WEBVTT

NOTE duration: ”01:04:46.520”

NOTE Confidence: 0.9763165

00:00:14.315 --> 00:00:14.815 Alright.

NOTE Confidence: 0.9836875

00:00:19.595 --> 00:00:20.095 Hello?

NOTE Confidence: 0.99620026

00:00:22.235 --> 00:00:23.215 Hello? Hello?

NOTE Confidence: 0.98466134

00:00:23.994 --> 00:00:25.055 Can you hear me?

NOTE Confidence: 0.9785013

00:00:28.289 --> 00:00:28.789 Yes.

NOTE Confidence: 0.99836254

00:00:32.370 --> 00:00:34.150 Alright. We're gonna get going.

NOTE Confidence: 0.9456029

00:00:38.075 --> 00:00:39.934 Thank you all for, coming,

NOTE Confidence: 0.93047583

00:00:40.715 --> 00:00:41.534 to our,

NOTE Confidence: 0.97752076

00:00:42.235 --> 00:00:43.354 for the next month, we're

NOTE Confidence: 0.97752076

00:00:43.354 --> 00:00:44.795 gonna have what we are

NOTE Confidence: 0.97752076

00:00:44.795 --> 00:00:45.695 calling our,

NOTE Confidence: 0.810457

00:00:47.354 --> 00:00:47.854 research,

NOTE Confidence: 0.98756033

00:00:49.595 --> 00:00:50.095 symposiums

NOTE Confidence: 0.70165944

00:00:50.715 --> 00:00:52.979 or bridging clinic what wasn't

NOTE Confidence: 0.70165944

00:00:52.979 --> 00:00:53.380 the

NOTE Confidence: 0.89381707

00:00:54.340 --> 00:00:56.440 I forgot about it. Bridging,

NOTE Confidence: 0.9583942

00:00:57.220 --> 00:00:58.120 you know, clinical,

NOTE Confidence: 0.97451895

00:00:58.900 --> 00:00:59.400 translational,

NOTE Confidence: 0.92177266

00:00:59.780 --> 00:01:00.440 and research,

NOTE Confidence: 0.9397097

00:01:01.940 --> 00:01:02.840 in our department

NOTE Confidence: 0.95522624

00:01:03.220 --> 00:01:04.500 and, sort of get to

NOTE Confidence: 0.95522624

00:01:04.500 --> 00:01:04.660 know,

NOTE Confidence: 0.9998817

00:01:05.745 --> 00:01:06.885 some of our researchers

NOTE Confidence: 0.8127397

00:01:07.825 --> 00:01:08.145 and,

NOTE Confidence: 0.9789988

00:01:09.025 --> 00:01:11.345 hopefully, ask questions and, you

NOTE Confidence: 0.9789988

00:01:11.345 --> 00:01:13.125 know, bring friend you know,

NOTE Confidence: 0.96917474

00:01:13.825 --> 00:01:15.265 find some common areas of

NOTE Confidence: 0.96917474

00:01:15.265 --> 00:01:16.705 interest. And, hopefully, this is

NOTE Confidence: 0.96917474

00:01:16.705 --> 00:01:17.685 gonna lead to

NOTE Confidence: 0.9982925

00:01:17.985 --> 00:01:19.765 some exciting research and

NOTE Confidence: 0.8636167

00:01:20.369 --> 00:01:20.869 translation,

NOTE Confidence: 0.99715805

00:01:21.329 --> 00:01:21.829 ultimately.

NOTE Confidence: 0.83058494

00:01:23.409 --> 00:01:25.189 So or friendship or friendship.

NOTE Confidence: 0.83058494

00:01:25.329 --> 00:01:25.990 Yeah. Exactly.

NOTE Confidence: 0.9730794

00:01:26.530 --> 00:01:27.030 Grants

NOTE Confidence: 0.7485461

00:01:28.049 --> 00:01:28.709 and etcetera.

NOTE Confidence: 0.96008706

00:01:29.810 --> 00:01:30.310 So,

NOTE Confidence: 0.89928055

00:01:31.569 --> 00:01:32.770 just to get going quickly,

NOTE Confidence: 0.89928055

00:01:32.770 --> 00:01:33.490 I mean, we have two

NOTE Confidence: 0.89928055

00:01:33.490 --> 00:01:34.549 distinguished, investigators from our

NOTE Confidence: 0.96067375

00:01:37.875 --> 00:01:38.755 there's gonna be a lot

NOTE Confidence: 0.96067375

00:01:38.755 --> 00:01:39.255 about,

NOTE Confidence: 0.98081124

00:01:39.715 --> 00:01:41.415 Parkinson's disease and neurodegeneration.

NOTE Confidence: 0.9851946

00:01:42.194 --> 00:01:43.095 And I'm gonna,

NOTE Confidence: 0.99889976

00:01:43.555 --> 00:01:45.555 have Vanessa introduce our distinguished

NOTE Confidence: 0.99889976

00:01:45.555 --> 00:01:46.055 speakers.

NOTE Confidence: 0.982903

00:01:49.799 --> 00:01:51.560 Hello, everyone. Good afternoon. For

NOTE Confidence: 0.982903

00:01:51.560 --> 00:01:52.520 those who don't know me,

NOTE Confidence: 0.982903

00:01:52.520 --> 00:01:53.640 I'm Vanessa, one of the

NOTE Confidence: 0.982903

00:01:53.640 --> 00:01:55.259 fourth year neurology residents,

NOTE Confidence: 0.988011

00:01:55.720 --> 00:01:56.540 and welcome.

NOTE Confidence: 0.981336

00:01:57.159 --> 00:01:58.360 Today, we're gonna have two

NOTE Confidence: 0.981336

00:01:58.360 --> 00:01:59.579 for the price of one.

NOTE Confidence: 0.95180786

00:02:00.200 --> 00:02:01.720 So first, we're gonna have

NOTE Confidence: 0.95180786

00:02:01.720 --> 00:02:02.780 doctor, Bierder.

NOTE Confidence: 0.92392683

00:02:03.555 --> 00:02:05.075 He received a PhD in

NOTE Confidence: 0.92392683

00:02:05.075 --> 00:02:05.814 cell biology

NOTE Confidence: 0.69928247

00:02:06.195 --> 00:02:06.695 from,

NOTE Confidence: 0.82360643

00:02:07.395 --> 00:02:08.355 pardon my,

NOTE Confidence: 0.9286582

00:02:09.155 --> 00:02:09.655 German,

NOTE Confidence: 0.88557863

00:02:10.595 --> 00:02:11.894 the Humboldt Universitat,

NOTE Confidence: 0.84203005

00:02:12.435 --> 00:02:13.815 zu Berlin in Germany.

NOTE Confidence: 0.92818147

00:02:14.514 --> 00:02:15.575 After his postdoctoral,

NOTE Confidence: 0.94000626

00:02:16.275 --> 00:02:17.735 training with doctor Thomas,

NOTE Confidence: 0.81339

00:02:18.114 --> 00:02:18.614 Sudoff,

NOTE Confidence: 0.7412329

00:02:19.500 --> 00:02:20.400 Doctor Bitter,

NOTE Confidence: 0.96755904

00:02:20.860 --> 00:02:22.540 became a faculty member here

NOTE Confidence: 0.96755904

00:02:22.540 --> 00:02:23.580 at Yale in two thousand

NOTE Confidence: 0.96755904

00:02:23.580 --> 00:02:24.860 and three. He took a

NOTE Confidence: 0.96755904

00:02:24.860 --> 00:02:26.540 position at Tufts in twenty

NOTE Confidence: 0.96755904

00:02:26.540 --> 00:02:28.300 thirteen before returning to Yale

NOTE Confidence: 0.96755904

00:02:28.300 --> 00:02:29.280 in twenty nineteen

NOTE Confidence: 0.9411104

00:02:29.820 --> 00:02:31.020 to join the faculty at

NOTE Confidence: 0.9411104

00:02:31.020 --> 00:02:32.320 the department of neurology.

NOTE Confidence: 0.9986542

00:02:33.225 --> 00:02:34.445 His current research

NOTE Confidence: 0.9586055

00:02:34.825 --> 00:02:36.905 addresses central questions to understand

NOTE Confidence: 0.9586055

00:02:36.905 --> 00:02:38.285 the biology of synopsis,

NOTE Confidence: 0.9968143

00:02:39.145 --> 00:02:41.325 the cellular structures that connect

NOTE Confidence: 0.9968143

00:02:41.385 --> 00:02:42.845 neurons into networks.

NOTE Confidence: 0.9543012

00:02:43.465 --> 00:02:45.885 First, how are new synapses

NOTE Confidence: 0.9543012

00:02:46.025 --> 00:02:46.525 formed?

NOTE Confidence: 0.97733694

00:02:46.940 --> 00:02:49.500 And second, which mechanisms control

NOTE Confidence: 0.97733694

00:02:49.500 --> 00:02:50.000 synapse,

NOTE Confidence: 0.77379173

00:02:50.540 --> 00:02:51.040 maintenance,

NOTE Confidence: 0.99952114

00:02:51.340 --> 00:02:52.959 and what makes them vulnerable

NOTE Confidence: 0.99433446

00:02:53.260 --> 00:02:54.879 and resilient in neurodegenerative

NOTE Confidence: 0.9840251

00:02:55.340 --> 00:02:55.840 disorders?

NOTE Confidence: 0.9841765

00:02:56.620 --> 00:02:57.919 To address these questions,

NOTE Confidence: 0.9992034

00:02:58.220 --> 00:03:00.239 his research group combines molecular

NOTE Confidence: 0.9992034

00:03:00.379 --> 00:03:00.879 studies

NOTE Confidence: 0.97760856

00:03:01.235 --> 00:03:03.254 with analysis of synaptic connectivity

NOTE Confidence: 0.97760856

00:03:03.474 --> 00:03:05.094 in the cortex and hippocampus,

NOTE Confidence: 0.90295535

00:03:07.314 --> 00:03:08.534 and mouse models.

NOTE Confidence: 0.9969521

00:03:08.915 --> 00:03:10.294 He leads a multidisciplinary

NOTE Confidence: 0.9958589

00:03:10.915 --> 00:03:12.694 team to address brain connectivity

NOTE Confidence: 0.9958589

00:03:12.915 --> 00:03:15.314 changes in Parkinson's disease, which

NOTE Confidence: 0.9958589

00:03:15.314 --> 00:03:16.775 he will talk about today.

NOTE Confidence: 0.93869656

00:03:17.530 --> 00:03:18.750 And doctor Chandra,

NOTE Confidence: 0.98363286

00:03:19.210 --> 00:03:20.270 our second speaker,

NOTE Confidence: 0.95577955

00:03:20.810 --> 00:03:22.830 received her PhD in chemistry

NOTE Confidence: 0.95577955

00:03:22.970 --> 00:03:24.350 from Purdue University.

NOTE Confidence: 0.90241814

00:03:25.370 --> 00:03:26.810 She pursued her interest in

NOTE Confidence: 0.90241814

00:03:26.810 --> 00:03:27.310 neuronal

NOTE Confidence: 0.9948386

00:03:27.770 --> 00:03:29.230 cell biology and neurodegeneration

NOTE Confidence: 0.9661717

00:03:30.010 --> 00:03:31.069 during her postdoctoral

NOTE Confidence: 0.99783087

00:03:31.450 --> 00:03:31.950 research.

NOTE Confidence: 0.99504894

00:03:33.084 --> 00:03:35.084 Doctor Chandra became a faculty

NOTE Confidence: 0.99504894

00:03:35.084 --> 00:03:36.305 member here at Yale,

NOTE Confidence: 0.97335017

00:03:36.765 --> 00:03:38.145 in two thousand and seven,

NOTE Confidence: 0.97335017

00:03:38.205 --> 00:03:39.665 where she's currently a professor

NOTE Confidence: 0.97335017

00:03:39.724 --> 00:03:41.105 in the department of neurology

NOTE Confidence: 0.97335017

00:03:41.325 --> 00:03:43.185 departments of neurology and neuroscience.

NOTE Confidence: 0.99960536

00:03:43.885 --> 00:03:45.905 Her research focuses on two

NOTE Confidence: 0.99960536

00:03:45.965 --> 00:03:46.465 interconnected

NOTE Confidence: 0.9738152

00:03:46.765 --> 00:03:47.265 themes,

NOTE Confidence: 0.8267358

00:03:47.640 --> 00:03:49.819 synapse man maintenance and neurodegeneration,

NOTE Confidence: 0.99829626

00:03:50.599 --> 00:03:52.519 with a specific emphasis on

NOTE Confidence: 0.99829626

00:03:52.519 --> 00:03:54.780 Parkinson's disease and related disorders.

NOTE Confidence: 0.90366316

00:03:55.159 --> 00:03:56.540 Doctor Chandra's lab

NOTE Confidence: 0.9806968

00:03:56.920 --> 00:03:59.400 specifically studies familial Parkinson's disease

NOTE Confidence: 0.9806968

00:03:59.400 --> 00:04:01.900 genes that encode synaptic proteins.

NOTE Confidence: 0.9442076

00:04:02.555 --> 00:04:04.235 She also explores the, the

NOTE Confidence: 0.9442076

00:04:04.235 --> 00:04:05.455 role of the endolysisomal

NOTE Confidence: 0.9143985

00:04:05.915 --> 00:04:07.835 pathway in the disease and

NOTE Confidence: 0.9143985

00:04:07.835 --> 00:04:08.895 examine presynaptic

NOTE Confidence: 0.9850672

00:04:09.355 --> 00:04:09.855 proteostasis

NOTE Confidence: 0.97870785

00:04:10.395 --> 00:04:11.135 and dysfunction,

NOTE Confidence: 0.98309785

00:04:11.435 --> 00:04:12.575 which they hypothesize

NOTE Confidence: 0.98575693

00:04:12.955 --> 00:04:14.555 are central to the early

NOTE Confidence: 0.98575693

00:04:14.555 --> 00:04:15.535 synaptic events,

NOTE Confidence: 0.8482149

00:04:16.154 --> 00:04:17.135 of this neurodegenerative

NOTE Confidence: 0.999401

00:04:17.595 --> 00:04:18.095 disorders.

NOTE Confidence: 0.9866095

00:04:18.660 --> 00:04:20.420 Today, doctor Chandra will be

NOTE Confidence: 0.9866095

00:04:20.420 --> 00:04:22.340 discussing her research, in her

NOTE Confidence: 0.9866095

00:04:22.340 --> 00:04:23.380 talk named,

NOTE Confidence: 0.9436707

00:04:23.779 --> 00:04:26.040 elucidating the mechanisms of GBA

NOTE Confidence: 0.9436707

00:04:26.100 --> 00:04:28.420 linked Parkinson's and dementia with

NOTE Confidence: 0.9436707

00:04:28.420 --> 00:04:29.240 LVEE bodies.

NOTE Confidence: 0.9616372

00:04:30.580 --> 00:04:32.180 Now, well, help me to

NOTE Confidence: 0.9616372

00:04:32.180 --> 00:04:33.400 welcome them both.

NOTE Confidence: 0.99765366

00:04:42.275 --> 00:04:42.775 So

NOTE Confidence: 0.8748224

00:04:43.715 --> 00:04:45.015 thank everyone for,

NOTE Confidence: 0.9943574

00:04:45.715 --> 00:04:47.955 joining our research talks today.

NOTE Confidence: 0.9943574

00:04:47.955 --> 00:04:49.339 I think it's a splendid

NOTE Confidence: 0.9943574

00:04:49.400 --> 00:04:50.380 idea to,

NOTE Confidence: 0.9813517

00:04:51.000 --> 00:04:53.080 make, these efforts to better

NOTE Confidence: 0.9813517

00:04:53.080 --> 00:04:53.580 connect,

NOTE Confidence: 0.9978594

00:04:54.279 --> 00:04:56.040 clinical and basic research here

NOTE Confidence: 0.9978594

00:04:56.040 --> 00:04:57.020 within the department.

NOTE Confidence: 0.965624

00:04:58.760 --> 00:04:59.639 As you can as you

NOTE Confidence: 0.965624

00:04:59.639 --> 00:05:00.135 just heard,

NOTE Confidence: 0.72381175

00:05:01.735 --> 00:05:02.475 the, shared,

NOTE Confidence: 0.9951439

00:05:03.335 --> 00:05:05.175 area for both the talks

NOTE Confidence: 0.9951439

00:05:05.175 --> 00:05:05.675 today,

NOTE Confidence: 0.9614684

00:05:06.375 --> 00:05:07.755 is Parkinson's disease.

NOTE Confidence: 0.97740877

00:05:08.214 --> 00:05:08.535 And,

NOTE Confidence: 0.9537412

00:05:09.095 --> 00:05:10.295 I would like to start

NOTE Confidence: 0.9537412

00:05:10.295 --> 00:05:11.975 out by highlighting that,

NOTE Confidence: 0.991942

00:05:12.889 --> 00:05:14.889 our research is actually in

NOTE Confidence: 0.991942

00:05:14.889 --> 00:05:15.550 a part

NOTE Confidence: 0.9775715

00:05:15.930 --> 00:05:16.330 that,

NOTE Confidence: 0.9624211

00:05:16.730 --> 00:05:17.930 of the brain that normally

NOTE Confidence: 0.9624211

00:05:17.930 --> 00:05:19.950 not commonly studied in Parkinson's

NOTE Confidence: 0.9624211

00:05:20.089 --> 00:05:21.550 disease, namely in the cortex.

NOTE Confidence: 0.9258107

00:05:22.250 --> 00:05:22.570 And,

NOTE Confidence: 0.9856305

00:05:23.690 --> 00:05:25.290 the reason for this, is

NOTE Confidence: 0.9856305

00:05:25.290 --> 00:05:25.790 that,

NOTE Confidence: 0.9861283

00:05:26.605 --> 00:05:28.464 the majority of PD patients

NOTE Confidence: 0.9861283

00:05:28.525 --> 00:05:30.464 will experience cognitive impairments

NOTE Confidence: 0.97155815

00:05:31.085 --> 00:05:33.025 or even dementia. The trajectory,

NOTE Confidence: 0.97155815

00:05:33.165 --> 00:05:34.685 of course, depends is different

NOTE Confidence: 0.97155815

00:05:34.685 --> 00:05:35.904 for each of the patients,

NOTE Confidence: 0.97155815

00:05:36.205 --> 00:05:36.525 but,

NOTE Confidence: 0.94652325

00:05:37.005 --> 00:05:38.125 estimates are that up to

NOTE Confidence: 0.94652325

00:05:38.125 --> 00:05:40.044 eighty percent of patients will

NOTE Confidence: 0.94652325

00:05:40.044 --> 00:05:41.425 experience these cognitive

NOTE Confidence: 0.9736062

00:05:42.580 --> 00:05:43.080 challenges.

NOTE Confidence: 0.93068945

00:05:43.940 --> 00:05:44.180 And,

NOTE Confidence: 0.97609764

00:05:46.180 --> 00:05:47.400 we wanted to understand,

NOTE Confidence: 0.9612178

00:05:48.420 --> 00:05:50.260 what the mechanisms the cellular

NOTE Confidence: 0.9612178

00:05:50.260 --> 00:05:52.260 mechanisms are that underlie these

NOTE Confidence: 0.9612178

00:05:52.260 --> 00:05:54.100 cognitive impairments because there's really,

NOTE Confidence: 0.9612178

00:05:54.100 --> 00:05:55.720 at this point, no therapeutic

NOTE Confidence: 0.9612178

00:05:55.940 --> 00:05:58.255 intervention for these, problems.

NOTE Confidence: 0.9891214

00:06:00.154 --> 00:06:01.115 What you see here on

NOTE Confidence: 0.9891214

00:06:01.115 --> 00:06:02.395 the right is actually one

NOTE Confidence: 0.9891214

00:06:02.395 --> 00:06:03.435 of the leads that we

NOTE Confidence: 0.9891214

00:06:03.435 --> 00:06:04.255 already had.

NOTE Confidence: 0.8962092

00:06:04.794 --> 00:06:06.235 What you see here is

NOTE Confidence: 0.8962092

00:06:06.235 --> 00:06:08.014 a tissue section from cortex

NOTE Confidence: 0.8962092

00:06:08.074 --> 00:06:09.214 of a PD patients.

NOTE Confidence: 0.9960429

00:06:09.770 --> 00:06:12.170 And, what you see in

NOTE Confidence: 0.9960429

00:06:12.170 --> 00:06:12.670 green

NOTE Confidence: 0.98120075

00:06:13.290 --> 00:06:14.570 is the staining for a

NOTE Confidence: 0.98120075

00:06:14.570 --> 00:06:15.070 protein,

NOTE Confidence: 0.8571889

00:06:15.610 --> 00:06:17.130 named synuclein. It's actually, in

NOTE Confidence: 0.8571889

00:06:17.130 --> 00:06:18.570 this case, it's be a

NOTE Confidence: 0.8571889

00:06:18.570 --> 00:06:19.610 form of the protein that

NOTE Confidence: 0.8571889

00:06:19.610 --> 00:06:20.270 is phosphorylated,

NOTE Confidence: 0.9975921

00:06:20.810 --> 00:06:22.410 which marks the aggregated forms

NOTE Confidence: 0.9975921

00:06:22.410 --> 00:06:23.150 of synuclein.

NOTE Confidence: 0.9531

00:06:23.975 --> 00:06:25.575 And the abundance of these

NOTE Confidence: 0.9531

00:06:25.575 --> 00:06:27.575 synuclein aggregates is not only

NOTE Confidence: 0.9531

00:06:27.575 --> 00:06:29.335 a hallmark of PDs or

NOTE Confidence: 0.9531

00:06:29.335 --> 00:06:30.615 as Lewy bodies or as

NOTE Confidence: 0.9531

00:06:30.615 --> 00:06:31.355 Lewy neurites.

NOTE Confidence: 0.98594075

00:06:31.735 --> 00:06:32.955 Also, the abundance

NOTE Confidence: 0.9839971

00:06:33.575 --> 00:06:35.175 correlates with the extent of

NOTE Confidence: 0.9839971

00:06:35.175 --> 00:06:37.175 cognitive decline. So the project

NOTE Confidence: 0.9839971

00:06:37.175 --> 00:06:38.375 that I will present today

NOTE Confidence: 0.9839971

00:06:38.375 --> 00:06:40.650 is really based on modeling

NOTE Confidence: 0.9839971

00:06:40.710 --> 00:06:42.170 these synuclein pathologies.

NOTE Confidence: 0.986889

00:06:44.790 --> 00:06:46.870 And, just to recap a

NOTE Confidence: 0.986889

00:06:46.870 --> 00:06:48.089 little bit of the literature,

NOTE Confidence: 0.986889

00:06:48.389 --> 00:06:49.210 as I mentioned,

NOTE Confidence: 0.93908733

00:06:50.070 --> 00:06:52.169 dementia or mild cognitive impairments

NOTE Confidence: 0.93908733

00:06:52.230 --> 00:06:53.350 at least is very common

NOTE Confidence: 0.93908733

00:06:53.350 --> 00:06:54.010 in PD.

NOTE Confidence: 0.93974483

00:06:55.305 --> 00:06:56.665 And there already have been

NOTE Confidence: 0.93974483

00:06:56.665 --> 00:06:58.585 studies, in human patients that

NOTE Confidence: 0.93974483

00:06:58.585 --> 00:07:00.585 showed that activity patterns in

NOTE Confidence: 0.93974483

00:07:00.585 --> 00:07:02.125 the cortex are also disrupted.

NOTE Confidence: 0.960581

00:07:02.825 --> 00:07:04.445 And, as I just said,

NOTE Confidence: 0.960581

00:07:04.505 --> 00:07:04.985 the best,

NOTE Confidence: 0.6794528

00:07:05.625 --> 00:07:06.125 indicator

NOTE Confidence: 0.9196941

00:07:06.585 --> 00:07:08.585 of, dementia or progression to

NOTE Confidence: 0.9196941

00:07:08.585 --> 00:07:09.085 dementia

NOTE Confidence: 0.9567948

00:07:09.450 --> 00:07:10.730 is then the abundance of

NOTE Confidence: 0.9567948

00:07:10.730 --> 00:07:12.330 the synuclein aggregates in the

NOTE Confidence: 0.9567948

00:07:12.330 --> 00:07:12.830 cortex.

NOTE Confidence: 0.94607323

00:07:13.770 --> 00:07:14.590 And so together,

NOTE Confidence: 0.9936803

00:07:15.050 --> 00:07:16.510 our hypothesis is

NOTE Confidence: 0.9739123

00:07:16.890 --> 00:07:17.790 that these,

NOTE Confidence: 0.98420453

00:07:18.410 --> 00:07:19.630 synuclein pathologies,

NOTE Confidence: 0.8723096

00:07:21.130 --> 00:07:23.130 cause damage to vulnerable neuron

NOTE Confidence: 0.8723096

00:07:23.130 --> 00:07:24.810 types and vulnerable synapses and

NOTE Confidence: 0.8723096

00:07:24.810 --> 00:07:26.235 that underlies or at least

NOTE Confidence: 0.8723096

00:07:26.235 --> 00:07:26.735 contributes

NOTE Confidence: 0.9930096

00:07:27.275 --> 00:07:28.815 to the cognitive impairments.

NOTE Confidence: 0.9434648

00:07:30.795 --> 00:07:32.175 Now with this,

NOTE Confidence: 0.8159223

00:07:33.595 --> 00:07:34.715 big question of how has

NOTE Confidence: 0.8159223

00:07:34.715 --> 00:07:35.215 connectivity

NOTE Confidence: 0.8939205

00:07:35.755 --> 00:07:37.515 changed, we try to simplify

NOTE Confidence: 0.8939205

00:07:37.515 --> 00:07:38.795 it and we go back

NOTE Confidence: 0.8939205

00:07:38.795 --> 00:07:40.255 to a synaptic level.

NOTE Confidence: 0.7687963

00:07:41.550 --> 00:07:42.290 And there's,

NOTE Confidence: 0.9636116

00:07:42.910 --> 00:07:44.750 ample data that support that,

NOTE Confidence: 0.98822194

00:07:45.470 --> 00:07:46.750 this is a relevant factor

NOTE Confidence: 0.98822194

00:07:46.750 --> 00:07:48.290 in in human PD patients.

NOTE Confidence: 0.97779614

00:07:48.669 --> 00:07:49.550 What you see on the

NOTE Confidence: 0.97779614

00:07:49.550 --> 00:07:50.830 left is an older study

NOTE Confidence: 0.97779614

00:07:50.830 --> 00:07:51.889 that used immunostaining

NOTE Confidence: 0.905346

00:07:52.190 --> 00:07:53.490 for a synaptic protein,

NOTE Confidence: 0.9755075

00:07:53.835 --> 00:07:54.955 and that showed that the

NOTE Confidence: 0.9755075

00:07:54.955 --> 00:07:56.794 extent of synapse loss that

NOTE Confidence: 0.9755075

00:07:56.794 --> 00:07:58.074 occurs in the cortex in

NOTE Confidence: 0.9755075

00:07:58.074 --> 00:07:59.675 PD patients is almost as

NOTE Confidence: 0.9755075

00:07:59.675 --> 00:08:00.875 high as the extent of

NOTE Confidence: 0.9755075

00:08:00.875 --> 00:08:02.315 synapse loss in patients with

NOTE Confidence: 0.9755075

00:08:02.315 --> 00:08:03.294 Alzheimer's disease.

NOTE Confidence: 0.9881747

00:08:04.715 --> 00:08:05.935 Here on the right,

NOTE Confidence: 0.9984221

00:08:06.640 --> 00:08:08.260 much more advanced studies

NOTE Confidence: 0.9900789

00:08:08.720 --> 00:08:10.320 pioneered by colleagues here at

NOTE Confidence: 0.9900789

00:08:10.320 --> 00:08:10.820 Yale.

NOTE Confidence: 0.9531175

00:08:11.360 --> 00:08:12.240 In this case, this is

NOTE Confidence: 0.9531175

00:08:12.240 --> 00:08:13.620 a paper by Dave Matuski,

NOTE Confidence: 0.9770033

00:08:14.480 --> 00:08:16.640 using the PET ligand that

NOTE Confidence: 0.9770033

00:08:16.640 --> 00:08:17.920 was developed here at Yale

NOTE Confidence: 0.9770033

00:08:17.920 --> 00:08:18.660 to visualize,

NOTE Confidence: 0.92208296

00:08:19.600 --> 00:08:21.360 the presynaptic protein s v

NOTE Confidence: 0.92208296

00:08:21.360 --> 00:08:21.860 two,

NOTE Confidence: 0.8772748

00:08:22.775 --> 00:08:24.615 which is a wonderful tool

NOTE Confidence: 0.8772748

00:08:24.615 --> 00:08:25.115 to,

NOTE Confidence: 0.6456757

00:08:26.455 --> 00:08:26.955 represent,

NOTE Confidence: 0.77330554

00:08:27.495 --> 00:08:27.995 synapses

NOTE Confidence: 0.89140946

00:08:28.375 --> 00:08:29.895 in line in humans and

NOTE Confidence: 0.89140946

00:08:29.895 --> 00:08:31.595 actually do longitudinal studies.

NOTE Confidence: 0.9944395

00:08:31.895 --> 00:08:32.775 For me, this is still

NOTE Confidence: 0.9944395

00:08:32.775 --> 00:08:34.375 breathtaking that you can visualize

NOTE Confidence: 0.9944395

00:08:34.375 --> 00:08:35.735 synapses in a living brain

NOTE Confidence: 0.9944395

00:08:35.735 --> 00:08:37.735 and analyze synapse density. And

NOTE Confidence: 0.9944395

00:08:37.735 --> 00:08:39.070 what Dave and his colleagues

NOTE Confidence: 0.9944395

00:08:39.070 --> 00:08:40.350 found is that one of

NOTE Confidence: 0.9944395

00:08:40.350 --> 00:08:42.130 the areas that is impacted

NOTE Confidence: 0.9944395

00:08:42.270 --> 00:08:43.410 in PD patients

NOTE Confidence: 0.98488605

00:08:43.790 --> 00:08:45.650 as they undergo cognitive impairments

NOTE Confidence: 0.9305133

00:08:46.510 --> 00:08:47.730 is, the cortex.

