

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 endolysosomal

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 glucocerebrosidase.
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, glucosyl 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 glucosphagolipids
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, phosphocinogreltin

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 glucosyl 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 1 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.