.545 --> 00:00:55.385 of vulnerability in Alzheimer's disease

NOTE Confidence: 0.9729028

00:00:55.385 --> 00:00:56.670 and related dementia. So if

NOTE Confidence: 0.9729028

00:00:56.670 --> 00:00:57.710 all of you picture someone

NOTE Confidence: 0.9729028

00:00:57.710 --> 00:00:59.470 with Alzheimer's, you're probably picturing

NOTE Confidence: 0.9729028

00:00:59.470 --> 00:01:00.990 someone elderly with short term

NOTE Confidence: 0.9729028

00:01:00.990 --> 00:01:01.890 memory deficits,

NOTE Confidence: 0.9940125

00:01:02.270 --> 00:01:03.390 but there's also this period

NOTE Confidence: 0.9940125

00:01:03.390 --> 00:01:04.590 before that onset of clinical

NOTE Confidence: 0.9940125

00:01:04.590 --> 00:01:05.790 illness, right, where someone has

NOTE Confidence: 0.9940125

00:01:05.790 --> 00:01:07.150 a lot of Alzheimer's pathology

NOTE Confidence: 0.9940125

00:01:07.150 --> 00:01:08.610 in the brain, especially amyloid,

NOTE Confidence: 0.9940125

00:01:08.745 --> 00:01:10.365 but doesn't have clinically recognizable

NOTE Confidence: 0.9920935

00:01:10.825 --> 00:01:11.325 symptomatology

NOTE Confidence: 0.98765856

00:01:11.705 --> 00:01:13.145 yet. And even before that,

NOTE Confidence: 0.98765856

00:01:13.145 --> 00:01:14.105 there are groups of people

NOTE Confidence: 0.98765856

00:01:14.105 --> 00:01:15.305 who are much more vulnerable

NOTE Confidence: 0.98765856

00:01:15.305 --> 00:01:16.665 for a variety of reasons.

NOTE Confidence: 0.98765856

00:01:16.665 --> 00:01:17.944 So we're interested in that

NOTE Confidence: 0.98765856

00:01:17.944 --> 00:01:19.485 entire dimension in the lab.

NOTE Confidence: 0.9618165

00:01:19.785 --> 00:01:20.585 Many of you may know

NOTE Confidence: 0.9618165

00:01:20.585 --> 00:01:21.465 that age is the single

NOTE Confidence: 0.9618165

00:01:21.465 --> 00:01:23.065 biggest risk factor for Alzheimer's

NOTE Confidence: 0.9618165

00:01:23.065 --> 00:01:24.120 disease. You may not know

NOTE Confidence: 0.9618165

00:01:24.120 --> 00:01:25.560 that female sex is number

NOTE Confidence: 0.9618165

00:01:25.560 --> 00:01:27.319 two and that even common

NOTE Confidence: 0.9618165

00:01:27.319 --> 00:01:28.520 genotypes that we've all we're

NOTE Confidence: 0.9618165

00:01:28.520 --> 00:01:29.319 all aware of like the

NOTE Confidence: 0.9618165

00:01:29.319 --> 00:01:29.819 APOE4

NOTE Confidence: 0.9423194

00:01:30.120 --> 00:01:32.200 allele, heterozygotes where women have

NOTE Confidence: 0.9423194

00:01:32.200 --> 00:01:33.479 much more risk than men

NOTE Confidence: 0.9423194

00:01:33.479 --> 00:01:35.240 do, so we're interested in

NOTE Confidence: 0.9423194

00:01:35.240 --> 00:01:35.740 vulnerability

NOTE Confidence: 0.97464687

00:01:36.200 --> 00:01:37.185 like that as well. And

NOTE Confidence: 0.97464687

00:01:37.345 --> 00:01:38.225 in the next few minutes

NOTE Confidence: 0.97464687

00:01:38.225 --> 00:01:38.865 I'm going to take you

NOTE Confidence: 0.97464687

00:01:38.865 --> 00:01:39.505 on a bit of a

NOTE Confidence: 0.97464687

00:01:39.505 --> 00:01:41.024 whirlwind tour of several projects

NOTE Confidence: 0.97464687

00:01:41.024 --> 00:01:42.064 in my lab that look

NOTE Confidence: 0.97464687

00:01:42.064 --> 00:01:42.725 at vulnerability,

NOTE Confidence: 0.9650394

00:01:43.424 --> 00:01:45.125 from different different dimensions.

NOTE Confidence: 0.96491414

00:01:45.584 --> 00:01:46.545 The first we'll talk about

NOTE Confidence: 0.96491414

00:01:46.545 --> 00:01:47.825 what the functional connectome can

NOTE Confidence: 0.96491414

00:01:47.825 --> 00:01:49.185 tell us about vulnerability to

NOTE Confidence: 0.96491414

00:01:49.185 --> 00:01:50.625 Alzheimer's disease and how that

NOTE Confidence: 0.96491414

00:01:50.625 --> 00:01:52.085 may actually present some opportunities.

NOTE Confidence: 0.99499613

00:01:52.670 --> 00:01:53.469 Next, we'll talk a little

NOTE Confidence: 0.99499613

00:01:53.469 --> 00:01:54.429 bit more about why women

NOTE Confidence: 0.99499613

00:01:54.429 --> 00:01:55.390 may be at greater risk

NOTE Confidence: 0.99499613

00:01:55.390 --> 00:01:57.090 for aggressive Alzheimer's disease.

NOTE Confidence: 0.96097887

00:01:57.390 --> 00:01:58.429 We'll take a detour away

NOTE Confidence: 0.96097887

00:01:58.429 --> 00:01:59.469 from Alzheimer's and into the

NOTE Confidence: 0.96097887

00:01:59.469 --> 00:02:00.450 world of alpha synucleinopathy,

NOTE Confidence: 0.96860176

00:02:00.750 --> 00:02:02.369 and in particular, the preclinical

NOTE Confidence: 0.96860176

00:02:02.590 --> 00:02:04.109 state of alpha synucleinopathy called

NOTE Confidence: 0.96860176

00:02:04.109 --> 00:02:05.170 REM behavior disorder.