NOTE Confidence: 0.96075076

00:08:48.270 --> 00:08:49.790 And, actually, also, he could

NOTE Confidence: 0.96075076

00:08:49.790 --> 00:08:51.390 find that, the extent of

NOTE Confidence: 0.96075076

00:08:51.390 --> 00:08:53.070 synapse loss correlates with cognitive

NOTE Confidence: 0.96075076

00:08:53.070 --> 00:08:53.570 impairments.

NOTE Confidence: 0.9490164

00:08:54.725 --> 00:08:56.665 So there's a strong precedent

NOTE Confidence: 0.9490164

00:08:56.725 --> 00:08:58.165 that from human patients that

NOTE Confidence: 0.9490164

00:08:58.165 --> 00:08:59.765 is relevant to analyze,

NOTE Confidence: 0.96735406

00:09:00.404 --> 00:09:01.545 synaptic vulnerability

NOTE Confidence: 0.97898346

00:09:02.084 --> 00:09:03.385 in Parkinson's disease.

NOTE Confidence: 0.971736

00:09:05.125 --> 00:09:05.925 Together with,

NOTE Confidence: 0.9346588

00:09:07.370 --> 00:09:09.050 several colleagues, we try to

NOTE Confidence: 0.9346588

00:09:09.050 --> 00:09:10.830 get at the molecular underpinnings.

NOTE Confidence: 0.89288956

00:09:11.370 --> 00:09:12.170 And what I show you

NOTE Confidence: 0.89288956

00:09:12.170 --> 00:09:13.929 here are data generated by

NOTE Confidence: 0.89288956

00:09:13.929 --> 00:09:15.210 Mike Henderson at the Fan

NOTE Confidence: 0.89288956

00:09:15.210 --> 00:09:15.950 Adel Institute.

NOTE Confidence: 0.98773384

00:09:17.050 --> 00:09:19.390 He tried to obtain mechanistic

NOTE Confidence: 0.98773384

00:09:19.529 --> 00:09:20.890 leads by looking at gene

NOTE Confidence: 0.98773384

00:09:20.890 --> 00:09:21.870 expression patterns,

NOTE Confidence: 0.84257364

00:09:22.695 --> 00:09:23.755 and he analyzed,

NOTE Confidence: 0.9670512

00:09:24.135 --> 00:09:25.995 the cortex of PD patients,

NOTE Confidence: 0.7139382

00:09:27.815 --> 00:09:29.434 typically patients with dementia,

NOTE Confidence: 0.9721221

00:09:30.295 --> 00:09:31.495 and compared this to a

NOTE Confidence: 0.9721221

00:09:31.495 --> 00:09:32.695 mouse model. I will introduce

NOTE Confidence: 0.9721221

00:09:32.695 --> 00:09:33.575 the mouse model in the

NOTE Confidence: 0.9721221

00:09:33.575 --> 00:09:34.855 next slide. But,

NOTE Confidence: 0.9708869

00:09:35.735 --> 00:09:37.255 the theme is that there's

NOTE Confidence: 0.9708869

00:09:37.255 --> 00:09:38.510 very strongly

NOTE Confidence: 0.9102904

00:09:38.970 --> 00:09:39.290 shared,

NOTE Confidence: 0.9897204

00:09:40.170 --> 00:09:42.429 gene expression changes in both

NOTE Confidence: 0.9897204

00:09:42.490 --> 00:09:43.770 the human patients and in

NOTE Confidence: 0.9897204

00:09:43.770 --> 00:09:44.830 our mouse model.

NOTE Confidence: 0.9819962

00:09:45.610 --> 00:09:46.910 And one of the,

NOTE Confidence: 0.85719407

00:09:47.610 --> 00:09:50.030 clusters that was, down regulated

NOTE Confidence: 0.9789491

00:09:50.735 --> 00:09:51.454 in both,

NOTE Confidence: 0.98147255

00:09:52.014 --> 00:09:53.475 humans and the mouse model

NOTE Confidence: 0.98147255

00:09:53.774 --> 00:09:55.535 are synaptic genes. And I

NOTE Confidence: 0.98147255

00:09:55.535 --> 00:09:56.495 can show you this here.

NOTE Confidence: 0.98147255

00:09:56.495 --> 00:09:57.695 So this is the area

NOTE Confidence: 0.98147255

00:09:57.695 --> 00:09:59.235 that is here highlighted.

NOTE Confidence: 0.97341514

00:10:00.095 --> 00:10:01.235 What you see here,

NOTE Confidence: 0.9604847

00:10:01.615 --> 00:10:02.255 is named,

NOTE Confidence: 0.9727689

00:10:02.975 --> 00:10:04.495 genes. These are all genes

NOTE Confidence: 0.9727689

00:10:04.495 --> 00:10:05.820 that are downregulated when they

NOTE Confidence: 0.9727689

00:10:05.820 --> 00:10:06.800 are shown in blue.

NOTE Confidence: 0.8824417

00:10:07.900 --> 00:10:09.420 And as you can see,

NOTE Confidence: 0.8824417

00:10:09.420 --> 00:10:11.600 it's involves both presynaptic

NOTE Confidence: 0.9984583

00:10:12.059 --> 00:10:13.679 and postsynaptic proteins.

NOTE Confidence: 0.9418145

00:10:14.700 --> 00:10:16.059 One protein that I can

NOTE Confidence: 0.9418145

00:10:16.059 --> 00:10:17.420 already highlight because it will

NOTE Confidence: 0.9418145

00:10:17.420 --> 00:10:18.080 show up

NOTE Confidence: 0.9573978

00:10:18.455 --> 00:10:19.575 in, at the end of

NOTE Confidence: 0.9573978

00:10:19.575 --> 00:10:21.415 my presentation. I hear these

NOTE Confidence: 0.9573978

00:10:21.415 --> 00:10:21.915 transsynaptic

NOTE Confidence: 0.7801477

00:10:22.295 --> 00:10:22.795 interactions.

NOTE Confidence: 0.9949355

00:10:23.575 --> 00:10:24.455 So I will come back

NOTE Confidence: 0.9949355

00:10:24.455 --> 00:10:25.275 to that later.

NOTE Confidence: 0.95335823

00:10:25.975 --> 00:10:26.934 But we have a number

NOTE Confidence: 0.95335823

00:10:26.934 --> 00:10:28.695 of of of leads. And

NOTE Confidence: 0.95335823

00:10:28.695 --> 00:10:30.475 when we use gene ontology

NOTE Confidence: 0.95335823

00:10:30.535 --> 00:10:31.035 analysis,

NOTE Confidence: 0.9867459

00:10:31.590 --> 00:10:33.110 we can pinpoint that these,

NOTE Confidence: 0.9867459

00:10:33.510 --> 00:10:34.010 changes

NOTE Confidence: 0.9664862

00:10:34.470 --> 00:10:37.050 affect both the synaptic vesicle

NOTE Confidence: 0.9664862

00:10:37.350 --> 00:10:38.790 cycle or proteins involved in

NOTE Confidence: 0.9664862

00:10:38.790 --> 00:10:40.630 the synaptic vesicle cycle and

NOTE Confidence: 0.9664862

00:10:40.630 --> 00:10:42.490 also proteins involved in postsynaptic

NOTE Confidence: 0.9664862

00:10:42.710 --> 00:10:44.090 organization. So the,

NOTE Confidence: 0.9957717

00:10:44.710 --> 00:10:46.070 damage hits on both sides

NOTE Confidence: 0.9957717

00:10:46.070 --> 00:10:46.890 of the synapse.

NOTE Confidence: 0.85179317

00:10:47.774 --> 00:10:48.975 Now we try to,

NOTE Confidence: 0.9246285

00:10:51.214 --> 00:10:52.334 analyze this. And so the

NOTE Confidence: 0.9246285

00:10:52.334 --> 00:10:54.915 first question then larger, so

NOTE Confidence: 0.9246285

00:10:55.054 --> 00:10:56.415 the the main part of

NOTE Confidence: 0.9246285

00:10:56.415 --> 00:10:57.074 my talk,

NOTE Confidence: 0.9578239

00:10:57.615 --> 00:10:58.815 is how we can,

NOTE Confidence: 0.9453565

00:10:59.375 --> 00:11:00.300 analyze or what what we

NOTE Confidence: 0.9453565

00:11:00.300 --> 00:11:01.360 can learn about

NOTE Confidence: 0.95422566

00:11:01.740 --> 00:11:02.940 synapse loss in this p

NOTE Confidence: 0.95422566

00:11:02.940 --> 00:11:03.840 d in PD.

NOTE Confidence: 0.9844364

00:11:05.420 --> 00:11:07.179 And here, I would like

NOTE Confidence: 0.9844364

00:11:07.179 --> 00:11:08.240 to briefly introduce,

NOTE Confidence: 0.9990794

00:11:08.940 --> 00:11:09.980 the model that we are

NOTE Confidence: 0.9990794

00:11:09.980 --> 00:11:10.480 using,

NOTE Confidence: 0.94878644

00:11:10.860 --> 00:11:11.980 which, as I mentioned, is

NOTE Confidence: 0.94878644

00:11:11.980 --> 00:11:14.000 based on, synuclein pathology.

NOTE Confidence: 0.9253735

00:11:14.585 --> 00:11:15.385 And the data that I

NOTE Confidence: 0.9253735

00:11:15.385 --> 00:11:16.905 show here are generated by

NOTE Confidence: 0.9253735

00:11:16.905 --> 00:11:18.345 Saroj Sar, who is here

NOTE Confidence: 0.9253735

00:11:18.345 --> 00:11:19.085 in the audience.

NOTE Confidence: 0.9663995

00:11:20.025 --> 00:11:20.765 What we,

NOTE Confidence: 0.9887356

00:11:21.145 --> 00:11:22.505 utilize is a model where

NOTE Confidence: 0.9887356

00:11:22.505 --> 00:11:23.245 we take

NOTE Confidence: 0.8903785

00:11:23.945 --> 00:11:24.445 fibrils,

NOTE Confidence: 0.9238314

00:11:24.985 --> 00:11:27.625 so artificially generated aggregates of

NOTE Confidence: 0.9238314

00:11:27.625 --> 00:11:29.304 this disease linked protein alpha

NOTE Confidence: 0.9238314

00:11:29.304 --> 00:11:29.804 synuclein,

NOTE Confidence: 0.9686325

00:11:30.559 --> 00:11:31.920 and we generate them under

NOTE Confidence: 0.9686325

00:11:31.920 --> 00:11:33.360 highly controlled conditions. They have

NOTE Confidence: 0.9686325

00:11:33.360 --> 00:11:34.500 to have a very specific

NOTE Confidence: 0.9686325

00:11:34.559 --> 00:11:35.700 size to be bioactive,

NOTE Confidence: 0.95580894

00:11:36.320 --> 00:11:37.440 and we are also very

NOTE Confidence: 0.95580894

00:11:37.440 --> 00:11:38.800 careful handling them in the

NOTE Confidence: 0.95580894

00:11:38.800 --> 00:11:39.920 cell culture hood as you

NOTE Confidence: 0.95580894

00:11:39.920 --> 00:11:41.380 probably can imagine. And,

NOTE Confidence: 0.9722722

00:11:41.840 --> 00:11:44.160 so we then inject these

NOTE Confidence: 0.9722722

00:11:44.160 --> 00:11:45.220 into animals.

NOTE Confidence: 0.94213724

00:11:45.675 --> 00:11:47.355 Specifically, we target the dorsal

NOTE Confidence: 0.94213724

00:11:47.355 --> 00:11:48.255 lateral striatum.

NOTE Confidence: 0.9531198

00:11:48.875 --> 00:11:49.915 And the reason that we

NOTE Confidence: 0.9531198

00:11:49.915 --> 00:11:51.675 target that area is because

NOTE Confidence: 0.9531198

00:11:51.675 --> 00:11:52.815 here we have

NOTE Confidence: 0.99946964

00:11:53.195 --> 00:11:54.175 very precise

NOTE Confidence: 0.99686784

00:11:54.715 --> 00:11:55.775 regional control

NOTE Confidence: 0.86770153

00:11:56.235 --> 00:11:57.780 because that means that the

NOTE Confidence: 0.9401471

00:11:58.260 --> 00:11:59.860 cortical neurons in layer five

NOTE Confidence: 0.9401471

00:11:59.860 --> 00:12:01.700 that projected the striatum, these

NOTE Confidence: 0.9401471

00:12:01.700 --> 00:12:02.660 are the first ones who

NOTE Confidence: 0.9401471

00:12:02.660 --> 00:12:03.800 will be exposed,

NOTE Confidence: 0.90609485

00:12:04.660 --> 00:12:06.580 to the synuclein pathology. And

NOTE Confidence: 0.90609485

00:12:06.580 --> 00:12:08.020 indeed, we can then show

NOTE Confidence: 0.90609485

00:12:08.020 --> 00:12:09.400 that these, neurons,

NOTE Confidence: 0.85124415

00:12:10.565 --> 00:12:12.425 build on themselves, develop aggregates.

NOTE Confidence: 0.85124415

00:12:12.725 --> 00:12:13.865 So in a sense, it's,

NOTE Confidence: 0.8893818

00:12:14.645 --> 00:12:16.825 reminiscent of the prior hypothesis

NOTE Confidence: 0.8893818

00:12:17.045 --> 00:12:19.605 that the proteins synuclein that

NOTE Confidence: 0.8893818

00:12:19.605 --> 00:12:20.985 we inject in its aggregated

NOTE Confidence: 0.8893818

00:12:21.045 --> 00:12:22.105 form can template

NOTE Confidence: 0.9948795

00:12:22.405 --> 00:12:23.785 the endogenous synuclein

NOTE Confidence: 0.97765183

00:12:24.440 --> 00:12:26.040 and stem cause pathology. And

NOTE Confidence: 0.97765183

00:12:26.040 --> 00:12:27.320 this is very likely what

NOTE Confidence: 0.97765183

00:12:27.320 --> 00:12:28.679 happens in the in the

NOTE Confidence: 0.97765183

00:12:28.679 --> 00:12:29.179 patients,

NOTE Confidence: 0.88733244

00:12:29.800 --> 00:12:31.480 because, for example, the Braque

NOTE Confidence: 0.88733244

00:12:31.480 --> 00:12:31.980 staging,

NOTE Confidence: 0.9615239

00:12:32.679 --> 00:12:33.179 really,

NOTE Confidence: 0.95622635

00:12:33.959 --> 00:12:35.399 tracks all of these changes

NOTE Confidence: 0.95622635

00:12:35.399 --> 00:12:37.500 in the progression across synaptically

NOTE Confidence: 0.9997204

00:12:37.880 --> 00:12:38.380 connected

NOTE Confidence: 0.84078383

00:12:38.754 --> 00:12:39.574 neural populations.

NOTE Confidence: 0.97245455

00:12:40.035 --> 00:12:41.314 So we use this approach

NOTE Confidence: 0.97245455

00:12:41.314 --> 00:12:42.855 to specifically set,

NOTE Confidence: 0.9485693

00:12:43.314 --> 00:12:45.314 pathology in the cortex of

NOTE Confidence: 0.9485693

00:12:45.314 --> 00:12:46.694 temporal and spatial control.

NOTE Confidence: 0.89715195

00:12:47.475 --> 00:12:48.995 And, the way these data

NOTE Confidence: 0.89715195

00:12:48.995 --> 00:12:50.035 look like in this mouse

NOTE Confidence: 0.89715195

00:12:50.035 --> 00:12:51.394 model, here's data from the

NOTE Confidence: 0.89715195

00:12:51.394 --> 00:12:52.834 cortex. And I would ask

NOTE Confidence: 0.89715195

00:12:52.834 --> 00:12:54.160 you just focus on the

NOTE Confidence: 0.89715195

00:12:54.160 --> 00:12:56.160 bottom row because here, you

NOTE Confidence: 0.89715195

00:12:56.160 --> 00:12:56.980 see the synuclein

NOTE Confidence: 0.9863857

00:12:57.760 --> 00:12:58.260 aggregates

NOTE Confidence: 0.9870669

00:12:58.640 --> 00:13:00.240 easier because they are marked

NOTE Confidence: 0.9870669

00:13:00.240 --> 00:13:01.059 in red.

NOTE Confidence: 0.86851853

00:13:01.600 --> 00:13:03.140 And, when quantifies

NOTE Confidence: 0.98169655

00:13:03.840 --> 00:13:05.360 the progression of pathology, you

NOTE Confidence: 0.98169655

00:13:05.360 --> 00:13:07.220 see a significant increase

NOTE Confidence: 0.9984786

00:13:07.575 --> 00:13:08.075 between

NOTE Confidence: 0.77301645

00:13:08.815 --> 00:13:09.315 the,

NOTE Confidence: 0.8975254

00:13:10.135 --> 00:13:11.735 starting, like, one month post

NOTE Confidence: 0.8975254

00:13:11.735 --> 00:13:13.415 injection to later time point.

NOTE Confidence: 0.8975254

00:13:13.415 --> 00:13:14.455 So that's a model to

NOTE Confidence: 0.8975254

00:13:14.455 --> 00:13:15.515 analyze progression,

NOTE Confidence: 0.9964691

00:13:15.895 --> 00:13:17.495 and we heavily utilize it

NOTE Confidence: 0.9964691

00:13:17.495 --> 00:13:18.315 for that reason.

NOTE Confidence: 0.9943068

00:13:20.670 --> 00:13:22.510 Now when we analyze how

NOTE Confidence: 0.9943068

00:13:22.510 --> 00:13:24.290 this model then replicates,

NOTE Confidence: 0.9949728

00:13:25.070 --> 00:13:26.990 synapse changes or synapse loss

NOTE Confidence: 0.9949728

00:13:26.990 --> 00:13:27.809 in the patients,

NOTE Confidence: 0.98966336

00:13:28.670 --> 00:13:29.890 we can find that,

NOTE Confidence: 0.9267301

00:13:30.750 --> 00:13:32.190 also here, just like the

NOTE Confidence: 0.9267301

00:13:32.190 --> 00:13:33.170 synuclein pathology,

NOTE Confidence: 0.9753947

00:13:33.710 --> 00:13:35.330 the synapse loss is progressive.

NOTE Confidence: 0.98611915

00:13:35.834 --> 00:13:36.875 I don't show the data

NOTE Confidence: 0.98611915

00:13:36.875 --> 00:13:37.995 here, but in the first

NOTE Confidence: 0.98611915

00:13:37.995 --> 00:13:39.274 stages, we do not yet

NOTE Confidence: 0.98611915

00:13:39.274 --> 00:13:40.954 see synapse loss. But then

NOTE Confidence: 0.98611915

00:13:40.954 --> 00:13:42.175 as soon as the pathology

NOTE Confidence: 0.98611915

00:13:42.475 --> 00:13:44.394 has, been around for, let's

NOTE Confidence: 0.98611915

00:13:44.394 --> 00:13:45.995 say, four weeks, we then

NOTE Confidence: 0.98611915

00:13:45.995 --> 00:13:46.394 see,

NOTE Confidence: 0.880067

00:13:47.514 --> 00:13:49.035 a a gradual increase since,

NOTE Confidence: 0.880067

00:13:49.355 --> 00:13:50.910 gradual loss of synapses. Synapses.

NOTE Confidence: 0.880067

00:13:50.910 --> 00:13:52.350 The way we quantify this

NOTE Confidence: 0.880067

00:13:52.350 --> 00:13:55.390 is, we take three d

NOTE Confidence: 0.880067

00:13:55.390 --> 00:13:55.890 reconstructions.

NOTE Confidence: 0.9491454

00:13:56.270 --> 00:13:58.110 These are images that are

NOTE Confidence: 0.9491454

00:13:58.110 --> 00:13:58.610 obtained,

NOTE Confidence: 0.91773194

00:13:58.990 --> 00:14:00.750 using a super resolved imaging

NOTE Confidence: 0.91773194

00:14:00.750 --> 00:14:01.250 approach.

NOTE Confidence: 0.9044119

00:14:01.630 --> 00:14:03.070 So these allow us to

NOTE Confidence: 0.9044119

00:14:03.070 --> 00:14:05.330 separately analyze pre and postsynaptic

NOTE Confidence: 0.9044119

00:14:05.550 --> 00:14:07.685 sites. I mean, analyze synapses

NOTE Confidence: 0.9044119

00:14:07.685 --> 00:14:08.885 as structures that has,

NOTE Confidence: 0.984293

00:14:09.605 --> 00:14:11.365 appeared in space. So this

NOTE Confidence: 0.984293

00:14:11.365 --> 00:14:12.985 is a highly, computationally,

NOTE Confidence: 0.9790539

00:14:14.245 --> 00:14:16.725 driven analysis of of synaptic

NOTE Confidence: 0.9790539

00:14:16.725 --> 00:14:17.225 connectivity.

NOTE Confidence: 0.97507304

00:14:17.765 --> 00:14:18.645 And we see that both

NOTE Confidence: 0.97507304

00:14:18.645 --> 00:14:19.525 at three months and then

NOTE Confidence: 0.97507304

00:14:19.525 --> 00:14:20.645 later at six months, so

NOTE Confidence: 0.97507304

00:14:20.645 --> 00:14:21.785 left and right side,

NOTE Confidence: 0.8769388

00:14:22.400 --> 00:14:23.860 that synopsis are lost.

NOTE Confidence: 0.96927804

00:14:24.880 --> 00:14:26.640 Now importantly, it depends on

NOTE Confidence: 0.96927804

00:14:26.640 --> 00:14:28.100 what markers you're analyzing.

NOTE Confidence: 0.935407

00:14:28.480 --> 00:14:30.000 These are the synopsis that

NOTE Confidence: 0.935407

00:14:30.000 --> 00:14:31.440 are marked by the protein

NOTE Confidence: 0.935407

00:14:31.440 --> 00:14:32.640 big load one. These are

NOTE Confidence: 0.935407

00:14:32.640 --> 00:14:34.960 short range local excitatory connections

NOTE Confidence: 0.935407

00:14:34.960 --> 00:14:35.700 in the cortex.

NOTE Confidence: 0.98783207

00:14:36.255 --> 00:14:37.615 However, when we analyze long

NOTE Confidence: 0.98783207

00:14:37.615 --> 00:14:39.215 range connections, so inputs, for

NOTE Confidence: 0.98783207

00:14:39.215 --> 00:14:40.435 example, from the thalamus

NOTE Confidence: 0.9838257

00:14:40.895 --> 00:14:43.075 to the cortex, those inputs

NOTE Confidence: 0.9838257

00:14:43.135 --> 00:14:45.475 are spared. So synaptic vulnerability

NOTE Confidence: 0.99016756

00:14:45.855 --> 00:14:47.055 is not across the board.

NOTE Confidence: 0.99016756

00:14:47.055 --> 00:14:48.655 Certain synapse types are more

NOTE Confidence: 0.99016756

00:14:48.655 --> 00:14:50.279 vulnerable than others. And that's

NOTE Confidence: 0.99016756

00:14:50.279 --> 00:14:51.980 actually very interesting for therapeutic

NOTE Confidence: 0.99016756

00:14:52.120 --> 00:14:53.560 interventions because it means there

NOTE Confidence: 0.99016756

00:14:53.560 --> 00:14:54.920 are factors that protect the

NOTE Confidence: 0.99016756

00:14:54.920 --> 00:14:56.440 other synapses. So we just

NOTE Confidence: 0.99016756

00:14:56.440 --> 00:14:57.640 have to figure out what

NOTE Confidence: 0.99016756

00:14:57.640 --> 00:14:59.660 makes these long range inputs

NOTE Confidence: 0.99016756

00:14:59.720 --> 00:15:00.220 stable,

NOTE Confidence: 0.8591956

00:15:01.000 --> 00:15:02.680 versus, what makes the short

NOTE Confidence: 0.8591956

00:15:02.680 --> 00:15:04.665 range inputs vulnerable. But that's,

NOTE Confidence: 0.9962461

00:15:05.105 --> 00:15:05.905 this is one of the

NOTE Confidence: 0.9962461

00:15:05.905 --> 00:15:07.205 reasons why we analyze,

NOTE Confidence: 0.94198245

00:15:08.065 --> 00:15:09.685 synapse specific vulnerabilities.

NOTE Confidence: 0.99299484

00:15:11.985 --> 00:15:12.485 Now

NOTE Confidence: 0.9535718

00:15:13.345 --> 00:15:14.625 we not only have synapse

NOTE Confidence: 0.9535718

00:15:14.625 --> 00:15:15.665 loss. So as you could

NOTE Confidence: 0.9535718

00:15:15.665 --> 00:15:17.905 see, it's, a relatively small

NOTE Confidence: 0.9535718

00:15:17.905 --> 00:15:19.585 portion of synapses that is,

NOTE Confidence: 0.9784088

00:15:20.420 --> 00:15:20.920 removed.

NOTE Confidence: 0.97963154

00:15:21.700 --> 00:15:23.060 We also have broad effects

NOTE Confidence: 0.97963154

00:15:23.060 --> 00:15:24.899 on the remaining synopsis. And

NOTE Confidence: 0.97963154

00:15:24.899 --> 00:15:26.339 among those effects are that,

NOTE Confidence: 0.97963154

00:15:26.660 --> 00:15:27.940 the synopsis, even if they

NOTE Confidence: 0.97963154

00:15:27.940 --> 00:15:28.440 stay,

NOTE Confidence: 0.81737304

00:15:28.899 --> 00:15:30.440 show ultra structural aberrations.

NOTE Confidence: 0.9265495

00:15:30.899 --> 00:15:33.195 These involve include a separation

NOTE Confidence: 0.9265495

00:15:33.255 --> 00:15:34.695 of pre and postsynaptic sites.

NOTE Confidence: 0.9265495

00:15:34.695 --> 00:15:35.575 And as you can imagine,

NOTE Confidence: 0.9265495

00:15:35.575 --> 00:15:36.315 that must,

NOTE Confidence: 0.9662368

00:15:36.935 --> 00:15:39.415 massively affect, the ability to

NOTE Confidence: 0.9662368

00:15:39.415 --> 00:15:40.954 release and detect neurotransmitters.

NOTE Confidence: 0.9776682

00:15:41.575 --> 00:15:43.014 But we also see changes

NOTE Confidence: 0.9776682

00:15:43.014 --> 00:15:45.014 in the presynaptic organization, and

NOTE Confidence: 0.9776682

00:15:45.014 --> 00:15:45.915 these are data

NOTE Confidence: 0.98786247

00:15:46.589 --> 00:15:47.569 obtained in the bottom

NOTE Confidence: 0.9704022

00:15:47.949 --> 00:15:49.410 by, our collaborator,

NOTE Confidence: 0.8765306

00:15:49.949 --> 00:15:52.290 Laura Volpicelli, at the University

NOTE Confidence: 0.8765306

00:15:52.350 --> 00:15:53.569 of Alabama in Birmingham.

NOTE Confidence: 0.9295025

00:15:54.670 --> 00:15:56.110 And so even though these

NOTE Confidence: 0.9295025

00:15:56.110 --> 00:15:58.269 are relatively modest changes in

NOTE Confidence: 0.9295025

00:15:58.269 --> 00:16:00.509 synaptic vascular size, they will

NOTE Confidence: 0.9295025

00:16:00.509 --> 00:16:02.555 also impact synaptic transmission.

NOTE Confidence: 0.9619017

00:16:05.495 --> 00:16:06.695 So PD in the cortex

NOTE Confidence: 0.9619017

00:16:06.695 --> 00:16:07.975 involves both the loss of

NOTE Confidence: 0.9619017

00:16:07.975 --> 00:16:10.295 synopsis and structural changes of

NOTE Confidence: 0.9619017

00:16:10.295 --> 00:16:12.055 the remaining synopsis, both of

NOTE Confidence: 0.9619017

00:16:12.055 --> 00:16:13.115 which will impact,

NOTE Confidence: 0.99875754

00:16:13.655 --> 00:16:14.155 connectivity.

NOTE Confidence: 0.9603106

00:16:15.400 --> 00:16:16.540 Now we try to get

NOTE Confidence: 0.9603106

00:16:16.600 --> 00:16:17.400 a little bit more on

NOTE Confidence: 0.9603106

00:16:17.400 --> 00:16:19.420 the molecular underpinnings of that.

NOTE Confidence: 0.8836893

00:16:19.880 --> 00:16:21.160 And here we have,

NOTE Confidence: 0.9674816

00:16:21.880 --> 00:16:23.000 both in our own lab

NOTE Confidence: 0.9674816

00:16:23.000 --> 00:16:24.760 and also in collaboration with

NOTE Confidence: 0.9674816

00:16:24.760 --> 00:16:26.140 the lab of Terry Kumar,

NOTE Confidence: 0.91779613

00:16:26.600 --> 00:16:27.260 at WashU,

NOTE Confidence: 0.8989928

00:16:28.040 --> 00:16:29.880 performed a number of different,

NOTE Confidence: 0.8989928

00:16:30.200 --> 00:16:30.700 analysis.

NOTE Confidence: 0.94758606

00:16:31.295 --> 00:16:32.415 And it goes back to

NOTE Confidence: 0.94758606

00:16:32.415 --> 00:16:33.855 the role of synuclein in

NOTE Confidence: 0.94758606

00:16:33.855 --> 00:16:35.375 this type of pathology. As

NOTE Confidence: 0.94758606

00:16:35.375 --> 00:16:36.834 I mentioned, we use synuclein

NOTE Confidence: 0.94758606

00:16:36.975 --> 00:16:38.595 aggregates to trigger this pathology

NOTE Confidence: 0.94758606

00:16:38.654 --> 00:16:39.855 and to trigger the synapse

NOTE Confidence: 0.94758606

00:16:39.855 --> 00:16:41.375 loss, but we can also

NOTE Confidence: 0.94758606

00:16:41.375 --> 00:16:44.015 detect whether synuclein itself has

NOTE Confidence: 0.94758606

00:16:44.015 --> 00:16:45.855 a, a local role at

NOTE Confidence: 0.94758606

00:16:45.855 --> 00:16:47.450 these, these, vulnerable synapses.

