

WEBVTT

NOTE duration: "00:21:43.466"

NOTE Confidence: 0.8267018

00:00:00.480 --> 00:00:03.139 Our next speaker is Srirangachandra,

NOTE Confidence: 0.97293574

00:00:04.640 --> 00:00:05.140 professor

NOTE Confidence: 0.94423103

00:00:05.440 --> 00:00:06.980 in the department of neurology

NOTE Confidence: 0.94423103

00:00:07.040 --> 00:00:07.859 and neuroscience,

NOTE Confidence: 0.9433185

00:00:09.119 --> 00:00:11.039 and she previously trained with

NOTE Confidence: 0.9433185

00:00:11.039 --> 00:00:12.019 Nobel laureate,

NOTE Confidence: 0.9015852

00:00:12.595 --> 00:00:14.935 doctor Tom Sudhoff, and received

NOTE Confidence: 0.9127375

00:00:15.235 --> 00:00:16.935 a PhD actually in chemistry

NOTE Confidence: 0.9815061

00:00:17.555 --> 00:00:19.495 of from Purdue University.

NOTE Confidence: 0.5552976

00:00:21.075 --> 00:00:21.575 Srikanga?

NOTE Confidence: 0.73760235

00:00:24.435 --> 00:00:25.475 Can I just probably take

NOTE Confidence: 0.73760235

00:00:25.475 --> 00:00:26.454 this part back?

NOTE Confidence: 0.9695927

00:00:28.250 --> 00:00:29.130 One of the part back.

NOTE Confidence: 0.9695927

00:00:29.130 --> 00:00:30.169 Right? Are you guys gonna

NOTE Confidence: 0.9695927

00:00:30.169 --> 00:00:31.210 need them? Can you hear
NOTE Confidence: 0.9695927

00:00:31.210 --> 00:00:33.210 me? Okay. So I'd like
NOTE Confidence: 0.9695927

00:00:33.210 --> 00:00:34.890 to begin by thanking and
NOTE Confidence: 0.9695927

00:00:34.890 --> 00:00:35.390 congratulating
NOTE Confidence: 0.9062715

00:00:35.930 --> 00:00:37.530 Clemons on sort of kick
NOTE Confidence: 0.9062715

00:00:37.530 --> 00:00:39.390 starting the Adams and recruiting
NOTE Confidence: 0.9062715

00:00:39.449 --> 00:00:39.854 all
NOTE Confidence: 0.9543085

00:00:40.255 --> 00:00:42.175 faculty. So I'm gonna tell
NOTE Confidence: 0.9543085

00:00:42.175 --> 00:00:44.415 you about synaptic dysfunction in
NOTE Confidence: 0.9543085

00:00:44.415 --> 00:00:45.715 Parkinson's disease.
NOTE Confidence: 0.9959195

00:00:46.895 --> 00:00:48.175 As all of you know,
NOTE Confidence: 0.9959195

00:00:48.175 --> 00:00:50.254 the two hallmarks of the
NOTE Confidence: 0.9959195

00:00:50.254 --> 00:00:51.475 disease are
NOTE Confidence: 0.95240843

00:00:53.920 --> 00:00:55.220 are are the death of
NOTE Confidence: 0.8509459

00:00:56.320 --> 00:00:57.680 neurons in the nigra that
NOTE Confidence: 0.8509459

00:00:57.680 --> 00:00:58.180 project,

NOTE Confidence: 0.82489264

00:00:58.520 --> 00:00:59.920 to the put putamen in

NOTE Confidence: 0.82489264

00:00:59.920 --> 00:01:00.660 the cortex.

NOTE Confidence: 0.9891488

00:01:01.040 --> 00:01:02.820 And as you already heard,

NOTE Confidence: 0.93691134

00:01:03.600 --> 00:01:05.520 Lewy body pathology, which is

NOTE Confidence: 0.93691134

00:01:05.520 --> 00:01:07.220 characterized by this characteristic

NOTE Confidence: 0.9414125

00:01:07.585 --> 00:01:09.745 phosphorylation that's serine one twenty

NOTE Confidence: 0.9414125

00:01:09.745 --> 00:01:10.245 nine.

NOTE Confidence: 0.9929844

00:01:10.865 --> 00:01:13.444 So, the other feature of,

NOTE Confidence: 0.9850063

00:01:13.745 --> 00:01:15.585 sort of early Parkinson's disease

NOTE Confidence: 0.9850063

00:01:15.585 --> 00:01:16.485 is not just,

NOTE Confidence: 0.89761895

00:01:16.944 --> 00:01:18.225 the death of neurons and

NOTE Confidence: 0.89761895

00:01:18.225 --> 00:01:18.725 pathology,

NOTE Confidence: 0.972473

00:01:19.265 --> 00:01:20.085 but also

NOTE Confidence: 0.9760544

00:01:20.680 --> 00:01:22.520 the dying back of these

NOTE Confidence: 0.9760544

00:01:22.520 --> 00:01:23.020 dopenergetic

NOTE Confidence: 0.9045426

00:01:23.319 --> 00:01:23.819 synapses,
NOTE Confidence: 0.9876694

00:01:24.679 --> 00:01:26.280 at the striatum. And this
NOTE Confidence: 0.9876694

00:01:26.280 --> 00:01:27.560 is such a sort of
NOTE Confidence: 0.9876694

00:01:27.560 --> 00:01:28.859 profound and striking,
NOTE Confidence: 0.9806768

00:01:29.880 --> 00:01:31.979 phenotype. It is used clinically
NOTE Confidence: 0.95290446

00:01:32.600 --> 00:01:33.259 to diagnose,
NOTE Confidence: 0.89470696

00:01:33.799 --> 00:01:35.479 early Parkinson's. So as soon
NOTE Confidence: 0.89470696

00:01:35.479 --> 00:01:36.625 as you're diagnosed, you you
NOTE Confidence: 0.89470696

00:01:36.625 --> 00:01:37.065 are,
NOTE Confidence: 0.97796506

00:01:37.505 --> 00:01:38.944 you know, you get imaging,
NOTE Confidence: 0.97796506

00:01:38.944 --> 00:01:39.825 and this is a way
NOTE Confidence: 0.97796506

00:01:39.825 --> 00:01:41.424 of determining for sure that
NOTE Confidence: 0.97796506

00:01:41.424 --> 00:01:42.244 you have Parkinson's.
NOTE Confidence: 0.93553

00:01:43.104 --> 00:01:44.084 And so, traditionally,
NOTE Confidence: 0.9728783

00:01:44.784 --> 00:01:46.164 what has been oh, sorry.
NOTE Confidence: 0.99597293

00:01:46.865 --> 00:01:48.625 Traditionally, what has been used

NOTE Confidence: 0.99597293
00:01:48.625 --> 00:01:49.125 is
NOTE Confidence: 0.9300912
00:01:49.490 --> 00:01:51.009 f eighteen dopa, which is
NOTE Confidence: 0.9300912
00:01:51.009 --> 00:01:52.790 the precursor for dopamine.
NOTE Confidence: 0.9796476
00:01:53.330 --> 00:01:54.369 And, as,
NOTE Confidence: 0.9083527
00:01:55.170 --> 00:01:56.689 dopa is then converted to
NOTE Confidence: 0.9083527
00:01:56.689 --> 00:01:57.189 dopamine
NOTE Confidence: 0.9596963
00:01:57.490 --> 00:01:59.430 and then packaged into synaptic
NOTE Confidence: 0.9596963
00:01:59.490 --> 00:02:01.590 vesicles by the vesicular monoamine
NOTE Confidence: 0.9596963
00:02:01.810 --> 00:02:03.855 transporter, VMAT two. And you
NOTE Confidence: 0.9596963
00:02:03.855 --> 00:02:06.015 can also image VMAT two
NOTE Confidence: 0.9596963
00:02:06.015 --> 00:02:07.875 by using this ligand DTBS.
NOTE Confidence: 0.96435034
00:02:08.575 --> 00:02:09.695 And you can see on
NOTE Confidence: 0.96435034
00:02:09.695 --> 00:02:11.235 the top panels are healthy,
NOTE Confidence: 0.9709304
00:02:12.175 --> 00:02:13.615 healthy imaging, and then the
NOTE Confidence: 0.9709304
00:02:13.615 --> 00:02:15.055 bottom is PD. And you
NOTE Confidence: 0.9709304

00:02:15.055 --> 00:02:16.335 can see that the disease
NOTE Confidence: 0.9709304

00:02:16.335 --> 00:02:16.835 starts
NOTE Confidence: 0.9941161

00:02:17.180 --> 00:02:17.680 asymmetrically
NOTE Confidence: 0.9393239

00:02:18.060 --> 00:02:19.440 in the in patients,
NOTE Confidence: 0.97860515

00:02:19.980 --> 00:02:21.340 typically on one side. And
NOTE Confidence: 0.97860515

00:02:21.340 --> 00:02:22.460 you can see that there's
NOTE Confidence: 0.97860515

00:02:22.460 --> 00:02:23.680 a loss of both
NOTE Confidence: 0.84697455

00:02:24.139 --> 00:02:25.919 f dopa and d, DTBS,
NOTE Confidence: 0.99776316

00:02:26.540 --> 00:02:27.040 staining.
NOTE Confidence: 0.99436164

00:02:27.419 --> 00:02:28.300 And the other,
NOTE Confidence: 0.9576976

00:02:28.700 --> 00:02:30.460 other way to monitor this
NOTE Confidence: 0.9576976

00:02:30.460 --> 00:02:32.125 sort of both the dysfunction
NOTE Confidence: 0.9576976

00:02:32.345 --> 00:02:34.285 and the loss of, termini
NOTE Confidence: 0.9576976

00:02:34.505 --> 00:02:35.405 early in disease
NOTE Confidence: 0.96806824

00:02:35.705 --> 00:02:36.425 is using,
NOTE Confidence: 0.9368499

00:02:36.905 --> 00:02:37.725 DAT imaging.