NOTE Confidence: 0.9710487

00:02:05.485 --> 00:02:06.204 And then I also wanna

NOTE Confidence: 0.9710487

00:02:06.204 --> 00:02:07.485 touch on some really exciting

NOTE Confidence: 0.9710487

00:02:07.485 --> 00:02:08.525 work by my colleagues at

NOTE Confidence: 0.9710487

00:02:08.525 --> 00:02:09.565 the Pet Center looking at

NOTE Confidence: 0.9710487

00:02:09.565 --> 00:02:11.485 the relationship between perfusion and

NOTE Confidence: 0.9710487

00:02:11.485 --> 00:02:11.985 tau.

NOTE Confidence: 0.9599661

00:02:13.245 --> 00:02:14.205 So to start off with

NOTE Confidence: 0.9599661

00:02:14.205 --> 00:02:15.165 in terms of the functional

NOTE Confidence: 0.9599661

00:02:15.165 --> 00:02:16.125 connectome and what it can

NOTE Confidence: 0.9599661

00:02:16.125 --> 00:02:17.565 tell us about vulnerability to

NOTE Confidence: 0.9599661

00:02:17.565 --> 00:02:18.989 Alzheimer's disease, The work I'm

NOTE Confidence: 0.9599661

00:02:18.989 --> 00:02:20.189 gonna share with you is

NOTE Confidence: 0.9599661

00:02:20.189 --> 00:02:21.709 spearheaded by a graduate student

NOTE Confidence: 0.9599661

00:02:21.709 --> 00:02:22.909 in my and Todd Constable's

NOTE Confidence: 0.9599661

00:02:22.909 --> 00:02:24.349 lab who just defended defended

NOTE Confidence: 0.9599661

00:02:24.349 --> 00:02:26.129 his dissertation, Hamid Abu Warda.

NOTE Confidence: 0.9599661

00:02:26.349 --> 00:02:27.870 And Hamid took advantage of

NOTE Confidence: 0.9599661

00:02:27.870 --> 00:02:29.230 a technique developed by Todd

NOTE Confidence: 0.9599661

00:02:29.230 --> 00:02:30.829 Constable's group called connectome based

NOTE Confidence: 0.9599661

00:02:30.829 --> 00:02:32.189 predictive modeling, which many of

NOTE Confidence: 0.9599661

00:02:32.189 --> 00:02:33.389 you here may be familiar

NOTE Confidence: 0.9599661

00:02:33.389 --> 00:02:35.065 with, essentially a linear machine

NOTE Confidence: 0.9599661

00:02:35.065 --> 00:02:37.005 based machine learning based model

NOTE Confidence: 0.9599661

00:02:37.065 --> 00:02:38.264 that allows us to predict

NOTE Confidence: 0.9599661

00:02:38.264 --> 00:02:39.785 measures like how the edges

NOTE Confidence: 0.9599661

00:02:39.785 --> 00:02:41.065 of the functional connectome can

NOTE Confidence: 0.9599661

00:02:41.065 --> 00:02:43.145 predict fluid intelligence or scores

NOTE Confidence: 0.9599661

00:02:43.145 --> 00:02:44.764 on cognitive or functional

NOTE Confidence: 0.99030864

00:02:45.225 --> 00:02:46.285 behavioral assays.

NOTE Confidence: 0.98342156

00:02:46.600 --> 00:02:47.320 For me, it had the

NOTE Confidence: 0.98342156

00:02:47.320 --> 00:02:48.360 idea that perhaps we could

NOTE Confidence: 0.98342156

00:02:48.360 --> 00:02:49.639 use this method to predict

NOTE Confidence: 0.98342156

00:02:49.639 --> 00:02:50.700 pathology instead.

NOTE Confidence: 0.93903583

00:02:51.000 --> 00:02:51.960 So in people in this

NOTE Confidence: 0.93903583

00:02:51.960 --> 00:02:53.560 preclinical cohort, this is from

NOTE Confidence: 0.93903583

00:02:53.560 --> 00:02:54.600 the A four study, which

NOTE Confidence: 0.93903583

00:02:54.600 --> 00:02:55.639 is a study of anti

NOTE Confidence: 0.93903583

00:02:55.639 --> 00:02:57.000 amyloid antibody in people with

NOTE Confidence: 0.93903583

00:02:57.000 --> 00:02:59.084 preclinical Alzheimer's disease, The study

NOTE Confidence: 0.93903583

00:02:59.084 --> 00:03:00.444 unfortunately failed, but the data

NOTE Confidence: 0.93903583

00:03:00.444 --> 00:03:01.565 were released to the research

NOTE Confidence: 0.93903583

00:03:01.565 --> 00:03:02.065 community.

NOTE Confidence: 0.98793995

00:03:02.444 --> 00:03:03.165 So we have this huge

NOTE Confidence: 0.98793995

00:03:03.165 --> 00:03:04.205 cohort of people in this

NOTE Confidence: 0.98793995

00:03:04.205 --> 00:03:05.724 preclinical stage of disease, and

NOTE Confidence: 0.98793995

00:03:05.724 --> 00:03:07.325 Hameed developed models based on

NOTE Confidence: 0.98793995

00:03:07.325 --> 00:03:08.685 the connections between the brain

NOTE Confidence: 0.98793995

00:03:08.685 --> 00:03:10.044 from fMRI to see if

NOTE Confidence: 0.98793995

00:03:10.044 --> 00:03:11.325 we could predict focal tau

NOTE Confidence: 0.98793995

00:03:11.325 --> 00:03:12.364 in different regions of the

NOTE Confidence: 0.98793995

00:03:12.364 --> 00:03:12.864 brain.