NOTE Confidence: 0.9606387

00:16:48.149 --> 00:16:49.110 The way we test this

NOTE Confidence: 0.9606387

00:16:49.110 --> 00:16:50.490 is, again, like high resolution

NOTE Confidence: 0.9606387

00:16:50.550 --> 00:16:52.950 imaging, and we track what

NOTE Confidence: 0.9606387

00:16:52.950 --> 00:16:54.550 happens in the vicinity of

NOTE Confidence: 0.9606387

00:16:54.550 --> 00:16:55.850 these synuclein aggregates.

NOTE Confidence: 0.92211884

00:16:56.550 --> 00:16:57.670 What we can find is,

NOTE Confidence: 0.92211884

00:16:58.149 --> 00:16:59.910 as shown here, that the

NOTE Confidence: 0.92211884

00:16:59.910 --> 00:17:01.770 synapses that are very close

NOTE Confidence: 0.92211884

00:17:01.965 --> 00:17:02.865 to these aggregates,

NOTE Confidence: 0.97618407

00:17:03.485 --> 00:17:04.385 and these are,

NOTE Confidence: 0.9637278

00:17:04.845 --> 00:17:06.525 shown here in magenta on

NOTE Confidence: 0.9637278

00:17:06.525 --> 00:17:08.205 the left. So the synapses

NOTE Confidence: 0.9637278

00:17:08.205 --> 00:17:08.845 that are very close to

NOTE Confidence: 0.9637278

00:17:08.845 --> 00:17:10.365 these aggregates are the first

NOTE Confidence: 0.9637278

00:17:10.365 --> 00:17:11.805 ones to be lost. So

NOTE Confidence: 0.9637278

00:17:11.805 --> 00:17:13.585 even at the earliest stages

NOTE Confidence: 0.9637278

00:17:13.805 --> 00:17:15.244 when we can't see broad

NOTE Confidence: 0.9637278

00:17:15.244 --> 00:17:16.619 synapse loss, when you look

NOTE Confidence: 0.9637278

00:17:16.619 --> 00:17:18.300 very closely at the sites

NOTE Confidence: 0.9637278

00:17:18.300 --> 00:17:19.280 of these aggregations,

NOTE Confidence: 0.9597003

00:17:19.740 --> 00:17:20.880 that's where synapse,

NOTE Confidence: 0.98683274

00:17:21.340 --> 00:17:21.840 number,

NOTE Confidence: 0.9558338

00:17:22.380 --> 00:17:23.980 goes down. Oh, sorry. I

NOTE Confidence: 0.9558338

00:17:23.980 --> 00:17:25.020 got the order wrong. What

NOTE Confidence: 0.9558338

00:17:25.020 --> 00:17:25.820 I show you here is

NOTE Confidence: 0.9558338

00:17:25.820 --> 00:17:28.080 actually the data that synaptics

NOTE Confidence: 0.9558338

00:17:28.300 --> 00:17:29.520 synuclein accumulates

NOTE Confidence: 0.97337335

00:17:30.325 --> 00:17:31.605 at these aggregate sites. And

NOTE Confidence: 0.97337335

00:17:31.605 --> 00:17:32.484 then here, these are the

NOTE Confidence: 0.97337335

00:17:32.484 --> 00:17:34.325 data that synapses are lost

NOTE Confidence: 0.97337335

00:17:34.325 --> 00:17:36.005 close to these aggregates. But

NOTE Confidence: 0.97337335

00:17:36.005 --> 00:17:36.744 there's a

NOTE Confidence: 0.9011541

00:17:37.045 --> 00:17:38.505 a correlation between,

NOTE Confidence: 0.9988833

00:17:40.005 --> 00:17:41.145 synuclein aggregation

NOTE Confidence: 0.9832987

00:17:41.525 --> 00:17:42.665 and synapse loss.

NOTE Confidence: 0.65362906

00:17:42.970 --> 00:17:43.470 And,

NOTE Confidence: 0.99035317

00:17:44.010 --> 00:17:45.530 recently has found that the

NOTE Confidence: 0.99035317

00:17:45.530 --> 00:17:46.670 vulnerable synapses

NOTE Confidence: 0.9845016

00:17:47.050 --> 00:17:48.490 actually have ten times more

NOTE Confidence: 0.9845016

00:17:48.490 --> 00:17:50.170 synuclein than the non than

NOTE Confidence: 0.9845016

00:17:50.170 --> 00:17:51.950 the protected ones. So synuclein

NOTE Confidence: 0.9845016

00:17:52.090 --> 00:17:53.530 certainly is a risk factor.

NOTE Confidence: 0.9845016

00:17:53.530 --> 00:17:55.070 So the accumulation of synuclein

NOTE Confidence: 0.9845016

00:17:55.130 --> 00:17:55.790 is probably,

NOTE Confidence: 0.99984884

00:17:56.570 --> 00:17:57.470 a good candidate

NOTE Confidence: 0.92523956

00:17:57.815 --> 00:17:59.275 as, for causal,

NOTE Confidence: 0.94115466

00:17:59.655 --> 00:18:00.795 to cause the loss.

NOTE Confidence: 0.6849977

00:18:02.455 --> 00:18:03.095 And as,

NOTE Confidence: 0.72602665

00:18:03.415 --> 00:18:04.775 we wanted to test,

NOTE Confidence: 0.77404964

00:18:05.494 --> 00:18:06.234 however, this,

NOTE Confidence: 0.94343996

00:18:07.255 --> 00:18:08.315 impacts function,

NOTE Confidence: 0.9165915

00:18:09.335 --> 00:18:11.095 I could, rely on our,

NOTE Confidence: 0.971446

00:18:11.800 --> 00:18:13.320 excellent collaboration that we have

NOTE Confidence: 0.971446

00:18:13.320 --> 00:18:14.200 with Mike Higley in the

NOTE Confidence: 0.971446

00:18:14.200 --> 00:18:15.260 neuroscience department

NOTE Confidence: 0.9024704

00:18:15.960 --> 00:18:17.720 where, Mike, in this case,

NOTE Confidence: 0.9024704

00:18:17.800 --> 00:18:19.900 for example, analyzed slice physiology

NOTE Confidence: 0.8355811

00:18:20.440 --> 00:18:21.640 in this peer in this,

NOTE Confidence: 0.9076306

00:18:22.359 --> 00:18:23.660 fibril mouse model.

NOTE Confidence: 0.9121422

00:18:24.225 --> 00:18:26.725 And, consistent with our, histochemical

NOTE Confidence: 0.9121422

00:18:26.945 --> 00:18:28.625 data, you could show that,

NOTE Confidence: 0.9121422

00:18:29.025 --> 00:18:30.165 exhalatory transmission

NOTE Confidence: 0.9970364

00:18:30.785 --> 00:18:31.924 is strongly reduced

NOTE Confidence: 0.9876959

00:18:32.225 --> 00:18:33.285 in these animals.

NOTE Confidence: 0.9352921

00:18:33.665 --> 00:18:34.625 What you see what you

NOTE Confidence: 0.9352921

00:18:34.625 --> 00:18:36.465 see here is actually plotted

NOTE Confidence: 0.9352921

00:18:36.465 --> 00:18:38.300 the time it takes between

NOTE Confidence: 0.9352921

00:18:38.360 --> 00:18:40.140 excitatory transmission events.

NOTE Confidence: 0.9901814

00:18:40.600 --> 00:18:41.640 So as you see here

NOTE Confidence: 0.9901814

00:18:41.640 --> 00:18:42.700 in the second graph,

NOTE Confidence: 0.9799139

00:18:44.920 --> 00:18:46.280 that timing gets longer and

NOTE Confidence: 0.9799139

00:18:46.280 --> 00:18:46.780 longer.

NOTE Confidence: 0.9738268

00:18:47.080 --> 00:18:47.740 That means,

NOTE Confidence: 0.9884422

00:18:48.120 --> 00:18:49.640 fewer and fewer events. So

NOTE Confidence: 0.9884422

00:18:49.640 --> 00:18:51.015 that's how we quantify

NOTE Confidence: 0.9757452

00:18:51.475 --> 00:18:51.875 the,

NOTE Confidence: 0.90176105

00:18:52.275 --> 00:18:55.175 frequency of, synaptic transmission events.

NOTE Confidence: 0.99683136

00:18:56.115 --> 00:18:56.615 Now

NOTE Confidence: 0.9499382

00:19:01.955 --> 00:19:03.975 analyzing the vulnerability of synopsis

NOTE Confidence: 0.9499382

00:19:04.035 --> 00:19:04.934 is one thing,

NOTE Confidence: 0.98024994

00:19:05.410 --> 00:19:06.450 but we also want to

NOTE Confidence: 0.98024994

00:19:06.450 --> 00:19:06.950 analyze

NOTE Confidence: 0.97552586

00:19:07.810 --> 00:19:09.510 how different cell types

NOTE Confidence: 0.9543398

00:19:09.810 --> 00:19:11.910 are vulnerable to PD pathology.

NOTE Confidence: 0.97473276

00:19:13.570 --> 00:19:13.970 And,

NOTE Confidence: 0.93243694

00:19:14.770 --> 00:19:16.609 we here rely on or

NOTE Confidence: 0.93243694

00:19:16.609 --> 00:19:17.490 can rely on,

NOTE Confidence: 0.96901983

00:19:18.050 --> 00:19:19.350 information about neuroanatomical

NOTE Confidence: 0.9989214

00:19:20.175 --> 00:19:21.475 connectivity of the cortex.

NOTE Confidence: 0.96274656

00:19:21.855 --> 00:19:23.715 As we know, layer five,

NOTE Confidence: 0.96274656

00:19:23.855 --> 00:19:25.455 where these projection neurons live

NOTE Confidence: 0.96274656

00:19:25.455 --> 00:19:26.915 that project to the striatum,

NOTE Confidence: 0.96274656

00:19:27.135 --> 00:19:28.175 is the first layer that

NOTE Confidence: 0.96274656

00:19:28.175 --> 00:19:30.115 shows, significant pathology.

NOTE Confidence: 0.9970914

00:19:31.055 --> 00:19:32.895 And, so we also have

NOTE Confidence: 0.9970914

00:19:32.895 --> 00:19:34.735 information that the neurons that

NOTE Confidence: 0.9970914

00:19:34.735 --> 00:19:35.910 are in layer five

NOTE Confidence: 0.8471354

00:19:36.390 --> 00:19:38.330 is, particularly these intertendencephalic,

NOTE Confidence: 0.95159787

00:19:39.350 --> 00:19:40.790 projection neurons that are shown

NOTE Confidence: 0.95159787

00:19:40.790 --> 00:19:41.609 here in gray,

NOTE Confidence: 0.99843

00:19:42.070 --> 00:19:43.210 that they project

NOTE Confidence: 0.98478657

00:19:43.590 --> 00:19:45.930 bilaterally. So they project,

NOTE Confidence: 0.78599983

00:19:47.030 --> 00:19:48.650 if the ipsio contralateral

NOTE Confidence: 0.92336047

00:19:48.950 --> 00:19:49.830 to the same side of

NOTE Confidence: 0.92336047

00:19:49.830 --> 00:19:51.190 the striatum, they will inject

NOTE Confidence: 0.92336047

00:19:51.190 --> 00:19:52.365 it, project to,

NOTE Confidence: 0.9510654

00:19:53.465 --> 00:19:54.025 the same,

NOTE Confidence: 0.96463376

00:19:54.904 --> 00:19:56.205 area of the striatum.

NOTE Confidence: 0.9721721

00:19:56.904 --> 00:19:58.825 But that allows us to

NOTE Confidence: 0.9721721

00:19:58.825 --> 00:20:00.284 test this in our model,

NOTE Confidence: 0.98721725

00:20:00.984 --> 00:20:02.765 is what happens if we

NOTE Confidence: 0.98721725

00:20:03.065 --> 00:20:04.984 use this unilateral injection to

NOTE Confidence: 0.98721725

00:20:04.984 --> 00:20:05.645 the striatum

NOTE Confidence: 0.9120106

00:20:06.109 --> 00:20:07.730 and then see how pathology

NOTE Confidence: 0.9120106

00:20:07.790 --> 00:20:09.570 progresses? Do we see pathology

NOTE Confidence: 0.9120106

00:20:09.630 --> 00:20:10.510 only in the side of

NOTE Confidence: 0.9120106

00:20:10.510 --> 00:20:12.290 the cortex for the injected

NOTE Confidence: 0.9120106

00:20:12.350 --> 00:20:14.270 striatum that sits, or do

NOTE Confidence: 0.9120106

00:20:14.270 --> 00:20:14.830 we see,

NOTE Confidence: 0.9631523

00:20:15.310 --> 00:20:16.850 pathology on both sides?

NOTE Confidence: 0.9678419

00:20:17.950 --> 00:20:19.230 And we actually do see

NOTE Confidence: 0.9678419

00:20:19.230 --> 00:20:20.290 Sanukian pathology

NOTE Confidence: 0.90079385

00:20:20.794 --> 00:20:22.715 both ipsy and contralaterally to

NOTE Confidence: 0.90079385

00:20:22.715 --> 00:20:23.934 the injected striatum.

NOTE Confidence: 0.7709414

00:20:24.395 --> 00:20:25.855 Here again in layer five.

NOTE Confidence: 0.9957702

00:20:26.234 --> 00:20:27.375 And so that's consistent

NOTE Confidence: 0.92974275

00:20:27.914 --> 00:20:30.154 with the layer five projection

NOTE Confidence: 0.92974275

00:20:30.154 --> 00:20:30.654 neurons,

NOTE Confidence: 0.99660295

00:20:31.515 --> 00:20:33.215 to be the primary targets

NOTE Confidence: 0.99660295

00:20:33.275 --> 00:20:33.934 of pathology

NOTE Confidence: 0.90932256

00:20:34.234 --> 00:20:35.054 in the cortex,

NOTE Confidence: 0.96302986

00:20:36.040 --> 00:20:37.240 because these are the only

NOTE Confidence: 0.96302986

00:20:37.240 --> 00:20:39.340 ones that really project dorsolateral,

NOTE Confidence: 0.96302986

00:20:39.560 --> 00:20:41.240 both ipsi and contralaterally to

NOTE Confidence: 0.96302986

00:20:41.240 --> 00:20:41.980 the striatum.

NOTE Confidence: 0.9591984

00:20:43.240 --> 00:20:45.320 And this is accompanied also

NOTE Confidence: 0.9591984

00:20:45.320 --> 00:20:46.760 in the contralateral side with

NOTE Confidence: 0.9591984

00:20:46.760 --> 00:20:48.040 synapse loss, just what I

NOTE Confidence: 0.9591984

00:20:48.040 --> 00:20:49.340 showed you for the ipsilateral

NOTE Confidence: 0.9591984

00:20:49.480 --> 00:20:50.300 side before.

NOTE Confidence: 0.94501805

00:20:50.674 --> 00:20:51.554 So it's not just that

NOTE Confidence: 0.94501805

00:20:51.554 --> 00:20:53.475 synuclein pathology appears, but also

NOTE Confidence: 0.94501805

00:20:53.475 --> 00:20:55.554 then connectivity is impaired even

NOTE Confidence: 0.94501805

00:20:55.554 --> 00:20:57.255 though this is a hemisphere

NOTE Confidence: 0.94501805

00:20:57.395 --> 00:20:58.835 that has been spared by

NOTE Confidence: 0.94501805

00:20:58.835 --> 00:20:59.575 our injection.

NOTE Confidence: 0.99758554

00:21:01.475 --> 00:21:01.975 Now

NOTE Confidence: 0.94848585

00:21:03.250 --> 00:21:04.450 this is all data in

NOTE Confidence: 0.94848585

00:21:04.450 --> 00:21:05.350 the mouse model.

NOTE Confidence: 0.9484128

00:21:06.929 --> 00:21:08.130 The question now is how

NOTE Confidence: 0.9484128

00:21:08.130 --> 00:21:09.330 can we validate this in

NOTE Confidence: 0.9484128

00:21:09.330 --> 00:21:10.309 the human tissue?

NOTE Confidence: 0.96202886

00:21:10.929 --> 00:21:13.190 And here, again, our collaborators,

NOTE Confidence: 0.7758768

00:21:14.369 --> 00:21:15.750 so Terry Kumar and Rousalbek

NOTE Confidence: 0.7758768

00:21:16.049 --> 00:21:16.710 stepped in

NOTE Confidence: 0.9639728

00:21:17.284 --> 00:21:19.125 and have pulled off some,

NOTE Confidence: 0.9639728

00:21:19.125 --> 00:21:20.585 what I find, very impressive

NOTE Confidence: 0.9639728

00:21:20.645 --> 00:21:22.164 approaches. What you see here

NOTE Confidence: 0.9639728

00:21:22.164 --> 00:21:23.525 on the left is, human

NOTE Confidence: 0.9639728

00:21:23.525 --> 00:21:24.345 PD tissue,

NOTE Confidence: 0.99780124

00:21:26.244 --> 00:21:26.744 analyzed

NOTE Confidence: 0.86234623

00:21:27.205 --> 00:21:28.825 by synaptic marker staining.

NOTE Confidence: 0.988308

00:21:29.380 --> 00:21:30.260 And this is not your

NOTE Confidence: 0.988308

00:21:30.260 --> 00:21:32.020 regular confocal. This is high

NOTE Confidence: 0.988308

00:21:32.020 --> 00:21:33.640 resolution meso scans

NOTE Confidence: 0.9603267

00:21:34.179 --> 00:21:36.419 at synaptic resolution. So wherever

NOTE Confidence: 0.9603267

00:21:36.419 --> 00:21:37.880 you go in this image,

NOTE Confidence: 0.9603267

00:21:38.100 --> 00:21:39.299 you can zoom in and

NOTE Confidence: 0.9603267

00:21:39.299 --> 00:21:40.520 have this at a subsynaptic

NOTE Confidence: 0.9603267

00:21:40.820 --> 00:21:41.940 resolution where you see the

NOTE Confidence: 0.9603267

00:21:41.940 --> 00:21:43.515 pre and the postsynaptic sides.

NOTE Confidence: 0.9603267

00:21:43.835 --> 00:21:45.135 So this is incredibly

NOTE Confidence: 0.9505019

00:21:45.595 --> 00:21:46.575 rich in detail.

NOTE Confidence: 0.99535716

00:21:46.955 --> 00:21:48.075 So you can look at

NOTE Confidence: 0.99535716

00:21:48.075 --> 00:21:48.815 the whole,

NOTE Confidence: 0.98869574

00:21:49.355 --> 00:21:51.135 across all cortical layers

NOTE Confidence: 0.95369655

00:21:51.515 --> 00:21:53.275 from the meso scan down

NOTE Confidence: 0.95369655

00:21:53.275 --> 00:21:55.035 to the synaptic level and

NOTE Confidence: 0.95369655

00:21:55.035 --> 00:21:57.435 analyze synaptic aberrations in the

NOTE Confidence: 0.95369655

00:21:57.435 --> 00:21:58.335 in the patients.

NOTE Confidence: 0.95250595

00:21:58.710 --> 00:22:00.169 This is a really

NOTE Confidence: 0.90941536

00:22:00.549 --> 00:22:01.049 impressive,

NOTE Confidence: 0.97872895

00:22:01.830 --> 00:22:03.510 advance that they have. So

NOTE Confidence: 0.97872895

00:22:03.510 --> 00:22:04.809 we're now in the position

NOTE Confidence: 0.97872895

00:22:04.950 --> 00:22:06.409 to test all of our

NOTE Confidence: 0.97872895

00:22:06.470 --> 00:22:06.970 approaches

NOTE Confidence: 0.9974925

00:22:08.149 --> 00:22:08.970 in the patients.

NOTE Confidence: 0.9954893

00:22:09.909 --> 00:22:11.450 And I wanted to add,

NOTE Confidence: 0.9997659

00:22:11.990 --> 00:22:12.730 two slides

NOTE Confidence: 0.9109243

00:22:13.395 --> 00:22:13.875 because,

NOTE Confidence: 0.99935657

00:22:14.675 --> 00:22:15.175 I

NOTE Confidence: 0.9789298

00:22:16.515 --> 00:22:17.975 am trained as a biochemist,

NOTE Confidence: 0.9789298

00:22:18.115 --> 00:22:19.315 so I want to have,

NOTE Confidence: 0.9981513

00:22:19.955 --> 00:22:20.455 mechanisms.

NOTE Confidence: 0.9762659

00:22:21.475 --> 00:22:23.415 And, here again, the transcriptional

NOTE Confidence: 0.9187162

00:22:23.795 --> 00:22:24.275 changes,

NOTE Confidence: 0.97243696

00:22:24.835 --> 00:22:25.795 helped us to,

NOTE Confidence: 0.99829173

00:22:26.195 --> 00:22:27.895 identify target pathways.

NOTE Confidence: 0.99464464

00:22:28.559 --> 00:22:29.299 As I mentioned,

NOTE Confidence: 0.85073245

00:22:30.000 --> 00:22:30.820 earlier on,

NOTE Confidence: 0.96137524

00:22:31.200 --> 00:22:32.240 among the genes that are

NOTE Confidence: 0.96137524

00:22:32.240 --> 00:22:32.740 downregulated

NOTE Confidence: 0.9701579

00:22:33.519 --> 00:22:35.440 in the, PD in the

NOTE Confidence: 0.9701579

00:22:35.440 --> 00:22:35.940 pathological

NOTE Confidence: 0.9244723

00:22:36.320 --> 00:22:38.260 neurons in human PD tissue,

NOTE Confidence: 0.9244723

00:22:38.480 --> 00:22:39.440 as well as now a

NOTE Confidence: 0.9244723

00:22:39.440 --> 00:22:41.065 mouse model, are these trans

NOTE Confidence: 0.9244723

00:22:41.065 --> 00:22:42.585 synaptic proteins that are here

NOTE Confidence: 0.9244723

00:22:42.585 --> 00:22:43.785 marked with this red circle

NOTE Confidence: 0.9244723

00:22:43.785 --> 00:22:44.525 on the left.

NOTE Confidence: 0.9624849

00:22:45.305 --> 00:22:46.365 These are called neurexins.

NOTE Confidence: 0.9465701

00:22:46.744 --> 00:22:47.885 These are on the presynaptic

NOTE Confidence: 0.9465701

00:22:48.025 --> 00:22:49.385 side, and they are down

NOTE Confidence: 0.9465701

00:22:49.385 --> 00:22:50.744 regulated both in the mouse

NOTE Confidence: 0.9465701

00:22:50.744 --> 00:22:51.945 model and in the human

NOTE Confidence: 0.9465701

00:22:51.945 --> 00:22:52.445 tissue.

NOTE Confidence: 0.9612596

00:22:53.930 --> 00:22:56.170 So we asked whether they

NOTE Confidence: 0.9612596

00:22:56.170 --> 00:22:57.530 have a role, and that's

NOTE Confidence: 0.9612596

00:22:57.530 --> 00:22:58.810 driven by the fact that

NOTE Confidence: 0.9612596

00:22:58.810 --> 00:23:00.030 pathology progresses

NOTE Confidence: 0.99156463

00:23:00.650 --> 00:23:01.630 between synaptically

NOTE Confidence: 0.95354855

00:23:02.010 --> 00:23:03.530 connected populations. So we want

NOTE Confidence: 0.95354855

00:23:03.530 --> 00:23:05.230 to know whether synapses themselves

NOTE Confidence: 0.98312116

00:23:05.690 --> 00:23:06.990 are sites of pathological

NOTE Confidence: 0.99668765

00:23:07.290 --> 00:23:07.790 transmission.

NOTE Confidence: 0.9992544

00:23:09.804 --> 00:23:10.765 And for that,

NOTE Confidence: 0.9779187

00:23:11.404 --> 00:23:12.385 we have established,

NOTE Confidence: 0.90361995

00:23:12.765 --> 00:23:13.885 both in vitro and in

NOTE Confidence: 0.90361995

00:23:13.885 --> 00:23:15.085 vivo approach. I'll show you

NOTE Confidence: 0.90361995

00:23:15.085 --> 00:23:16.605 what today the data for

NOTE Confidence: 0.90361995

00:23:16.605 --> 00:23:17.744 the in vitro approach.

NOTE Confidence: 0.99901736

00:23:18.365 --> 00:23:19.984 And these experiments are performed

NOTE Confidence: 0.9306771

00:23:20.365 --> 00:23:22.044 by Maria Juliano, who's also

NOTE Confidence: 0.9306771

00:23:22.044 --> 00:23:22.865 here in the audience.

NOTE Confidence: 0.9421593

00:23:24.240 --> 00:23:25.600 So and I just keep

NOTE Confidence: 0.9421593

00:23:25.600 --> 00:23:26.980 this, very straightforward.

NOTE Confidence: 0.97891617

00:23:27.359 --> 00:23:28.880 And in a nutshell, we

NOTE Confidence: 0.97891617

00:23:28.880 --> 00:23:30.320 could show that,

NOTE Confidence: 0.98862296

00:23:31.200 --> 00:23:32.560 cultured neurons that we use

NOTE Confidence: 0.98862296

00:23:32.560 --> 00:23:33.380 in this model

NOTE Confidence: 0.9399428

00:23:33.760 --> 00:23:36.000 show strong pathological responses to

NOTE Confidence: 0.9399428

00:23:36.000 --> 00:23:37.184 the addition to the of

NOTE Confidence: 0.9399428

00:23:37.184 --> 00:23:39.024 this, synuclein fibrils, just what

NOTE Confidence: 0.9399428

00:23:39.024 --> 00:23:39.904 I have shown you in

NOTE Confidence: 0.9399428

00:23:39.904 --> 00:23:40.404 vivo.

NOTE Confidence: 0.94043577

00:23:40.784 --> 00:23:42.244 Let's see on the top,

NOTE Confidence: 0.9643825

00:23:42.705 --> 00:23:43.664 where you see these,

NOTE Confidence: 0.9927033

00:23:44.065 --> 00:23:45.764 aggregates marked in green.

NOTE Confidence: 0.9052029

00:23:46.065 --> 00:23:46.865 What you see in blue

NOTE Confidence: 0.9052029

00:23:46.865 --> 00:23:48.244 is just a neural morphology,

NOTE Confidence: 0.9052029

00:23:48.384 --> 00:23:49.684 specifically the dendrites.

NOTE Confidence: 0.9520559

00:23:50.220 --> 00:23:51.820 And so we quantify the

NOTE Confidence: 0.9520559

00:23:51.820 --> 00:23:53.500 typical pathology as you see

NOTE Confidence: 0.9520559

00:23:53.500 --> 00:23:54.300 here on the graph on

NOTE Confidence: 0.9520559

00:23:54.300 --> 00:23:55.580 the left. But if you

NOTE Confidence: 0.9520559

00:23:55.580 --> 00:23:57.260 knock down Eurexin, you see

NOTE Confidence: 0.9520559

00:23:57.260 --> 00:23:58.240 a drastic,

NOTE Confidence: 0.96430874

00:23:59.179 --> 00:24:01.600 reduction in how the pathology

NOTE Confidence: 0.96430874

00:24:01.740 --> 00:24:02.240 appears.

NOTE Confidence: 0.7894496

00:24:02.780 --> 00:24:03.100 And,

NOTE Confidence: 0.91009974

00:24:04.095 --> 00:24:05.294 there is, at least to

NOTE Confidence: 0.91009974

00:24:05.294 --> 00:24:06.835 my knowledge, no other intervention

NOTE Confidence: 0.91009974

00:24:06.975 --> 00:24:08.515 that can reduce the synuclein

NOTE Confidence: 0.91009974

00:24:08.575 --> 00:24:10.835 pathology in any comparable way.

NOTE Confidence: 0.91009974

00:24:11.054 --> 00:24:13.234 So, these new reactions are

NOTE Confidence: 0.99988794

00:24:13.695 --> 00:24:14.195 critical

NOTE Confidence: 0.999723

00:24:14.655 --> 00:24:15.155 for

NOTE Confidence: 0.7647433

00:24:15.615 --> 00:24:16.275 the pathology

NOTE Confidence: 0.9794281

00:24:16.975 --> 00:24:19.554 appearance in these excitatory neurons.

NOTE Confidence: 0.9403389

00:24:20.040 --> 00:24:20.540 And,

NOTE Confidence: 0.93726516

00:24:21.400 --> 00:24:23.020 I just, wanted to,

NOTE Confidence: 0.9305377

00:24:23.400 --> 00:24:24.280 end with this. We have

NOTE Confidence: 0.9305377

00:24:24.280 --> 00:24:25.960 done structure function analysis on

NOTE Confidence: 0.9305377

00:24:25.960 --> 00:24:27.160 this. We do this in

NOTE Confidence: 0.9305377

00:24:27.160 --> 00:24:28.760 the in the neuroexon knockout

NOTE Confidence: 0.9305377

00:24:28.760 --> 00:24:30.200 mouse model right now. But,

NOTE Confidence: 0.9305377

00:24:30.440 --> 00:24:31.560 I think this is one

NOTE Confidence: 0.9305377

00:24:31.560 --> 00:24:33.080 way to communicate how we

NOTE Confidence: 0.9305377

00:24:33.080 --> 00:24:34.140 try to get at molecular

NOTE Confidence: 0.9305377

00:24:34.280 --> 00:24:34.780 approaches.

NOTE Confidence: 0.94215566

00:24:35.495 --> 00:24:36.395 And just to,

NOTE Confidence: 0.9925661

00:24:36.855 --> 00:24:37.355 conclude,

NOTE Confidence: 0.9357448

00:24:38.695 --> 00:24:39.995 what we know is,

NOTE Confidence: 0.96398216

00:24:41.415 --> 00:24:43.575 synapses are not only vulnerable,

NOTE Confidence: 0.96398216

00:24:43.575 --> 00:24:45.575 but also show synapse type

NOTE Confidence: 0.96398216

00:24:45.575 --> 00:24:47.275 specific vulnerability patterns.