NOTE Confidence: 0.8805968
00:02:38.105 --> 00:02:39.805 That is the dopamine transporter,
NOTE Confidence: 0.994943
00:02:40.345 --> 00:02:42.044 which is used to reuptake
NOTE Confidence: 0.994943
00:02:42.264 --> 00:02:44.205 dopamine as a clearance mechanism,
NOTE Confidence: 0.9679926
00:02:45.225 --> 00:02:47.460 and, allow for cycling.
NOTE Confidence: 0.9114755
00:02:47.760 --> 00:02:49.440 And so, traditionally, there have
NOTE Confidence: 0.9114755
00:02:49.440 --> 00:02:50.480 been there have been many
NOTE Confidence: 0.9114755
00:02:50.480 --> 00:02:52.919 modalities for imaging this, and,
NOTE Confidence: 0.9114755
00:02:53.280 --> 00:02:54.480 to date now, the DAT
NOTE Confidence: 0.9114755
00:02:54.480 --> 00:02:55.780 scan, which is this,
NOTE Confidence: 0.9581131
00:02:56.320 --> 00:02:57.919 iodine one twenty three,
NOTE Confidence: 0.5340257
00:02:58.320 --> 00:02:58.720 iron,
NOTE Confidence: 0.9558487
00:03:00.685 --> 00:03:02.764 ligand is traditionally used now
NOTE Confidence: 0.9558487
00:03:02.764 --> 00:03:03.505 to identify,
NOTE Confidence: 0.9996606
00:03:04.605 --> 00:03:05.425 new patients
NOTE Confidence: 0.911384
00:03:05.885 --> 00:03:07.805 for, for with which have
NOTE Confidence: 0.911384

00:03:07.805 --> 00:03:08.465 a Parkinson's.
NOTE Confidence: 0.9318214

00:03:10.365 --> 00:03:11.965 So there's a now new
NOTE Confidence: 0.9318214

00:03:11.965 --> 00:03:14.044 brand new imaging modality, actually,
NOTE Confidence: 0.9318214

00:03:14.044 --> 00:03:16.180 which is pioneered here, which
NOTE Confidence: 0.9318214

00:03:16.180 --> 00:03:17.480 is called UCBJ.
NOTE Confidence: 0.9643039

00:03:18.180 --> 00:03:19.300 And this is a study
NOTE Confidence: 0.9643039

00:03:19.300 --> 00:03:21.459 by David Matuski's lab in
NOTE Confidence: 0.9643039

00:03:21.459 --> 00:03:21.959 psychiatry.
NOTE Confidence: 0.98275566

00:03:22.500 --> 00:03:23.940 And this is a ligand
NOTE Confidence: 0.98275566

00:03:23.940 --> 00:03:26.180 that actually just looks which
NOTE Confidence: 0.98275566

00:03:26.180 --> 00:03:28.485 binds the synaptic vesicle. So
NOTE Confidence: 0.98275566

00:03:28.485 --> 00:03:30.004 this is not specific only
NOTE Confidence: 0.98275566

00:03:30.004 --> 00:03:31.764 for dopamine, but just all,
NOTE Confidence: 0.98275566

00:03:32.084 --> 00:03:33.305 all synaptic vesicles,
NOTE Confidence: 0.9260955

00:03:33.764 --> 00:03:34.965 and it binds s v
NOTE Confidence: 0.9260955

00:03:34.965 --> 00:03:36.485 two. And even in using

NOTE Confidence: 0.9260955

00:03:36.485 --> 00:03:37.224 a generic,

NOTE Confidence: 0.99686253

00:03:38.245 --> 00:03:40.325 synaptic vesicle marker, you can

NOTE Confidence: 0.99686253

00:03:40.325 --> 00:03:41.545 see that in the

NOTE Confidence: 0.87228656

00:03:42.170 --> 00:03:42.910 in Parkinson's

NOTE Confidence: 0.9254046

00:03:43.210 --> 00:03:45.130 patients, there's less signal, and

NOTE Confidence: 0.9254046

00:03:45.130 --> 00:03:46.170 this is sort of s

NOTE Confidence: 0.9254046

00:03:46.170 --> 00:03:48.190 v two density actually correlates

NOTE Confidence: 0.9819708

00:03:48.650 --> 00:03:50.350 very nicely with movement,

NOTE Confidence: 0.8233696

00:03:51.770 --> 00:03:53.470 severity in these patients.

NOTE Confidence: 0.9224603

00:03:54.755 --> 00:03:56.275 So so the question really

NOTE Confidence: 0.9224603

00:03:56.275 --> 00:03:57.395 is and that what one

NOTE Confidence: 0.9224603

00:03:57.395 --> 00:03:58.835 of the questions that animates

NOTE Confidence: 0.9224603

00:03:58.835 --> 00:04:00.455 us is to figure out

NOTE Confidence: 0.9224603

00:04:00.595 --> 00:04:02.855 why are synapses being dysfunctional

NOTE Confidence: 0.97600883

00:04:03.155 --> 00:04:04.775 and lost in the disease.

NOTE Confidence: 0.97600883

00:04:04.835 --> 00:04:06.775 And this holds the promise
NOTE Confidence: 0.97600883

00:04:06.835 --> 00:04:07.495 of actually
NOTE Confidence: 0.9756617

00:04:08.280 --> 00:04:10.520 disease modifying therapies because this
NOTE Confidence: 0.9756617

00:04:10.520 --> 00:04:12.300 is occurring in the prodromal
NOTE Confidence: 0.9756617

00:04:12.520 --> 00:04:13.500 phase of the disease
NOTE Confidence: 0.966671

00:04:13.800 --> 00:04:15.740 even before the onset of
NOTE Confidence: 0.6776908

00:04:16.120 --> 00:04:16.620 movement,
NOTE Confidence: 0.79116344

00:04:18.040 --> 00:04:19.020 you know, deficits.
NOTE Confidence: 0.9229376

00:04:19.400 --> 00:04:20.520 And therefore, if we can
NOTE Confidence: 0.9229376

00:04:20.520 --> 00:04:21.900 understand these mechanisms,
NOTE Confidence: 0.9839107

00:04:22.534 --> 00:04:23.735 it holds the promise of
NOTE Confidence: 0.9839107

00:04:23.735 --> 00:04:25.115 sort of disease modifying,
NOTE Confidence: 0.99632466

00:04:26.134 --> 00:04:26.634 therapy.
NOTE Confidence: 0.97558784

00:04:27.414 --> 00:04:28.955 So we are getting clues
NOTE Confidence: 0.97558784

00:04:29.014 --> 00:04:30.935 to understand this from the
NOTE Confidence: 0.97558784

00:04:30.935 --> 00:04:32.474 genetics. So as,

NOTE Confidence: 0.99875236

00:04:32.854 --> 00:04:34.314 was alluded to earlier,

NOTE Confidence: 0.93649024

00:04:34.699 --> 00:04:36.620 Pietro and I study familial

NOTE Confidence: 0.93649024

00:04:36.620 --> 00:04:38.560 genes and really big risk

NOTE Confidence: 0.93649024

00:04:38.620 --> 00:04:40.060 genes because we can model

NOTE Confidence: 0.93649024

00:04:40.060 --> 00:04:41.760 them readily in the lab.

NOTE Confidence: 0.9881096

00:04:42.380 --> 00:04:43.199 And so

NOTE Confidence: 0.81084746

00:04:43.660 --> 00:04:45.600 it includes that that indeed,

NOTE Confidence: 0.9239249

00:04:46.220 --> 00:04:48.160 why why are synapses dysfunctioning

NOTE Confidence: 0.9239249

00:04:48.300 --> 00:04:50.265 from the genetics? So as

NOTE Confidence: 0.9239249

00:04:50.265 --> 00:04:51.865 this was shown earlier on

NOTE Confidence: 0.9239249

00:04:52.025 --> 00:04:53.385 here is the FX size.

NOTE Confidence: 0.9239249

00:04:53.385 --> 00:04:55.145 So on the very top

NOTE Confidence: 0.9239249

00:04:55.145 --> 00:04:56.985 quartered are familial genes. There

NOTE Confidence: 0.9239249

00:04:56.985 --> 00:04:58.845 are twenty four familial genes.

NOTE Confidence: 0.9239249

00:04:59.145 --> 00:05:00.345 And then there are two

NOTE Confidence: 0.9239249

00:05:00.345 --> 00:05:02.125 medium to high risk allele,
NOTE Confidence: 0.9239249

00:05:02.185 --> 00:05:02.685 GBLERB
NOTE Confidence: 0.94143397

00:05:03.000 --> 00:05:04.200 two, which you've already heard
NOTE Confidence: 0.94143397

00:05:04.200 --> 00:05:05.880 about, and then all the
NOTE Confidence: 0.94143397

00:05:05.880 --> 00:05:07.260 many genes that,
NOTE Confidence: 0.98179245

00:05:07.800 --> 00:05:09.320 that are risk alleles that
NOTE Confidence: 0.98179245

00:05:09.320 --> 00:05:10.279 are shown in this,
NOTE Confidence: 0.9937695

00:05:10.839 --> 00:05:11.740 bottom cluster.
NOTE Confidence: 0.91017354

00:05:12.200 --> 00:05:14.279 So in here, listed the
NOTE Confidence: 0.91017354

00:05:14.279 --> 00:05:15.880 genes and the gene name
NOTE Confidence: 0.91017354

00:05:15.880 --> 00:05:17.480 and the proteins, the encode
NOTE Confidence: 0.91017354

00:05:17.480 --> 00:05:18.460 that are actually
NOTE Confidence: 0.949563

00:05:19.154 --> 00:05:20.535 functioning at the presynaptic.
NOTE Confidence: 0.972691

00:05:21.154 --> 00:05:22.275 So I should add that
NOTE Confidence: 0.972691

00:05:22.275 --> 00:05:23.015 in Parkinson's,
NOTE Confidence: 0.9738598

00:05:23.714 --> 00:05:25.955 the vast majority of,

NOTE Confidence: 0.4802398
00:05:26.355 --> 00:05:26.855 effects
NOTE Confidence: 0.988238
00:05:27.315 --> 00:05:28.595 of the synapse are occurring
NOTE Confidence: 0.988238
00:05:28.595 --> 00:05:29.415 on the presynaptic
NOTE Confidence: 0.92878246
00:05:29.795 --> 00:05:31.895 side and actually not surprisingly
NOTE Confidence: 0.92878246
00:05:32.115 --> 00:05:34.100 on the postsynaptic side. So
NOTE Confidence: 0.92878246
00:05:34.100 --> 00:05:35.380 the genes that are shown
NOTE Confidence: 0.92878246
00:05:35.380 --> 00:05:37.060 here, you've already heard of
NOTE Confidence: 0.92878246
00:05:37.060 --> 00:05:37.880 alpha synuclein,
NOTE Confidence: 0.94088423
00:05:38.740 --> 00:05:40.100 oxalin, which you heard of
NOTE Confidence: 0.94088423
00:05:40.100 --> 00:05:40.900 in the form of a
NOTE Confidence: 0.94088423
00:05:40.900 --> 00:05:42.680 circular RNA, synaptogenin,
NOTE Confidence: 0.95543385
00:05:43.140 --> 00:05:45.380 which, Pietro works on. And
NOTE Confidence: 0.95543385
00:05:45.380 --> 00:05:47.025 so some of these obviously,
NOTE Confidence: 0.95543385
00:05:47.025 --> 00:05:48.385 like Lerp two also work
NOTE Confidence: 0.95543385
00:05:48.385 --> 00:05:49.745 on the lysosome, but also
NOTE Confidence: 0.95543385