NOTE Confidence: 0.965854

00:03:13.180 --> 00:03:14.220 And now you might expect

NOTE Confidence: 0.965854

00:03:14.220 --> 00:03:14.940 that we'd be best at

NOTE Confidence: 0.965854

00:03:14.940 --> 00:03:16.139 predicting tau in the very

NOTE Confidence: 0.965854

00:03:16.139 --> 00:03:17.340 early Brock stage regions of

NOTE Confidence: 0.965854

00:03:17.340 --> 00:03:18.480 the brain, such as entorhinal

NOTE Confidence: 0.965854

00:03:18.540 --> 00:03:19.040 cortex,

NOTE Confidence: 0.6505829

00:03:19.419 --> 00:03:19.919 perhepocampal

NOTE Confidence: 0.98056567

00:03:20.220 --> 00:03:21.260 gyrus, because these people are

NOTE Confidence: 0.98056567

00:03:21.260 --> 00:03:22.540 so early in illness. That

NOTE Confidence: 0.98056567

00:03:22.540 --> 00:03:23.419 is not what we found,

NOTE Confidence: 0.98056567

00:03:23.419 --> 00:03:24.540 and those models were actually

NOTE Confidence: 0.98056567

00:03:24.540 --> 00:03:25.580 some of the worst performing

NOTE Confidence: 0.98056567

00:03:25.580 --> 00:03:26.620 that Hamid built, and those

NOTE Confidence: 0.98056567

00:03:26.620 --> 00:03:27.585 are in the blue box.

NOTE Confidence: 0.98056567

00:03:27.745 --> 00:03:28.865 Instead, we were best able

NOTE Confidence: 0.98056567

00:03:28.865 --> 00:03:30.145 to model tau in regions

NOTE Confidence: 0.98056567

00:03:30.145 --> 00:03:31.585 like the posterior cingulate and

NOTE Confidence: 0.98056567

00:03:31.585 --> 00:03:32.085 precuneus,

NOTE Confidence: 0.9659889

00:03:32.545 --> 00:03:33.505 which are important hubs in

NOTE Confidence: 0.9659889

00:03:33.505 --> 00:03:34.625 the default mode network, a

NOTE Confidence: 0.9659889

00:03:34.625 --> 00:03:35.585 network that seems to be

NOTE Confidence: 0.9659889

00:03:35.585 --> 00:03:37.425 preferentially targeted in Alzheimer's and

NOTE Confidence: 0.9659889

00:03:37.425 --> 00:03:38.625 that's observed short term memory

NOTE Confidence: 0.9659889

00:03:38.625 --> 00:03:40.145 function, but also are two

NOTE Confidence: 0.9659889

00:03:40.145 --> 00:03:41.345 of the biggest brain hubs

NOTE Confidence: 0.9659889

00:03:41.345 --> 00:03:42.165 just in general,

NOTE Confidence: 0.98979306

00:03:42.770 --> 00:03:43.730 in terms of the sheer

NOTE Confidence: 0.98979306

00:03:43.730 --> 00:03:45.170 number and importance of connections

NOTE Confidence: 0.98979306

00:03:45.170 --> 00:03:46.050 they have with other brain

NOTE Confidence: 0.98979306

00:03:46.050 --> 00:03:47.730 regions. So in retrospect, it

NOTE Confidence: 0.98979306

00:03:47.730 --> 00:03:48.690 may make sense that we're

NOTE Confidence: 0.98979306

00:03:48.690 --> 00:03:49.810 able to use the functional

NOTE Confidence: 0.98979306

00:03:49.810 --> 00:03:51.330 connectome best to predict tau

NOTE Confidence: 0.98979306

00:03:51.330 --> 00:03:52.290 in areas with the most

NOTE Confidence: 0.98979306

00:03:52.290 --> 00:03:53.190 functional connections.

NOTE Confidence: 0.97933644

00:03:54.130 --> 00:03:55.410 So building on that work,

NOTE Confidence: 0.97933644

00:03:55.410 --> 00:03:57.170 Mead wanted to move forward

NOTE Confidence: 0.97933644

00:03:57.170 --> 00:03:58.315 and see if we could

NOTE Confidence: 0.97933644

00:03:58.315 --> 00:03:58.815 identify,

NOTE Confidence: 0.99083287

00:03:59.195 --> 00:04:00.715 based on these functional connections,

NOTE Confidence: 0.99083287

00:04:00.715 --> 00:04:01.675 patients who might be more

NOTE Confidence: 0.99083287

00:04:01.675 --> 00:04:03.275 vulnerable to aggressive disease or

NOTE Confidence: 0.99083287

00:04:03.275 --> 00:04:04.635 patients who might benefit from

NOTE Confidence: 0.99083287

00:04:04.635 --> 00:04:05.535 specific treatments.

NOTE Confidence: 0.9720343

00:04:06.075 --> 00:04:07.115 And to do this, I

NOTE Confidence: 0.9720343

00:04:07.115 --> 00:04:08.155 should also say he he

NOTE Confidence: 0.9720343

00:04:08.155 --> 00:04:09.275 took this work and externally

NOTE Confidence: 0.9720343

00:04:09.275 --> 00:04:10.555 validated it in a clinical

NOTE Confidence: 0.9720343

00:04:10.555 --> 00:04:12.300 cohort, the ADNI cohort. So

NOTE Confidence: 0.9720343

00:04:12.300 --> 00:04:13.739 these models still apply for

NOTE Confidence: 0.9720343

00:04:13.739 --> 00:04:15.180 people who have clinical disease,

NOTE Confidence: 0.9720343

00:04:15.180 --> 00:04:16.080 not just preclinical.