NOTE Confidence: 0.94526327

00:24:48.649 --> 00:24:50.250 We have, not just loss,

NOTE Confidence: 0.94526327

00:24:50.250 --> 00:24:51.769 but also changes. So the

NOTE Confidence: 0.94526327

00:24:51.769 --> 00:24:53.210 structure of synapses in the

NOTE Confidence: 0.94526327

00:24:53.210 --> 00:24:55.389 PD pathology, so the pathology

NOTE Confidence: 0.94526327

00:24:55.450 --> 00:24:57.130 will have broad effects on

NOTE Confidence: 0.94526327

00:24:57.130 --> 00:24:58.109 cortical function.

NOTE Confidence: 0.9845931

00:24:59.609 --> 00:25:01.470 In agreement, we see altered,

NOTE Confidence: 0.9571215

00:25:01.929 --> 00:25:02.990 synaptic transmission

NOTE Confidence: 0.94981456

00:25:03.484 --> 00:25:04.865 in this mouse model.

NOTE Confidence: 0.95787555

00:25:05.325 --> 00:25:07.265 And we have evidence that

NOTE Confidence: 0.95787555

00:25:07.405 --> 00:25:09.805 the that, certain proteins, including,

NOTE Confidence: 0.95787555

00:25:10.125 --> 00:25:11.725 these transsynaptic proteins have a

NOTE Confidence: 0.95787555

00:25:11.725 --> 00:25:13.484 role in pathology progression. So

NOTE Confidence: 0.95787555

00:25:13.484 --> 00:25:14.765 this could be another way

NOTE Confidence: 0.95787555

00:25:14.765 --> 00:25:16.145 of slowing down progression

NOTE Confidence: 0.9980971

00:25:16.525 --> 00:25:17.345 in the patients.

NOTE Confidence: 0.8656371

00:25:18.090 --> 00:25:19.049 And the things we we

NOTE Confidence: 0.8656371

00:25:19.049 --> 00:25:19.790 don't know,

NOTE Confidence: 0.91281086

00:25:20.650 --> 00:25:22.109 really have to understand

NOTE Confidence: 0.9540647

00:25:22.490 --> 00:25:24.030 how in our mouse model,

NOTE Confidence: 0.9927522

00:25:24.570 --> 00:25:26.109 cortical circuits are impacted.

NOTE Confidence: 0.9188478

00:25:26.570 --> 00:25:27.869 We have to move beyond

NOTE Confidence: 0.9188478

00:25:28.010 --> 00:25:29.369 recordings to really look at

NOTE Confidence: 0.9188478

00:25:29.369 --> 00:25:30.650 activity patterns in the whole

NOTE Confidence: 0.9188478

00:25:30.650 --> 00:25:31.130 cortex, and,

NOTE Confidence: 0.994098

00:25:32.065 --> 00:25:33.865 that's currently something that we

NOTE Confidence: 0.994098

00:25:33.865 --> 00:25:34.285 test.

NOTE Confidence: 0.96275204

00:25:34.705 --> 00:25:36.005 We also need to know,

NOTE Confidence: 0.9989646

00:25:36.865 --> 00:25:37.845 to what extent

NOTE Confidence: 0.9095065

00:25:38.225 --> 00:25:38.705 does,

NOTE Confidence: 0.74467397

00:25:39.105 --> 00:25:39.605 synaptic,

NOTE Confidence: 0.7970827

00:25:40.625 --> 00:25:41.685 biology or synaptic,

NOTE Confidence: 0.964814

00:25:42.065 --> 00:25:43.505 proteins, to what extent do

NOTE Confidence: 0.964814

00:25:43.505 --> 00:25:43.890 they

NOTE Confidence: 0.9989463

00:25:44.369 --> 00:25:44.869 modulate

NOTE Confidence: 0.92730767

00:25:45.170 --> 00:25:47.250 or even, drive progressions? Or

NOTE Confidence: 0.92730767

00:25:47.250 --> 00:25:48.390 are they really targets?

NOTE Confidence: 0.91634125

00:25:49.890 --> 00:25:51.910 And then, the last question,

NOTE Confidence: 0.91634125

00:25:51.970 --> 00:25:52.930 and that's a question that

NOTE Confidence: 0.91634125

00:25:52.930 --> 00:25:53.590 I've already

NOTE Confidence: 0.9861542

00:25:53.970 --> 00:25:54.869 discussed at

NOTE Confidence: 0.8414087

00:25:55.170 --> 00:25:56.470 length with Jaime,

NOTE Confidence: 0.7880586

00:25:57.494 --> 00:25:57.975 It's,

NOTE Confidence: 0.9756082

00:25:58.455 --> 00:25:59.494 okay. So we have this

NOTE Confidence: 0.9756082

00:25:59.494 --> 00:26:01.335 model. It replicates one aspect

NOTE Confidence: 0.9756082

00:26:01.335 --> 00:26:02.535 of PD, which is the

NOTE Confidence: 0.9756082

00:26:02.535 --> 00:26:03.035 synuclein,

NOTE Confidence: 0.93410844

00:26:03.415 --> 00:26:03.915 aggregates,

NOTE Confidence: 0.96047276

00:26:04.375 --> 00:26:05.335 but that's not what happens

NOTE Confidence: 0.96047276

00:26:05.335 --> 00:26:06.615 in the patients. You often

NOTE Confidence: 0.96047276

00:26:06.615 --> 00:26:07.275 have copathology,

NOTE Confidence: 0.9171412

00:26:07.575 --> 00:26:09.015 whether it's tau, or whether

NOTE Confidence: 0.9171412

00:26:09.015 --> 00:26:10.315 it's amyloid copathology.

NOTE Confidence: 0.97481817

00:26:11.730 --> 00:26:13.250 Are they just living separately

NOTE Confidence: 0.97481817

00:26:13.250 --> 00:26:14.609 and doing the individual damage,

NOTE Confidence: 0.97481817

00:26:14.609 --> 00:26:15.750 or do they have synergistic

NOTE Confidence: 0.97481817

00:26:15.890 --> 00:26:16.929 effects? And we have already

NOTE Confidence: 0.97481817

00:26:16.929 --> 00:26:18.230 started the first experiments,

NOTE Confidence: 0.9196544

00:26:18.530 --> 00:26:20.369 and it, is, quite,

NOTE Confidence: 0.96278334

00:26:21.090 --> 00:26:22.230 promising that,

NOTE Confidence: 0.92420495

00:26:23.090 --> 00:26:25.270 amyloid pathology and synutin pathology

NOTE Confidence: 0.9729617

00:26:26.335 --> 00:26:27.695 are not just additive, but

NOTE Confidence: 0.9729617

00:26:27.695 --> 00:26:28.355 could actually,

NOTE Confidence: 0.95263726

00:26:29.055 --> 00:26:30.175 at least that the amyloid

NOTE Confidence: 0.95263726

00:26:30.175 --> 00:26:31.795 pathology could drive the synuclein

NOTE Confidence: 0.95263726

00:26:31.855 --> 00:26:32.355 pathology.

NOTE Confidence: 0.97452635

00:26:32.815 --> 00:26:34.495 So that's a active area

NOTE Confidence: 0.97452635

00:26:34.495 --> 00:26:36.015 of investigation that I think

NOTE Confidence: 0.97452635

00:26:36.015 --> 00:26:37.295 is also very important for

NOTE Confidence: 0.97452635

00:26:37.295 --> 00:26:37.955 the patients.

NOTE Confidence: 0.8508863

00:26:38.335 --> 00:26:39.135 After that, I would like

NOTE Confidence: 0.8508863

00:26:39.135 --> 00:26:39.635 to,

NOTE Confidence: 0.9497123

00:26:40.320 --> 00:26:40.820 acknowledge,

NOTE Confidence: 0.9807359

00:26:41.359 --> 00:26:42.179 my lab,

NOTE Confidence: 0.94939375

00:26:43.600 --> 00:26:45.279 who are here. And I

NOTE Confidence: 0.94939375

00:26:45.279 --> 00:26:46.799 also wanted to acknowledge the

NOTE Confidence: 0.94939375

00:26:46.799 --> 00:26:48.000 ASAP team. This is a

NOTE Confidence: 0.94939375

00:26:48.000 --> 00:26:49.520 team picture that we,

NOTE Confidence: 0.9686924

00:26:49.840 --> 00:26:51.140 took at one of our,

NOTE Confidence: 0.9940493

00:26:51.679 --> 00:26:52.179 retreats,

NOTE Confidence: 0.9974783

00:26:52.945 --> 00:26:54.244 which really brings together

NOTE Confidence: 0.9831481

00:26:54.625 --> 00:26:56.165 a large range of interdisciplinary,

NOTE Confidence: 0.9887089

00:26:57.265 --> 00:26:57.765 researchers

NOTE Confidence: 0.92837965

00:26:58.305 --> 00:27:00.065 that, some of us are

NOTE Confidence: 0.92837965

00:27:00.065 --> 00:27:01.185 new to the PD field,

NOTE Confidence: 0.92837965

00:27:01.185 --> 00:27:02.785 others are experiencing it. So

NOTE Confidence: 0.92837965

00:27:02.785 --> 00:27:04.645 it's a a very enjoyable

NOTE Confidence: 0.8778086

00:27:04.945 --> 00:27:05.345 and,

NOTE Confidence: 0.9461337

00:27:06.385 --> 00:27:07.905 great environment to learn about

NOTE Confidence: 0.9461337

00:27:07.905 --> 00:27:09.359 PD and to apply our

NOTE Confidence: 0.9461337

00:27:09.359 --> 00:27:10.580 our research interests.

NOTE Confidence: 0.9700697

00:27:11.040 --> 00:27:11.840 That, I would like to

NOTE Confidence: 0.9700697

00:27:11.840 --> 00:27:13.140 thank you for your attention.

NOTE Confidence: 0.8982636

00:27:21.634 --> 00:27:22.534 Right. Good.

NOTE Confidence: 0.5658817

00:27:22.994 --> 00:27:24.134 Kumar. Yeah.

NOTE Confidence: 0.9911225

00:27:24.514 --> 00:27:25.715 So if you were to

NOTE Confidence: 0.9911225

00:27:25.715 --> 00:27:26.215 superimpose

NOTE Confidence: 0.95385015

00:27:26.674 --> 00:27:28.195 the g g b the

NOTE Confidence: 0.95385015

00:27:28.195 --> 00:27:30.195 GWAS data onto your synaptic

NOTE Confidence: 0.95385015

00:27:30.195 --> 00:27:31.634 protein, you know, that slide

NOTE Confidence: 0.95385015

00:27:31.634 --> 00:27:33.575 that you had, is there

NOTE Confidence: 0.95785224

00:27:34.034 --> 00:27:35.494 a map? Do they match?

NOTE Confidence: 0.9686282

00:27:36.980 --> 00:27:38.419 It's not that straightforward. So

NOTE Confidence: 0.9686282

00:27:38.419 --> 00:27:40.200 the GBOS data are less

NOTE Confidence: 0.995974

00:27:40.580 --> 00:27:41.080 informative

NOTE Confidence: 0.9904064

00:27:41.539 --> 00:27:43.299 than the the the expression

NOTE Confidence: 0.9904064

00:27:43.299 --> 00:27:44.659 data. The expression data have

NOTE Confidence: 0.9904064

00:27:44.659 --> 00:27:46.440 one advantage. We specifically

NOTE Confidence: 0.9519012

00:27:46.820 --> 00:27:48.019 and I didn't I I

NOTE Confidence: 0.9519012

00:27:48.019 --> 00:27:49.455 explained this in detail. We

NOTE Confidence: 0.9519012

00:27:49.455 --> 00:27:51.855 specifically analyzed gene expression changes

NOTE Confidence: 0.9519012

00:27:51.855 --> 00:27:53.475 in pathology bearing neurons.

NOTE Confidence: 0.8658964

00:27:53.855 --> 00:27:54.895 But at some point, it

NOTE Confidence: 0.8658964

00:27:54.895 --> 00:27:56.414 becomes super streamlined. So we

NOTE Confidence: 0.8658964

00:27:56.414 --> 00:27:57.534 look we look at that

NOTE Confidence: 0.8658964

00:27:57.534 --> 00:27:58.975 subpopulation of neurons that have

NOTE Confidence: 0.8658964

00:27:58.975 --> 00:28:00.575 the synuclein aggregates so we've

NOTE Confidence: 0.8658964

00:28:00.575 --> 00:28:01.715 had much better resolution.

NOTE Confidence: 0.9220355

00:28:02.240 --> 00:28:03.840 And then does neurons seem

NOTE Confidence: 0.9220355

00:28:03.840 --> 00:28:04.960 to bind? I didn't get

NOTE Confidence: 0.9220355

00:28:04.960 --> 00:28:06.000 that. Did you say it

NOTE Confidence: 0.9220355

00:28:06.000 --> 00:28:08.260 binds to I didn't. Reform?

NOTE Confidence: 0.9638184

00:28:08.640 --> 00:28:09.680 I didn't say it, but,

NOTE Confidence: 0.9609735

00:28:10.240 --> 00:28:11.520 because I didn't want to

NOTE Confidence: 0.9609735

00:28:11.520 --> 00:28:12.480 cover too much of the

NOTE Confidence: 0.9609735

00:28:12.480 --> 00:28:13.840 mechanism. But, yes, your your

NOTE Confidence: 0.9609735

00:28:13.840 --> 00:28:15.119 hunch is absolutely right. That's

NOTE Confidence: 0.9609735

00:28:15.119 --> 00:28:16.400 what we observe, and,

NOTE Confidence: 0.98179996

00:28:16.994 --> 00:28:17.955 that's what we are currently

NOTE Confidence: 0.98179996

00:28:17.955 --> 00:28:20.055 quantifying. But there is evidence,

NOTE Confidence: 0.8519879

00:28:20.915 --> 00:28:22.275 including also from other labs

NOTE Confidence: 0.8519879

00:28:22.275 --> 00:28:23.875 that synuclein and fibrils can

NOTE Confidence: 0.8519879

00:28:23.875 --> 00:28:25.315 bind to the surface of

NOTE Confidence: 0.8519879

00:28:25.315 --> 00:28:27.315 neurexin. And we have also

NOTE Confidence: 0.8519879

00:28:27.315 --> 00:28:29.015 with the structure functional identified

NOTE Confidence: 0.82988626

00:28:29.555 --> 00:28:31.015 modifications in neurexins

NOTE Confidence: 0.9673116

00:28:31.555 --> 00:28:32.730 that are required for

NOTE Confidence: 0.89100736

00:28:34.730 --> 00:28:35.850 them. It's a precedent. Right?

NOTE Confidence: 0.89100736

00:28:35.850 --> 00:28:37.049 So some of the toxins

NOTE Confidence: 0.89100736

00:28:37.049 --> 00:28:38.410 like botulism and stuff like

NOTE Confidence: 0.89100736

00:28:38.410 --> 00:28:40.350 that bind to synaptic proteins.

NOTE Confidence: 0.89100736

00:28:40.570 --> 00:28:41.390 Yeah. Protein.

NOTE Confidence: 0.91105765

00:28:44.935 --> 00:28:46.555 Okay. Go ahead. David, please.

NOTE Confidence: 0.91105765

00:28:46.775 --> 00:28:47.275 Do

NOTE Confidence: 0.6530515

00:28:47.655 --> 00:28:49.255 the advocates of the alpha

NOTE Confidence: 0.6530515

00:28:49.255 --> 00:28:51.435 SNP induced any microglia activation?

NOTE Confidence: 0.9992048

00:28:52.535 --> 00:28:53.035 We

NOTE Confidence: 0.9994068

00:28:53.655 --> 00:28:54.155 have

NOTE Confidence: 0.8910747

00:28:54.855 --> 00:28:55.355 only,

NOTE Confidence: 0.9937874

00:28:56.615 --> 00:28:58.155 we are planning these experiments

NOTE Confidence: 0.9937874

00:28:58.295 --> 00:28:59.035 right now.

NOTE Confidence: 0.95486563

00:29:00.090 --> 00:29:01.210 So we have the tissue

NOTE Confidence: 0.95486563

00:29:01.210 --> 00:29:02.410 in our mouse model. We

NOTE Confidence: 0.95486563

00:29:02.410 --> 00:29:03.770 are starting to analyze this,

NOTE Confidence: 0.95486563

00:29:03.770 --> 00:29:04.730 and we also want to

NOTE Confidence: 0.95486563

00:29:04.730 --> 00:29:06.270 analyze the role of microglia

NOTE Confidence: 0.95486563

00:29:06.410 --> 00:29:07.870 and the loss of synapses

NOTE Confidence: 0.95486563

00:29:07.930 --> 00:29:09.130 that we have here. But,

NOTE Confidence: 0.95486563

00:29:09.450 --> 00:29:11.050 that's that's the next step

NOTE Confidence: 0.95486563

00:29:11.050 --> 00:29:12.730 for us, leaving our neuron

NOTE Confidence: 0.95486563

00:29:12.730 --> 00:29:14.110 centric view of the world.

NOTE Confidence: 0.95486563

00:29:14.375 --> 00:29:14.855 And,

NOTE Confidence: 0.9892458

00:29:15.335 --> 00:29:15.895 and that's,

NOTE Confidence: 0.9073335

00:29:16.775 --> 00:29:18.875 yeah. We have started to

NOTE Confidence: 0.9073335

00:29:19.015 --> 00:29:19.775 to to,

NOTE Confidence: 0.5997156

00:29:20.215 --> 00:29:21.035 these experiments.

NOTE Confidence: 0.59336674

00:29:22.935 --> 00:29:23.435 Please.

NOTE Confidence: 0.90576804

00:29:23.895 --> 00:29:26.055 The role of dopamine and

NOTE Confidence: 0.90576804

00:29:26.055 --> 00:29:27.195 GABA. So

NOTE Confidence: 0.87054884

00:29:28.170 --> 00:29:29.790 I mean, in clinical practice,

NOTE Confidence: 0.9146632

00:29:30.090 --> 00:29:31.290 those are the main things,

NOTE Confidence: 0.9146632

00:29:31.290 --> 00:29:33.210 and dopamine interaction without this

NOTE Confidence: 0.9146632

00:29:33.210 --> 00:29:34.750 nuclei. And then in terms

NOTE Confidence: 0.9912097

00:29:35.130 --> 00:29:36.810 of synapse loss, have you

NOTE Confidence: 0.9912097

00:29:36.810 --> 00:29:38.110 quantitated whether

NOTE Confidence: 0.97384995

00:29:38.650 --> 00:29:39.550 it is more,

NOTE Confidence: 0.84785396

00:29:40.410 --> 00:29:41.470 GABA type of

NOTE Confidence: 0.93317497

00:29:41.945 --> 00:29:43.545 synopsis, or is it a

NOTE Confidence: 0.93317497

00:29:43.545 --> 00:29:45.785 excitatory synopsis? We have quantified

NOTE Confidence: 0.93317497

00:29:45.785 --> 00:29:46.745 this. I just didn't go

NOTE Confidence: 0.93317497

00:29:46.745 --> 00:29:47.945 into the details. We have

NOTE Confidence: 0.93317497

00:29:47.945 --> 00:29:49.625 analyzed different synapse types. So

NOTE Confidence: 0.93317497

00:29:49.625 --> 00:29:50.905 if I just ask answer

NOTE Confidence: 0.93317497

00:29:50.905 --> 00:29:52.525 first about the GABAergic synopsis.

NOTE Confidence: 0.93317497

00:29:52.665 --> 00:29:54.665 Inhibitory synapses are among those

NOTE Confidence: 0.93317497

00:29:54.665 --> 00:29:56.365 synapse types that are completely

NOTE Confidence: 0.93317497

00:29:56.505 --> 00:29:58.000 protected. So even at the

NOTE Confidence: 0.93317497

00:29:58.000 --> 00:29:59.040 latest time points that we've

NOTE Confidence: 0.93317497

00:29:59.040 --> 00:30:00.320 analyzed so far, we have

NOTE Confidence: 0.93317497

00:30:00.320 --> 00:30:02.000 not seen a loss of

NOTE Confidence: 0.93317497

00:30:02.000 --> 00:30:03.679 GABAergic synapse. So it seems

NOTE Confidence: 0.93317497

00:30:03.679 --> 00:30:04.340 to be

NOTE Confidence: 0.91128063

00:30:04.799 --> 00:30:06.820 pretty restricted to local inhibitory

NOTE Confidence: 0.91128063

00:30:07.040 --> 00:30:08.580 to local acceptory synapse.

NOTE Confidence: 0.9723056

00:30:09.360 --> 00:30:12.100 Interplay with, dopamine, we have

NOTE Confidence: 0.9723056

00:30:12.184 --> 00:30:14.044 not yet tested. So we,

NOTE Confidence: 0.9930379

00:30:15.544 --> 00:30:16.585 at this point, we don't

NOTE Confidence: 0.9930379

00:30:16.585 --> 00:30:17.325 have evidence,

NOTE Confidence: 0.9249413

00:30:17.865 --> 00:30:19.085 about, dopaminergic

NOTE Confidence: 0.82199025

00:30:19.544 --> 00:30:21.304 dopa dopamine release

NOTE Confidence: 0.98106974

00:30:21.625 --> 00:30:23.145 loss of of dopamine release

NOTE Confidence: 0.98106974

00:30:23.145 --> 00:30:23.645 sites,

NOTE Confidence: 0.96126485

00:30:24.105 --> 00:30:24.924 in the cortex,

NOTE Confidence: 0.95964354

00:30:26.010 --> 00:30:27.470 in our model. But then

NOTE Confidence: 0.9413351

00:30:27.930 --> 00:30:28.430 we,

NOTE Confidence: 0.9995952

00:30:29.450 --> 00:30:30.510 we do not

NOTE Confidence: 0.9093807

00:30:31.050 --> 00:30:32.810 aim to replicate that aspect

NOTE Confidence: 0.9093807

00:30:32.810 --> 00:30:34.270 of PPE at all.

NOTE Confidence: 0.95267

00:30:37.705 --> 00:30:40.025 That's in clinical practice, dopamine

NOTE Confidence: 0.95267

00:30:40.025 --> 00:30:41.465 is dopamine. I mean, that's,

NOTE Confidence: 0.95267

00:30:41.465 --> 00:30:42.905 like, ninety nine percent of

NOTE Confidence: 0.95267

00:30:43.225 --> 00:30:44.505 Oh, yeah. I'm I'm very

NOTE Confidence: 0.95267

00:30:44.505 --> 00:30:45.725 used to having to justify

NOTE Confidence: 0.95267

00:30:45.865 --> 00:30:46.605 my data.

NOTE Confidence: 0.86694837

00:30:49.865 --> 00:30:50.185 But,

NOTE Confidence: 0.95521754

00:30:51.865 --> 00:30:52.605 I personally

NOTE Confidence: 0.9895399

00:30:53.260 --> 00:30:55.200 I I would, like to

NOTE Confidence: 0.9895399

00:30:55.260 --> 00:30:55.760 suggest

NOTE Confidence: 0.9376192

00:30:56.299 --> 00:30:57.760 that these are parallel processes,

NOTE Confidence: 0.9700355

00:30:58.460 --> 00:31:00.220 that they do not actually

NOTE Confidence: 0.9700355

00:31:00.220 --> 00:31:01.660 directly impact each other. So

NOTE Confidence: 0.9700355

00:31:01.660 --> 00:31:03.580 that PD pathology could progress

NOTE Confidence: 0.9700355

00:31:03.580 --> 00:31:05.419 in different regions using in

NOTE Confidence: 0.9700355

00:31:05.419 --> 00:31:06.860 in different ways. So

NOTE Confidence: 0.995088

00:31:07.565 --> 00:31:09.265 That's not I think that

NOTE Confidence: 0.766618

00:31:09.805 --> 00:31:10.305 dopamine,

NOTE Confidence: 0.989439

00:31:11.405 --> 00:31:13.265 because it's highly oxidative,

NOTE Confidence: 0.9915028

00:31:13.725 --> 00:31:14.465 it actually

NOTE Confidence: 0.8698719

00:31:15.645 --> 00:31:17.425 accentuates the role of albasyanuclide

NOTE Confidence: 0.73085976

00:31:18.845 --> 00:31:19.825 to map.

NOTE Confidence: 0.9647131

00:31:20.490 --> 00:31:22.190 And especially in the synapses

NOTE Confidence: 0.9647131

00:31:22.250 --> 00:31:24.190 with dopamine, that's why substantia

NOTE Confidence: 0.9647131

00:31:24.250 --> 00:31:25.710 nigra dies first.

NOTE Confidence: 0.9739995

00:31:26.970 --> 00:31:28.250 We have no evidence for

NOTE Confidence: 0.9739995

00:31:28.250 --> 00:31:29.610 synapse for neuron loss in

NOTE Confidence: 0.9739995

00:31:29.610 --> 00:31:30.730 the cortex. So I think

NOTE Confidence: 0.9739995

00:31:30.730 --> 00:31:32.190 it's really a different mechanism.

NOTE Confidence: 0.8600439

00:31:36.275 --> 00:31:37.555 If, what you're saying is

NOTE Confidence: 0.8600439

00:31:37.555 --> 00:31:38.675 true that the binding of

NOTE Confidence: 0.8600439

00:31:38.675 --> 00:31:40.155 alpha synuclein with the norexin

NOTE Confidence: 0.8600439

00:31:40.435 --> 00:31:42.215 Yep. Person in vivo,

NOTE Confidence: 0.9932578

00:31:43.075 --> 00:31:44.515 are you thinking about ways

NOTE Confidence: 0.9932578

00:31:44.515 --> 00:31:44.915 to,

NOTE Confidence: 0.9327895

00:31:45.395 --> 00:31:46.915 interfere with that binding? I

NOTE Confidence: 0.9327895

00:31:46.915 --> 00:31:47.715 mean, would that be a

NOTE Confidence: 0.9327895

00:31:47.715 --> 00:31:48.775 good feasible

NOTE Confidence: 0.94906574

00:31:49.820 --> 00:31:52.059 or translatable mechanism? Yeah. So

NOTE Confidence: 0.94906574

00:31:52.059 --> 00:31:52.559 we

NOTE Confidence: 0.7521432

00:31:53.020 --> 00:31:53.980 hear what it works. Yeah.

NOTE Confidence: 0.7521432

00:31:53.980 --> 00:31:55.120 That's really worked.

NOTE Confidence: 0.39377484

00:31:55.740 --> 00:31:56.720 The mic. They're actually

NOTE Confidence: 0.82224387

00:32:00.380 --> 00:32:01.280 So we,

NOTE Confidence: 0.9724354

00:32:01.740 --> 00:32:03.100 we are currently testing this

NOTE Confidence: 0.9724354

00:32:03.100 --> 00:32:05.125 again, led by Maria. So

NOTE Confidence: 0.9724354

00:32:05.125 --> 00:32:06.664 we have evidence that

NOTE Confidence: 0.68842024

00:32:07.125 --> 00:32:07.625 the,

NOTE Confidence: 0.8689115

00:32:10.565 --> 00:32:11.924 the role of neurexin in

NOTE Confidence: 0.8689115

00:32:11.924 --> 00:32:14.184 pathology progression involves an extracellular

NOTE Confidence: 0.8689115

00:32:14.325 --> 00:32:16.265 modification of heparan sulfate proteoglycans.

NOTE Confidence: 0.9971056

00:32:17.269 --> 00:32:18.009 And we

NOTE Confidence: 0.9714238

00:32:18.309 --> 00:32:20.330 are collaborating with a colleague,

NOTE Confidence: 0.9705337

00:32:21.590 --> 00:32:21.750 who has,

NOTE Confidence: 0.99039024

00:32:23.509 --> 00:32:25.110 glycan arrays, and he will

NOTE Confidence: 0.99039024

00:32:25.110 --> 00:32:26.950 then map to what type

NOTE Confidence: 0.99039024

00:32:26.950 --> 00:32:27.690 of glycans

NOTE Confidence: 0.9274256

00:32:28.149 --> 00:32:30.070 so subtypes of glycans these

NOTE Confidence: 0.9274256

00:32:30.070 --> 00:32:32.205 synuclein propels can bind. And

NOTE Confidence: 0.9274256

00:32:32.205 --> 00:32:33.965 that could pros could give

NOTE Confidence: 0.9274256

00:32:33.965 --> 00:32:35.985 us a specific molecular lead

NOTE Confidence: 0.9274256

00:32:36.284 --> 00:32:38.044 for what types of heparan

NOTE Confidence: 0.9274256

00:32:38.044 --> 00:32:40.044 sulfate glycans are targeted by

NOTE Confidence: 0.9274256

00:32:40.044 --> 00:32:40.705 the synuclein,

NOTE Confidence: 0.9455382

00:32:41.245 --> 00:32:42.625 and that, can,

NOTE Confidence: 0.8562296

00:32:43.325 --> 00:32:44.945 that could be then possible

NOTE Confidence: 0.8260412

00:32:45.404 --> 00:32:46.465 a site of intervention.

NOTE Confidence: 0.91224474

00:32:46.765 --> 00:32:48.259 For example, we're targeting the

NOTE Confidence: 0.91224474

00:32:48.259 --> 00:32:49.860 specific enzymes that may need

NOTE Confidence: 0.91224474

00:32:49.860 --> 00:32:51.860 this particular type of glycan

NOTE Confidence: 0.91224474

00:32:51.860 --> 00:32:53.460 modification because these are so

NOTE Confidence: 0.91224474

00:32:53.460 --> 00:32:55.220 complex. There are hundreds of

NOTE Confidence: 0.91224474

00:32:55.220 --> 00:32:56.039 different options

NOTE Confidence: 0.97459775

00:32:56.500 --> 00:32:57.860 that should be possible to

NOTE Confidence: 0.97459775

00:32:57.860 --> 00:32:58.899 target them if they are

NOTE Confidence: 0.97459775

00:32:58.899 --> 00:32:59.399 specific.

NOTE Confidence: 0.62469125

00:33:00.855 --> 00:33:01.355 Yes.