00:05:49.745 --> 00:05:51.585 have impacts on synaptic function,
NOTE Confidence: 0.95543385

00:05:51.585 --> 00:05:52.625 but the ones in red
NOTE Confidence: 0.95543385

00:05:52.625 --> 00:05:54.165 are exclusively presynaptic.
NOTE Confidence: 0.96843153

00:05:55.265 --> 00:05:56.545 So today, I wanna sort
NOTE Confidence: 0.96843153

00:05:56.545 --> 00:05:57.445 of tell you,
NOTE Confidence: 0.9970969

00:05:57.985 --> 00:05:59.285 sort of three vignettes
NOTE Confidence: 0.9849332

00:05:59.790 --> 00:06:01.230 using these genes and trying
NOTE Confidence: 0.9849332

00:06:01.230 --> 00:06:02.750 to understand how these,
NOTE Confidence: 0.95374376

00:06:03.150 --> 00:06:05.650 genes impact actually synaptic function
NOTE Confidence: 0.95374376

00:06:05.790 --> 00:06:07.070 and sort of relate to
NOTE Confidence: 0.95374376

00:06:07.070 --> 00:06:09.169 you there's a convergence of
NOTE Confidence: 0.95374376

00:06:09.389 --> 00:06:11.389 pathways among these various genes
NOTE Confidence: 0.95374376

00:06:11.389 --> 00:06:13.470 that actually impact, synaptic terms.
NOTE Confidence: 0.95374376

00:06:13.470 --> 00:06:14.685 I'm gonna tell you about
NOTE Confidence: 0.95374376

00:06:14.845 --> 00:06:15.665 alpha synuclein,
NOTE Confidence: 0.90003693

00:06:16.365 --> 00:06:17.885 which is and then DNA

NOTE Confidence: 0.90003693
00:06:17.885 --> 00:06:19.665 j six, which encodes oxalate,
NOTE Confidence: 0.89980596
00:06:20.125 --> 00:06:21.725 and then GBA, which is
NOTE Confidence: 0.89980596
00:06:21.725 --> 00:06:23.725 not a presynaptic gene, exactly,
NOTE Confidence: 0.89980596
00:06:23.725 --> 00:06:25.105 as you've heard, a lysosomal,
NOTE Confidence: 0.9203062
00:06:25.725 --> 00:06:28.445 protein, but actually surprisingly impacts
NOTE Confidence: 0.9203062
00:06:28.445 --> 00:06:29.505 synaptic function.
NOTE Confidence: 0.96675915
00:06:30.839 --> 00:06:32.360 Okay. So let's before I
NOTE Confidence: 0.96675915
00:06:32.360 --> 00:06:33.480 make this case, I wanna
NOTE Confidence: 0.96675915
00:06:33.480 --> 00:06:34.940 make the case that synapses
NOTE Confidence: 0.96675915
00:06:35.240 --> 00:06:37.260 in general are highly vulnerable
NOTE Confidence: 0.96675915
00:06:37.400 --> 00:06:39.640 to synapse loss partly because
NOTE Confidence: 0.96675915
00:06:39.640 --> 00:06:40.460 they're executing
NOTE Confidence: 0.94086677
00:06:41.320 --> 00:06:43.515 the synaptic vesicle cycle, which
NOTE Confidence: 0.9384362
00:06:43.915 --> 00:06:45.915 in a tonically firing synapse
NOTE Confidence: 0.9384362
00:06:45.915 --> 00:06:46.815 like the dopaminergic
NOTE Confidence: 0.9390422

00:06:47.115 --> 00:06:48.875 synapse is occurring many times
NOTE Confidence: 0.9390422

00:06:48.875 --> 00:06:49.535 a second.
NOTE Confidence: 0.99615985

00:06:49.995 --> 00:06:51.515 And so the vesicles have
NOTE Confidence: 0.99615985

00:06:51.515 --> 00:06:52.975 to be filled with neurotransmitter
NOTE Confidence: 0.46262154

00:06:53.355 --> 00:06:53.855 fused
NOTE Confidence: 0.96949744

00:06:54.155 --> 00:06:55.755 and then be retrieved by
NOTE Confidence: 0.96949744

00:06:55.755 --> 00:06:57.295 synaptic vesicle endocytosis.
NOTE Confidence: 0.9665569

00:06:58.160 --> 00:06:59.440 So they have they have
NOTE Confidence: 0.9665569

00:06:59.440 --> 00:07:01.440 a very specialized component of
NOTE Confidence: 0.9665569

00:07:01.440 --> 00:07:03.040 proteins, such as synaptic vesicle
NOTE Confidence: 0.9665569

00:07:03.040 --> 00:07:03.540 proteins.
NOTE Confidence: 0.9975878

00:07:04.000 --> 00:07:05.360 And because of the synaptic
NOTE Confidence: 0.9975878

00:07:05.360 --> 00:07:06.260 vesicle cycle,
NOTE Confidence: 0.9910257

00:07:06.720 --> 00:07:07.380 they occur
NOTE Confidence: 0.9671515

00:07:07.760 --> 00:07:09.279 they undergo high rates of
NOTE Confidence: 0.9671515

00:07:09.279 --> 00:07:11.360 conformational changes, and these changes

NOTE Confidence: 0.9671515
00:07:11.360 --> 00:07:12.639 need to be precise in
NOTE Confidence: 0.9671515
00:07:12.639 --> 00:07:14.115 order to allow for fusion
NOTE Confidence: 0.9671515
00:07:14.115 --> 00:07:14.615 at,
NOTE Confidence: 0.9510854
00:07:15.715 --> 00:07:16.995 sort of being linked to
NOTE Confidence: 0.9510854
00:07:16.995 --> 00:07:18.055 the action potential.
NOTE Confidence: 0.97581804
00:07:18.595 --> 00:07:19.415 And as,
NOTE Confidence: 0.9477807
00:07:19.795 --> 00:07:21.575 as as sort of exemplified
NOTE Confidence: 0.9909978
00:07:21.955 --> 00:07:22.595 by the nigra
NOTE Confidence: 0.9270471
00:07:23.795 --> 00:07:25.795 stridal synapse, that the cell
NOTE Confidence: 0.9270471
00:07:25.795 --> 00:07:27.235 body and the synapse can
NOTE Confidence: 0.9270471
00:07:27.235 --> 00:07:29.150 be very far away. So
NOTE Confidence: 0.9270471
00:07:29.150 --> 00:07:31.069 here, the synapse is, the
NOTE Confidence: 0.9270471
00:07:31.069 --> 00:07:32.270 cell body is in the
NOTE Confidence: 0.9270471
00:07:32.270 --> 00:07:33.710 Niagara, but the synapse is
NOTE Confidence: 0.9270471
00:07:33.710 --> 00:07:34.930 at the striatum.
NOTE Confidence: 0.9529602

00:07:35.710 --> 00:07:38.050 And axonal transport actually is
NOTE Confidence: 0.9529602

00:07:38.189 --> 00:07:40.449 pretty slow. Even fast axonal
NOTE Confidence: 0.9529602

00:07:40.509 --> 00:07:42.210 transport is slow to maintain
NOTE Confidence: 0.9529602

00:07:42.430 --> 00:07:43.250 this quality
NOTE Confidence: 0.9355207

00:07:43.710 --> 00:07:44.025 of,
NOTE Confidence: 0.97534406

00:07:44.665 --> 00:07:46.505 quality in this terminal is
NOTE Confidence: 0.97534406

00:07:46.505 --> 00:07:47.865 difficult because of that. You're
NOTE Confidence: 0.97534406

00:07:47.865 --> 00:07:49.725 not getting new protein constantly.
NOTE Confidence: 0.97552586

00:07:50.425 --> 00:07:52.104 And there's while there is,
NOTE Confidence: 0.97552586

00:07:52.425 --> 00:07:54.345 protein translation mostly on the
NOTE Confidence: 0.97552586

00:07:54.345 --> 00:07:54.845 postsynaptic
NOTE Confidence: 0.95534235

00:07:55.225 --> 00:07:56.745 side, its role in the
NOTE Confidence: 0.95534235

00:07:56.745 --> 00:07:58.664 presynaptic side is much more
NOTE Confidence: 0.95534235

00:07:58.664 --> 00:07:59.164 limited.
NOTE Confidence: 0.8818065

00:07:59.620 --> 00:08:01.860 And, obviously, there are presence
NOTE Confidence: 0.8818065

00:08:01.860 --> 00:08:03.880 of aggregation prone proteins.

NOTE Confidence: 0.9362088
00:08:04.340 --> 00:08:05.620 And so this is best
NOTE Confidence: 0.9362088
00:08:05.620 --> 00:08:06.840 obviously exemplified
NOTE Confidence: 0.9976806
00:08:07.540 --> 00:08:08.680 by alpha synuclein.
NOTE Confidence: 0.98052865
00:08:09.140 --> 00:08:10.740 So you saw this right
NOTE Confidence: 0.98052865
00:08:10.740 --> 00:08:12.280 hand side of the graph,
NOTE Confidence: 0.97513974
00:08:13.824 --> 00:08:15.104 earlier. So but on the
NOTE Confidence: 0.97513974
00:08:15.104 --> 00:08:16.485 left hand side is just
NOTE Confidence: 0.97513974
00:08:16.544 --> 00:08:19.185 disease risk versus expression. And
NOTE Confidence: 0.97513974
00:08:19.185 --> 00:08:20.324 you can see that
NOTE Confidence: 0.97417176
00:08:20.625 --> 00:08:21.685 the the
NOTE Confidence: 0.8126677
00:08:22.384 --> 00:08:23.925 the duplication and the triplication
NOTE Confidence: 0.8126677
00:08:24.145 --> 00:08:25.365 which increase expression
NOTE Confidence: 0.95389736
00:08:26.050 --> 00:08:28.770 linearly increase disease risk, while
NOTE Confidence: 0.95389736
00:08:28.770 --> 00:08:29.510 the mutations
NOTE Confidence: 0.9838069
00:08:29.810 --> 00:08:31.510 actually increase aggregation.
NOTE Confidence: 0.9446709

00:08:32.290 --> 00:08:33.990 So they all increase aggregation.