NOTE Confidence: 0.9827273

00:04:17.820 --> 00:04:19.100 So moving forward, he used

NOTE Confidence: 0.9827273

00:04:19.100 --> 00:04:20.620 a clustering approach that was,

NOTE Confidence: 0.9827273

00:04:20.940 --> 00:04:22.540 actually pioneered by Leanne Williams

NOTE Confidence: 0.9827273

00:04:22.540 --> 00:04:23.339 right here at Yale and

NOTE Confidence: 0.9827273

00:04:23.339 --> 00:04:24.700 published in Nature Medicine last

NOTE Confidence: 0.9827273

00:04:24.700 --> 00:04:26.714 summer, and that essentially uses

NOTE Confidence: 0.9827273

00:04:26.714 --> 00:04:28.475 the functional connectivity scores of

NOTE Confidence: 0.9827273

00:04:28.475 --> 00:04:29.755 individuals that were derived from

NOTE Confidence: 0.9827273

00:04:29.755 --> 00:04:31.514 connectome based predictive modeling and

NOTE Confidence: 0.9827273

00:04:31.514 --> 00:04:33.035 puts them into clusters based

NOTE Confidence: 0.9827273

00:04:33.035 --> 00:04:33.914 on how much their edge

NOTE Confidence: 0.9827273

00:04:33.914 --> 00:04:35.755 weights resemble each other. So

NOTE Confidence: 0.9827273

00:04:35.755 --> 00:04:37.354 for our particular study, the

NOTE Confidence: 0.9827273

00:04:37.354 --> 00:04:38.955 best model was, was a

NOTE Confidence: 0.9827273

00:04:38.955 --> 00:04:40.095 two cluster model.

NOTE Confidence: 0.9704363

00:04:40.690 --> 00:04:41.730 And no need to read

NOTE Confidence: 0.9704363

00:04:41.730 --> 00:04:42.770 through this in-depth, but just

NOTE Confidence: 0.9704363

00:04:42.770 --> 00:04:43.650 to say that the patients

NOTE Confidence: 0.9704363

00:04:43.650 --> 00:04:44.529 who were in cluster one

NOTE Confidence: 0.9704363

00:04:44.529 --> 00:04:45.890 versus cluster two didn't differ

NOTE Confidence: 0.9704363

00:04:45.890 --> 00:04:47.010 in terms of their APOE

NOTE Confidence: 0.9704363

00:04:47.010 --> 00:04:48.290 status or how much amyloid

NOTE Confidence: 0.9704363

00:04:48.290 --> 00:04:49.330 they had in the brain.

NOTE Confidence: 0.9704363

00:04:49.330 --> 00:04:50.290 None of these sort of

NOTE Confidence: 0.9704363

00:04:50.290 --> 00:04:51.650 obvious factors that you might

NOTE Confidence: 0.9704363

00:04:51.650 --> 00:04:52.150 measure.

NOTE Confidence: 0.94214964

00:04:52.755 --> 00:04:53.875 However, when he looked at

NOTE Confidence: 0.94214964

00:04:53.875 --> 00:04:55.155 where their tau was, and

NOTE Confidence: 0.94214964

00:04:55.155 --> 00:04:56.435 again these clusters were derived

NOTE Confidence: 0.94214964

00:04:56.435 --> 00:04:58.135 using the functional edges only,

NOTE Confidence: 0.98428935

00:04:58.515 --> 00:04:59.875 they look quite different. So

NOTE Confidence: 0.98428935

00:04:59.875 --> 00:05:01.075 cluster one is individuals who

NOTE Confidence: 0.98428935

00:05:01.075 --> 00:05:02.695 have a very typical distribution

NOTE Confidence: 0.98428935

00:05:02.755 --> 00:05:03.715 of tau for someone with

NOTE Confidence: 0.98428935

00:05:03.715 --> 00:05:05.075 early Alzheimer's disease. They have

NOTE Confidence: 0.98428935

00:05:05.075 --> 00:05:05.795 a lot of it in

NOTE Confidence: 0.98428935

00:05:05.795 --> 00:05:07.235 the limbic regions, mesial and

NOTE Confidence: 0.98428935

00:05:07.235 --> 00:05:09.339 lateral temporal lobes. Cluster two

NOTE Confidence: 0.98428935

00:05:09.339 --> 00:05:10.639 looks really different, right?

NOTE Confidence: 0.9773322

00:05:10.940 --> 00:05:11.979 Even if you're not a

NOTE Confidence: 0.9773322

00:05:11.979 --> 00:05:13.339 brain imager you can appreciate

NOTE Confidence: 0.9773322

00:05:13.339 --> 00:05:14.460 that there's there's a bunch

NOTE Confidence: 0.9773322

00:05:14.460 --> 00:05:15.660 more tau in these these

NOTE Confidence: 0.9773322

00:05:15.660 --> 00:05:17.500 cortical regions, especially the parietal

NOTE Confidence: 0.9773322

00:05:17.500 --> 00:05:18.539 nodes that we talked about

NOTE Confidence: 0.9773322

00:05:18.539 --> 00:05:19.039 before,

NOTE Confidence: 0.99926215

00:05:19.419 --> 00:05:20.620 that are such important brain

NOTE Confidence: 0.99926215

00:05:20.620 --> 00:05:21.105 hubs.

NOTE Confidence: 0.9787188

00:05:21.585 --> 00:05:23.105 So Hamid next asked so

NOTE Confidence: 0.9787188

00:05:23.105 --> 00:05:24.145 the a four study, again,

NOTE Confidence: 0.9787188

00:05:24.145 --> 00:05:25.265 is the dataset we're using.

NOTE Confidence: 0.9787188

00:05:25.265 --> 00:05:25.904 They had a bunch of

NOTE Confidence: 0.9787188

00:05:25.904 --> 00:05:26.705 people who were just kept

NOTE Confidence: 0.9787188

00:05:26.705 --> 00:05:27.825 on placebo through the course

NOTE Confidence: 0.9787188

00:05:27.825 --> 00:05:28.625 of the study, so we

NOTE Confidence: 0.9787188

00:05:28.625 --> 00:05:29.345 can sort of see what

NOTE Confidence: 0.9787188

00:05:29.345 --> 00:05:30.865 the natural history is for

NOTE Confidence: 0.9787188

00:05:30.865 --> 00:05:31.904 people who are in cluster

NOTE Confidence: 0.9787188

00:05:31.904 --> 00:05:33.185 one or cluster two based

NOTE Confidence: 0.9787188

00:05:33.185 --> 00:05:34.464 on their functional connectomes at

NOTE Confidence: 0.9787188

00:05:34.464 --> 00:05:34.964 baseline.