NOTE Confidence: 0.96195155

00:33:01.735 --> 00:33:03.255 Please. I initially had a

NOTE Confidence: 0.96195155

00:33:03.255 --> 00:33:04.695 dopamine related question, but you

NOTE Confidence: 0.96195155

00:33:04.695 --> 00:33:06.295 answered that. My second question

NOTE Confidence: 0.96195155

00:33:06.295 --> 00:33:07.035 would be,

NOTE Confidence: 0.9389605

00:33:07.495 --> 00:33:08.695 have you look have you

NOTE Confidence: 0.9389605

00:33:08.695 --> 00:33:10.615 done any behavioral tasks in

NOTE Confidence: 0.9389605

00:33:10.615 --> 00:33:11.275 the mice

NOTE Confidence: 0.95107573

00:33:11.975 --> 00:33:13.335 to determine what,

NOTE Confidence: 0.996587

00:33:13.735 --> 00:33:14.875 abilities are affected?

NOTE Confidence: 0.9834362

00:33:16.180 --> 00:33:17.940 We have stayed clear of

NOTE Confidence: 0.9834362

00:33:17.940 --> 00:33:20.820 behavioral tests because they can

NOTE Confidence: 0.9834362

00:33:20.820 --> 00:33:21.320 be,

NOTE Confidence: 0.9514283

00:33:22.500 --> 00:33:24.760 not robust, and so we

NOTE Confidence: 0.99912

00:33:25.140 --> 00:33:26.900 wanted to focus on the

NOTE Confidence: 0.99912

00:33:26.900 --> 00:33:27.400 physiology

NOTE Confidence: 0.9990431

00:33:27.780 --> 00:33:28.280 instead.

NOTE Confidence: 0.9160552

00:33:29.955 --> 00:33:31.315 We are considering now to

NOTE Confidence: 0.9160552

00:33:31.315 --> 00:33:33.095 do go into behavioral essays,

NOTE Confidence: 0.9596794

00:33:34.355 --> 00:33:34.595 but,

NOTE Confidence: 0.8525698

00:33:35.315 --> 00:33:36.435 I think for us, the

NOTE Confidence: 0.8525698

00:33:36.435 --> 00:33:37.955 physiology comes first as a

NOTE Confidence: 0.8525698

00:33:37.955 --> 00:33:38.935 function of really.

NOTE Confidence: 0.59138834

00:33:41.250 --> 00:33:41.750 Alright?

NOTE Confidence: 0.9830273

00:33:53.835 --> 00:33:54.655 Hello, everybody.

NOTE Confidence: 0.94180554

00:33:55.275 --> 00:33:57.115 Thank you to Jaime for

NOTE Confidence: 0.94180554

00:33:57.115 --> 00:33:58.635 sort of spearheading this, and

NOTE Confidence: 0.94180554

00:33:58.635 --> 00:33:59.835 thank you for Puja to

NOTE Confidence: 0.94180554

00:33:59.835 --> 00:34:00.655 doing this.

NOTE Confidence: 0.7592529

00:34:02.315 --> 00:34:02.815 Okay.

NOTE Confidence: 0.92168283

00:34:03.595 --> 00:34:04.875 So today, I'm gonna tell

NOTE Confidence: 0.92168283

00:34:04.875 --> 00:34:06.975 you about GBA link Parkinson

NOTE Confidence: 0.95763695

00:34:07.355 --> 00:34:09.329 and dementia with Lewy bodies.

NOTE Confidence: 0.95763695

00:34:09.390 --> 00:34:10.109 And a lot of the

NOTE Confidence: 0.95763695

00:34:10.109 --> 00:34:11.630 themes that Thomas has sort

NOTE Confidence: 0.95763695

00:34:11.630 --> 00:34:12.849 of already reiterated

NOTE Confidence: 0.9772869

00:34:13.469 --> 00:34:14.910 will sort of come up

NOTE Confidence: 0.9772869

00:34:14.910 --> 00:34:15.869 again in my talk, so

NOTE Confidence: 0.9772869

00:34:15.869 --> 00:34:16.750 I don't have to give

NOTE Confidence: 0.9772869

00:34:16.750 --> 00:34:17.890 you lots of introductions.

NOTE Confidence: 0.9255201

00:34:19.469 --> 00:34:20.670 So what the outline of

NOTE Confidence: 0.9255201

00:34:20.670 --> 00:34:21.869 my talk will be sort

NOTE Confidence: 0.9255201

00:34:21.869 --> 00:34:23.390 of threefold. Let's see if

NOTE Confidence: 0.9255201

00:34:23.390 --> 00:34:24.285 this pointer

NOTE Confidence: 0.9882295

00:34:24.825 --> 00:34:25.325 works.

NOTE Confidence: 0.6125729

00:34:25.745 --> 00:34:26.245 No.

NOTE Confidence: 0.9729013

00:34:26.665 --> 00:34:28.364 There's no pointer. Sorry.

NOTE Confidence: 0.9261376

00:34:29.145 --> 00:34:30.344 So I'm gonna introduce to

NOTE Confidence: 0.9261376

00:34:30.344 --> 00:34:31.645 you what GB a is.

NOTE Confidence: 0.9261376

00:34:31.864 --> 00:34:33.705 It's links to Gaucher disease,

NOTE Confidence: 0.9261376

00:34:33.705 --> 00:34:35.245 which are very well established,

NOTE Confidence: 0.9261376

00:34:35.465 --> 00:34:36.985 and the more recent links

NOTE Confidence: 0.9261376

00:34:36.985 --> 00:34:38.940 to Parkinson and dementia with

NOTE Confidence: 0.9261376

00:34:38.940 --> 00:34:39.680 Lewy bodies.

NOTE Confidence: 0.9142128

00:34:39.980 --> 00:34:41.100 And then tell you because

NOTE Confidence: 0.9142128

00:34:41.100 --> 00:34:42.480 I'm a mouse and iPSC

NOTE Confidence: 0.9142128

00:34:42.540 --> 00:34:43.660 lab, I'm gonna tell you

NOTE Confidence: 0.9142128

00:34:43.660 --> 00:34:45.180 about our mouse studies on

NOTE Confidence: 0.9142128

00:34:45.180 --> 00:34:46.700 how to model GBL link

NOTE Confidence: 0.9142128

00:34:46.700 --> 00:34:48.000 Parkinson and dementia,

NOTE Confidence: 0.9680936

00:34:49.020 --> 00:34:50.775 with Lewy bodies in using

NOTE Confidence: 0.9680936

00:34:50.775 --> 00:34:52.214 mice, and then also what

NOTE Confidence: 0.9680936

00:34:52.214 --> 00:34:53.755 we've gained as insights

NOTE Confidence: 0.99412555

00:34:54.055 --> 00:34:55.594 by doing these mice studies.

NOTE Confidence: 0.9976971

00:34:56.454 --> 00:34:56.954 Okay.

NOTE Confidence: 0.9822463

00:34:57.255 --> 00:34:59.094 So just to begin with,

NOTE Confidence: 0.9822463

00:34:59.094 --> 00:35:00.395 GBA is a lysosomal

NOTE Confidence: 0.91603976

00:35:00.775 --> 00:35:02.234 enzyme called glucocerabrosidase.

NOTE Confidence: 0.98557043

00:35:03.390 --> 00:35:05.469 It's abbreviated commonly as GKS,

NOTE Confidence: 0.98557043

00:35:05.469 --> 00:35:06.270 so you may have heard

NOTE Confidence: 0.98557043

00:35:06.270 --> 00:35:08.029 that. And it's an enzyme

NOTE Confidence: 0.98557043

00:35:08.029 --> 00:35:09.410 that sits in the lysosome

NOTE Confidence: 0.94499654

00:35:09.710 --> 00:35:10.750 and is part of the

NOTE Confidence: 0.94499654

00:35:10.750 --> 00:35:11.250 sphingolipid,

NOTE Confidence: 0.8743298

00:35:12.190 --> 00:35:13.170 salvage pathway.

NOTE Confidence: 0.9688123

00:35:13.549 --> 00:35:15.069 And it's a glucosidase. So

NOTE Confidence: 0.9688123

00:35:15.069 --> 00:35:16.130 it'll take complex

NOTE Confidence: 0.924434

00:35:16.430 --> 00:35:18.369 ceramides, glucosal ceramides,

NOTE Confidence: 0.99043804

00:35:18.805 --> 00:35:20.645 and hydrolyze the glucose of

NOTE Confidence: 0.99043804

00:35:20.645 --> 00:35:22.265 it to release ceramide.

NOTE Confidence: 0.9803541

00:35:22.725 --> 00:35:23.925 And so what happens when

NOTE Confidence: 0.9803541

00:35:23.925 --> 00:35:25.125 you have loss of function

NOTE Confidence: 0.9803541

00:35:25.125 --> 00:35:26.425 mutations in GBA,

NOTE Confidence: 0.9875615

00:35:26.725 --> 00:35:27.925 you get a disease called

NOTE Confidence: 0.9875615

00:35:27.925 --> 00:35:29.445 Gaucher disease, which all of

NOTE Confidence: 0.9875615

00:35:29.445 --> 00:35:31.045 you are more familiar than

NOTE Confidence: 0.9875615

00:35:31.045 --> 00:35:31.785 I am.

NOTE Confidence: 0.85427

00:35:32.085 --> 00:35:33.864 So you this is a

NOTE Confidence: 0.95810574

00:35:34.530 --> 00:35:36.850 primarily a childhood disease of

NOTE Confidence: 0.95810574

00:35:36.850 --> 00:35:38.630 liver and spleen and bone.

NOTE Confidence: 0.95810574

00:35:38.850 --> 00:35:40.290 And in in this Gaucher

NOTE Confidence: 0.95810574

00:35:40.290 --> 00:35:42.050 disease, you have two things

NOTE Confidence: 0.95810574

00:35:42.050 --> 00:35:42.950 that are happening.

NOTE Confidence: 0.9453056

00:35:43.410 --> 00:35:44.870 One is that the complex

NOTE Confidence: 0.9453056

00:35:45.090 --> 00:35:45.590 glucosophagolipids

NOTE Confidence: 0.7554624

00:35:46.530 --> 00:35:47.030 accumulate,

NOTE Confidence: 0.8797257

00:35:48.065 --> 00:35:50.164 primarily peripherally in macrophages,

NOTE Confidence: 0.9824915

00:35:50.545 --> 00:35:51.585 and this is how you

NOTE Confidence: 0.9824915

00:35:51.585 --> 00:35:52.565 stain for them,

NOTE Confidence: 0.9940569

00:35:52.944 --> 00:35:54.164 as Gaucher cells.

NOTE Confidence: 0.9455353

00:35:54.704 --> 00:35:56.065 And also you have a

NOTE Confidence: 0.9455353

00:35:56.065 --> 00:35:58.384 ceramide deficiency because there's not

NOTE Confidence: 0.9455353

00:35:58.384 --> 00:36:00.224 ceramide not being released. And

NOTE Confidence: 0.9455353

00:36:00.224 --> 00:36:00.724 ceramide,

NOTE Confidence: 0.98138034

00:36:01.320 --> 00:36:02.840 as you all know, is

NOTE Confidence: 0.98138034

00:36:02.840 --> 00:36:04.840 necessary for barrier function of

NOTE Confidence: 0.98138034

00:36:04.840 --> 00:36:06.120 skin. So they also have

NOTE Confidence: 0.98138034

00:36:06.120 --> 00:36:06.860 skin issues.

NOTE Confidence: 0.94371027

00:36:07.400 --> 00:36:09.000 And Gaucher's in the US

NOTE Confidence: 0.94371027

00:36:09.000 --> 00:36:11.400 is largely treated. You there's

NOTE Confidence: 0.94371027

00:36:11.400 --> 00:36:13.020 very good enzyme replacement

NOTE Confidence: 0.990103

00:36:13.320 --> 00:36:13.820 therapy

NOTE Confidence: 0.94857377

00:36:14.280 --> 00:36:15.915 options. And there are also

NOTE Confidence: 0.94857377

00:36:15.915 --> 00:36:16.415 options

NOTE Confidence: 0.9231502

00:36:16.715 --> 00:36:18.495 to what are called substrate

NOTE Confidence: 0.9231502

00:36:18.635 --> 00:36:20.875 reduction therapies. That meaning that

NOTE Confidence: 0.9231502

00:36:20.875 --> 00:36:22.555 you try and reduce the

NOTE Confidence: 0.9231502

00:36:22.555 --> 00:36:23.775 amount of glucosylceramides

NOTE Confidence: 0.98555845

00:36:24.715 --> 00:36:26.175 that are actually synthesized.

NOTE Confidence: 0.98345935

00:36:26.715 --> 00:36:28.235 And both these strategies are

NOTE Confidence: 0.98345935

00:36:28.235 --> 00:36:29.055 very efficacious.

NOTE Confidence: 0.9457677

00:36:29.600 --> 00:36:31.520 And so patients can manage

NOTE Confidence: 0.9457677

00:36:31.520 --> 00:36:32.500 Gaucher disease

NOTE Confidence: 0.9514926

00:36:32.960 --> 00:36:33.600 all the while

NOTE Confidence: 0.969803

00:36:34.320 --> 00:36:35.460 all the way through adulthood.

NOTE Confidence: 0.8657652

00:36:37.360 --> 00:36:38.180 So GBA,

NOTE Confidence: 0.8910076

00:36:38.640 --> 00:36:40.640 the reason GBA and Gaucher

NOTE Confidence: 0.8910076

00:36:40.640 --> 00:36:42.640 is very well established, and

NOTE Confidence: 0.8910076

00:36:42.640 --> 00:36:44.640 GBA mutations due to founder

NOTE Confidence: 0.8910076

00:36:44.640 --> 00:36:46.635 effects are very common in

NOTE Confidence: 0.8910076

00:36:46.635 --> 00:36:48.495 the population. So for instance,

NOTE Confidence: 0.8910076

00:36:48.715 --> 00:36:49.835 if you're asked a Nazi

NOTE Confidence: 0.8910076

00:36:49.835 --> 00:36:52.094 Jewish or for instance Norwegian,

NOTE Confidence: 0.93768466

00:36:52.715 --> 00:36:54.475 they're huge founder effects. And

NOTE Confidence: 0.93768466

00:36:54.475 --> 00:36:56.315 so these mutations are very,

NOTE Confidence: 0.93768466

00:36:56.315 --> 00:36:58.410 very common. And especially two

NOTE Confidence: 0.93768466

00:36:58.410 --> 00:36:59.770 mutations I'm gonna talk to

NOTE Confidence: 0.93768466

00:36:59.770 --> 00:37:00.810 you about is just called

NOTE Confidence: 0.93768466

00:37:00.810 --> 00:37:02.010 the n three seventy s

NOTE Confidence: 0.93768466

00:37:02.010 --> 00:37:02.510 mutation

NOTE Confidence: 0.99329007

00:37:02.890 --> 00:37:04.089 and the l triple four

NOTE Confidence: 0.99329007

00:37:04.089 --> 00:37:04.910 p mutation.

NOTE Confidence: 0.9778935

00:37:06.489 --> 00:37:08.010 So even though the link

NOTE Confidence: 0.9778935

00:37:08.010 --> 00:37:10.489 between Gaucher and GBA was

NOTE Confidence: 0.9778935

00:37:10.489 --> 00:37:12.170 very well established, the link

NOTE Confidence: 0.9778935

00:37:12.170 --> 00:37:12.670 between,

NOTE Confidence: 0.93197227

00:37:13.565 --> 00:37:15.964 GBA and Parkinson and Gaucher

NOTE Confidence: 0.93197227

00:37:15.964 --> 00:37:17.644 is very recent. It's actually

NOTE Confidence: 0.93197227

00:37:17.644 --> 00:37:18.765 in two thousand nine it

NOTE Confidence: 0.93197227

00:37:18.765 --> 00:37:19.884 actually came only at a

NOTE Confidence: 0.93197227

00:37:19.884 --> 00:37:21.025 clinical practice

NOTE Confidence: 0.88240224

00:37:21.325 --> 00:37:22.704 even though we have GWAS

NOTE Confidence: 0.88240224

00:37:22.844 --> 00:37:23.244 and,

NOTE Confidence: 0.9895662

00:37:23.724 --> 00:37:25.505 GWAS and, you know, familial

NOTE Confidence: 0.9948403

00:37:26.125 --> 00:37:26.625 genetics.

NOTE Confidence: 0.96547043

00:37:27.000 --> 00:37:28.520 So this was a study

NOTE Confidence: 0.96547043

00:37:28.520 --> 00:37:30.060 that came from Ellen Sidransky's

NOTE Confidence: 0.9320733

00:37:30.360 --> 00:37:31.580 lab at the NIH,

NOTE Confidence: 0.9885691

00:37:32.280 --> 00:37:33.980 and she led a multicenter

NOTE Confidence: 0.8829779

00:37:34.920 --> 00:37:36.700 study which showed that GBA

NOTE Confidence: 0.8829779

00:37:36.760 --> 00:37:37.260 mutations

NOTE Confidence: 0.985605

00:37:37.560 --> 00:37:39.340 are actually causing Parkinson.

NOTE Confidence: 0.87169796

00:37:39.800 --> 00:37:41.320 And in fact, they showed

NOTE Confidence: 0.87169796

00:37:41.320 --> 00:37:41.775 that,

NOTE Confidence: 0.9796936

00:37:42.335 --> 00:37:44.194 Gaucher patients, which are homozygous

NOTE Confidence: 0.8139971

00:37:44.494 --> 00:37:44.974 GBA,

NOTE Confidence: 0.8850912

00:37:46.015 --> 00:37:48.194 patients, have homozygous mutations,

NOTE Confidence: 0.9212211

00:37:48.575 --> 00:37:49.775 are at a twenty four

NOTE Confidence: 0.9212211

00:37:49.775 --> 00:37:52.174 risk for developing Parkinson. And

NOTE Confidence: 0.9212211

00:37:52.174 --> 00:37:53.775 the parents of these patients,

NOTE Confidence: 0.9212211

00:37:53.775 --> 00:37:54.674 who are heterozygous

NOTE Confidence: 0.9005421

00:37:55.055 --> 00:37:56.670 carriers, are at a five

NOTE Confidence: 0.9005421

00:37:56.670 --> 00:37:59.010 fold risk for developing Parkinson.

NOTE Confidence: 0.8617617

00:37:59.390 --> 00:38:00.830 And the GBA link part

NOTE Confidence: 0.8617617

00:38:00.830 --> 00:38:02.849 of Parkinson is actually associated

NOTE Confidence: 0.8617617

00:38:02.989 --> 00:38:04.290 with synuclein pathology,

NOTE Confidence: 0.9374957

00:38:04.670 --> 00:38:06.510 the Lewy body pathology. That's

NOTE Confidence: 0.9374957

00:38:06.510 --> 00:38:08.690 the defining feature of sarisporadic

NOTE Confidence: 0.9984506

00:38:09.310 --> 00:38:09.810 disease.

NOTE Confidence: 0.9655214

00:38:10.805 --> 00:38:12.505 So sort of flash forward,

NOTE Confidence: 0.9655214

00:38:12.565 --> 00:38:14.265 this is the genetic landscape

NOTE Confidence: 0.9655214

00:38:14.325 --> 00:38:16.245 of Parkinson today. So in

NOTE Confidence: 0.9655214

00:38:16.245 --> 00:38:17.845 the top cluster are all

NOTE Confidence: 0.9655214

00:38:17.845 --> 00:38:19.925 the, familial genes. We have

NOTE Confidence: 0.9655214

00:38:19.925 --> 00:38:21.605 twenty three PARC genes, PARC

NOTE Confidence: 0.9655214

00:38:21.605 --> 00:38:22.739 one through twenty three.

NOTE Confidence: 0.99467576

00:38:23.219 --> 00:38:24.360 And then in the middle

NOTE Confidence: 0.9554155

00:38:24.739 --> 00:38:26.580 are the medium to high

NOTE Confidence: 0.9554155

00:38:26.580 --> 00:38:28.280 risk genes, which are fairly

NOTE Confidence: 0.9554155

00:38:28.340 --> 00:38:29.860 common in the population, and

NOTE Confidence: 0.9554155

00:38:29.860 --> 00:38:31.080 I've circled GBA,

NOTE Confidence: 0.9594935

00:38:31.460 --> 00:38:32.820 and the other being LERP

NOTE Confidence: 0.9594935

00:38:32.820 --> 00:38:34.020 two, which you also heard

NOTE Confidence: 0.9594935

00:38:34.020 --> 00:38:35.300 of. And in the very

NOTE Confidence: 0.9594935

00:38:35.460 --> 00:38:37.320 this sort of corner here

NOTE Confidence: 0.9594935

00:38:37.585 --> 00:38:39.265 are common variants that are

NOTE Confidence: 0.9594935

00:38:39.265 --> 00:38:41.125 all in the sporadic population.

NOTE Confidence: 0.9785992

00:38:42.065 --> 00:38:43.265 So you can see that

NOTE Confidence: 0.9785992

00:38:43.265 --> 00:38:45.505 GBA is, turns out to

NOTE Confidence: 0.9785992

00:38:45.505 --> 00:38:46.785 be one of the most

NOTE Confidence: 0.9785992

00:38:46.785 --> 00:38:48.705 common genetic risk factor for

NOTE Confidence: 0.9785992

00:38:48.705 --> 00:38:49.205 Parkinson.

NOTE Confidence: 0.98851365

00:38:49.745 --> 00:38:51.344 In fact, five percent of

NOTE Confidence: 0.98851365

00:38:51.344 --> 00:38:52.085 all GBA,

NOTE Confidence: 0.984171

00:38:52.545 --> 00:38:53.285 all Parkinson

NOTE Confidence: 0.9960456

00:38:53.640 --> 00:38:55.420 patients have GBA mutations.

NOTE Confidence: 0.9530871

00:38:55.960 --> 00:38:57.579 And because of this link

NOTE Confidence: 0.9530871

00:38:57.640 --> 00:38:59.160 of this founder effects, there

NOTE Confidence: 0.9530871

00:38:59.160 --> 00:39:00.219 are certain ethnicities

NOTE Confidence: 0.9452501

00:39:00.520 --> 00:39:02.359 that are actually very at

NOTE Confidence: 0.9452501

00:39:02.359 --> 00:39:04.440 high risk for developing GBA

NOTE Confidence: 0.9452501

00:39:04.440 --> 00:39:05.180 link pockets.

NOTE Confidence: 0.9465321

00:39:06.215 --> 00:39:08.295 So since this two thousand

NOTE Confidence: 0.9465321

00:39:08.295 --> 00:39:08.795 nine,

NOTE Confidence: 0.9246876

00:39:09.335 --> 00:39:10.395 landmark paper,

NOTE Confidence: 0.9821043

00:39:10.695 --> 00:39:11.575 there have been a lot

NOTE Confidence: 0.9821043

00:39:11.575 --> 00:39:13.815 of follow-up clinical studies to

NOTE Confidence: 0.9821043

00:39:13.815 --> 00:39:14.315 understand

NOTE Confidence: 0.89062977

00:39:14.775 --> 00:39:16.635 whether sporadic Parkinson,

NOTE Confidence: 0.9758519

00:39:17.094 --> 00:39:18.375 which is the eighty five

NOTE Confidence: 0.9758519

00:39:18.375 --> 00:39:19.515 percent of population,

NOTE Confidence: 0.9880333

00:39:20.135 --> 00:39:20.635 and

NOTE Confidence: 0.97849894

00:39:21.160 --> 00:39:22.920 peep, patients that have GBM

NOTE Confidence: 0.97849894

00:39:22.920 --> 00:39:24.940 mutations, is there anything clinically

NOTE Confidence: 0.97849894

00:39:25.000 --> 00:39:26.920 different between them? And what

NOTE Confidence: 0.97849894

00:39:26.920 --> 00:39:28.520 is sort of a clear

NOTE Confidence: 0.97849894

00:39:28.520 --> 00:39:29.020 consensus

NOTE Confidence: 0.97698545

00:39:29.400 --> 00:39:30.600 is that if you have

NOTE Confidence: 0.97698545

00:39:30.600 --> 00:39:32.520 GBM mutations that is driving

NOTE Confidence: 0.97698545

00:39:32.520 --> 00:39:34.085 your disease, you have a

NOTE Confidence: 0.97698545

00:39:34.085 --> 00:39:35.844 faster decline and you have

NOTE Confidence: 0.97698545

00:39:35.844 --> 00:39:36.984 much more cognitive

NOTE Confidence: 0.9334105

00:39:37.364 --> 00:39:39.285 deficits. So there is it

NOTE Confidence: 0.9334105

00:39:39.285 --> 00:39:40.664 it is actually predisposing

NOTE Confidence: 0.95977944

00:39:41.204 --> 00:39:42.505 you to having,

NOTE Confidence: 0.99755996

00:39:43.045 --> 00:39:43.545 dementia.

NOTE Confidence: 0.96263

00:39:45.204 --> 00:39:46.344 So when in,

NOTE Confidence: 0.9754831

00:39:46.890 --> 00:39:48.589 in two thousand twenty three,

NOTE Confidence: 0.99580765

00:39:49.369 --> 00:39:49.869 the

NOTE Confidence: 0.95717835

00:39:50.170 --> 00:39:52.170 GWAS studies for Lewy body

NOTE Confidence: 0.95717835

00:39:52.170 --> 00:39:53.469 dementia, the related

NOTE Confidence: 0.8392981

00:39:54.250 --> 00:39:54.750 synucleonopathy

NOTE Confidence: 0.9743977

00:39:55.289 --> 00:39:57.130 was actually published. And you

NOTE Confidence: 0.9743977

00:39:57.130 --> 00:39:58.089 can see this is a

NOTE Confidence: 0.9743977

00:39:58.089 --> 00:39:59.864 Manhattan bot. And you can

NOTE Confidence: 0.9743977

00:39:59.864 --> 00:40:01.385 see that GBA is one

NOTE Confidence: 0.9743977

00:40:01.385 --> 00:40:02.585 of the genes that is

NOTE Confidence: 0.9743977

00:40:02.585 --> 00:40:03.645 actually driving,

NOTE Confidence: 0.94491655

00:40:04.825 --> 00:40:06.265 dementia with Lewy bodies. The

NOTE Confidence: 0.94491655

00:40:06.265 --> 00:40:07.864 other being SNCA, which is

NOTE Confidence: 0.94491655

00:40:07.864 --> 00:40:09.005 the gene for synuclein.

NOTE Confidence: 0.95358145

00:40:09.465 --> 00:40:11.005 And this being a dementia

NOTE Confidence: 0.9338501

00:40:11.680 --> 00:40:13.700 sort of across between Parkinson

NOTE Confidence: 0.9338501

00:40:13.840 --> 00:40:15.280 and Alzheimer's, you can see

NOTE Confidence: 0.9338501

00:40:15.280 --> 00:40:17.300 APOE and BIN1 are also,

NOTE Confidence: 0.9456761

00:40:18.080 --> 00:40:19.280 genes that are linked to

NOTE Confidence: 0.9456761

00:40:19.280 --> 00:40:20.500 Alzheimer are also,

NOTE Confidence: 0.93854207

00:40:21.440 --> 00:40:22.660 genes linked to,

NOTE Confidence: 0.8701608

00:40:23.360 --> 00:40:24.820 dementia with Lewy bodies.

NOTE Confidence: 0.99217725

00:40:25.415 --> 00:40:26.455 So if you just look

NOTE Confidence: 0.99217725

00:40:26.455 --> 00:40:28.375 at the familial forms of

NOTE Confidence: 0.99217725

00:40:28.375 --> 00:40:29.974 Lewy body dementia, you can

NOTE Confidence: 0.99217725

00:40:29.974 --> 00:40:31.494 see that GBA is the

NOTE Confidence: 0.99217725

00:40:31.494 --> 00:40:33.175 only gene linked to this,

NOTE Confidence: 0.9998418

00:40:33.575 --> 00:40:34.075 disorder.

NOTE Confidence: 0.99964845

00:40:34.855 --> 00:40:35.355 So

NOTE Confidence: 0.92438704

00:40:35.815 --> 00:40:36.315 because

NOTE Confidence: 0.9818451

00:40:36.935 --> 00:40:38.295 the GBA is linked to

NOTE Confidence: 0.9818451

00:40:38.295 --> 00:40:39.035 two synucleopathies,

NOTE Confidence: 0.94992393

00:40:39.810 --> 00:40:41.730 you know, Parkinson and Lewy

NOTE Confidence: 0.94992393

00:40:41.730 --> 00:40:42.550 body dementia,

NOTE Confidence: 0.96063936

00:40:43.010 --> 00:40:44.050 you know, there's a lot

NOTE Confidence: 0.96063936

00:40:44.050 --> 00:40:45.810 of interest farmers you know,

NOTE Confidence: 0.96063936

00:40:45.810 --> 00:40:47.090 in pharma to sort of

NOTE Confidence: 0.96063936

00:40:47.090 --> 00:40:49.410 develop GBA therapies. And because

NOTE Confidence: 0.96063936

00:40:49.410 --> 00:40:50.390 of all the

NOTE Confidence: 0.9995278

00:40:50.770 --> 00:40:51.270 therapeutic

NOTE Confidence: 0.97931063

00:40:51.570 --> 00:40:53.730 advances already for Gaucher, they

NOTE Confidence: 0.97931063

00:40:53.730 --> 00:40:55.915 can actually use those leads

NOTE Confidence: 0.97931063

00:40:55.975 --> 00:40:57.815 to actually treat this. I

NOTE Confidence: 0.97931063

00:40:57.815 --> 00:40:59.275 should say at this point,

NOTE Confidence: 0.97931063

00:40:59.415 --> 00:41:01.355 the reason why Gaucher patients,

NOTE Confidence: 0.9607103

00:41:01.735 --> 00:41:02.775 even though they are on

NOTE Confidence: 0.9607103

00:41:02.775 --> 00:41:04.795 drugs and can manage their

NOTE Confidence: 0.9607103

00:41:04.855 --> 00:41:05.755 Gaucher symptoms,

NOTE Confidence: 0.88563424

00:41:06.930 --> 00:41:08.609 still develop Parkinson or Lew

NOTE Confidence: 0.88563424

00:41:08.609 --> 00:41:10.210 body dementia is because those

NOTE Confidence: 0.88563424

00:41:10.210 --> 00:41:11.730 drugs don't cross the blood

NOTE Confidence: 0.88563424

00:41:11.730 --> 00:41:12.469 brain barrier.