NOTE Confidence: 0.9446709

00:08:34.130 --> 00:08:35.250 And the question is, but

NOTE Confidence: 0.9446709

00:08:35.250 --> 00:08:36.929 does aggregation occur at the

NOTE Confidence: 0.9446709

00:08:36.929 --> 00:08:37.429 synapse?

NOTE Confidence: 0.9486494

00:08:38.475 --> 00:08:40.154 So we previously and we

NOTE Confidence: 0.9486494

00:08:40.154 --> 00:08:41.434 and others have shown that

NOTE Confidence: 0.9486494

00:08:41.434 --> 00:08:41.934 synuclein,

NOTE Confidence: 0.90410465

00:08:43.675 --> 00:08:44.955 since its discovery when it

NOTE Confidence: 0.90410465

00:08:45.035 --> 00:08:46.875 as a torpedo vesicle protein

NOTE Confidence: 0.90410465

00:08:46.875 --> 00:08:48.795 is a synaptic vesicle protein,

NOTE Confidence: 0.90410465

00:08:48.795 --> 00:08:50.475 so it binds powerfully to

NOTE Confidence: 0.90410465

00:08:50.475 --> 00:08:51.535 synaptic vesicles.

NOTE Confidence: 0.94475454

00:08:51.929 --> 00:08:53.290 And this is shown by

NOTE Confidence: 0.94475454

00:08:53.290 --> 00:08:54.730 immunogold, which are these little

NOTE Confidence: 0.94475454

00:08:54.730 --> 00:08:55.630 black dots,

NOTE Confidence: 0.9379432

00:08:56.010 --> 00:08:57.529 and that synuclein is at

NOTE Confidence: 0.9379432

00:08:57.529 --> 00:08:58.890 rest is always found on

NOTE Confidence: 0.9379432

00:08:58.890 --> 00:09:00.330 synaptic vesicles. And this is

NOTE Confidence: 0.9379432

00:09:00.330 --> 00:09:02.029 quantified here at the bottom.

NOTE Confidence: 0.9379432

00:09:02.089 --> 00:09:03.370 So sixty percent of them

NOTE Confidence: 0.9379432

00:09:03.370 --> 00:09:04.350 are on the vesicle

NOTE Confidence: 0.9462773

00:09:04.875 --> 00:09:06.635 with around third, twenty five

NOTE Confidence: 0.9462773

00:09:06.635 --> 00:09:08.255 percent on plasma membrane.

NOTE Confidence: 0.8829053

00:09:08.715 --> 00:09:10.575 But, surprisingly, what we discussed,

NOTE Confidence: 0.8829053

00:09:10.635 --> 00:09:11.535 if you stimulate,

NOTE Confidence: 0.95018995

00:09:12.635 --> 00:09:14.155 nerve terminals, what happens is

NOTE Confidence: 0.95018995

00:09:14.155 --> 00:09:16.075 the synuclein comes off, and

NOTE Confidence: 0.95018995

00:09:16.075 --> 00:09:17.915 then it's it's found mainly

NOTE Confidence: 0.95018995

00:09:17.915 --> 00:09:19.480 on the membrane. And then

NOTE Confidence: 0.95018995

00:09:19.480 --> 00:09:21.400 when you repolarize the terminal,

NOTE Confidence: 0.95018995

00:09:21.400 --> 00:09:22.760 then the vessel it goes

NOTE Confidence: 0.95018995

00:09:22.760 --> 00:09:24.120 back onto the vesicle. So
NOTE Confidence: 0.95018995

00:09:24.120 --> 00:09:24.700 it's synuclein,
NOTE Confidence: 0.9960122

00:09:25.640 --> 00:09:26.140 localization
NOTE Confidence: 0.99127465

00:09:26.760 --> 00:09:28.620 within the terminal is dynamic
NOTE Confidence: 0.99127465

00:09:28.679 --> 00:09:30.220 and and linked to synaptic
NOTE Confidence: 0.99127465

00:09:30.360 --> 00:09:30.860 activity.
NOTE Confidence: 0.9740082

00:09:31.355 --> 00:09:32.815 So our control is synapto
NOTE Confidence: 0.9740082

00:09:32.875 --> 00:09:34.335 brevin, which is an integral
NOTE Confidence: 0.9740082

00:09:34.395 --> 00:09:35.835 vesicle protein, and you can
NOTE Confidence: 0.9740082

00:09:35.835 --> 00:09:36.875 see it's mainly on the
NOTE Confidence: 0.9740082

00:09:36.875 --> 00:09:37.375 vessel.
NOTE Confidence: 0.9522203

00:09:39.035 --> 00:09:40.235 So why why does this
NOTE Confidence: 0.9522203

00:09:40.235 --> 00:09:42.015 matter? So this matters because
NOTE Confidence: 0.9522203

00:09:42.155 --> 00:09:43.595 there's some very nice work
NOTE Confidence: 0.9522203

00:09:43.595 --> 00:09:45.515 from Ulf Detmer's lab at
NOTE Confidence: 0.9522203

00:09:45.515 --> 00:09:46.575 Harvard at Brigham,

NOTE Confidence: 0.992307

00:09:47.620 --> 00:09:49.700 showed that that this that

NOTE Confidence: 0.992307

00:09:49.700 --> 00:09:51.959 synuclein is actually being phosphorylated

NOTE Confidence: 0.978014

00:09:52.339 --> 00:09:53.380 as a function of the

NOTE Confidence: 0.978014

00:09:53.380 --> 00:09:55.140 synaptic vesicle. So they showed

NOTE Confidence: 0.978014

00:09:55.140 --> 00:09:57.160 that that as the vesicle

NOTE Confidence: 0.978014

00:09:57.380 --> 00:09:59.540 cycles, that synuclein is being

NOTE Confidence: 0.978014

00:09:59.540 --> 00:10:00.040 phosphorylated

NOTE Confidence: 0.9846815

00:10:00.420 --> 00:10:02.085 as serine one twenty nine.

NOTE Confidence: 0.98778254

00:10:03.045 --> 00:10:04.985 Historically, we actually thought this

NOTE Confidence: 0.98778254

00:10:05.125 --> 00:10:05.625 phosphorylation

NOTE Confidence: 0.9552867

00:10:05.925 --> 00:10:07.225 was purely pathological,

NOTE Confidence: 0.99224997

00:10:08.005 --> 00:10:09.765 but now it's appreciated that

NOTE Confidence: 0.99224997

00:10:09.765 --> 00:10:11.125 this is occurring as part

NOTE Confidence: 0.99224997

00:10:11.125 --> 00:10:12.725 of the normal physiology of

NOTE Confidence: 0.99224997

00:10:12.725 --> 00:10:14.245 the protein. Every time the

NOTE Confidence: 0.99224997

00:10:14.245 --> 00:10:15.765 protein comes off the vessel,
NOTE Confidence: 0.99224997

00:10:15.765 --> 00:10:16.960 it's getting phosphorylated
NOTE Confidence: 0.62597495

00:10:17.340 --> 00:10:18.300 up for polo
NOTE Confidence: 0.9660203

00:10:18.860 --> 00:10:20.300 polo like kinase two, and
NOTE Confidence: 0.9660203

00:10:20.300 --> 00:10:21.900 then the phosphorylation can be
NOTE Confidence: 0.9660203

00:10:21.900 --> 00:10:23.820 removed. And this was what
NOTE Confidence: 0.9660203

00:10:23.820 --> 00:10:25.600 is resulting in actually
NOTE Confidence: 0.9973484

00:10:25.900 --> 00:10:26.640 the aggregation
NOTE Confidence: 0.9995492

00:10:27.020 --> 00:10:27.840 of the protein
NOTE Confidence: 0.9559899

00:10:28.300 --> 00:10:29.845 in the terminal. So there's
NOTE Confidence: 0.9559899

00:10:29.845 --> 00:10:31.365 been long standing data in
NOTE Confidence: 0.9559899

00:10:31.365 --> 00:10:33.125 the field that actually why
NOTE Confidence: 0.9559899

00:10:33.125 --> 00:10:34.725 you can see Lewy bodies,
NOTE Confidence: 0.9559899

00:10:34.725 --> 00:10:35.845 which are these sort of
NOTE Confidence: 0.9559899

00:10:35.845 --> 00:10:38.405 bright objects in, in in
NOTE Confidence: 0.9559899

00:10:38.405 --> 00:10:38.905 pathology.