NOTE Confidence: 0.97007746

00:05:35.689 --> 00:05:36.810 And what he found is

NOTE Confidence: 0.97007746

00:05:36.810 --> 00:05:38.330 that both groups do more

NOTE Confidence: 0.97007746

00:05:38.330 --> 00:05:39.210 poorly over time as you

NOTE Confidence: 0.97007746

00:05:39.210 --> 00:05:40.490 would expect for anyone with

NOTE Confidence: 0.97007746

00:05:40.490 --> 00:05:41.389 Alzheimer's disease,

NOTE Confidence: 0.9742915

00:05:41.770 --> 00:05:42.810 but that cluster one has

NOTE Confidence: 0.9742915

00:05:42.810 --> 00:05:44.089 a much slower progression, the

NOTE Confidence: 0.9742915

00:05:44.089 --> 00:05:45.370 ones with the typical tau

NOTE Confidence: 0.9742915

00:05:45.370 --> 00:05:46.889 distribution, whereas cluster two has

NOTE Confidence: 0.9742915

00:05:46.889 --> 00:05:48.509 a much more dramatic decline

NOTE Confidence: 0.9742915

00:05:48.784 --> 00:05:50.485 on this primary out endpoint,

NOTE Confidence: 0.958629

00:05:51.345 --> 00:05:52.944 composite cognitive measure that the

NOTE Confidence: 0.958629

00:05:52.944 --> 00:05:54.145 a four study reports, the

NOTE Confidence: 0.958629

00:05:54.145 --> 00:05:54.645 PAC.

NOTE Confidence: 0.9908582

00:05:56.305 --> 00:05:57.425 This is the data from

NOTE Confidence: 0.9908582

00:05:57.425 --> 00:05:58.724 the entire phase three,

NOTE Confidence: 0.905078

00:05:59.185 --> 00:06:00.464 study that that report of

NOTE Confidence: 0.905078

00:06:00.464 --> 00:06:01.844 the negative study. So solanizumab

NOTE Confidence: 0.905078

00:06:01.985 --> 00:06:03.185 in general failed to delay

NOTE Confidence: 0.905078

00:06:03.185 --> 00:06:03.264 cognitive decline. You can see

NOTE Confidence: 0.905078

00:06:03.264 --> 00:06:03.344 there's no separation between the

NOTE Confidence: 0.905078

00:06:03.344 --> 00:06:04.240 placebo and decline. You can

NOTE Confidence: 0.905078

00:06:04.240 --> 00:06:05.520 see there's no separation between

NOTE Confidence: 0.905078

00:06:05.520 --> 00:06:07.380 the placebo and solenozumab groups

NOTE Confidence: 0.905078

00:06:07.520 --> 00:06:08.339 at any point.

NOTE Confidence: 0.98243934

00:06:08.960 --> 00:06:10.080 And this was an expensive

NOTE Confidence: 0.98243934

00:06:10.080 --> 00:06:12.400 study too, so a big

NOTE Confidence: 0.98243934

00:06:12.400 --> 00:06:13.360 disappointment to all of us

NOTE Confidence: 0.98243934

00:06:13.360 --> 00:06:14.639 in the field. What if

NOTE Confidence: 0.98243934

00:06:14.639 --> 00:06:15.520 you look at how people

NOTE Confidence: 0.98243934

00:06:15.520 --> 00:06:16.800 do in cluster one versus

NOTE Confidence: 0.98243934

00:06:16.800 --> 00:06:18.339 cluster two on the drug?

NOTE Confidence: 0.98243934

00:06:18.595 --> 00:06:20.115 And this fascinated us. So

NOTE Confidence: 0.98243934

00:06:20.115 --> 00:06:20.915 if you look at people

NOTE Confidence: 0.98243934

00:06:20.915 --> 00:06:22.535 with that typical tau pattern,

NOTE Confidence: 0.98243934

00:06:22.755 --> 00:06:24.275 they show a similar response

NOTE Confidence: 0.98243934

00:06:24.275 --> 00:06:25.235 or lack of response to

NOTE Confidence: 0.98243934

00:06:25.235 --> 00:06:26.275 the drug as the overall

NOTE Confidence: 0.98243934

00:06:26.275 --> 00:06:27.475 study did. But when you

NOTE Confidence: 0.98243934

00:06:27.475 --> 00:06:28.435 look at those people with

NOTE Confidence: 0.98243934

00:06:28.435 --> 00:06:30.115 the more aggressive clinical course

NOTE Confidence: 0.98243934

00:06:30.115 --> 00:06:31.395 and that cortical pattern of

NOTE Confidence: 0.98243934

00:06:31.395 --> 00:06:32.595 tau who ended up sorted

NOTE Confidence: 0.98243934

00:06:32.595 --> 00:06:34.230 into cluster two, they actually

NOTE Confidence: 0.98243934

00:06:34.230 --> 00:06:35.510 do really well on this

NOTE Confidence: 0.98243934

00:06:35.510 --> 00:06:36.010 drug.

NOTE Confidence: 0.9801486

00:06:36.470 --> 00:06:37.350 So they have a forty

NOTE Confidence: 0.9801486

00:06:37.350 --> 00:06:38.630 eight percent reduction in cognitive

NOTE Confidence: 0.9801486

00:06:38.630 --> 00:06:39.610 decline on solenozumab

NOTE Confidence: 0.95573574

00:06:39.910 --> 00:06:41.110 versus placebo, and this is

NOTE Confidence: 0.95573574

00:06:41.110 --> 00:06:41.910 about a third of those

NOTE Confidence: 0.95573574

00:06:41.910 --> 00:06:43.130 who enrolled in the study.