NOTE Confidence: 0.9571296

00:41:12.770 --> 00:41:14.130 So then right now, there's

NOTE Confidence: 0.9571296

00:41:14.130 --> 00:41:15.190 a huge impetus

NOTE Confidence: 0.97860414

00:41:15.730 --> 00:41:16.930 to try and convert, you

NOTE Confidence: 0.97860414

00:41:16.930 --> 00:41:19.190 know, convert the Gaucher drugs

NOTE Confidence: 0.9611725

00:41:19.535 --> 00:41:20.735 to cross the blood brain

NOTE Confidence: 0.9611725

00:41:20.735 --> 00:41:22.015 barrier because you know that

NOTE Confidence: 0.9611725

00:41:22.015 --> 00:41:23.155 they're actually efficacious

NOTE Confidence: 0.8962059

00:41:23.695 --> 00:41:25.155 because they can treat Gaucher.

NOTE Confidence: 0.8962059

00:41:25.215 --> 00:41:26.015 So I I mean, I

NOTE Confidence: 0.8962059

00:41:26.015 --> 00:41:26.515 won't,

NOTE Confidence: 0.98083514

00:41:26.975 --> 00:41:28.735 belabor this, but there are

NOTE Confidence: 0.98083514

00:41:28.735 --> 00:41:29.555 very interesting,

NOTE Confidence: 0.9622723

00:41:30.415 --> 00:41:32.700 therapeutic strategies in the pipeline.

NOTE Confidence: 0.9872971

00:41:33.080 --> 00:41:34.520 And so far, they all

NOTE Confidence: 0.9872971

00:41:34.520 --> 00:41:35.820 look very promising.

NOTE Confidence: 0.9071111

00:41:36.280 --> 00:41:38.200 One is AAV based therapies,

NOTE Confidence: 0.9071111

00:41:38.200 --> 00:41:40.300 which they're actually inject injecting

NOTE Confidence: 0.9071111

00:41:40.440 --> 00:41:40.940 intrathecally,

NOTE Confidence: 0.95727444

00:41:41.480 --> 00:41:42.840 and the other is using

NOTE Confidence: 0.95727444

00:41:42.840 --> 00:41:44.520 small molecules because a lot

NOTE Confidence: 0.95727444

00:41:44.520 --> 00:41:45.980 of the GBM mutations

NOTE Confidence: 0.9776236

00:41:46.594 --> 00:41:47.255 are actually,

NOTE Confidence: 0.9787003

00:41:48.594 --> 00:41:50.275 trafficking mutants. So they don't

NOTE Confidence: 0.9787003

00:41:50.275 --> 00:41:52.055 go to the lysosome properly.

NOTE Confidence: 0.9715184

00:41:52.355 --> 00:41:53.395 And so if you can

NOTE Confidence: 0.9715184

00:41:53.395 --> 00:41:54.594 make it go to the

NOTE Confidence: 0.9715184

00:41:54.594 --> 00:41:56.355 right place within the neuron,

NOTE Confidence: 0.9715184

00:41:56.355 --> 00:41:57.714 then you can actually treat

NOTE Confidence: 0.9715184

00:41:57.714 --> 00:41:58.870 the cell. Okay.

NOTE Confidence: 0.9804395

00:41:59.330 --> 00:42:00.370 And the last thing that

NOTE Confidence: 0.9804395

00:42:00.370 --> 00:42:01.410 I wanna sort of plug

NOTE Confidence: 0.9804395

00:42:01.410 --> 00:42:02.150 is ambroxol,

NOTE Confidence: 0.93418056

00:42:02.530 --> 00:42:04.370 which is a, over the

NOTE Confidence: 0.93418056

00:42:04.370 --> 00:42:04.870 counter,

NOTE Confidence: 0.97644526

00:42:05.730 --> 00:42:06.230 drug,

NOTE Confidence: 0.95617896

00:42:07.170 --> 00:42:09.590 cough medicine that's available worldwide,

NOTE Confidence: 0.95617896

00:42:09.730 --> 00:42:11.010 but that is now actually

NOTE Confidence: 0.95617896

00:42:11.010 --> 00:42:12.310 in phase two trial,

NOTE Confidence: 0.91404134

00:42:12.690 --> 00:42:14.594 for GBL link park ins.

NOTE Confidence: 0.91404134

00:42:14.594 --> 00:42:15.955 It's not available here, but

NOTE Confidence: 0.91404134

00:42:15.955 --> 00:42:16.695 it's available

NOTE Confidence: 0.9981073

00:42:17.155 --> 00:42:18.295 elsewhere in the world.

NOTE Confidence: 0.9785685

00:42:18.755 --> 00:42:20.594 Okay. Okay. So okay. So

NOTE Confidence: 0.9785685

00:42:20.594 --> 00:42:22.055 the question really is

NOTE Confidence: 0.83081365

00:42:22.594 --> 00:42:24.055 why do GBA mutations

NOTE Confidence: 0.9993677

00:42:24.435 --> 00:42:24.935 predispose

NOTE Confidence: 0.96212274

00:42:25.235 --> 00:42:27.650 you to both, PD and

NOTE Confidence: 0.96212274

00:42:27.869 --> 00:42:28.369 DLB?

NOTE Confidence: 0.913177

00:42:28.829 --> 00:42:29.550 So this,

NOTE Confidence: 0.9868738

00:42:30.030 --> 00:42:31.310 there has been sort of

NOTE Confidence: 0.9868738

00:42:31.310 --> 00:42:33.710 a very synuclein centric model

NOTE Confidence: 0.9868738

00:42:33.710 --> 00:42:35.310 because it causes Lewy bodies

NOTE Confidence: 0.9868738

00:42:35.310 --> 00:42:36.670 in this. And one of

NOTE Confidence: 0.9868738

00:42:36.670 --> 00:42:38.290 the ideas that was actually,

NOTE Confidence: 0.9319503

00:42:38.904 --> 00:42:40.744 put forward by Dimitri Cronk,

NOTE Confidence: 0.9319503

00:42:40.744 --> 00:42:42.285 who's the head of neurology

NOTE Confidence: 0.9319503

00:42:42.344 --> 00:42:43.085 in Northwestern,

NOTE Confidence: 0.99631953

00:42:43.785 --> 00:42:44.525 is that,

NOTE Confidence: 0.96866655

00:42:45.384 --> 00:42:47.305 a, that the lipids that

NOTE Confidence: 0.96866655

00:42:47.305 --> 00:42:49.805 accumulate can actually template synuclein

NOTE Confidence: 0.96866655

00:42:49.944 --> 00:42:51.464 aggregation, which is we we

NOTE Confidence: 0.96866655

00:42:51.464 --> 00:42:53.070 could also show this. And

NOTE Confidence: 0.96866655

00:42:53.070 --> 00:42:54.830 because the lysosome, which is

NOTE Confidence: 0.96866655

00:42:54.830 --> 00:42:56.590 where, you know, proteins are

NOTE Confidence: 0.96866655

00:42:56.590 --> 00:42:58.290 degraded is not functioning,

NOTE Confidence: 0.97013396

00:42:58.590 --> 00:42:59.870 sort of this two hit

NOTE Confidence: 0.97013396

00:42:59.870 --> 00:43:01.550 model that, you know, alpha

NOTE Confidence: 0.97013396

00:43:01.550 --> 00:43:03.570 synuclein is no longer degraded

NOTE Confidence: 0.97013396

00:43:03.630 --> 00:43:06.050 plus aggregating causing Lewy bodies.

NOTE Confidence: 0.96532875

00:43:06.645 --> 00:43:07.685 So this was in two

NOTE Confidence: 0.96532875

00:43:07.685 --> 00:43:09.225 thousand eleven, but subsequently,

NOTE Confidence: 0.93452835

00:43:10.165 --> 00:43:11.844 it's we have on as

NOTE Confidence: 0.93452835

00:43:11.844 --> 00:43:13.864 a field have understood that

NOTE Confidence: 0.93452835

00:43:14.005 --> 00:43:15.605 it's much more complex. It's

NOTE Confidence: 0.93452835

00:43:15.605 --> 00:43:16.985 just not about synuclein

NOTE Confidence: 0.9253671

00:43:17.285 --> 00:43:17.785 alone.

NOTE Confidence: 0.8485173

00:43:18.405 --> 00:43:20.245 And therefore, it's now realized

NOTE Confidence: 0.8485173

00:43:20.245 --> 00:43:21.305 that there because,

NOTE Confidence: 0.9663176

00:43:21.760 --> 00:43:23.860 the proteins are misfolded, there's

NOTE Confidence: 0.9663176

00:43:24.080 --> 00:43:24.900 ER stress.

NOTE Confidence: 0.9919833

00:43:25.200 --> 00:43:26.239 And what I will come

NOTE Confidence: 0.9919833

00:43:26.239 --> 00:43:27.360 back to later is that

NOTE Confidence: 0.9919833

00:43:27.360 --> 00:43:28.239 there are a lot of

NOTE Confidence: 0.9919833

00:43:28.239 --> 00:43:29.220 lipid imbalances

NOTE Confidence: 0.9965629

00:43:29.840 --> 00:43:31.360 with because this is an

NOTE Confidence: 0.9965629

00:43:31.360 --> 00:43:33.280 enzyme that's involved in lipid

NOTE Confidence: 0.9965629

00:43:33.280 --> 00:43:33.780 homeostasis.

NOTE Confidence: 0.9209436

00:43:34.239 --> 00:43:34.739 Yeah.

NOTE Confidence: 0.9495742

00:43:35.605 --> 00:43:37.285 Okay. So at this point,

NOTE Confidence: 0.9495742

00:43:37.285 --> 00:43:38.405 I wanna just sort of

NOTE Confidence: 0.9495742

00:43:38.405 --> 00:43:39.525 make a plug for our

NOTE Confidence: 0.9495742

00:43:39.525 --> 00:43:41.045 story that came out last

NOTE Confidence: 0.9495742

00:43:41.045 --> 00:43:41.545 week.

NOTE Confidence: 0.9427821

00:43:42.005 --> 00:43:43.864 So we we are using

NOTE Confidence: 0.9427821

00:43:43.925 --> 00:43:45.625 mouse models to understand

NOTE Confidence: 0.86150575

00:43:46.325 --> 00:43:47.545 GBLINK Parkinson,

NOTE Confidence: 0.96407366

00:43:48.245 --> 00:43:49.685 and we have sort of,

NOTE Confidence: 0.99745935

00:43:50.670 --> 00:43:51.170 used

NOTE Confidence: 0.9327225

00:43:51.630 --> 00:43:53.309 the, what we learned from

NOTE Confidence: 0.9327225

00:43:53.309 --> 00:43:54.910 human genetics that the l

NOTE Confidence: 0.9327225

00:43:54.910 --> 00:43:56.750 triple four p mutation in

NOTE Confidence: 0.9327225

00:43:56.750 --> 00:43:57.250 particular

NOTE Confidence: 0.9829585

00:43:57.869 --> 00:43:59.089 is actually predisposed

NOTE Confidence: 0.99890214

00:43:59.390 --> 00:44:00.130 to cognitive

NOTE Confidence: 0.9420904

00:44:00.430 --> 00:44:02.210 deficits. So we've made mice,

NOTE Confidence: 0.9857773

00:44:03.239 --> 00:44:05.364 that have this mutation on

NOTE Confidence: 0.9857773

00:44:05.364 --> 00:44:07.125 a null background to model

NOTE Confidence: 0.9857773

00:44:07.125 --> 00:44:08.744 basically Gaucher patients.

NOTE Confidence: 0.99740845

00:44:09.204 --> 00:44:10.025 And because,

NOTE Confidence: 0.9763558

00:44:10.724 --> 00:44:12.644 you need ceramide for barrier

NOTE Confidence: 0.9763558

00:44:12.644 --> 00:44:14.005 function of skin, if you

NOTE Confidence: 0.9763558

00:44:14.005 --> 00:44:15.684 just make these mutations, the

NOTE Confidence: 0.9763558

00:44:15.684 --> 00:44:17.444 mice get skin phenotypes and

NOTE Confidence: 0.9763558

00:44:17.444 --> 00:44:19.219 they die. So we've rescued

NOTE Confidence: 0.93660396

00:44:19.760 --> 00:44:22.000 the Gaucher, GBA expression in

NOTE Confidence: 0.93660396

00:44:22.000 --> 00:44:22.900 skin. Okay.

NOTE Confidence: 0.9413573

00:44:23.200 --> 00:44:24.320 But what we can show

NOTE Confidence: 0.9413573

00:44:24.320 --> 00:44:25.760 is these are really good

NOTE Confidence: 0.9413573

00:44:25.760 --> 00:44:27.360 models. They can, in the

NOTE Confidence: 0.9413573

00:44:27.360 --> 00:44:29.760 previously we before this, before

NOTE Confidence: 0.9413573

00:44:29.760 --> 00:44:31.335 we made these mice, most

NOTE Confidence: 0.9413573

00:44:31.335 --> 00:44:32.495 of the mice would only

NOTE Confidence: 0.9413573

00:44:32.495 --> 00:44:33.695 live three weeks, so we

NOTE Confidence: 0.9413573

00:44:33.695 --> 00:44:34.735 could not because of the

NOTE Confidence: 0.9413573

00:44:34.735 --> 00:44:35.555 skin issues.

NOTE Confidence: 0.992996

00:44:35.935 --> 00:44:37.315 So we could not study,

NOTE Confidence: 0.992996

00:44:37.375 --> 00:44:39.155 like, age related phenotypes.

NOTE Confidence: 0.9906867

00:44:39.614 --> 00:44:41.295 So in this case, these

NOTE Confidence: 0.9906867

00:44:41.295 --> 00:44:43.395 these mice, you know, accumulate

NOTE Confidence: 0.8977405

00:44:43.935 --> 00:44:44.435 the

NOTE Confidence: 0.8949413

00:44:44.870 --> 00:44:45.530 the lipids.

NOTE Confidence: 0.970341

00:44:45.830 --> 00:44:47.270 They're like you would expect,

NOTE Confidence: 0.970341

00:44:47.270 --> 00:44:49.270 like patients do. They have

NOTE Confidence: 0.970341

00:44:49.270 --> 00:44:50.870 very little protein because they

NOTE Confidence: 0.970341

00:44:50.870 --> 00:44:51.770 have the mutations,

NOTE Confidence: 0.9656334

00:44:52.150 --> 00:44:53.530 and they have no enzymatic

NOTE Confidence: 0.9656334

00:44:53.750 --> 00:44:55.830 activity because the because it's

NOTE Confidence: 0.9656334

00:44:55.830 --> 00:44:57.190 a mutant protein. So they're

NOTE Confidence: 0.9656334

00:44:57.190 --> 00:44:58.730 really a very good model.

NOTE Confidence: 0.9653195

00:44:59.114 --> 00:45:00.475 And what we've done is

NOTE Confidence: 0.9653195

00:45:00.475 --> 00:45:02.395 taken these mice and crossed

NOTE Confidence: 0.9653195

00:45:02.395 --> 00:45:04.475 them to synuclein transgenic. So

NOTE Confidence: 0.9653195

00:45:04.475 --> 00:45:05.455 we can compare,

NOTE Confidence: 0.9674743

00:45:06.075 --> 00:45:07.435 the black mice, which is

NOTE Confidence: 0.9674743

00:45:07.435 --> 00:45:08.635 the wild type mice, to

NOTE Confidence: 0.9674743

00:45:08.635 --> 00:45:10.094 the GBA, the amber.

NOTE Confidence: 0.9597566

00:45:10.555 --> 00:45:11.935 And then we can cross,

NOTE Confidence: 0.9597566

00:45:12.155 --> 00:45:13.295 compare the same

NOTE Confidence: 0.95558393

00:45:13.630 --> 00:45:15.170 impact of this GBA mutation

NOTE Confidence: 0.95558393

00:45:15.230 --> 00:45:16.530 on a wild type background

NOTE Confidence: 0.9860314

00:45:16.830 --> 00:45:18.830 or a synuclein background. So

NOTE Confidence: 0.9860314

00:45:18.830 --> 00:45:20.130 red versus green.

NOTE Confidence: 0.98450005

00:45:21.469 --> 00:45:22.750 So what we've done in

NOTE Confidence: 0.98450005

00:45:22.750 --> 00:45:24.190 using these mice is sort

NOTE Confidence: 0.98450005

00:45:24.190 --> 00:45:26.109 of behavioral assays to sort

NOTE Confidence: 0.98450005

00:45:26.109 --> 00:45:28.130 of understand how,

NOTE Confidence: 0.8270221

00:45:28.665 --> 00:45:30.685 GBA impacts motor functions

NOTE Confidence: 0.9714268

00:45:31.145 --> 00:45:33.005 as well as cognitive functions.

NOTE Confidence: 0.9949789

00:45:33.465 --> 00:45:34.425 And so if you can

NOTE Confidence: 0.9949789

00:45:34.425 --> 00:45:36.105 just look at the colors,

NOTE Confidence: 0.9949789

00:45:36.105 --> 00:45:37.145 if you look at the

NOTE Confidence: 0.9949789

00:45:37.145 --> 00:45:38.445 amber colors versus

NOTE Confidence: 0.9221626

00:45:38.745 --> 00:45:40.344 the black colors, these are

NOTE Confidence: 0.9221626

00:45:40.344 --> 00:45:40.844 longitudinal

NOTE Confidence: 0.9632374

00:45:41.305 --> 00:45:42.905 motor behavior tests. So at

NOTE Confidence: 0.9632374

00:45:42.905 --> 00:45:44.860 the, in panel a is

NOTE Confidence: 0.9632374

00:45:44.860 --> 00:45:46.460 balanced beam. So you make

NOTE Confidence: 0.9632374

00:45:46.460 --> 00:45:48.060 the mice cross from one

NOTE Confidence: 0.9632374

00:45:48.060 --> 00:45:49.580 end of the very narrow

NOTE Confidence: 0.9632374

00:45:49.580 --> 00:45:50.940 beam to the other and

NOTE Confidence: 0.9632374

00:45:50.940 --> 00:45:52.700 quantitate how many runs they

NOTE Confidence: 0.9632374

00:45:52.700 --> 00:45:53.820 can do in a given

NOTE Confidence: 0.9632374

00:45:53.820 --> 00:45:54.320 time.

NOTE Confidence: 0.973271

00:45:54.780 --> 00:45:56.380 And here on the panel

NOTE Confidence: 0.973271

00:45:56.380 --> 00:45:57.280 b is,

NOTE Confidence: 0.9292536

00:45:57.695 --> 00:45:59.135 the grip strength. How long

NOTE Confidence: 0.9292536

00:45:59.135 --> 00:46:00.335 a mouse can hold on

NOTE Confidence: 0.9292536

00:46:00.335 --> 00:46:02.195 to a grip strength meter.

NOTE Confidence: 0.9292536

00:46:02.415 --> 00:46:03.455 And you can see in

NOTE Confidence: 0.9292536

00:46:03.455 --> 00:46:05.135 this as this is the

NOTE Confidence: 0.9292536

00:46:05.135 --> 00:46:07.075 same cohort of mice analyzed

NOTE Confidence: 0.9292536

00:46:07.135 --> 00:46:08.655 over one year. And you

NOTE Confidence: 0.9292536

00:46:08.655 --> 00:46:10.015 can see in wild type

NOTE Confidence: 0.9292536

00:46:10.015 --> 00:46:11.535 that they are fine in

NOTE Confidence: 0.9292536

00:46:11.535 --> 00:46:12.835 black. In amber,

NOTE Confidence: 0.95329773

00:46:13.210 --> 00:46:14.410 you can see the GBA

NOTE Confidence: 0.95329773

00:46:14.410 --> 00:46:15.850 mice are also fine. They

NOTE Confidence: 0.95329773

00:46:15.850 --> 00:46:17.690 have no motor deficits. But

NOTE Confidence: 0.95329773

00:46:17.690 --> 00:46:19.450 the synuclein transgenic, which are

NOTE Confidence: 0.95329773

00:46:19.450 --> 00:46:21.310 in red, can show progressive

NOTE Confidence: 0.95329773

00:46:21.530 --> 00:46:22.030 phenotypes.

NOTE Confidence: 0.99526423

00:46:22.410 --> 00:46:23.530 But if you cross in

NOTE Confidence: 0.99526423

00:46:23.530 --> 00:46:24.030 GBA,

NOTE Confidence: 0.99706113

00:46:24.330 --> 00:46:25.450 which is in green, they

NOTE Confidence: 0.99706113

00:46:25.450 --> 00:46:26.510 get much worse.

NOTE Confidence: 0.9659242

00:46:27.075 --> 00:46:28.675 Yeah? So it says that

NOTE Confidence: 0.9659242

00:46:28.675 --> 00:46:30.035 GBM mice on their own

NOTE Confidence: 0.9659242

00:46:30.035 --> 00:46:31.715 don't get any motor phenotypes,

NOTE Confidence: 0.9659242

00:46:31.715 --> 00:46:32.755 but on a on a

NOTE Confidence: 0.9659242

00:46:32.755 --> 00:46:34.515 synuclein background, they can make

NOTE Confidence: 0.9659242

00:46:34.515 --> 00:46:35.415 things worse.

NOTE Confidence: 0.9636716

00:46:35.875 --> 00:46:37.715 We've done this using variety

NOTE Confidence: 0.9636716

00:46:37.715 --> 00:46:39.474 of other motor behaviors. In

NOTE Confidence: 0.9636716

00:46:39.474 --> 00:46:40.994 this case, hyaline clasp and

NOTE Confidence: 0.9636716

00:46:40.994 --> 00:46:42.710 open field. And the same

NOTE Confidence: 0.9636716

00:46:42.710 --> 00:46:45.049 story holds. As as you

NOTE Confidence: 0.9161957

00:46:45.510 --> 00:46:47.049 on their own, they're fine.

NOTE Confidence: 0.9161957

00:46:47.270 --> 00:46:48.069 But in a on a

NOTE Confidence: 0.9161957

00:46:48.069 --> 00:46:49.910 synthetic background, they make things

NOTE Confidence: 0.9161957

00:46:49.910 --> 00:46:50.410 worse.

NOTE Confidence: 0.9869622

00:46:51.190 --> 00:46:52.410 So what about cognition?

NOTE Confidence: 0.9683887

00:46:52.789 --> 00:46:54.309 Because, you know, GBA is

NOTE Confidence: 0.9683887

00:46:54.309 --> 00:46:56.575 linked in particular to cognitive

NOTE Confidence: 0.9683887

00:46:56.714 --> 00:46:58.315 deficits, we were very interested

NOTE Confidence: 0.9683887

00:46:58.315 --> 00:46:59.755 in doing this. And so

NOTE Confidence: 0.9683887

00:46:59.755 --> 00:47:00.954 the way we've done this

NOTE Confidence: 0.9683887

00:47:00.954 --> 00:47:02.494 is using fear conditioning.

NOTE Confidence: 0.97970355

00:47:02.875 --> 00:47:03.835 So if you put a

NOTE Confidence: 0.97970355

00:47:03.835 --> 00:47:05.515 mouse in a in a

NOTE Confidence: 0.97970355

00:47:05.515 --> 00:47:07.114 box and then pair a

NOTE Confidence: 0.97970355

00:47:07.114 --> 00:47:08.940 tone with the shock, then

NOTE Confidence: 0.97970355

00:47:08.940 --> 00:47:10.700 they remember that this was

NOTE Confidence: 0.97970355

00:47:10.700 --> 00:47:11.760 a very aversive

NOTE Confidence: 0.97788036

00:47:12.060 --> 00:47:13.420 environment. So the next day,

NOTE Confidence: 0.97788036

00:47:13.420 --> 00:47:14.940 if you bring them and

NOTE Confidence: 0.97788036

00:47:14.940 --> 00:47:16.300 just give them the tone,

NOTE Confidence: 0.97788036

00:47:16.300 --> 00:47:18.140 no shock, then they will

NOTE Confidence: 0.97788036

00:47:18.140 --> 00:47:19.260 freeze, you know. So we

NOTE Confidence: 0.97788036

00:47:19.260 --> 00:47:20.859 can calculate how long they

NOTE Confidence: 0.97788036

00:47:20.859 --> 00:47:22.535 freeze as a measure of

NOTE Confidence: 0.97788036

00:47:22.535 --> 00:47:24.135 how much they remember this

NOTE Confidence: 0.97788036

00:47:24.135 --> 00:47:25.975 fear fear memory. And you

NOTE Confidence: 0.97788036

00:47:25.975 --> 00:47:27.275 can see on the panels

NOTE Confidence: 0.97788036

00:47:27.335 --> 00:47:29.195 on the on the, e

NOTE Confidence: 0.9795176

00:47:29.495 --> 00:47:30.535 that if you look at

NOTE Confidence: 0.9795176

00:47:30.535 --> 00:47:32.775 the amber bars between the

NOTE Confidence: 0.9795176

00:47:32.775 --> 00:47:34.295 training day and the testing

NOTE Confidence: 0.9795176

00:47:34.295 --> 00:47:35.495 day, both at three and

NOTE Confidence: 0.9795176

00:47:35.495 --> 00:47:37.290 twelve months, that they are

NOTE Confidence: 0.9795176

00:47:37.290 --> 00:47:39.230 showing no significant differences

NOTE Confidence: 0.94549114

00:47:39.770 --> 00:47:41.710 in so they don't remember

NOTE Confidence: 0.94549114

00:47:41.930 --> 00:47:43.630 this fear, fear condition.

NOTE Confidence: 0.93767405

00:47:44.330 --> 00:47:45.850 So because there were some

NOTE Confidence: 0.93767405

00:47:45.850 --> 00:47:47.770 differences in already on the

NOTE Confidence: 0.93767405

00:47:47.770 --> 00:47:49.530 training day, we did another

NOTE Confidence: 0.93767405

00:47:49.530 --> 00:47:51.630 essay called novel object recognition.

NOTE Confidence: 0.91848594

00:47:52.484 --> 00:47:53.525 This is what what you

NOTE Confidence: 0.91848594

00:47:53.525 --> 00:47:54.404 do is you put a

NOTE Confidence: 0.91848594

00:47:54.404 --> 00:47:55.204 mouse with,

NOTE Confidence: 0.77584255

00:47:56.164 --> 00:47:56.904 two objects

NOTE Confidence: 0.97668105

00:47:57.204 --> 00:47:58.505 on one day, and you

NOTE Confidence: 0.97668105

00:47:58.724 --> 00:48:00.325 calculate how much time they

NOTE Confidence: 0.97668105

00:48:00.325 --> 00:48:01.384 spend with each

NOTE Confidence: 0.96426195

00:48:01.765 --> 00:48:03.364 object. And then the next

NOTE Confidence: 0.96426195

00:48:03.364 --> 00:48:04.565 day, you swap out one

NOTE Confidence: 0.96426195

00:48:04.565 --> 00:48:05.525 of the objects, and you

NOTE Confidence: 0.96426195

00:48:05.525 --> 00:48:06.724 put a new object, a

NOTE Confidence: 0.96426195

00:48:06.724 --> 00:48:08.880 novel object. And then normally,

NOTE Confidence: 0.96426195

00:48:09.020 --> 00:48:10.380 mice are curious, so they

NOTE Confidence: 0.96426195

00:48:10.380 --> 00:48:11.500 will go to the novel

NOTE Confidence: 0.96426195

00:48:11.500 --> 00:48:13.040 object if they remembered,

NOTE Confidence: 0.96499825

00:48:13.340 --> 00:48:14.460 these were the one was

NOTE Confidence: 0.96499825

00:48:14.460 --> 00:48:15.900 an old object. And you

NOTE Confidence: 0.96499825

00:48:15.900 --> 00:48:17.260 can see in this very

NOTE Confidence: 0.96499825

00:48:17.260 --> 00:48:17.760 clearly

NOTE Confidence: 0.89387155

00:48:18.060 --> 00:48:19.739 that GBM mice, even at

NOTE Confidence: 0.89387155

00:48:19.739 --> 00:48:21.119 three months, have a cognitive

NOTE Confidence: 0.89387155

00:48:21.260 --> 00:48:21.760 deficits.

NOTE Confidence: 0.973897

00:48:22.655 --> 00:48:23.555 But on a synuclein

NOTE Confidence: 0.92079675

00:48:23.855 --> 00:48:24.355 transgenic

NOTE Confidence: 0.9870615

00:48:24.655 --> 00:48:26.415 background, they still have the

NOTE Confidence: 0.9870615

00:48:26.415 --> 00:48:26.915 same,

NOTE Confidence: 0.98742425

00:48:27.375 --> 00:48:28.815 effect. So it says that

NOTE Confidence: 0.98742425

00:48:28.815 --> 00:48:30.895 very clearly that we can

NOTE Confidence: 0.98742425

00:48:30.895 --> 00:48:31.395 dissociate

NOTE Confidence: 0.99232984

00:48:31.855 --> 00:48:33.155 both motor and cognitive,

NOTE Confidence: 0.70897347

00:48:34.734 --> 00:48:36.435 phenotypes with genotype.

NOTE Confidence: 0.92332625

00:48:37.350 --> 00:48:38.390 So a wild type are

NOTE Confidence: 0.92332625

00:48:38.390 --> 00:48:40.730 normal. GBA only have cognitive

NOTE Confidence: 0.92332625

00:48:40.790 --> 00:48:41.290 deficits.

NOTE Confidence: 0.9771042

00:48:41.830 --> 00:48:42.890 Synuclein transgenic

NOTE Confidence: 0.9480278

00:48:43.190 --> 00:48:44.790 only motor deficits. And when

NOTE Confidence: 0.9480278

00:48:44.790 --> 00:48:46.250 you have a double cross,

NOTE Confidence: 0.9480278

00:48:46.310 --> 00:48:47.050 you have

NOTE Confidence: 0.9985861

00:48:47.350 --> 00:48:49.430 cognitive deficits that are driven

NOTE Confidence: 0.9985861

00:48:49.430 --> 00:48:50.170 by GBA

NOTE Confidence: 0.9178151

00:48:50.470 --> 00:48:52.490 and then worsen motor deficits.