NOTE Confidence: 0.95262146
00:10:39.365 --> 00:10:41.205 There's a lot larger and
NOTE Confidence: 0.95262146
00:10:41.205 --> 00:10:43.205 vast more amount of sort
NOTE Confidence: 0.95262146
00:10:43.205 --> 00:10:44.985 of smaller oligomeric
NOTE Confidence: 0.9652951
00:10:45.470 --> 00:10:46.750 species that are found in
NOTE Confidence: 0.9652951
00:10:46.750 --> 00:10:48.750 presynaptic terminal, and this is
NOTE Confidence: 0.9652951
00:10:48.750 --> 00:10:50.350 sort of explaining that the
NOTE Confidence: 0.9652951
00:10:50.350 --> 00:10:50.850 phosphorylation
NOTE Confidence: 0.9979131
00:10:51.309 --> 00:10:52.370 event that precipitates
NOTE Confidence: 0.9911131
00:10:52.670 --> 00:10:54.590 this is actually occurring at
NOTE Confidence: 0.9911131
00:10:54.590 --> 00:10:55.170 the terminal.
NOTE Confidence: 0.92701125
00:10:55.550 --> 00:10:56.910 So the question is what
NOTE Confidence: 0.92701125
00:10:56.910 --> 00:10:58.050 what are the consequences
NOTE Confidence: 0.9451972
00:10:58.429 --> 00:10:59.890 to the synaptic function,
NOTE Confidence: 0.9690583
00:11:00.505 --> 00:11:01.565 for this aggregation?
NOTE Confidence: 0.9625289
00:11:02.665 --> 00:11:04.024 So we we show this
NOTE Confidence: 0.9625289

00:11:04.024 --> 00:11:05.225 when I first started my
NOTE Confidence: 0.9625289

00:11:05.225 --> 00:11:06.665 lab here, Dale, that if
NOTE Confidence: 0.9625289

00:11:06.665 --> 00:11:08.425 you overexpress and you aggregate
NOTE Confidence: 0.9625289

00:11:08.425 --> 00:11:10.745 synuclein internals, you actually get
NOTE Confidence: 0.9625289

00:11:10.745 --> 00:11:12.445 profound effects on neurotransmission.
NOTE Confidence: 0.939404

00:11:13.140 --> 00:11:14.260 So here in blue, which
NOTE Confidence: 0.939404

00:11:14.260 --> 00:11:15.380 is hidden is the wild
NOTE Confidence: 0.939404

00:11:15.380 --> 00:11:16.740 type. And then if you
NOTE Confidence: 0.939404

00:11:16.740 --> 00:11:17.240 overexpress
NOTE Confidence: 0.9855746

00:11:17.860 --> 00:11:19.400 if you delete all synucleins,
NOTE Confidence: 0.9855746

00:11:19.700 --> 00:11:22.040 actually, synaptic transmission gets better.
NOTE Confidence: 0.9945867

00:11:22.420 --> 00:11:23.559 But if you overexpress
NOTE Confidence: 0.96717334

00:11:23.860 --> 00:11:24.360 human,
NOTE Confidence: 0.96098393

00:11:24.980 --> 00:11:27.000 alpha synuclein and cause aggregation
NOTE Confidence: 0.96098393

00:11:27.059 --> 00:11:28.505 in the tunnel, neurotransmission
NOTE Confidence: 0.9840264

00:11:28.965 --> 00:11:30.405 goes down. And this is

NOTE Confidence: 0.9840264
00:11:30.405 --> 00:11:32.265 actually specific for the human
NOTE Confidence: 0.9840264
00:11:32.325 --> 00:11:33.785 subtype, which can aggregate
NOTE Confidence: 0.9433214
00:11:34.165 --> 00:11:36.485 unlike the mouse, which doesn't
NOTE Confidence: 0.9433214
00:11:36.485 --> 00:11:38.265 readily aggregate in the system.
NOTE Confidence: 0.9433214
00:11:38.405 --> 00:11:39.780 It's just like wild type.
NOTE Confidence: 0.9433214
00:11:40.020 --> 00:11:41.380 So this this data has
NOTE Confidence: 0.9433214
00:11:41.380 --> 00:11:43.400 been replicated by many labs.
NOTE Confidence: 0.9433214
00:11:43.620 --> 00:11:45.060 And so that the bottom
NOTE Confidence: 0.9433214
00:11:45.060 --> 00:11:46.520 line is that you overexpress
NOTE Confidence: 0.9433214
00:11:46.740 --> 00:11:47.960 and aggregate synuclein
NOTE Confidence: 0.8895658
00:11:48.340 --> 00:11:49.460 in the nerve zone, you
NOTE Confidence: 0.8895658
00:11:49.460 --> 00:11:51.400 get neuro decrease in neurotransmission.
NOTE Confidence: 0.90016073
00:11:52.095 --> 00:11:53.054 So this is shown by
NOTE Confidence: 0.90016073
00:11:53.054 --> 00:11:54.915 Stephanie Craig's dad at the
NOTE Confidence: 0.90016073
00:11:55.054 --> 00:11:55.554 nigrostriatal
NOTE Confidence: 0.8533142

00:11:56.014 --> 00:11:56.514 synapse.
NOTE Confidence: 0.83209485

00:11:56.894 --> 00:11:57.934 And you can see that
NOTE Confidence: 0.83209485

00:11:57.934 --> 00:11:59.855 overexpression of synuclein and thus
NOTE Confidence: 0.83209485

00:11:59.855 --> 00:12:01.214 for it will dampen trans
NOTE Confidence: 0.785385

00:12:03.214 --> 00:12:03.714 oh,
NOTE Confidence: 0.9274617

00:12:04.130 --> 00:12:05.649 so what what are the
NOTE Confidence: 0.9274617

00:12:05.809 --> 00:12:06.870 why is neurotransmission
NOTE Confidence: 0.9838926

00:12:07.330 --> 00:12:09.429 input output curves actually decreasing?
NOTE Confidence: 0.9838926

00:12:09.649 --> 00:12:10.769 So one of the ways
NOTE Confidence: 0.9838926

00:12:10.769 --> 00:12:12.130 it's doing this is because
NOTE Confidence: 0.9838926

00:12:12.130 --> 00:12:14.130 of structural reorganization of the
NOTE Confidence: 0.9838926

00:12:14.130 --> 00:12:15.330 synapse, which I'm not gonna
NOTE Confidence: 0.9838926

00:12:15.330 --> 00:12:16.755 talk about today, But the
NOTE Confidence: 0.9838926

00:12:16.755 --> 00:12:18.615 other is because it dampens,
NOTE Confidence: 0.91713214

00:12:19.395 --> 00:12:21.155 and retrieval of the membrane
NOTE Confidence: 0.91713214

00:12:21.155 --> 00:12:22.855 and synaptic vesicle endocytosis

NOTE Confidence: 0.64495754
00:12:23.395 --> 00:12:24.855 and nerve terminals as shown
NOTE Confidence: 0.8683799
00:12:25.235 --> 00:12:27.015 by fluorin imaging, which is,
NOTE Confidence: 0.9578537
00:12:27.395 --> 00:12:29.555 a pH sensitive GFP that's
NOTE Confidence: 0.9578537
00:12:29.555 --> 00:12:31.335 monitoring vesicle trafficking.
NOTE Confidence: 0.9654117
00:12:31.790 --> 00:12:32.990 And as the curves get
NOTE Confidence: 0.9654117
00:12:33.230 --> 00:12:34.590 as the tau as the
NOTE Confidence: 0.9654117
00:12:34.590 --> 00:12:35.090 vesicle
NOTE Confidence: 0.8982303
00:12:35.710 --> 00:12:37.230 retrieval is happening, it
NOTE Confidence: 0.9677462
00:12:37.790 --> 00:12:39.150 the GFP is sort of
NOTE Confidence: 0.9677462
00:12:39.150 --> 00:12:40.690 quenched. And therefore,
NOTE Confidence: 0.9815365
00:12:40.990 --> 00:12:42.190 if this is slower, this
NOTE Confidence: 0.9815365
00:12:42.190 --> 00:12:43.250 means that endocytosis
NOTE Confidence: 0.9482485
00:12:43.710 --> 00:12:45.175 is slower, and you can
NOTE Confidence: 0.9482485
00:12:45.175 --> 00:12:46.694 calculate this as a decay
NOTE Confidence: 0.9482485
00:12:46.694 --> 00:12:47.995 constant of tau.
NOTE Confidence: 0.95107853

00:12:49.095 --> 00:12:50.554 So this is what synuclein
NOTE Confidence: 0.95107853

00:12:50.615 --> 00:12:51.975 is doing at the terminal.
NOTE Confidence: 0.95107853

00:12:51.975 --> 00:12:53.735 It also has profound struct
NOTE Confidence: 0.95107853

00:12:54.214 --> 00:12:56.454 structural changes to the pool
NOTE Confidence: 0.95107853

00:12:56.615 --> 00:12:58.700 vesicle pool dynamics, which which
NOTE Confidence: 0.95107853

00:12:58.700 --> 00:13:00.220 are already published, and many
NOTE Confidence: 0.95107853

00:13:00.220 --> 00:13:01.440 groups can show this.
NOTE Confidence: 0.9480049

00:13:02.380 --> 00:13:03.740 So okay. So that's that's
NOTE Confidence: 0.9480049

00:13:03.740 --> 00:13:05.500 one vignette. So the second
NOTE Confidence: 0.9480049

00:13:05.500 --> 00:13:07.100 vignette I wanna talk about
NOTE Confidence: 0.9480049

00:13:07.100 --> 00:13:09.020 is auxilin, which is DNA
NOTE Confidence: 0.9480049

00:13:09.020 --> 00:13:10.059 j c six, which is
NOTE Confidence: 0.9480049

00:13:10.059 --> 00:13:11.520 of great interest to you.
NOTE Confidence: 0.9480049

00:13:11.820 --> 00:13:12.320 So
NOTE Confidence: 0.9779558

00:13:14.165 --> 00:13:15.545 so this was a gene
NOTE Confidence: 0.9779558

00:13:15.605 --> 00:13:17.845 identified in families which have

NOTE Confidence: 0.9779558
00:13:17.845 --> 00:13:19.064 early onset Parkinson's.
NOTE Confidence: 0.9411295
00:13:19.764 --> 00:13:21.285 And what we what it
NOTE Confidence: 0.9411295
00:13:21.285 --> 00:13:23.204 has one known function. It's
NOTE Confidence: 0.9411295
00:13:23.204 --> 00:13:23.944 a chaperone.
NOTE Confidence: 0.993744
00:13:24.404 --> 00:13:25.144 It basically
NOTE Confidence: 0.9381664
00:13:25.524 --> 00:13:27.970 uncoats this clathrin coated vesicles
NOTE Confidence: 0.9381664
00:13:28.030 --> 00:13:29.550 that are formed as as
NOTE Confidence: 0.9381664
00:13:29.550 --> 00:13:31.070 a part of synaptic vesicle
NOTE Confidence: 0.9381664
00:13:31.070 --> 00:13:31.570 endocytosis
NOTE Confidence: 0.99307764
00:13:32.110 --> 00:13:34.050 to generate a nascent vesicle
NOTE Confidence: 0.9286436
00:13:34.510 --> 00:13:36.050 allowing it to be actually
NOTE Confidence: 0.9286436
00:13:36.110 --> 00:13:37.410 refilled with neurotransmitter.
NOTE Confidence: 0.99094045
00:13:38.735 --> 00:13:39.215 So,
NOTE Confidence: 0.99827707
00:13:39.695 --> 00:13:41.395 what happens is that,
NOTE Confidence: 0.9433422
00:13:42.095 --> 00:13:44.175 it's already Pietro and Loyce
NOTE Confidence: 0.9433422

00:13:44.175 --> 00:13:45.775 Green's lab previously showed that

NOTE Confidence: 0.9433422

00:13:45.775 --> 00:13:47.615 if you in in mice

NOTE Confidence: 0.9433422

00:13:47.615 --> 00:13:48.755 that lack oxalyn,

NOTE Confidence: 0.9991156

00:13:49.135 --> 00:13:49.635 endocytosis

NOTE Confidence: 0.9342645

00:13:50.095 --> 00:13:52.050 is not surprisingly slow using

NOTE Confidence: 0.9342645

00:13:52.050 --> 00:13:53.570 the same fluoren assay, which

NOTE Confidence: 0.9342645

00:13:53.570 --> 00:13:55.330 is this pH sensitive hooked

NOTE Confidence: 0.9342645

00:13:55.330 --> 00:13:57.190 to a synaptic vesicle protein.