NOTE Confidence: 0.9903067

00:06:44.070 --> 00:06:45.190 Hamid then went back and

NOTE Confidence: 0.9903067

00:06:45.190 --> 00:06:46.470 looked at how much tau

NOTE Confidence: 0.9903067

00:06:46.470 --> 00:06:47.805 was in that that region

NOTE Confidence: 0.9903067

00:06:47.805 --> 00:06:49.005 that includes the precuneus and

NOTE Confidence: 0.9903067

00:06:49.005 --> 00:06:50.764 posterior cingulate. And it turns

NOTE Confidence: 0.9903067

00:06:50.764 --> 00:06:52.285 out that individuals who had

NOTE Confidence: 0.9903067

00:06:52.285 --> 00:06:53.645 a high baseline level of

NOTE Confidence: 0.9903067

00:06:53.645 --> 00:06:54.685 tau in those regions are

NOTE Confidence: 0.9903067

00:06:54.685 --> 00:06:56.125 the ones who benefit most

NOTE Confidence: 0.9903067

00:06:56.125 --> 00:06:57.005 from the drug, as you

NOTE Confidence: 0.9903067

00:06:57.005 --> 00:06:57.884 can see in this heat

NOTE Confidence: 0.9903067

00:06:57.884 --> 00:06:58.544 map here.

NOTE Confidence: 0.98953736

00:06:59.529 --> 00:07:00.810 So we're really excited about

NOTE Confidence: 0.98953736

00:07:00.810 --> 00:07:01.850 this finding, and I think

NOTE Confidence: 0.98953736

00:07:01.850 --> 00:07:02.830 that it'll be,

NOTE Confidence: 0.9619597

00:07:03.450 --> 00:07:04.410 it has the potential to

NOTE Confidence: 0.9619597

00:07:04.410 --> 00:07:05.210 open up a new era

NOTE Confidence: 0.9619597

00:07:05.210 --> 00:07:06.430 where we can use fMRI

NOTE Confidence: 0.9619597

00:07:06.490 --> 00:07:08.010 to identify individuals who may

NOTE Confidence: 0.9619597

00:07:08.010 --> 00:07:09.450 more be maybe more vulnerable

NOTE Confidence: 0.9619597

00:07:09.450 --> 00:07:10.570 to aggressive disease or may

NOTE Confidence: 0.9619597

00:07:10.570 --> 00:07:12.330 be more responsive to specific

NOTE Confidence: 0.9619597

00:07:12.330 --> 00:07:12.830 treatments,

NOTE Confidence: 0.96864396

00:07:13.315 --> 00:07:14.195 at a fraction of the

NOTE Confidence: 0.96864396

00:07:14.195 --> 00:07:15.255 cost of Taupep.

NOTE Confidence: 0.97190934

00:07:17.635 --> 00:07:19.155 Moving on and and turning

NOTE Confidence: 0.97190934

00:07:19.155 --> 00:07:20.775 completely to a different topic,

NOTE Confidence: 0.97190934

00:07:20.915 --> 00:07:22.115 we are also very interested

NOTE Confidence: 0.97190934

00:07:22.115 --> 00:07:22.915 in why women are at

NOTE Confidence: 0.97190934

00:07:22.915 --> 00:07:24.275 more risk for aggressive AD,

NOTE Confidence: 0.97190934

00:07:24.275 --> 00:07:25.050 and this is work that

NOTE Confidence: 0.97190934

00:07:25.050 --> 00:07:26.050 I did soon after my

NOTE Confidence: 0.97190934

00:07:26.050 --> 00:07:27.430 arrival at Yale with Bronte

NOTE Confidence: 0.97190934

00:07:27.570 --> 00:07:28.930 Fisiktani, who is now an

NOTE Confidence: 0.97190934

00:07:28.930 --> 00:07:30.050 MD and about to start

NOTE Confidence: 0.97190934

00:07:30.050 --> 00:07:31.970 her psychiatry residency after graduating

NOTE Confidence: 0.97190934

00:07:31.970 --> 00:07:33.270 from the University of Washington.