NOTE Confidence: 0.9806785

00:48:53.375 --> 00:48:54.734 So what about how is

NOTE Confidence: 0.9806785

00:48:54.734 --> 00:48:56.755 this related to synuclein pathology?

NOTE Confidence: 0.9806785

00:48:56.815 --> 00:48:58.655 Because in Parkinson's field or

NOTE Confidence: 0.9806785

00:48:58.655 --> 00:49:00.094 Lewy body dementia, you can't

NOTE Confidence: 0.9806785

00:49:00.094 --> 00:49:02.194 get away from, synuclein pathology.

NOTE Confidence: 0.9731362

00:49:02.655 --> 00:49:04.035 So what we did is

NOTE Confidence: 0.9731362

00:49:04.094 --> 00:49:05.135 if you look at the

NOTE Confidence: 0.9731362

00:49:05.135 --> 00:49:06.895 column, the third column, just

NOTE Confidence: 0.9731362

00:49:06.895 --> 00:49:07.954 the green column,

NOTE Confidence: 0.96396375

00:49:08.310 --> 00:49:10.469 we stain the cortex and

NOTE Confidence: 0.96396375

00:49:10.469 --> 00:49:11.910 many other areas, but I'm

NOTE Confidence: 0.96396375

00:49:11.910 --> 00:49:12.790 just gonna show you the

NOTE Confidence: 0.96396375

00:49:12.790 --> 00:49:13.290 cortex,

NOTE Confidence: 0.96082795

00:49:14.070 --> 00:49:15.130 for phosphocinuclein,

NOTE Confidence: 0.9954295

00:49:16.230 --> 00:49:17.450 which is phosphorylated

NOTE Confidence: 0.92920715

00:49:17.830 --> 00:49:19.190 at a particular site at

NOTE Confidence: 0.92920715

00:49:19.190 --> 00:49:21.285 position one twenty nine. And

NOTE Confidence: 0.92920715

00:49:21.285 --> 00:49:23.444 this is the, is used,

NOTE Confidence: 0.92920715

00:49:23.444 --> 00:49:25.045 as Thomas said, to sort

NOTE Confidence: 0.92920715

00:49:25.045 --> 00:49:26.984 of distinguish normal synuclein

NOTE Confidence: 0.96356636

00:49:27.285 --> 00:49:29.364 from aggregated synuclein. And this

NOTE Confidence: 0.96356636

00:49:29.364 --> 00:49:30.645 is also used in the

NOTE Confidence: 0.96356636

00:49:30.645 --> 00:49:32.405 path labs to score for

NOTE Confidence: 0.96356636

00:49:32.405 --> 00:49:33.224 Lewy bodies.

NOTE Confidence: 0.8976805

00:49:33.719 --> 00:49:34.920 And you can see very

NOTE Confidence: 0.8976805

00:49:34.920 --> 00:49:36.300 clearly if you just go

NOTE Confidence: 0.8976805

00:49:36.440 --> 00:49:37.660 vertically down that

NOTE Confidence: 0.90980947

00:49:37.960 --> 00:49:39.340 wild type and GBMI,

NOTE Confidence: 0.9830859

00:49:39.800 --> 00:49:41.000 even at twelve months of

NOTE Confidence: 0.9830859

00:49:41.000 --> 00:49:42.280 age in which these pictures

NOTE Confidence: 0.9830859

00:49:42.280 --> 00:49:42.940 are taken,

NOTE Confidence: 0.8560508

00:49:43.320 --> 00:49:44.700 do not show any synuclein

NOTE Confidence: 0.8560508

00:49:44.920 --> 00:49:45.104 pathology. The synuclein transgenic does,

NOTE Confidence: 0.8560508

00:49:45.104 --> 00:49:45.289 but when you have a

NOTE Confidence: 0.8560508

00:49:45.289 --> 00:49:46.380 double transgenic, you get much,

NOTE Confidence: 0.8540412

00:49:46.995 --> 00:49:47.495 transgenic

NOTE Confidence: 0.7988258

00:49:47.915 --> 00:49:48.415 does,

NOTE Confidence: 0.90931183

00:49:48.835 --> 00:49:50.035 but when you have a

NOTE Confidence: 0.90931183

00:49:50.035 --> 00:49:51.155 double transgenic, you get much

NOTE Confidence: 0.90931183

00:49:51.155 --> 00:49:51.815 more pathology.

NOTE Confidence: 0.8986879

00:49:52.515 --> 00:49:53.475 And this is sort of

NOTE Confidence: 0.8986879

00:49:53.475 --> 00:49:55.095 quantified in these graphs

NOTE Confidence: 0.95819247

00:49:55.635 --> 00:49:57.015 here. And what is interesting

NOTE Confidence: 0.95819247

00:49:57.075 --> 00:49:58.755 is it's not the number

NOTE Confidence: 0.95819247

00:49:58.755 --> 00:50:00.295 of cells that are positive,

NOTE Confidence: 0.9949629

00:50:00.760 --> 00:50:02.040 but the cells that are

NOTE Confidence: 0.9949629

00:50:02.040 --> 00:50:04.200 actually positive become much more

NOTE Confidence: 0.9949629

00:50:04.200 --> 00:50:05.480 intense. And this is shown

NOTE Confidence: 0.9949629

00:50:05.480 --> 00:50:06.780 in sort of these histograms

NOTE Confidence: 0.9542839

00:50:07.400 --> 00:50:08.300 on this side.

NOTE Confidence: 0.9457343

00:50:08.840 --> 00:50:10.280 So the take home message

NOTE Confidence: 0.9457343

00:50:10.280 --> 00:50:12.440 is that GBM mice don't

NOTE Confidence: 0.9457343

00:50:12.440 --> 00:50:13.739 show, phosphocinogrelin

NOTE Confidence: 0.9949586

00:50:14.360 --> 00:50:14.860 pathology.

NOTE Confidence: 0.95675236

00:50:16.265 --> 00:50:17.305 And we've done this other

NOTE Confidence: 0.95675236

00:50:17.305 --> 00:50:18.585 ways. We've done this by

NOTE Confidence: 0.95675236

00:50:18.585 --> 00:50:20.265 western blotting, and we get

NOTE Confidence: 0.95675236

00:50:20.265 --> 00:50:21.705 a similar result. You can

NOTE Confidence: 0.95675236

00:50:21.705 --> 00:50:23.225 see that on their own

NOTE Confidence: 0.95675236

00:50:23.225 --> 00:50:25.005 wild type and GBM mice

NOTE Confidence: 0.95675236

00:50:25.225 --> 00:50:27.305 don't have any pathology, but

NOTE Confidence: 0.95675236

00:50:27.305 --> 00:50:29.650 synuclein transgenics do, and then

NOTE Confidence: 0.95675236

00:50:29.650 --> 00:50:31.030 many of the double transgenic,

NOTE Confidence: 0.95675236

00:50:31.170 --> 00:50:32.230 you have more pathology.

NOTE Confidence: 0.9819269

00:50:33.810 --> 00:50:35.750 So this tells us something

NOTE Confidence: 0.9271166

00:50:36.050 --> 00:50:38.050 rather surprising for us that

NOTE Confidence: 0.9271166

00:50:38.050 --> 00:50:40.150 the cognitive symptoms are actually

NOTE Confidence: 0.96243304

00:50:40.565 --> 00:50:41.305 occurring independent

NOTE Confidence: 0.997661

00:50:41.845 --> 00:50:43.205 in this mouse of alpha

NOTE Confidence: 0.997661

00:50:43.205 --> 00:50:44.345 synuclein pathology.

NOTE Confidence: 0.99181014

00:50:44.965 --> 00:50:46.165 So this is sort of

NOTE Confidence: 0.99181014

00:50:46.165 --> 00:50:46.665 counterintuitive

NOTE Confidence: 0.91155285

00:50:47.045 --> 00:50:48.325 to to what Thomas told

NOTE Confidence: 0.91155285

00:50:48.325 --> 00:50:49.465 you, like,

NOTE Confidence: 0.8371061

00:50:50.005 --> 00:50:51.545 a a few slides ago.

NOTE Confidence: 0.9990289

00:50:52.165 --> 00:50:53.705 But the motor symptoms

NOTE Confidence: 0.9982799

00:50:54.670 --> 00:50:56.590 are very tightly linked to

NOTE Confidence: 0.9982799

00:50:56.590 --> 00:50:57.410 alpha synuclein

NOTE Confidence: 0.99573416

00:50:58.190 --> 00:50:58.690 pathology

NOTE Confidence: 0.99483776

00:50:58.989 --> 00:51:00.670 load. So the more the

NOTE Confidence: 0.99483776

00:51:00.670 --> 00:51:01.170 pathology,

NOTE Confidence: 0.96039623

00:51:01.469 --> 00:51:03.150 more the motor symptoms. This

NOTE Confidence: 0.96039623

00:51:03.150 --> 00:51:04.930 is just for GBLINK Parkinson.

NOTE Confidence: 0.96039623

00:51:05.070 --> 00:51:06.130 This is not for

NOTE Confidence: 0.94062966

00:51:06.510 --> 00:51:07.010 linked

NOTE Confidence: 0.7840155

00:51:07.550 --> 00:51:08.050 models.

NOTE Confidence: 0.8788383

00:51:08.350 --> 00:51:08.850 Okay.

NOTE Confidence: 0.9985948

00:51:09.525 --> 00:51:10.025 Okay.

NOTE Confidence: 0.942188

00:51:10.325 --> 00:51:12.165 Okay. So while we were

NOTE Confidence: 0.942188

00:51:12.165 --> 00:51:14.005 doing this, we had an

NOTE Confidence: 0.942188

00:51:14.005 --> 00:51:16.265 an a competing lab, Gomiteng's

NOTE Confidence: 0.942188

00:51:16.484 --> 00:51:17.464 lab at Columbia,

NOTE Confidence: 0.82084066

00:51:17.924 --> 00:51:19.224 published this study,

NOTE Confidence: 0.8940637

00:51:19.525 --> 00:51:21.125 and they used l triple

NOTE Confidence: 0.8940637

00:51:21.125 --> 00:51:22.424 four p but heterozygous

NOTE Confidence: 0.9696141

00:51:22.805 --> 00:51:23.305 mice.

NOTE Confidence: 0.9565052

00:51:23.610 --> 00:51:25.230 And they also analyzed,

NOTE Confidence: 0.9372716

00:51:25.770 --> 00:51:26.270 cognitive,

NOTE Confidence: 0.8901056

00:51:27.370 --> 00:51:28.750 impairment in this mice.

NOTE Confidence: 0.99777675

00:51:29.050 --> 00:51:30.970 I won't belabor this, but

NOTE Confidence: 0.99777675

00:51:30.970 --> 00:51:32.350 they could show that

NOTE Confidence: 0.92448425

00:51:32.890 --> 00:51:34.410 they could in their mice

NOTE Confidence: 0.92448425

00:51:34.410 --> 00:51:36.030 also that they have issues

NOTE Confidence: 0.92448425

00:51:36.090 --> 00:51:37.770 in the panel a with

NOTE Confidence: 0.92448425

00:51:37.770 --> 00:51:38.510 fear conditioning.

NOTE Confidence: 0.99442714

00:51:38.915 --> 00:51:40.214 And they also did,

NOTE Confidence: 0.9279579

00:51:40.755 --> 00:51:42.275 Morris water mace if you

NOTE Confidence: 0.9279579

00:51:42.355 --> 00:51:43.795 whether you could figure out

NOTE Confidence: 0.9279579

00:51:43.795 --> 00:51:46.035 where the hidden platform was.

NOTE Confidence: 0.9279579

00:51:46.035 --> 00:51:46.994 And they could show that

NOTE Confidence: 0.9279579

00:51:46.994 --> 00:51:48.675 in the GBA mice that

NOTE Confidence: 0.9279579

00:51:48.675 --> 00:51:50.055 they do have a deficits

NOTE Confidence: 0.9279579

00:51:50.114 --> 00:51:51.575 at seven months a day.

NOTE Confidence: 0.9576299

00:51:52.460 --> 00:51:54.299 But most importantly, what they

NOTE Confidence: 0.9576299

00:51:54.299 --> 00:51:55.660 did is they crossed their

NOTE Confidence: 0.9576299

00:51:55.660 --> 00:51:56.160 mice

NOTE Confidence: 0.8952005

00:51:56.539 --> 00:51:58.539 to synuclein knockout. So they

NOTE Confidence: 0.8952005

00:51:58.619 --> 00:52:00.059 where in which synuclein has

NOTE Confidence: 0.8952005

00:52:00.059 --> 00:52:00.880 been deleted.

NOTE Confidence: 0.9972761

00:52:01.260 --> 00:52:02.619 And they still get these

NOTE Confidence: 0.9972761

00:52:02.619 --> 00:52:03.119 deficits.

NOTE Confidence: 0.9558415

00:52:03.420 --> 00:52:05.260 So saying that you do

NOTE Confidence: 0.9558415

00:52:05.260 --> 00:52:06.000 not need,

NOTE Confidence: 0.9473679

00:52:06.494 --> 00:52:08.914 in this mouse model any

NOTE Confidence: 0.9473679

00:52:09.135 --> 00:52:11.234 synuclein to drive the cognitive

NOTE Confidence: 0.9473679

00:52:11.454 --> 00:52:13.694 deficits. The GBA alone, by

NOTE Confidence: 0.9473679

00:52:13.694 --> 00:52:15.154 its function in the lysosome,

NOTE Confidence: 0.9473679

00:52:15.375 --> 00:52:16.674 can cause these deficits.

NOTE Confidence: 0.9685253

00:52:17.855 --> 00:52:19.135 Okay. So we are interested

NOTE Confidence: 0.9685253

00:52:19.135 --> 00:52:20.015 to try and figure out

NOTE Confidence: 0.9685253

00:52:20.015 --> 00:52:20.914 what the mechanisms

NOTE Confidence: 0.98962635

00:52:21.295 --> 00:52:22.920 are. And so to get

NOTE Confidence: 0.98962635

00:52:22.920 --> 00:52:24.520 some insights into this, we

NOTE Confidence: 0.98962635

00:52:24.520 --> 00:52:26.460 did single cell RNA sequencing

NOTE Confidence: 0.98962635

00:52:26.599 --> 00:52:28.280 that you're all familiar. This

NOTE Confidence: 0.98962635

00:52:28.280 --> 00:52:29.160 is just to get a

NOTE Confidence: 0.98962635

00:52:29.160 --> 00:52:29.660 transcriptional,

NOTE Confidence: 0.9000657

00:52:30.839 --> 00:52:31.339 definition,

NOTE Confidence: 0.9727666

00:52:31.640 --> 00:52:33.000 if it were, of the

NOTE Confidence: 0.9727666

00:52:33.000 --> 00:52:34.599 brain as a as at

NOTE Confidence: 0.9727666

00:52:34.599 --> 00:52:36.599 a single cell resolution in

NOTE Confidence: 0.9727666

00:52:36.599 --> 00:52:37.739 these four mice.

NOTE Confidence: 0.9626326

00:52:39.135 --> 00:52:40.175 So this is what what

NOTE Confidence: 0.9626326

00:52:40.255 --> 00:52:41.855 you you compress all this

NOTE Confidence: 0.9626326

00:52:41.855 --> 00:52:43.715 complex data into two dimensions

NOTE Confidence: 0.9626326

00:52:43.935 --> 00:52:44.675 called UMAPs,

NOTE Confidence: 0.9620152

00:52:44.975 --> 00:52:45.855 and this is what the

NOTE Confidence: 0.9620152

00:52:45.855 --> 00:52:47.614 data look like. And if

NOTE Confidence: 0.9620152

00:52:47.614 --> 00:52:49.135 we look in and sort

NOTE Confidence: 0.9620152

00:52:49.135 --> 00:52:50.655 of dive in only into

NOTE Confidence: 0.9620152

00:52:50.655 --> 00:52:52.859 neurons comparing wild type versus

NOTE Confidence: 0.9620152

00:52:52.859 --> 00:52:54.160 GBA and these transgenics.

NOTE Confidence: 0.99532765

00:52:54.700 --> 00:52:55.900 And if you look in

NOTE Confidence: 0.99532765

00:52:55.900 --> 00:52:57.200 the bottom here,

NOTE Confidence: 0.99896306

00:52:57.500 --> 00:52:58.380 if you look at what's

NOTE Confidence: 0.99896306

00:52:58.380 --> 00:53:00.079 happening in neuronal types,

NOTE Confidence: 0.93952554

00:53:00.380 --> 00:53:02.540 I was expecting because GBA

NOTE Confidence: 0.93952554

00:53:02.540 --> 00:53:03.440 is a lysosomal

NOTE Confidence: 0.9285954

00:53:03.819 --> 00:53:04.319 enzyme,

NOTE Confidence: 0.9882523

00:53:04.619 --> 00:53:06.400 it controls lipid homeostasis,

NOTE Confidence: 0.9921222

00:53:07.025 --> 00:53:08.385 that those would be the

NOTE Confidence: 0.9921222

00:53:08.385 --> 00:53:10.405 pathways that are most prominent.

NOTE Confidence: 0.8915046

00:53:10.945 --> 00:53:11.445 But,

NOTE Confidence: 0.827782

00:53:11.825 --> 00:53:13.425 surprised when you do unbiased

NOTE Confidence: 0.827782

00:53:13.425 --> 00:53:14.805 things, you get surprises.

NOTE Confidence: 0.99037766

00:53:15.265 --> 00:53:16.545 And the hits you get

NOTE Confidence: 0.99037766

00:53:16.545 --> 00:53:18.325 are all related to synaptic

NOTE Confidence: 0.99037766

00:53:18.385 --> 00:53:19.525 vesicle trafficking,

NOTE Confidence: 0.99221396

00:53:20.349 --> 00:53:21.329 synapse structure,

NOTE Confidence: 0.99052167

00:53:22.270 --> 00:53:23.469 and so forth. So we

NOTE Confidence: 0.99052167

00:53:23.469 --> 00:53:24.849 are now sort of,

NOTE Confidence: 0.94928664

00:53:25.950 --> 00:53:26.910 and if you can do

NOTE Confidence: 0.94928664

00:53:26.910 --> 00:53:28.589 more analysis, then this is

NOTE Confidence: 0.94928664

00:53:28.589 --> 00:53:29.869 exactly what you get. You

NOTE Confidence: 0.94928664

00:53:29.869 --> 00:53:31.310 get more and more synaptic

NOTE Confidence: 0.94928664

00:53:31.310 --> 00:53:32.535 pathways that are

NOTE Confidence: 0.9862519

00:53:33.015 --> 00:53:33.515 dysregulated

NOTE Confidence: 0.9993039

00:53:33.815 --> 00:53:35.174 when you actually have a

NOTE Confidence: 0.9993039

00:53:35.174 --> 00:53:35.674 lysosomal

NOTE Confidence: 0.9995058

00:53:36.214 --> 00:53:38.155 enzyme that is actually missing.

NOTE Confidence: 0.98832613

00:53:39.015 --> 00:53:40.795 So we've done some preliminary

NOTE Confidence: 0.98832613

00:53:40.855 --> 00:53:42.855 experiments to confirm that this

NOTE Confidence: 0.98832613

00:53:42.855 --> 00:53:45.015 indeed impacts synapses by doing

NOTE Confidence: 0.98832613

00:53:45.015 --> 00:53:45.994 electron microscopy.

NOTE Confidence: 0.99660856

00:53:46.830 --> 00:53:47.150 Like,

NOTE Confidence: 0.97559905

00:53:47.630 --> 00:53:49.150 Thomas showed you, we can

NOTE Confidence: 0.97559905

00:53:49.150 --> 00:53:50.830 show there are fewer synaptic

NOTE Confidence: 0.97559905

00:53:50.830 --> 00:53:52.350 connections in the cortex of

NOTE Confidence: 0.97559905

00:53:52.350 --> 00:53:52.850 GBMIs.

NOTE Confidence: 0.9704445

00:53:54.030 --> 00:53:55.469 We can also look at

NOTE Confidence: 0.9704445

00:53:55.469 --> 00:53:57.710 very detailed outer structure as

NOTE Confidence: 0.9704445

00:53:57.710 --> 00:53:59.790 a proxy for synaptic vesicle

NOTE Confidence: 0.9704445

00:53:59.790 --> 00:54:00.290 cycling

NOTE Confidence: 0.97166187

00:54:00.670 --> 00:54:02.030 to look at how many

NOTE Confidence: 0.97166187

00:54:02.030 --> 00:54:03.505 vesicles there are in each

NOTE Confidence: 0.97166187

00:54:03.505 --> 00:54:05.525 terminal and how many clathrin

NOTE Confidence: 0.97166187

00:54:05.585 --> 00:54:07.425 coated vesicles. These are vesicles

NOTE Confidence: 0.97166187

00:54:07.425 --> 00:54:09.285 that are sort of functionally

NOTE Confidence: 0.97166187

00:54:09.344 --> 00:54:11.025 turning over. And we can

NOTE Confidence: 0.97166187

00:54:11.025 --> 00:54:12.864 see very profound changes in

NOTE Confidence: 0.97166187

00:54:12.864 --> 00:54:14.805 these, GBA mutant synapses.

NOTE Confidence: 0.9829055

00:54:15.200 --> 00:54:16.640 But we're still left with

NOTE Confidence: 0.9829055

00:54:16.640 --> 00:54:18.240 a lot of questions. And

NOTE Confidence: 0.9829055

00:54:18.240 --> 00:54:19.680 this is what we're currently

NOTE Confidence: 0.9829055

00:54:19.680 --> 00:54:20.660 trying to tackle.

NOTE Confidence: 0.99961644

00:54:21.200 --> 00:54:23.120 The problem for us is

NOTE Confidence: 0.99961644

00:54:23.120 --> 00:54:23.620 that

NOTE Confidence: 0.9854083

00:54:24.960 --> 00:54:27.620 lysosomes and synapse synaptic vesicles

NOTE Confidence: 0.9854083

00:54:27.680 --> 00:54:29.805 are two organelles that have

NOTE Confidence: 0.9854083

00:54:29.805 --> 00:54:32.145 distinct identities in the neuron.

NOTE Confidence: 0.9854083

00:54:32.205 --> 00:54:34.205 So the lysosome is mainly

NOTE Confidence: 0.9854083

00:54:34.205 --> 00:54:35.725 in the cell body, and

NOTE Confidence: 0.9854083

00:54:35.725 --> 00:54:37.565 synaptic vesicles are at the

NOTE Confidence: 0.9854083

00:54:37.565 --> 00:54:38.065 terminal.

NOTE Confidence: 0.99966097

00:54:38.364 --> 00:54:39.885 And we don't understand how

NOTE Confidence: 0.99966097

00:54:39.885 --> 00:54:41.025 you can impact

NOTE Confidence: 0.98235166

00:54:41.430 --> 00:54:43.109 if you remove an enzyme

NOTE Confidence: 0.98235166

00:54:43.109 --> 00:54:44.550 that's sitting in the soma,

NOTE Confidence: 0.98235166

00:54:44.550 --> 00:54:46.250 how you're impacting this,

NOTE Confidence: 0.98811376

00:54:47.030 --> 00:54:48.810 you know, distinct organelle.

NOTE Confidence: 0.9986929

00:54:49.349 --> 00:54:50.950 And one idea is that

NOTE Confidence: 0.9986929

00:54:50.950 --> 00:54:53.369 it's controlling lipids. It's controlling

NOTE Confidence: 0.9986929

00:54:53.589 --> 00:54:54.329 key lipids

NOTE Confidence: 0.9497125

00:54:54.684 --> 00:54:56.704 that are necessary for synaptic

NOTE Confidence: 0.9497125

00:54:56.765 --> 00:54:58.525 function. And we have some

NOTE Confidence: 0.9497125

00:54:58.525 --> 00:55:00.364 beginning to get some answers

NOTE Confidence: 0.9497125

00:55:00.364 --> 00:55:01.724 into this. And if you

NOTE Confidence: 0.9497125

00:55:01.724 --> 00:55:02.765 look at the we've looked

NOTE Confidence: 0.9497125

00:55:02.765 --> 00:55:04.464 for some lipids called PIP2,

NOTE Confidence: 0.9497125

00:55:04.525 --> 00:55:05.344 the phosphoinositides,

NOTE Confidence: 0.8813597

00:55:06.045 --> 00:55:08.224 the essential for synaptic cycling.

NOTE Confidence: 0.9609892

00:55:08.750 --> 00:55:09.790 And you can see that

NOTE Confidence: 0.9609892

00:55:09.790 --> 00:55:11.309 in the GBM mice, there's

NOTE Confidence: 0.9609892

00:55:11.309 --> 00:55:11.809 less,

NOTE Confidence: 0.9834935

00:55:12.190 --> 00:55:13.710 PIP2. So now we're sort

NOTE Confidence: 0.9834935

00:55:13.710 --> 00:55:14.829 of on a quest to

NOTE Confidence: 0.9834935

00:55:14.829 --> 00:55:15.569 do lipidomics,

NOTE Confidence: 0.84955925

00:55:15.950 --> 00:55:18.109 sort of organella lipidomics to

NOTE Confidence: 0.84955925

00:55:18.109 --> 00:55:18.609 understand

NOTE Confidence: 0.95924634

00:55:19.150 --> 00:55:20.829 the basis for this, sort

NOTE Confidence: 0.95924634

00:55:20.829 --> 00:55:21.569 of fine.

NOTE Confidence: 0.9571586

00:55:22.255 --> 00:55:23.295 Okay. I how am I

NOTE Confidence: 0.9571586

00:55:23.295 --> 00:55:24.895 doing? Okay. So I'm just

NOTE Confidence: 0.9571586

00:55:24.895 --> 00:55:26.255 gonna wrap up and tell

NOTE Confidence: 0.9571586

00:55:26.255 --> 00:55:27.455 you that, you know, if

NOTE Confidence: 0.9571586

00:55:27.455 --> 00:55:28.895 there's one take home message

NOTE Confidence: 0.9571586

00:55:28.895 --> 00:55:30.015 that you can say that

NOTE Confidence: 0.9571586

00:55:30.015 --> 00:55:31.135 GBA can,

NOTE Confidence: 0.9567126

00:55:31.535 --> 00:55:33.375 cognitive deficits in GBA,

NOTE Confidence: 0.95979303

00:55:34.830 --> 00:55:36.930 occur independent of alpha synuclein

NOTE Confidence: 0.95979303

00:55:37.070 --> 00:55:38.670 pathology and that these are

NOTE Confidence: 0.95979303

00:55:38.670 --> 00:55:40.050 related to actually

NOTE Confidence: 0.8361574

00:55:40.670 --> 00:55:41.730 synaptic signatures.

NOTE Confidence: 0.9977336

00:55:42.510 --> 00:55:43.010 And

NOTE Confidence: 0.9859176

00:55:43.310 --> 00:55:45.090 that there are actually treatments

NOTE Confidence: 0.9859176

00:55:45.150 --> 00:55:46.270 that are in the pipeline,

NOTE Confidence: 0.9859176

00:55:46.270 --> 00:55:47.810 and I'm actually very hopeful

NOTE Confidence: 0.996843

00:55:48.110 --> 00:55:49.944 for this sort of five,

NOTE Confidence: 0.996843

00:55:49.944 --> 00:55:51.565 ten percent of the population

NOTE Confidence: 0.93876684

00:55:51.944 --> 00:55:53.405 that there will be actually

NOTE Confidence: 0.9736089

00:55:53.864 --> 00:55:56.025 effective treatments for that. And

NOTE Confidence: 0.9736089

00:55:56.025 --> 00:55:57.645 that we should actually look

NOTE Confidence: 0.9736089

00:55:57.785 --> 00:55:59.145 not just from the from

NOTE Confidence: 0.9736089

00:55:59.145 --> 00:55:59.964 the perspective

NOTE Confidence: 0.982402

00:56:00.265 --> 00:56:01.864 of PD or motor symptoms,

NOTE Confidence: 0.982402

00:56:01.864 --> 00:56:03.145 but also from this, you

NOTE Confidence: 0.982402

00:56:03.145 --> 00:56:05.130 know, perspective of cognitive symptoms.

NOTE Confidence: 0.9789289

00:56:06.329 --> 00:56:07.450 Okay. With that, I'd like

NOTE Confidence: 0.9789289

00:56:07.450 --> 00:56:08.569 to thank the people who

NOTE Confidence: 0.9789289

00:56:08.569 --> 00:56:09.769 did this. All the people

NOTE Confidence: 0.9789289

00:56:09.769 --> 00:56:11.049 who did this have gone

NOTE Confidence: 0.9789289

00:56:11.049 --> 00:56:12.910 to brighter and greener pastures.

NOTE Confidence: 0.8791911

00:56:13.529 --> 00:56:14.969 So Vidya Dara, who's now

NOTE Confidence: 0.8791911

00:56:14.969 --> 00:56:16.730 an assistant professor in Rosalind

NOTE Confidence: 0.8791911

00:56:16.730 --> 00:56:17.789 Franklin University,

NOTE Confidence: 0.999438

00:56:18.089 --> 00:56:18.589 David

NOTE Confidence: 0.9115312

00:56:19.035 --> 00:56:20.555 Backstrom, who's now back in

NOTE Confidence: 0.9115312

00:56:20.555 --> 00:56:22.174 Sweden in Umea University,

NOTE Confidence: 0.9043835

00:56:22.875 --> 00:56:24.474 Risha, who started as a

NOTE Confidence: 0.9043835

00:56:24.474 --> 00:56:25.375 MD PhD.

NOTE Confidence: 0.98953795

00:56:25.755 --> 00:56:27.114 I could she only wanted

NOTE Confidence: 0.98953795

00:56:27.114 --> 00:56:27.994 to be an MD, and

NOTE Confidence: 0.98953795

00:56:27.994 --> 00:56:29.275 I convinced her to be

NOTE Confidence: 0.98953795

00:56:29.275 --> 00:56:30.415 an MD PhD.