NOTE Confidence: 0.9574676

00:13:57.730 --> 00:13:59.010 And so the question what

NOTE Confidence: 0.9574676

00:13:59.010 --> 00:14:01.410 we tested is whether this

NOTE Confidence: 0.9574676

00:14:01.410 --> 00:14:01.910 oxalyn

NOTE Confidence: 0.9860345

00:14:02.290 --> 00:14:03.970 mice are actually a good

NOTE Confidence: 0.9860345

00:14:03.970 --> 00:14:05.110 model for Parkinson.

NOTE Confidence: 0.99950284

00:14:05.505 --> 00:14:06.965 So we did longitudinal

NOTE Confidence: 0.95329064

00:14:07.505 --> 00:14:09.905 behavioral analysis on large cohorts

NOTE Confidence: 0.95329064

00:14:09.905 --> 00:14:11.425 of mice, and we could

NOTE Confidence: 0.95329064
00:14:11.425 --> 00:14:12.625 show that in a wild
NOTE Confidence: 0.95329064
00:14:12.625 --> 00:14:13.665 type mouse, which you saw,
NOTE Confidence: 0.95329064
00:14:13.665 --> 00:14:15.105 it would scurry back across
NOTE Confidence: 0.95329064
00:14:15.105 --> 00:14:16.785 this balance beam. But the
NOTE Confidence: 0.95329064
00:14:16.785 --> 00:14:18.385 oxalate mice is still sort
NOTE Confidence: 0.95329064
00:14:18.385 --> 00:14:20.160 of getting across this beam.
NOTE Confidence: 0.95329064
00:14:20.399 --> 00:14:21.839 And so you can see
NOTE Confidence: 0.95329064
00:14:21.839 --> 00:14:23.759 that as a wild type
NOTE Confidence: 0.95329064
00:14:23.759 --> 00:14:25.139 as a function of age
NOTE Confidence: 0.95329064
00:14:25.279 --> 00:14:27.199 can do this assay even
NOTE Confidence: 0.95329064
00:14:27.199 --> 00:14:28.800 up to fifteen months, but
NOTE Confidence: 0.95329064
00:14:28.800 --> 00:14:30.639 the knockout is actually showing
NOTE Confidence: 0.95329064
00:14:30.639 --> 00:14:31.699 an age dependent
NOTE Confidence: 0.9619562
00:14:32.000 --> 00:14:33.620 decrement in motor function.
NOTE Confidence: 0.9670884
00:14:34.055 --> 00:14:35.115 And most importantly,
NOTE Confidence: 0.97535664

00:14:35.495 --> 00:14:37.095 this can be rescued by
NOTE Confidence: 0.97535664

00:14:37.095 --> 00:14:38.535 giving l dopa, which is
NOTE Confidence: 0.97535664

00:14:38.535 --> 00:14:40.634 the standard treatment for Parkinson
NOTE Confidence: 0.97535664

00:14:40.855 --> 00:14:42.295 patient. So you can see
NOTE Confidence: 0.97535664

00:14:42.295 --> 00:14:44.214 individual traces of mice that
NOTE Confidence: 0.97535664

00:14:44.214 --> 00:14:45.495 are nine to twelve months
NOTE Confidence: 0.97535664

00:14:45.495 --> 00:14:47.194 old that they can improve
NOTE Confidence: 0.97535664

00:14:47.334 --> 00:14:49.175 in their motor performance when
NOTE Confidence: 0.97535664

00:14:49.175 --> 00:14:50.170 they do this. And this
NOTE Confidence: 0.97535664

00:14:50.170 --> 00:14:51.630 is the cumulative data.
NOTE Confidence: 0.9732322

00:14:52.810 --> 00:14:54.810 We also tested and showed
NOTE Confidence: 0.9732322

00:14:54.810 --> 00:14:56.250 that in these mice, there's
NOTE Confidence: 0.9732322

00:14:56.250 --> 00:14:58.110 age dependent loss of dopaminergic
NOTE Confidence: 0.9732322

00:14:58.410 --> 00:15:00.090 neurons in the nigra, and
NOTE Confidence: 0.9732322

00:15:00.090 --> 00:15:00.990 this is quantified
NOTE Confidence: 0.9670756

00:15:01.690 --> 00:15:03.365 by sterology. So you can

NOTE Confidence: 0.9670756
00:15:03.365 --> 00:15:04.565 see there are forty percent
NOTE Confidence: 0.9670756
00:15:04.565 --> 00:15:05.765 loss of neurons as a
NOTE Confidence: 0.9670756
00:15:05.765 --> 00:15:06.825 function of age.
NOTE Confidence: 0.97379506
00:15:07.205 --> 00:15:09.045 And and the third feature
NOTE Confidence: 0.97379506
00:15:09.045 --> 00:15:10.725 of Parkinson's that everybody looks
NOTE Confidence: 0.97379506
00:15:10.725 --> 00:15:11.845 for is to see whether
NOTE Confidence: 0.97379506
00:15:11.845 --> 00:15:13.305 they have synuclein pathology,
NOTE Confidence: 0.95970684
00:15:13.925 --> 00:15:15.045 and we could show that
NOTE Confidence: 0.95970684
00:15:15.045 --> 00:15:16.905 in an age dependent manner
NOTE Confidence: 0.95970684
00:15:17.045 --> 00:15:18.370 in the nigra, which is
NOTE Confidence: 0.95970684
00:15:18.370 --> 00:15:20.209 labeled with t h, that
NOTE Confidence: 0.95970684
00:15:20.209 --> 00:15:21.829 there is increased phosphorous,
NOTE Confidence: 0.9622818
00:15:22.449 --> 00:15:24.149 serine one twenty nine phosphorylation.
NOTE Confidence: 0.9680502
00:15:25.009 --> 00:15:26.790 This phosphorylation is not restricted
NOTE Confidence: 0.9680502
00:15:26.930 --> 00:15:28.470 to t h positive cells,
NOTE Confidence: 0.9680502

00:15:28.769 --> 00:15:29.170 but,
NOTE Confidence: 0.9849262

00:15:29.730 --> 00:15:31.490 but is found throughout the
NOTE Confidence: 0.9849262

00:15:31.490 --> 00:15:32.930 brain. And it's not like
NOTE Confidence: 0.9849262

00:15:32.930 --> 00:15:35.055 the somatic aggregation of Lewy
NOTE Confidence: 0.9849262

00:15:35.055 --> 00:15:36.995 bodies, but much more presynaptic
NOTE Confidence: 0.9602604

00:15:37.375 --> 00:15:39.235 like aggregates that we see,
NOTE Confidence: 0.97377497

00:15:39.775 --> 00:15:40.815 in in the in the
NOTE Confidence: 0.97377497

00:15:40.815 --> 00:15:42.175 previous pictures that I showed
NOTE Confidence: 0.97377497

00:15:42.175 --> 00:15:43.215 you. And this is the
NOTE Confidence: 0.97377497

00:15:43.215 --> 00:15:45.135 quantification here shown on the,
NOTE Confidence: 0.97377497

00:15:45.375 --> 00:15:46.435 shown on the right.
NOTE Confidence: 0.97305566

00:15:47.839 --> 00:15:49.600 Okay. So because this data
NOTE Confidence: 0.97305566

00:15:49.600 --> 00:15:51.040 is published, I'm just gonna
NOTE Confidence: 0.97305566

00:15:51.040 --> 00:15:53.140 summarize what we see mechanistically
NOTE Confidence: 0.97305566

00:15:53.440 --> 00:15:55.440 in the oxalate mice. When
NOTE Confidence: 0.97305566

00:15:55.600 --> 00:15:56.959 so I already told you

NOTE Confidence: 0.97305566
00:15:56.959 --> 00:15:58.420 that they have this deficit
NOTE Confidence: 0.97305566
00:15:58.560 --> 00:15:59.885 in clathrin uncoating.
NOTE Confidence: 0.9927134
00:16:00.345 --> 00:16:01.465 And as a result, what
NOTE Confidence: 0.9927134
00:16:01.465 --> 00:16:03.405 happens is clathrin coated vesicles
NOTE Confidence: 0.9927134
00:16:03.625 --> 00:16:04.125 accumulate.
NOTE Confidence: 0.99166775
00:16:04.745 --> 00:16:06.205 The other thing that happens
NOTE Confidence: 0.99166775
00:16:06.265 --> 00:16:08.025 is that the synapse to
NOTE Confidence: 0.99166775
00:16:08.025 --> 00:16:10.345 generate these vesicles uses other
NOTE Confidence: 0.99166775
00:16:10.345 --> 00:16:11.405 modes of endocytosis,
NOTE Confidence: 0.99707955
00:16:11.785 --> 00:16:13.305 which don't have the same
NOTE Confidence: 0.99707955
00:16:13.305 --> 00:16:14.365 quality control.
NOTE Confidence: 0.99363136
00:16:14.790 --> 00:16:15.990 And as a result, if
NOTE Confidence: 0.99363136
00:16:15.990 --> 00:16:17.510 you look at proteomics of
NOTE Confidence: 0.99363136
00:16:17.510 --> 00:16:18.870 the vesicles that are in
NOTE Confidence: 0.99363136
00:16:18.870 --> 00:16:19.529 the knockout,
NOTE Confidence: 0.9455194

00:16:19.910 --> 00:16:21.670 their their composition is totally
NOTE Confidence: 0.9455194

00:16:21.670 --> 00:16:23.269 different. And we think that
NOTE Confidence: 0.9455194