NOTE Confidence: 0.95667005

00:07:33.570 --> 00:07:34.530 And what Bronte and I

NOTE Confidence: 0.95667005

00:07:34.530 --> 00:07:35.250 did was we looked at

NOTE Confidence: 0.95667005

00:07:35.250 --> 00:07:36.690 the Human Connectome Project Aging

NOTE Confidence: 0.95667005

00:07:36.690 --> 00:07:37.889 study, which looks at healthy

NOTE Confidence: 0.95667005

00:07:37.889 --> 00:07:38.770 men and women over the

NOTE Confidence: 0.95667005

00:07:38.770 --> 00:07:39.970 course of aging and obtains

NOTE Confidence: 0.95667005

00:07:39.970 --> 00:07:41.545 very high quality fMRI, we

NOTE Confidence: 0.95667005

00:07:41.545 --> 00:07:42.905 found this interesting pattern where

NOTE Confidence: 0.95667005

00:07:42.905 --> 00:07:44.025 these posterior nodes in the

NOTE Confidence: 0.95667005

00:07:44.025 --> 00:07:45.545 default mode network, again the

NOTE Confidence: 0.95667005

00:07:45.545 --> 00:07:47.145 network that serves short term

NOTE Confidence: 0.95667005

00:07:47.145 --> 00:07:48.505 memory performance and that seems

NOTE Confidence: 0.95667005

00:07:48.505 --> 00:07:49.785 to be especially targeted in

NOTE Confidence: 0.95667005

00:07:49.785 --> 00:07:50.845 amnestic disease,

NOTE Confidence: 0.9726761

00:07:51.225 --> 00:07:52.665 they have higher connectivity than

NOTE Confidence: 0.9726761

00:07:52.665 --> 00:07:53.705 men do in the posterior

NOTE Confidence: 0.9726761

00:07:53.705 --> 00:07:55.220 nodes of that network. We

NOTE Confidence: 0.9726761

00:07:55.220 --> 00:07:56.900 broke it down by, by

NOTE Confidence: 0.9726761

00:07:56.900 --> 00:07:57.860 decade and found that this

NOTE Confidence: 0.9726761

00:07:57.860 --> 00:07:59.139 was especially for women in

NOTE Confidence: 0.9726761

00:07:59.139 --> 00:08:00.180 their 50s, which of course

NOTE Confidence: 0.9726761

00:08:00.180 --> 00:08:01.300 is an interesting time in

NOTE Confidence: 0.9726761

00:08:01.300 --> 00:08:03.139 the reproductive life cycle for

NOTE Confidence: 0.9726761

00:08:03.139 --> 00:08:04.820 most women. This pattern still

NOTE Confidence: 0.9726761

00:08:04.820 --> 00:08:06.340 holds in the preclinical a

NOTE Confidence: 0.9726761

00:08:06.340 --> 00:08:07.575 four data set, So women

NOTE Confidence: 0.9726761

00:08:07.575 --> 00:08:09.255 who actually have amyloid pathology

NOTE Confidence: 0.9726761

00:08:09.255 --> 00:08:10.455 in their brains, if anything,

NOTE Confidence: 0.9726761

00:08:10.455 --> 00:08:12.215 have more so, this posterior

NOTE Confidence: 0.9726761

00:08:12.215 --> 00:08:12.715 hyperconnectivity.

NOTE Confidence: 0.9768792

00:08:13.895 --> 00:08:15.095 And now a very talented

NOTE Confidence: 0.9768792

00:08:15.095 --> 00:08:16.215 grad student in the lab,

NOTE Confidence: 0.9768792

00:08:16.215 --> 00:08:18.215 Jordan Galbraith, is taking this

NOTE Confidence: 0.9768792

00:08:18.215 --> 00:08:18.715 idea

NOTE Confidence: 0.9901582

00:08:19.015 --> 00:08:20.615 and looking into hormone levels

NOTE Confidence: 0.9901582

00:08:20.615 --> 00:08:21.275 in perimenopause

NOTE Confidence: 0.9813777

00:08:21.680 --> 00:08:22.720 to see whether levels of

NOTE Confidence: 0.9813777

00:08:22.720 --> 00:08:24.660 estrogen or FSH might correspond

NOTE Confidence: 0.9813777

00:08:24.800 --> 00:08:26.100 to some of these connectivity

NOTE Confidence: 0.9813777

00:08:26.160 --> 00:08:27.120 changes in women who are

NOTE Confidence: 0.9813777

00:08:27.120 --> 00:08:27.840 about to go through the

NOTE Confidence: 0.9813777

00:08:27.840 --> 00:08:29.840 menopausal transition and finding that,

NOTE Confidence: 0.9813777

00:08:29.840 --> 00:08:31.360 in fact, connectivity in the

NOTE Confidence: 0.9813777

00:08:31.360 --> 00:08:32.559 default mode network seems to

NOTE Confidence: 0.9813777

00:08:32.559 --> 00:08:34.000 correlate tightly with higher levels

NOTE Confidence: 0.9813777

00:08:34.000 --> 00:08:35.300 of FSH in perimenopause.

NOTE Confidence: 0.9787283

00:08:36.964 --> 00:08:38.005 I think that I am

NOTE Confidence: 0.9787283

00:08:38.005 --> 00:08:39.285 going too slowly, so I'm

NOTE Confidence: 0.9787283

00:08:39.285 --> 00:08:41.384 going to skip our detour,

NOTE Confidence: 0.7879467

00:08:41.764 --> 00:08:42.824 into alpha synuclein,

NOTE Confidence: 0.9285541

00:08:43.764 --> 00:08:44.964 but I would be delighted

NOTE Confidence: 0.9285541

00:08:44.964 --> 00:08:45.764 to talk about this work,

NOTE Confidence: 0.9285541

00:08:45.764 --> 00:08:46.884 which is in collaboration with

NOTE Confidence: 0.9285541

00:08:46.884 --> 00:08:48.084 Al Powers with our graduate

NOTE Confidence: 0.9285541

00:08:48.084 --> 00:08:49.524 student, Rena Vine, if we

NOTE Confidence: 0.9285541

00:08:49.524 --> 00:08:50.665 have time in the questions.

NOTE Confidence: 0.99131566

00:08:51.679 --> 00:08:52.960 And instead, I will share

NOTE Confidence: 0.99131566

00:08:52.960 --> 00:08:54.000 with you a little bit

NOTE Confidence: 0.99131566

00:08:54.000 --> 00:08:54.500 about,

NOTE Confidence: 0.8588039

00:08:55.040 --> 00:08:56.240 the use of MK sixty

NOTE Confidence: 0.8588039

00:08:56.240 --> 00:08:57.679 two forty by two colleagues

NOTE Confidence: 0.8588039

00:08:57.679 --> 00:08:59.040 in the pet center, Nicola

NOTE Confidence: 0.8588039

00:08:59.040 --> 00:09:00.660 Aigel and Meva Daneout.

NOTE Confidence: 0.9871248

00:09:01.679 --> 00:09:02.880 MK sixty two forty is

NOTE Confidence: 0.9871248

00:09:02.880 --> 00:09:04.580 a second generation tau tracer.

NOTE Confidence: 0.9871248

00:09:04.755 --> 00:09:05.875 It has a lot of

NOTE Confidence: 0.9871248

00:09:05.875 --> 00:09:07.315 selectivity and high affinity for

NOTE Confidence: 0.9871248

00:09:07.315 --> 00:09:08.434 tau, and it also shows

NOTE Confidence: 0.9871248

00:09:08.434 --> 00:09:09.975 relatively fast brain penetration,

NOTE Confidence: 0.9829457

00:09:10.355 --> 00:09:11.475 which allows us to use

NOTE Confidence: 0.9829457

00:09:11.475 --> 00:09:12.755 the early phase of dynamic

NOTE Confidence: 0.9829457

00:09:12.755 --> 00:09:14.595 scans to derive this r

NOTE Confidence: 0.9829457

00:09:14.595 --> 00:09:16.035 one parameter that essentially is

NOTE Confidence: 0.9829457

00:09:16.035 --> 00:09:17.235 an index of relative brain

NOTE Confidence: 0.9829457

00:09:17.235 --> 00:09:17.735 perfusion.