NOTE Confidence: 0.7925611

00:56:30.954 --> 00:56:31.454 Okay.

NOTE Confidence: 0.8683593

00:56:32.710 --> 00:56:34.150 And who's at Columbia, and

NOTE Confidence: 0.8683593

00:56:34.150 --> 00:56:35.830 then Jevin, who's a who's

NOTE Confidence: 0.8683593

00:56:35.830 --> 00:56:37.190 a PhD student. So and

NOTE Confidence: 0.8683593

00:56:37.190 --> 00:56:38.810 funding sources. Thank you.

NOTE Confidence: 0.64711064

00:56:44.484 --> 00:56:46.505 Yeah. Yeah. So

NOTE Confidence: 0.9623104

00:56:46.964 --> 00:56:48.085 thank you for a really

NOTE Confidence: 0.9623104

00:56:48.085 --> 00:56:49.605 nice talk. Thank you. Yeah.

NOTE Confidence: 0.9623104

00:56:49.605 --> 00:56:50.565 For those of us who

NOTE Confidence: 0.9623104

00:56:50.565 --> 00:56:52.405 study Alzheimer's disease and model

NOTE Confidence: 0.9623104

00:56:52.405 --> 00:56:53.445 that in mice, there is

NOTE Confidence: 0.9623104

00:56:53.525 --> 00:56:54.244 I mean, there is just

NOTE Confidence: 0.9623104

00:56:54.244 --> 00:56:56.165 so many thematic similarities in

NOTE Confidence: 0.9623104

00:56:56.165 --> 00:56:57.285 where you guys are and

NOTE Confidence: 0.9623104

00:56:57.285 --> 00:56:58.510 where we are. I mean,

NOTE Confidence: 0.9623104

00:56:58.510 --> 00:56:59.570 we have the APP,

NOTE Confidence: 0.8953924

00:57:00.190 --> 00:57:02.190 rare genetic variant for mutation

NOTE Confidence: 0.8953924

00:57:02.190 --> 00:57:03.250 that causes AD

NOTE Confidence: 0.8835152

00:57:03.630 --> 00:57:05.390 early onset, and then APOE,

NOTE Confidence: 0.8835152

00:57:05.390 --> 00:57:06.510 which is the strongest genetic

NOTE Confidence: 0.8835152

00:57:06.510 --> 00:57:08.030 risk factor. And now you

NOTE Confidence: 0.8835152

00:57:08.030 --> 00:57:09.950 have SNCA or synuclein alpha,

NOTE Confidence: 0.8835152

00:57:09.950 --> 00:57:11.250 which is your rare cause,

NOTE Confidence: 0.9587923

00:57:11.645 --> 00:57:12.925 then you've got GBA as

NOTE Confidence: 0.9587923

00:57:12.925 --> 00:57:14.625 your most common, most impactful.

NOTE Confidence: 0.8648848

00:57:15.405 --> 00:57:17.484 And in the APP APOE

NOTE Confidence: 0.8648848

00:57:17.484 --> 00:57:19.265 story, there's some biochemical

NOTE Confidence: 0.99255085

00:57:20.285 --> 00:57:22.045 functional relationship between those two

NOTE Confidence: 0.99255085

00:57:22.045 --> 00:57:22.545 proteins.

NOTE Confidence: 0.92580545

00:57:22.925 --> 00:57:23.964 Do you think you're gonna

NOTE Confidence: 0.92580545

00:57:23.964 --> 00:57:26.224 find some similar similarities across,

NOTE Confidence: 0.84146035

00:57:26.525 --> 00:57:27.569 you know, how it impacts

NOTE Confidence: 0.6464541

00:57:28.430 --> 00:57:28.930 ATP?

NOTE Confidence: 0.87429166

00:57:29.390 --> 00:57:30.616 Do you think GBA may

NOTE Confidence: 0.87429166

00:57:30.963 --> 00:57:32.670 you know, synuclein similar ways?

NOTE Confidence: 0.87429166

00:57:32.670 --> 00:57:34.829 So in the motor aspects

NOTE Confidence: 0.87429166

00:57:34.829 --> 00:57:36.349 of this, this is entirely

NOTE Confidence: 0.87429166

00:57:36.349 --> 00:57:37.490 true because,

NOTE Confidence: 0.98661476

00:57:38.190 --> 00:57:39.650 GBA makes synuclein

NOTE Confidence: 0.9841505

00:57:40.030 --> 00:57:40.530 aggregates

NOTE Confidence: 0.9728552

00:57:40.955 --> 00:57:42.895 much worse because the lipids

NOTE Confidence: 0.9728552

00:57:42.955 --> 00:57:45.295 themselves can template the the

NOTE Confidence: 0.9728552

00:57:45.435 --> 00:57:46.735 seeding of synuclein.

NOTE Confidence: 0.94094145

00:57:47.435 --> 00:57:49.855 And because in GBA mutations,

NOTE Confidence: 0.9029857

00:57:50.235 --> 00:57:50.735 lysosomes

NOTE Confidence: 0.9510729

00:57:51.275 --> 00:57:52.875 are not functional, the pH

NOTE Confidence: 0.9510729

00:57:52.875 --> 00:57:54.630 is off. So in that

NOTE Confidence: 0.9510729

00:57:54.630 --> 00:57:55.130 sense,

NOTE Confidence: 0.9967516

00:57:55.670 --> 00:57:57.670 yes. So there is very

NOTE Confidence: 0.9967516

00:57:57.670 --> 00:57:59.270 interesting data that even in

NOTE Confidence: 0.9967516

00:57:59.270 --> 00:58:00.569 sporadic disease,

NOTE Confidence: 0.9542954

00:58:00.950 --> 00:58:03.349 GBA levels are down even

NOTE Confidence: 0.9542954

00:58:03.349 --> 00:58:05.030 though there's no mutation in

NOTE Confidence: 0.9542954

00:58:05.030 --> 00:58:05.865 those patients,

NOTE Confidence: 0.9309717

00:58:06.325 --> 00:58:08.565 and that glucosal sphingosine, which

NOTE Confidence: 0.9309717

00:58:08.565 --> 00:58:10.485 is the biomarker of GBA

NOTE Confidence: 0.9309717

00:58:10.485 --> 00:58:11.865 deficiency, is high.

NOTE Confidence: 0.98549986

00:58:12.245 --> 00:58:13.225 So there is

NOTE Confidence: 0.98565865

00:58:13.765 --> 00:58:15.945 talk of trying these therapies

NOTE Confidence: 0.6970152

00:58:16.485 --> 00:58:17.610 also on sporadic.

NOTE Confidence: 0.92631143

00:58:18.810 --> 00:58:19.850 So and I think I

NOTE Confidence: 0.92631143

00:58:19.850 --> 00:58:21.450 would support that. I think

NOTE Confidence: 0.92631143

00:58:21.450 --> 00:58:22.890 the data to date would

NOTE Confidence: 0.92631143

00:58:22.890 --> 00:58:24.650 suggest that it would or

NOTE Confidence: 0.92631143

00:58:24.650 --> 00:58:26.190 maybe, Clemens, you think so?

NOTE Confidence: 0.90453154

00:58:26.570 --> 00:58:27.930 Is that yeah. Right? Yeah.

NOTE Confidence: 0.90453154

00:58:27.930 --> 00:58:29.210 That it would be to

NOTE Confidence: 0.90453154

00:58:29.210 --> 00:58:32.010 treat increase GK's activity even

NOTE Confidence: 0.90453154

00:58:32.010 --> 00:58:34.175 in sporadic would be would

NOTE Confidence: 0.90453154

00:58:34.175 --> 00:58:35.395 be my thought. Yeah.

NOTE Confidence: 0.60676897

00:58:36.895 --> 00:58:37.395 Congratulations

NOTE Confidence: 0.85414153

00:58:38.175 --> 00:58:39.615 to the wonderful dog and

NOTE Confidence: 0.85414153

00:58:39.615 --> 00:58:41.055 the awesome new paper. That's

NOTE Confidence: 0.85414153

00:58:41.055 --> 00:58:41.955 really great.

NOTE Confidence: 0.9791356

00:58:42.895 --> 00:58:44.335 I'd be curious if you

NOTE Confidence: 0.9791356

00:58:44.335 --> 00:58:45.235 could hypothesize

NOTE Confidence: 0.9390947

00:58:46.095 --> 00:58:47.395 how on a molecular,

NOTE Confidence: 0.9641797

00:58:47.775 --> 00:58:49.930 you know, precise level do

NOTE Confidence: 0.9641797

00:58:49.930 --> 00:58:50.590 you think,

NOTE Confidence: 0.8755096

00:58:51.690 --> 00:58:54.270 reduced g, GK's function

NOTE Confidence: 0.9578966

00:58:54.810 --> 00:58:55.950 impacts endocytosis?

NOTE Confidence: 0.9737037

00:58:57.050 --> 00:58:58.650 Yeah. So, I mean, I

NOTE Confidence: 0.9737037

00:58:58.650 --> 00:59:00.030 don't have a good answer.

NOTE Confidence: 0.9737037

00:59:00.090 --> 00:59:01.470 I mean, I think, currently,

NOTE Confidence: 0.9737037

00:59:01.530 --> 00:59:02.910 we're gonna see whether,

NOTE Confidence: 0.95526063

00:59:04.035 --> 00:59:05.875 if we're gonna purify vesicles

NOTE Confidence: 0.95526063

00:59:05.875 --> 00:59:06.934 from these mice

NOTE Confidence: 0.9825769

00:59:07.234 --> 00:59:08.214 and look at

NOTE Confidence: 0.92241144

00:59:08.675 --> 00:59:10.535 sort of unbiased lipidomics

NOTE Confidence: 0.9661064

00:59:10.835 --> 00:59:11.875 to see if that's the

NOTE Confidence: 0.9661064

00:59:11.875 --> 00:59:12.375 case.

NOTE Confidence: 0.94043845

00:59:12.994 --> 00:59:14.515 If that's we don't get

NOTE Confidence: 0.94043845

00:59:14.515 --> 00:59:16.035 clean answers there, then we

NOTE Confidence: 0.94043845

00:59:16.035 --> 00:59:17.980 have to really think. We

NOTE Confidence: 0.94043845

00:59:17.980 --> 00:59:19.500 we can get some insights

NOTE Confidence: 0.94043845

00:59:19.500 --> 00:59:20.400 from the transcriptional

NOTE Confidence: 0.96996146

00:59:21.340 --> 00:59:23.020 signatures. But right now, I

NOTE Confidence: 0.96996146

00:59:23.020 --> 00:59:25.120 don't have a clear answer.

NOTE Confidence: 0.96996146

00:59:25.340 --> 00:59:26.220 I wish I had a

NOTE Confidence: 0.96996146

00:59:26.220 --> 00:59:27.420 clear answer. I don't know

NOTE Confidence: 0.96996146

00:59:27.420 --> 00:59:28.640 that. Yeah. Yeah. Sorry.

NOTE Confidence: 0.89715785

00:59:29.355 --> 00:59:30.875 I don't The APOE I

NOTE Confidence: 0.89715785

00:59:30.875 --> 00:59:32.075 mean, it seems like APOE

NOTE Confidence: 0.89715785

00:59:32.075 --> 00:59:33.215 is also quite strong.

NOTE Confidence: 0.7051356

00:59:33.994 --> 00:59:35.535 Yes. Yes. Yes. You realize

NOTE Confidence: 0.7051356

00:59:35.595 --> 00:59:36.895 how strong about it.

NOTE Confidence: 0.8892021

00:59:37.515 --> 00:59:38.475 But you you think it's

NOTE Confidence: 0.8892021

00:59:38.475 --> 00:59:39.375 also lipid

NOTE Confidence: 0.873343

00:59:39.675 --> 00:59:40.175 mediated

NOTE Confidence: 0.8399741

00:59:40.475 --> 00:59:41.994 or because in Alzheimer's, it

NOTE Confidence: 0.8399741

00:59:41.994 --> 00:59:43.755 is still unclear what APOE

NOTE Confidence: 0.94427985

00:59:44.155 --> 00:59:45.810 is it affecting amyloid plaques?

NOTE Confidence: 0.94427985

00:59:45.810 --> 00:59:46.550 Is it affecting

NOTE Confidence: 0.9660569

00:59:46.930 --> 00:59:47.430 inflammation

NOTE Confidence: 0.74401844

00:59:48.210 --> 00:59:50.470 or directly on the synapses?

NOTE Confidence: 0.74401844

00:59:50.690 --> 00:59:51.750 So it's very confusing.

NOTE Confidence: 0.8902458

00:59:52.370 --> 00:59:53.810 I I You think there's

NOTE Confidence: 0.8902458

00:59:53.810 --> 00:59:55.250 any more clarity there? No.

NOTE Confidence: 0.8902458

00:59:55.250 --> 00:59:56.370 It's I don't think we

NOTE Confidence: 0.8902458

00:59:56.370 --> 00:59:57.570 have many because, you know,

NOTE Confidence: 0.8902458

00:59:57.570 --> 00:59:59.270 it's a two thing. One,

NOTE Confidence: 0.9979806

00:59:59.615 --> 01:00:00.674 you know, there is

NOTE Confidence: 0.9570242

01:00:01.135 --> 01:00:02.734 increased certain lipids, but there's

NOTE Confidence: 0.9570242

01:00:02.734 --> 01:00:04.755 a deficiency of other lipids

NOTE Confidence: 0.9024057

01:00:05.055 --> 01:00:06.895 and the lysosome down function.

NOTE Confidence: 0.9024057

01:00:06.895 --> 01:00:08.174 It's a it's not a

NOTE Confidence: 0.9024057

01:00:08.414 --> 01:00:09.694 and also I didn't talk

NOTE Confidence: 0.9024057

01:00:09.694 --> 01:00:10.994 about this, but GBA

NOTE Confidence: 0.97085404

01:00:11.454 --> 01:00:11.954 in

NOTE Confidence: 0.96403354

01:00:12.510 --> 01:00:14.110 immune cells does all kinds

NOTE Confidence: 0.96403354

01:00:14.110 --> 01:00:15.810 of things. So it's,

NOTE Confidence: 0.9630469

01:00:16.910 --> 01:00:18.190 I'm sort of looking very

NOTE Confidence: 0.9630469

01:00:18.190 --> 01:00:19.790 neurocentric, but I don't think

NOTE Confidence: 0.9630469

01:00:19.790 --> 01:00:21.250 that is actually the truth.

NOTE Confidence: 0.842853

01:00:21.630 --> 01:00:23.710 Yes, sir. Yeah. Okay. You

NOTE Confidence: 0.842853

01:00:23.710 --> 01:00:25.070 you just mentioned it, but

NOTE Confidence: 0.842853

01:00:25.070 --> 01:00:25.230 the

NOTE Confidence: 0.8948659

01:00:25.985 --> 01:00:27.265 like, if the main cell

NOTE Confidence: 0.8948659

01:00:27.265 --> 01:00:28.465 type is the main cell

NOTE Confidence: 0.8948659

01:00:28.465 --> 01:00:29.905 type in Gaucher disease that's

NOTE Confidence: 0.8948659

01:00:29.905 --> 01:00:31.845 affected to some macrophages Yep.

NOTE Confidence: 0.8215922

01:00:32.465 --> 01:00:33.445 So, like,

NOTE Confidence: 0.9355599

01:00:33.905 --> 01:00:35.445 what's the root of micro,

NOTE Confidence: 0.9744932

01:00:36.545 --> 01:00:37.045 microglia

NOTE Confidence: 0.85304385

01:00:37.345 --> 01:00:39.205 in the brain and, like,

NOTE Confidence: 0.9341017

01:00:40.290 --> 01:00:42.710 Yeah. We're we're, we are

NOTE Confidence: 0.91657466

01:00:43.010 --> 01:00:44.290 just beginning to look at

NOTE Confidence: 0.91657466

01:00:44.290 --> 01:00:45.250 that. There are other you

NOTE Confidence: 0.91657466

01:00:45.250 --> 01:00:46.770 know, Prime Mysteries Lab has

NOTE Confidence: 0.91657466

01:00:46.770 --> 01:00:48.370 looked at that, and they

NOTE Confidence: 0.91657466

01:00:48.370 --> 01:00:49.270 find that,

NOTE Confidence: 0.99842453

01:00:50.290 --> 01:00:50.790 microglia

NOTE Confidence: 0.7242725

01:00:51.170 --> 01:00:51.670 inflamed.

NOTE Confidence: 0.9491534

01:00:52.130 --> 01:00:52.630 There's

NOTE Confidence: 0.89219403

01:00:53.545 --> 01:00:54.825 there's you know, it's a

NOTE Confidence: 0.89219403

01:00:54.825 --> 01:00:57.145 complex one. David David wouldn't

NOTE Confidence: 0.89219403

01:00:57.145 --> 01:00:58.765 have access to those criteria.

NOTE Confidence: 0.89219403

01:00:58.985 --> 01:01:00.205 Does she behave a nutrition?

NOTE Confidence: 0.89219403

01:01:00.345 --> 01:01:01.785 Yes. Yes. Very much so.

NOTE Confidence: 0.89219403

01:01:01.785 --> 01:01:02.985 And that's why this you

NOTE Confidence: 0.89219403

01:01:02.985 --> 01:01:04.345 know, that's how they stain

NOTE Confidence: 0.89219403

01:01:04.345 --> 01:01:05.865 for them. They do they

NOTE Confidence: 0.89219403

01:01:05.865 --> 01:01:07.065 are called Gaucher cell. They're

NOTE Confidence: 0.89219403

01:01:07.065 --> 01:01:08.045 staining for

NOTE Confidence: 0.81621003

01:01:08.550 --> 01:01:10.310 macrophages that have full of

NOTE Confidence: 0.81621003

01:01:10.310 --> 01:01:11.750 lipid in them. So it's

NOTE Confidence: 0.81621003

01:01:11.750 --> 01:01:13.830 such a prominent phenylalanine. That

NOTE Confidence: 0.81621003

01:01:13.830 --> 01:01:15.510 they can use it. And

NOTE Confidence: 0.81621003

01:01:15.510 --> 01:01:16.870 also they have, you know,

NOTE Confidence: 0.81621003

01:01:16.870 --> 01:01:18.970 liver enlargement as Yes.

NOTE Confidence: 0.87826794

01:01:20.790 --> 01:01:22.390 One common thing among all

NOTE Confidence: 0.87826794

01:01:22.390 --> 01:01:24.010 of these is the autophagy.

NOTE Confidence: 0.93316483

01:01:24.444 --> 01:01:25.265 Yes. That's correct.

NOTE Confidence: 0.9339501

01:01:26.204 --> 01:01:27.025 Where you have

NOTE Confidence: 0.8407507

01:01:27.325 --> 01:01:28.765 proteins and the lipids and

NOTE Confidence: 0.8407507

01:01:28.765 --> 01:01:30.545 everything, and that's that's overwhelmed,

NOTE Confidence: 0.9349644

01:01:31.164 --> 01:01:31.984 then the

NOTE Confidence: 0.7556917

01:01:32.365 --> 01:01:33.724 secondary thing would be that

NOTE Confidence: 0.7556917

01:01:33.724 --> 01:01:34.605 the people tend to

NOTE Confidence: 0.979226

01:01:35.405 --> 01:01:36.765 this is this is correct.

NOTE Confidence: 0.979226

01:01:36.765 --> 01:01:38.065 There's a lot of autophagy

NOTE Confidence: 0.18076049

01:01:38.365 --> 01:01:38.700 finis

NOTE Confidence: 0.8295574

01:01:39.500 --> 01:01:41.119 phenotypes or in other, like,

NOTE Confidence: 0.8295574

01:01:41.339 --> 01:01:43.440 stem cell derived neuronal models.

NOTE Confidence: 0.926649

01:01:43.820 --> 01:01:46.240 And you could manipulate those

NOTE Confidence: 0.926649

01:01:46.380 --> 01:01:48.220 to to get some, at

NOTE Confidence: 0.926649

01:01:48.220 --> 01:01:49.420 least in a in in

NOTE Confidence: 0.926649

01:01:49.420 --> 01:01:51.280 vitro system, some benefit.

NOTE Confidence: 0.99350905

01:01:51.820 --> 01:01:53.119 Whether that will work

NOTE Confidence: 0.9799577

01:01:53.755 --> 01:01:55.835 in vivo, I don't know.

NOTE Confidence: 0.9799577

01:01:55.835 --> 01:01:57.595 No. It's not it's it's

NOTE Confidence: 0.9799577

01:01:57.994 --> 01:01:59.755 I should say that there

NOTE Confidence: 0.9799577

01:01:59.755 --> 01:02:00.734 is some data

NOTE Confidence: 0.99569863

01:02:01.275 --> 01:02:02.415 that all lysosomal

NOTE Confidence: 0.9533883

01:02:02.715 --> 01:02:03.775 storage diseases

NOTE Confidence: 0.7745258

01:02:04.075 --> 01:02:05.675 actually increase the risk for

NOTE Confidence: 0.7745258

01:02:05.675 --> 01:02:06.175 Parkinson's.

NOTE Confidence: 0.63552445

01:02:06.760 --> 01:02:08.620 It just negotiated a very

NOTE Confidence: 0.63552445

01:02:08.840 --> 01:02:09.340 prevalent

NOTE Confidence: 0.9966634

01:02:09.880 --> 01:02:10.380 lysosomal

NOTE Confidence: 0.8215417

01:02:10.760 --> 01:02:12.680 storage disease. And in other

NOTE Confidence: 0.8215417

01:02:12.680 --> 01:02:13.180 diseases,

NOTE Confidence: 0.79683006

01:02:13.640 --> 01:02:15.420 it's also much more fatal

NOTE Confidence: 0.79683006

01:02:15.560 --> 01:02:16.840 early on that they don't

NOTE Confidence: 0.79683006

01:02:16.840 --> 01:02:18.460 have. Yes. So yes.

NOTE Confidence: 0.79691964

01:02:19.640 --> 01:02:20.780 Yeah. No. Congratulation.

NOTE Confidence: 0.83786327

01:02:22.135 --> 01:02:23.655 But it's still being a

NOTE Confidence: 0.83786327

01:02:23.655 --> 01:02:25.495 career for GPA is a

NOTE Confidence: 0.83786327

01:02:25.495 --> 01:02:26.555 is a predisposition.

NOTE Confidence: 0.89629555

01:02:27.015 --> 01:02:28.855 Yeah. And it's, do you

NOTE Confidence: 0.89629555

01:02:28.855 --> 01:02:30.935 have any insight about genetic

NOTE Confidence: 0.89629555

01:02:30.935 --> 01:02:31.435 modifiers

NOTE Confidence: 0.9330704

01:02:31.815 --> 01:02:33.335 either in human or brain?

NOTE Confidence: 0.9330704

01:02:33.335 --> 01:02:34.695 Yeah. So the I didn't

NOTE Confidence: 0.9330704

01:02:34.695 --> 01:02:36.215 clarify this, but that what

NOTE Confidence: 0.9330704

01:02:36.215 --> 01:02:37.335 she brings up is a

NOTE Confidence: 0.9330704

01:02:37.335 --> 01:02:39.270 very important question. Is that,

NOTE Confidence: 0.999318

01:02:40.849 --> 01:02:41.670 not everybody

NOTE Confidence: 0.97300833

01:02:41.970 --> 01:02:44.690 who has GBM mutations will

NOTE Confidence: 0.97300833

01:02:44.690 --> 01:02:45.829 develop Parkinson.

NOTE Confidence: 0.9673083

01:02:46.770 --> 01:02:49.089 There's very strong genetic and

NOTE Confidence: 0.9673083

01:02:49.089 --> 01:02:50.950 even within the Gaucher, forget

NOTE Confidence: 0.9673083

01:02:51.010 --> 01:02:53.190 Parkinson, there's a huge phenotypic

NOTE Confidence: 0.98851544

01:02:53.655 --> 01:02:55.095 variability that you could be

NOTE Confidence: 0.98851544

01:02:55.095 --> 01:02:55.595 homozygous

NOTE Confidence: 0.9278114

01:02:55.975 --> 01:02:57.355 for l triple four p,

NOTE Confidence: 0.9278114

01:02:57.415 --> 01:02:59.335 but not actually only come

NOTE Confidence: 0.9278114

01:02:59.335 --> 01:03:00.795 to the clinic for Parkinson,

NOTE Confidence: 0.9278114

01:03:00.935 --> 01:03:02.295 you know, that you made

NOTE Confidence: 0.9278114

01:03:02.295 --> 01:03:03.895 it all through childhood just

NOTE Confidence: 0.9278114

01:03:03.895 --> 01:03:06.295 fine. In partly because the

NOTE Confidence: 0.9278114

01:03:06.295 --> 01:03:06.795 sphingolipid

NOTE Confidence: 0.9674345

01:03:07.690 --> 01:03:09.930 metabolism pathway is highly hairy

NOTE Confidence: 0.9674345

01:03:09.930 --> 01:03:10.670 and complex

NOTE Confidence: 0.9283938

01:03:10.970 --> 01:03:12.170 and that there are many

NOTE Confidence: 0.9283938

01:03:12.170 --> 01:03:12.670 modifiers.

NOTE Confidence: 0.92686015

01:03:13.210 --> 01:03:14.250 So there have been a

NOTE Confidence: 0.92686015

01:03:14.250 --> 01:03:16.110 huge quest to find modifiers,

NOTE Confidence: 0.99768203

01:03:16.970 --> 01:03:18.570 because they would make the

NOTE Confidence: 0.99768203

01:03:18.570 --> 01:03:19.630 perfect therapeutic

NOTE Confidence: 0.9044351

01:03:20.295 --> 01:03:22.214 target because in humans, they're

NOTE Confidence: 0.9044351

01:03:22.214 --> 01:03:22.714 actually

NOTE Confidence: 0.97320825

01:03:23.095 --> 01:03:24.155 modifying the disease.

NOTE Confidence: 0.99411494

01:03:24.615 --> 01:03:25.115 And

NOTE Confidence: 0.9879685

01:03:25.575 --> 01:03:26.775 we are also looking for

NOTE Confidence: 0.9879685

01:03:26.775 --> 01:03:27.275 those.

NOTE Confidence: 0.85848546

01:03:27.734 --> 01:03:28.875 We have a couple.

NOTE Confidence: 0.87345725

01:03:29.734 --> 01:03:30.694 We're not ready for a

NOTE Confidence: 0.87345725

01:03:30.694 --> 01:03:32.234 short time. But, you know,

NOTE Confidence: 0.87345725

01:03:32.375 --> 01:03:34.135 Dimitri Crunk's lab has done

NOTE Confidence: 0.87345725

01:03:34.135 --> 01:03:35.415 a lot on that front,

NOTE Confidence: 0.87345725

01:03:35.415 --> 01:03:36.960 and they found recently a

NOTE Confidence: 0.87345725

01:03:36.960 --> 01:03:38.240 command Khan's labs.

NOTE Confidence: 0.81838095

01:03:39.200 --> 01:03:41.380 Controls GK's activity in duets.

NOTE Confidence: 0.9518155

01:03:42.560 --> 01:03:43.700 And I think that

NOTE Confidence: 0.8627813

01:03:44.000 --> 01:03:45.220 therein will be

NOTE Confidence: 0.94095397

01:03:45.920 --> 01:03:46.900 new leads to

NOTE Confidence: 0.7580697

01:03:51.745 --> 01:03:52.245 This

NOTE Confidence: 0.98276436

01:03:52.545 --> 01:03:53.365 is exclusively

NOTE Confidence: 0.6530211

01:03:53.665 --> 01:03:55.365 seen in non neuropathic

NOTE Confidence: 0.8384626

01:03:57.025 --> 01:03:57.525 forms.

NOTE Confidence: 0.9178182

01:03:57.905 --> 01:03:58.785 That's it. Oh, yeah. Yeah.

NOTE Confidence: 0.9178182

01:03:58.785 --> 01:04:00.305 You're right. Okay. I didn't

NOTE Confidence: 0.9178182

01:04:00.305 --> 01:04:01.605 go into this either.

NOTE Confidence: 0.93728036

01:04:02.305 --> 01:04:03.985 But then yes. Because the

NOTE Confidence: 0.93728036

01:04:03.985 --> 01:04:04.485 neuropathic

NOTE Confidence: 0.85556096

01:04:04.800 --> 01:04:06.240 form, there are three forms

NOTE Confidence: 0.85556096

01:04:06.240 --> 01:04:06.900 of negotiate.

NOTE Confidence: 0.96891546

01:04:07.280 --> 01:04:08.800 Like, type one, type two,

NOTE Confidence: 0.96891546

01:04:08.800 --> 01:04:09.840 and type three, which is

NOTE Confidence: 0.96891546

01:04:09.840 --> 01:04:10.580 the neuropathic

NOTE Confidence: 0.7732627

01:04:10.880 --> 01:04:12.580 form. And after the four

NOTE Confidence: 0.7732627

01:04:12.640 --> 01:04:13.140 imputations

NOTE Confidence: 0.71450424

01:04:13.600 --> 01:04:14.260 are associated

NOTE Confidence: 0.9172118

01:04:14.960 --> 01:04:16.960 with neuropathic function. Yes. Because

NOTE Confidence: 0.9172118

01:04:16.960 --> 01:04:18.880 the neuropathic forms are by

NOTE Confidence: 0.9172118

01:04:18.880 --> 01:04:19.380 large,

NOTE Confidence: 0.99146783

01:04:20.165 --> 01:04:20.665 early

NOTE Confidence: 0.8745685

01:04:21.285 --> 01:04:23.125 infantile child and much more

NOTE Confidence: 0.8745685

01:04:23.125 --> 01:04:23.625 severe.

NOTE Confidence: 0.88886696

01:04:24.484 --> 01:04:26.484 So they don't live long

NOTE Confidence: 0.88886696

01:04:26.484 --> 01:04:27.465 enough. Yeah.

NOTE Confidence: 0.99089193

01:04:33.045 --> 01:04:34.265 Okay. Thank you.