00:16:23.269 --> 00:16:24.550 because of that, they don't
NOTE Confidence: 0.9455194

00:16:24.550 --> 00:16:26.330 have key proteins like vesicle
NOTE Confidence: 0.9455194

00:16:26.390 --> 00:16:27.209 amine transporter,
NOTE Confidence: 0.9862591

00:16:28.495 --> 00:16:30.575 and dopamine will accrue not
NOTE Confidence: 0.9862591

00:16:30.575 --> 00:16:32.095 within the vesicle, but in
NOTE Confidence: 0.9862591

00:16:32.095 --> 00:16:33.695 the cytosolic milieu of the
NOTE Confidence: 0.9862591

00:16:33.695 --> 00:16:34.995 presynaptic terminal.
NOTE Confidence: 0.9894536

00:16:35.455 --> 00:16:37.295 And dopamine is already known
NOTE Confidence: 0.9894536

00:16:37.295 --> 00:16:38.335 that if it it is
NOTE Confidence: 0.9894536

00:16:38.335 --> 00:16:39.315 very oxidative
NOTE Confidence: 0.8923166

00:16:39.615 --> 00:16:41.295 prone and that it forms
NOTE Confidence: 0.8923166

00:16:41.295 --> 00:16:43.510 these intermediates like called DOPAL
NOTE Confidence: 0.8923166

00:16:43.510 --> 00:16:44.329 and DOPAC.
NOTE Confidence: 0.9533116

00:16:44.709 --> 00:16:46.709 And DOPAL is very increased

NOTE Confidence: 0.9533116
00:16:46.709 --> 00:16:48.649 in these oxalate knockout mice,
NOTE Confidence: 0.9533116
00:16:48.870 --> 00:16:51.529 suggesting that dopamine forms adducts
NOTE Confidence: 0.9533116
00:16:51.589 --> 00:16:52.630 with a whole bunch of
NOTE Confidence: 0.9533116
00:16:52.630 --> 00:16:54.310 proteins in the terminal and
NOTE Confidence: 0.9533116
00:16:54.310 --> 00:16:55.290 causes toxicity.
NOTE Confidence: 0.9559914
00:16:56.345 --> 00:16:57.545 And what we also can
NOTE Confidence: 0.9559914
00:16:57.545 --> 00:16:59.805 show is that both synaptic
NOTE Confidence: 0.9559914
00:16:59.945 --> 00:17:01.965 vesicles and clathrin motor vesicles
NOTE Confidence: 0.9559914
00:17:02.105 --> 00:17:03.645 are being cleared by autophagy
NOTE Confidence: 0.9559914
00:17:03.785 --> 00:17:04.525 in the presynaptic
NOTE Confidence: 0.9798292
00:17:04.825 --> 00:17:05.325 terminal.
NOTE Confidence: 0.9767296
00:17:05.865 --> 00:17:06.905 And the last thing that
NOTE Confidence: 0.9767296
00:17:06.905 --> 00:17:08.505 we see is that DAT,
NOTE Confidence: 0.9767296
00:17:08.505 --> 00:17:10.125 which is the dopamine transporter,
NOTE Confidence: 0.9767296
00:17:10.185 --> 00:17:11.305 which is being used in
NOTE Confidence: 0.9767296

00:17:11.305 --> 00:17:12.470 the in the clinic,
NOTE Confidence: 0.9469624

00:17:12.929 --> 00:17:14.130 is trapped in these sort
NOTE Confidence: 0.9469624

00:17:14.130 --> 00:17:15.410 of large worlds. And some
NOTE Confidence: 0.9469624

00:17:15.410 --> 00:17:16.869 really beautiful imaging,
NOTE Confidence: 0.92565936

00:17:17.490 --> 00:17:19.250 EM data from Pedro's lab
NOTE Confidence: 0.92565936

00:17:19.250 --> 00:17:20.450 also showed this in their
NOTE Confidence: 0.92565936

00:17:20.450 --> 00:17:20.950 synaptogen
NOTE Confidence: 0.72565436

00:17:21.250 --> 00:17:21.830 in mice.
NOTE Confidence: 0.95454466

00:17:22.130 --> 00:17:23.010 And I show you a
NOTE Confidence: 0.95454466

00:17:23.010 --> 00:17:24.369 picture from our mice, the
NOTE Confidence: 0.95454466

00:17:24.369 --> 00:17:25.650 oxalate mice. You can see
NOTE Confidence: 0.95454466

00:17:25.650 --> 00:17:27.250 these large membrane worlds in
NOTE Confidence: 0.95454466

00:17:27.250 --> 00:17:28.415 which that is,
NOTE Confidence: 0.9969887

00:17:29.355 --> 00:17:30.555 is sequestered. And we think
NOTE Confidence: 0.9969887

00:17:30.555 --> 00:17:31.675 that this may be a
NOTE Confidence: 0.9969887

00:17:31.675 --> 00:17:32.735 common modality

NOTE Confidence: 0.9923012
00:17:33.515 --> 00:17:34.255 through which
NOTE Confidence: 0.9950746
00:17:34.635 --> 00:17:35.615 many Parkinsonian
NOTE Confidence: 0.9246418
00:17:35.995 --> 00:17:37.295 models are impacted,
NOTE Confidence: 0.95647097
00:17:37.675 --> 00:17:39.055 that that trafficking
NOTE Confidence: 0.9980696
00:17:39.435 --> 00:17:40.895 is controlled by endocytic
NOTE Confidence: 0.9347887
00:17:41.355 --> 00:17:42.875 pathways and that this is
NOTE Confidence: 0.9347887
00:17:42.875 --> 00:17:43.375 impacted
NOTE Confidence: 0.7702003
00:17:44.369 --> 00:17:45.570 across many PD,
NOTE Confidence: 0.8244181
00:17:45.970 --> 00:17:47.650 genetic forms of PD and
NOTE Confidence: 0.8244181
00:17:47.650 --> 00:17:49.410 maybe even sporadic forms of
NOTE Confidence: 0.8244181
00:17:49.410 --> 00:17:50.390 PD. Okay.
NOTE Confidence: 0.8942191
00:17:53.410 --> 00:17:54.850 So that's that's a little
NOTE Confidence: 0.8942191
00:17:54.850 --> 00:17:55.910 vignette about,
NOTE Confidence: 0.864237
00:17:56.770 --> 00:17:57.583 oxalate. And the last vignette
NOTE Confidence: 0.864237
00:17:57.583 --> 00:17:57.616 I wanna tell you is
NOTE Confidence: 0.864237

00:17:57.616 --> 00:17:57.650 about GBA. And as you
NOTE Confidence: 0.864237

00:17:57.650 --> 00:17:58.150 already
NOTE Confidence: 0.90173715

00:17:58.450 --> 00:17:59.505 heard, wanna tell you
NOTE Confidence: 0.9926338

00:17:59.965 --> 00:18:01.804 is about GBA. And as
NOTE Confidence: 0.9926338

00:18:01.804 --> 00:18:03.345 you already heard from Steve's,
NOTE Confidence: 0.9553269

00:18:04.205 --> 00:18:06.365 talk and, also alluded by
NOTE Confidence: 0.9553269

00:18:06.365 --> 00:18:08.385 Clement's talk, that GBA
NOTE Confidence: 0.967036

00:18:08.765 --> 00:18:10.625 is one of the biggest
NOTE Confidence: 0.967036

00:18:10.924 --> 00:18:12.684 risk factors with Lerp two
NOTE Confidence: 0.967036

00:18:12.684 --> 00:18:13.170 for
NOTE Confidence: 0.9661111

00:18:13.570 --> 00:18:16.050 Parkinson's disease. Around five percent
NOTE Confidence: 0.9661111

00:18:16.050 --> 00:18:17.890 of all PD patients have
NOTE Confidence: 0.9661111

00:18:17.890 --> 00:18:18.950 GBA mutations.
NOTE Confidence: 0.96323824

00:18:19.650 --> 00:18:21.010 And so we're we have
NOTE Confidence: 0.96323824

00:18:21.010 --> 00:18:22.390 been had a long standing
NOTE Confidence: 0.96323824

00:18:22.450 --> 00:18:23.670 interest in this gene.

NOTE Confidence: 0.94529027
00:18:24.130 --> 00:18:26.695 GBA encodes this lysosomal enzyme,
NOTE Confidence: 0.94529027
00:18:26.695 --> 00:18:27.895 so it's not found in
NOTE Confidence: 0.94529027
00:18:27.895 --> 00:18:29.195 the presynaptic terminal.
NOTE Confidence: 0.9865306
00:18:29.815 --> 00:18:31.115 It's it's basically
NOTE Confidence: 0.94018453
00:18:31.734 --> 00:18:32.715 it's a glucosidase
NOTE Confidence: 0.9882264
00:18:33.015 --> 00:18:33.755 that's removing,
NOTE Confidence: 0.8967948
00:18:34.774 --> 00:18:35.274 ceramide,
NOTE Confidence: 0.3109987
00:18:35.575 --> 00:18:36.075 glucose
NOTE Confidence: 0.7785249
00:18:36.774 --> 00:18:38.154 from glucose and ceramide.
NOTE Confidence: 0.934476
00:18:38.990 --> 00:18:40.609 So we we had previously
NOTE Confidence: 0.934476
00:18:40.750 --> 00:18:42.690 generated long lived mice,
NOTE Confidence: 0.90617687
00:18:43.070 --> 00:18:45.630 that are very accurate models
NOTE Confidence: 0.90617687
00:18:45.630 --> 00:18:47.250 for GBA linked Parkinson,
NOTE Confidence: 0.8788549
00:18:47.710 --> 00:18:49.310 and we have also crossed
NOTE Confidence: 0.8788549
00:18:49.310 --> 00:18:51.645 these mice to synuclein transgenic
NOTE Confidence: 0.8788549

00:18:51.645 --> 00:18:52.945 so so you can get,
NOTE Confidence: 0.899608

00:18:53.405 --> 00:18:55.244 wild type and GBA 1
NOTE Confidence: 0.899608

00:18:55.244 --> 00:18:57.005 triple four p mutation on
NOTE Confidence: 0.899608

00:18:57.005 --> 00:18:57.905 a null background,
NOTE Confidence: 0.8594452

00:18:59.405 --> 00:19:00.685 on a wild type background
NOTE Confidence: 0.8594452