NOTE Confidence: 0.90493286

00:09:18.200 --> 00:09:19.240 And Nicola and Meva and

NOTE Confidence: 0.90493286

00:09:19.240 --> 00:09:20.200 their group have shown that

NOTE Confidence: 0.90493286

00:09:20.200 --> 00:09:22.380 these R1 values reveal regional

NOTE Confidence: 0.90493286

00:09:22.440 --> 00:09:24.040 perfusion differences in people with

NOTE Confidence: 0.90493286

00:09:24.040 --> 00:09:26.040 Alzheimer's disease, including earlier stages,

NOTE Confidence: 0.90493286

00:09:26.040 --> 00:09:28.279 and cognitively unimpaired individuals, and

NOTE Confidence: 0.90493286

00:09:28.279 --> 00:09:29.720 that those correlate strongly with

NOTE Confidence: 0.90493286

00:09:29.720 --> 00:09:31.214 fifteen o water PET. So

NOTE Confidence: 0.90493286

00:09:31.214 --> 00:09:32.654 this is is supporting its

NOTE Confidence: 0.90493286

00:09:32.654 --> 00:09:34.255 uses to surrogate marker marker

NOTE Confidence: 0.90493286

00:09:34.255 --> 00:09:34.995 of perfusion.

NOTE Confidence: 0.95384413

00:09:35.774 --> 00:09:36.894 And that means that essentially

NOTE Confidence: 0.95384413

00:09:36.894 --> 00:09:37.615 if we get an MK

NOTE Confidence: 0.95384413

00:09:37.615 --> 00:09:38.574 scan we can measure both

NOTE Confidence: 0.95384413

00:09:38.574 --> 00:09:40.415 perfusion and tau single scan

NOTE Confidence: 0.95384413

00:09:40.415 --> 00:09:41.694 with no added cost or

NOTE Confidence: 0.95384413

00:09:41.694 --> 00:09:42.194 dose.

NOTE Confidence: 0.9590692

00:09:42.815 --> 00:09:43.774 What's very cool is the

NOTE Confidence: 0.9590692

00:09:43.774 --> 00:09:44.894 work that they've done in

NOTE Confidence: 0.9590692

00:09:44.894 --> 00:09:46.334 dizzy across disease stages of

NOTE Confidence: 0.9590692

00:09:46.334 --> 00:09:47.510 AD. So on the left

NOTE Confidence: 0.9590692

00:09:47.510 --> 00:09:48.790 you see controls who don't

NOTE Confidence: 0.9590692

00:09:48.790 --> 00:09:49.910 have amyloid in their brains

NOTE Confidence: 0.9590692

00:09:49.910 --> 00:09:51.750 there's no consistent correlation between

NOTE Confidence: 0.9590692

00:09:51.750 --> 00:09:53.429 perfusion that r1 parameter and

NOTE Confidence: 0.9590692

00:09:53.429 --> 00:09:54.550 tau, but then if you

NOTE Confidence: 0.9590692

00:09:54.550 --> 00:09:55.290 look at individuals

NOTE Confidence: 0.96699095

00:09:55.910 --> 00:09:57.350 with preclinical AD like the

NOTE Confidence: 0.96699095

00:09:57.350 --> 00:09:58.309 a four cohort we were

NOTE Confidence: 0.96699095

00:09:58.309 --> 00:09:59.905 talking about before you can

NOTE Confidence: 0.96699095

00:09:59.905 --> 00:10:01.184 see that higher perfusion is

NOTE Confidence: 0.96699095

00:10:01.184 --> 00:10:02.385 actually linked with early tau

NOTE Confidence: 0.96699095

00:10:02.385 --> 00:10:03.745 deposition, and this is thought

NOTE Confidence: 0.96699095

00:10:03.745 --> 00:10:04.885 to be maybe a compensatory

NOTE Confidence: 0.96699095

00:10:05.025 --> 00:10:06.385 response. Once you get into

NOTE Confidence: 0.96699095

00:10:06.385 --> 00:10:07.665 clinical illness in the patients

NOTE Confidence: 0.96699095

00:10:07.665 --> 00:10:09.265 with mild cognitive impairment and

NOTE Confidence: 0.96699095

00:10:09.265 --> 00:10:10.945 AD, high tau is associated

NOTE Confidence: 0.96699095

00:10:10.945 --> 00:10:12.400 with low perfusion, which might

NOTE Confidence: 0.96699095

00:10:12.400 --> 00:10:13.760 reflect a breakdown of that

NOTE Confidence: 0.96699095

00:10:13.760 --> 00:10:14.260 compensatory

NOTE Confidence: 0.99130136

00:10:14.720 --> 00:10:15.840 process and a shift towards

NOTE Confidence: 0.99130136

00:10:15.840 --> 00:10:16.340 neurodegeneration

NOTE Confidence: 0.9950361

00:10:16.720 --> 00:10:17.300 and decline.

NOTE Confidence: 0.96536267

00:10:17.760 --> 00:10:19.040 So taken together, r one

NOTE Confidence: 0.96536267

00:10:19.040 --> 00:10:19.760 seems to serve as a

NOTE Confidence: 0.96536267

00:10:19.760 --> 00:10:21.440 dual marker, compensation in early

NOTE Confidence: 0.96536267

00:10:21.440 --> 00:10:23.120 disease and dysfunction in later

NOTE Confidence: 0.96536267

00:10:23.120 --> 00:10:23.620 stages.

NOTE Confidence: 0.96111786

00:10:25.270 --> 00:10:26.230 With that, I want to

NOTE Confidence: 0.96111786

00:10:26.230 --> 00:10:27.350 thank all of you for

NOTE Confidence: 0.96111786

00:10:27.350 --> 00:10:28.390 for your attention and our

NOTE Confidence: 0.96111786

00:10:28.390 --> 00:10:29.910 sponsors and collaborators and the

NOTE Confidence: 0.96111786

00:10:29.910 --> 00:10:30.950 members of the lab. Thanks

NOTE Confidence: 0.96111786

00:10:30.950 --> 00:10:31.296 so much.