00:19:00.685 --> 00:19:02.065 and a and a synuclein,
NOTE Confidence: 0.9967234

00:19:03.005 --> 00:19:03.505 transgenic
NOTE Confidence: 0.99218374

00:19:03.805 --> 00:19:05.345 or a sensitized background.
NOTE Confidence: 0.9790627

00:19:05.840 --> 00:19:07.440 And we have done so,
NOTE Confidence: 0.9790627

00:19:07.440 --> 00:19:08.420 again, longitudinal
NOTE Confidence: 0.98278344

00:19:08.800 --> 00:19:10.240 analysis of these mice, but
NOTE Confidence: 0.98278344

00:19:10.240 --> 00:19:11.200 I'm not gonna show this
NOTE Confidence: 0.98278344

00:19:11.200 --> 00:19:12.080 to you, but to say
NOTE Confidence: 0.98278344

00:19:12.080 --> 00:19:12.580 that
NOTE Confidence: 0.8905128

00:19:13.040 --> 00:19:14.980 these mice have profound cognitive
NOTE Confidence: 0.9735958

00:19:15.280 --> 00:19:17.040 deficits on their own very

NOTE Confidence: 0.9735958

00:19:17.040 --> 00:19:18.734 early in life. So even

NOTE Confidence: 0.9735958

00:19:18.734 --> 00:19:19.855 at three months of age,

NOTE Confidence: 0.9735958

00:19:19.855 --> 00:19:21.715 GBM mice cannot do,

NOTE Confidence: 0.9687211

00:19:22.095 --> 00:19:24.655 many cognitive tasks, including fear

NOTE Confidence: 0.9687211

00:19:24.655 --> 00:19:26.835 condition and novel object recognition.

NOTE Confidence: 0.99751097

00:19:27.295 --> 00:19:28.915 But what is very surprising

NOTE Confidence: 0.99751097

00:19:29.055 --> 00:19:30.255 is that they have these

NOTE Confidence: 0.99751097

00:19:30.255 --> 00:19:31.475 profound deficits

NOTE Confidence: 0.995712

00:19:31.990 --> 00:19:33.350 even though they have no

NOTE Confidence: 0.995712

00:19:33.350 --> 00:19:34.250 alpha synuclein

NOTE Confidence: 0.9734614

00:19:34.630 --> 00:19:36.470 pathology in these mice. And

NOTE Confidence: 0.9734614

00:19:36.470 --> 00:19:37.529 this is the quantification,

NOTE Confidence: 0.9910179

00:19:38.070 --> 00:19:38.730 three months,

NOTE Confidence: 0.765011

00:19:39.429 --> 00:19:40.650 YOSAP and GBA.

NOTE Confidence: 0.9620106

00:19:41.029 --> 00:19:42.630 But interestingly, if you have

NOTE Confidence: 0.9620106

00:19:42.630 --> 00:19:44.230 a GBA mutation on a
NOTE Confidence: 0.9620106

00:19:44.230 --> 00:19:45.435 synuclein background,
NOTE Confidence: 0.99821246

00:19:45.755 --> 00:19:46.415 it greatly
NOTE Confidence: 0.9623683

00:19:46.715 --> 00:19:48.555 accelerates the pathology of the
NOTE Confidence: 0.9623683

00:19:48.555 --> 00:19:49.055 synuclein.
NOTE Confidence: 0.95919186

00:19:50.075 --> 00:19:51.195 And this is sort of
NOTE Confidence: 0.95919186

00:19:51.195 --> 00:19:52.795 increases with age. We've aged
NOTE Confidence: 0.95919186

00:19:52.795 --> 00:19:53.915 these mice out to now
NOTE Confidence: 0.95919186

00:19:53.915 --> 00:19:55.435 eighteen months, and they don't
NOTE Confidence: 0.95919186

00:19:55.435 --> 00:19:57.375 seem to have any, synuclein
NOTE Confidence: 0.95919186

00:19:57.595 --> 00:19:58.095 pathology.
NOTE Confidence: 0.9672902

00:19:58.680 --> 00:20:00.119 So we've done a single
NOTE Confidence: 0.9672902

00:20:00.119 --> 00:20:01.880 cell RNA sequencing trying to
NOTE Confidence: 0.9672902

00:20:01.880 --> 00:20:03.480 understand the basis for this
NOTE Confidence: 0.9672902

00:20:03.480 --> 00:20:04.700 cognitive phenotypes,
NOTE Confidence: 0.91050065

00:20:05.960 --> 00:20:07.720 and what we have done

NOTE Confidence: 0.91050065

00:20:07.720 --> 00:20:09.800 sort of a pathway analysis.

NOTE Confidence: 0.91050065

00:20:09.800 --> 00:20:11.740 And what's surprising for us

NOTE Confidence: 0.91050065

00:20:11.800 --> 00:20:13.640 is in neurons, the biggest

NOTE Confidence: 0.91050065

00:20:13.640 --> 00:20:14.140 pathways

NOTE Confidence: 0.98985326

00:20:14.674 --> 00:20:16.535 are all related to synaptic

NOTE Confidence: 0.98985326

00:20:16.595 --> 00:20:17.575 vesicle endocytosis.

NOTE Confidence: 0.93703455

00:20:18.195 --> 00:20:19.635 We actually do not see

NOTE Confidence: 0.93703455

00:20:19.635 --> 00:20:22.135 transcriptual changes associated with lysosomal

NOTE Confidence: 0.93703455

00:20:22.434 --> 00:20:24.535 proteins, but actually only,

NOTE Confidence: 0.93021333

00:20:25.155 --> 00:20:26.934 synaptic pathways in neuron.

NOTE Confidence: 0.8983726

00:20:28.869 --> 00:20:29.910 So I sort of sort

NOTE Confidence: 0.8983726

00:20:29.910 --> 00:20:31.510 of summarize, yeah, summarize all

NOTE Confidence: 0.8983726

00:20:31.510 --> 00:20:32.390 these three pieces of the

NOTE Confidence: 0.8983726

00:20:32.390 --> 00:20:33.990 thing is that the synaptic

NOTE Confidence: 0.8983726

00:20:33.990 --> 00:20:34.890 vesicle endocytosis

NOTE Confidence: 0.9180739

00:20:35.430 --> 00:20:37.270 is a major pathway in
NOTE Confidence: 0.9180739

00:20:37.270 --> 00:20:38.730 endo in Parkinson's
NOTE Confidence: 0.8387832

00:20:39.030 --> 00:20:39.525 disease.
NOTE Confidence: 0.90246147

00:20:39.845 --> 00:20:41.305 And, you know, we recently
NOTE Confidence: 0.90246147

00:20:41.445 --> 00:20:43.285 did a single cell and
NOTE Confidence: 0.90246147

00:20:43.285 --> 00:20:43.785 multiomic
NOTE Confidence: 0.9547307

00:20:44.085 --> 00:20:44.585 transcriptomic
NOTE Confidence: 0.9995829

00:20:45.125 --> 00:20:46.025 analysis of
NOTE Confidence: 0.97758347

00:20:46.484 --> 00:20:48.825 sporadic Parkinson patient brains,
NOTE Confidence: 0.93275845

00:20:49.445 --> 00:20:51.365 in collaboration with David and
NOTE Confidence: 0.93275845

00:20:51.365 --> 00:20:52.850 Le. And we could see
NOTE Confidence: 0.93275845

00:20:52.850 --> 00:20:54.230 that some of the proteins
NOTE Confidence: 0.93275845

00:20:54.290 --> 00:20:55.830 that genes that are actually,
NOTE Confidence: 0.8927338

00:20:56.530 --> 00:20:58.370 familial genes, they also show
NOTE Confidence: 0.8927338

00:20:58.370 --> 00:21:00.130 similar patterns in the sporadic.
NOTE Confidence: 0.8927338

00:21:00.130 --> 00:21:01.990 For instance, synuclein is expressed

NOTE Confidence: 0.8927338

00:21:02.290 --> 00:21:03.830 increased and for instance,

NOTE Confidence: 0.9354922

00:21:06.295 --> 00:21:08.135 oxalate is decreased. So we

NOTE Confidence: 0.9354922

00:21:08.135 --> 00:21:09.415 think that even though we're

NOTE Confidence: 0.9354922

00:21:09.415 --> 00:21:10.395 studying familial

NOTE Confidence: 0.97164714

00:21:10.935 --> 00:21:12.695 disease, that this has a

NOTE Confidence: 0.97164714

00:21:12.695 --> 00:21:14.715 bearing on sporadic disease.

NOTE Confidence: 0.99470454

00:21:15.335 --> 00:21:16.375 So with that, I would

NOTE Confidence: 0.99470454

00:21:16.375 --> 00:21:17.595 like to sort of

NOTE Confidence: 0.95009065

00:21:19.609 --> 00:21:20.890 thank the people who made

NOTE Confidence: 0.95009065

00:21:20.890 --> 00:21:22.510 the work. So the the

NOTE Confidence: 0.95009065

00:21:22.730 --> 00:21:24.570 project was actually spearheaded by

NOTE Confidence: 0.95009065

00:21:24.570 --> 00:21:25.850 Corina Vargas. She has her

NOTE Confidence: 0.95009065

00:21:25.850 --> 00:21:27.450 own lab in University of

NOTE Confidence: 0.95009065

00:21:27.450 --> 00:21:27.950 Pittsburgh,

NOTE Confidence: 0.8977197

00:21:28.330 --> 00:21:29.930 and then the GBA and

NOTE Confidence: 0.8977197

00:21:29.930 --> 00:21:31.930 work was spearheaded by Vidya

NOTE Confidence: 0.8977197

00:21:31.930 --> 00:21:33.050 Dara who just started his

NOTE Confidence: 0.8977197

00:21:33.050 --> 00:21:34.590 own lab in Roseland Franklin.

NOTE Confidence: 0.97189957

00:21:34.905 --> 00:21:36.105 All the people in red

NOTE Confidence: 0.97189957

00:21:36.105 --> 00:21:37.165 are team Synuclein,

NOTE Confidence: 0.9764465

00:21:38.265 --> 00:21:39.405 team GBA,

NOTE Confidence: 0.9562618

00:21:40.265 --> 00:21:41.145 and the rest of my

NOTE Confidence: 0.9562618

00:21:41.145 --> 00:21:43.065 labs and and collaborators. Thank

NOTE Confidence: 0.9562618

00:21:43.065 --> 00:21:43.466 you.