

WEBVTT

NOTE duration:"00:47:33.1600000"

NOTE recognizability:0.913

NOTE language:en-us

NOTE Confidence: 0.932705985

00:00:02.880 --> 00:00:06.040 No, no, we'll talk. Got it, got it.

NOTE Confidence: 0.93019015

00:00:10.640 --> 00:00:14.320 And the the very generous introductions,

NOTE Confidence: 0.950316928

00:00:16.920 --> 00:00:19.640 sorry for the 18 issues.

NOTE Confidence: 0.950316928

00:00:19.640 --> 00:00:21.850 Look at this, Alexa.

NOTE Confidence: 0.950316928

00:00:21.850 --> 00:00:23.320 Nicole might be able to do that.

NOTE Confidence: 0.950316928

00:00:23.320 --> 00:00:25.328 You try, you know,

NOTE Confidence: 0.950316928

00:00:25.328 --> 00:00:27.183 that don't gloat this.

NOTE Confidence: 0.950316928

00:00:27.183 --> 00:00:29.927 You hear a lot of disasters out there.

NOTE Confidence: 0.950316928

00:00:29.930 --> 00:00:31.286 Golden Gate Park is still fine

NOTE Confidence: 0.93320922

00:00:34.970 --> 00:00:36.818 and this is a view of Golden

NOTE Confidence: 0.93320922

00:00:36.818 --> 00:00:40.074 Gate Park for the hill were at

NOTE Confidence: 0.93320922

00:00:40.074 --> 00:00:44.368 UCSF Mount Parnassus campuses.

NOTE Confidence: 0.93320922

00:00:44.370 --> 00:00:46.302 So I'll be telling you about a

NOTE Confidence: 0.93320922

00:00:46.302 --> 00:00:48.648 transcription factor called TV R1 which

NOTE Confidence: 0.93320922

00:00:48.648 --> 00:00:51.684 is really important and early portable

NOTE Confidence: 0.93320922

00:00:51.684 --> 00:00:54.569 development in self based specification.

NOTE Confidence: 0.93320922

00:00:54.570 --> 00:00:57.481 But as you'll see it has several roles

NOTE Confidence: 0.93320922

00:00:57.481 --> 00:01:00.103 as time moves on in development.

NOTE Confidence: 0.93320922

00:01:00.110 --> 00:01:02.086 Roles that I think are perhaps,

NOTE Confidence: 0.93320922

00:01:02.086 --> 00:01:06.400 maybe even more remain to cognitive

NOTE Confidence: 0.93320922

00:01:06.400 --> 00:01:10.625 disorders and then psychiatric disorders,

NOTE Confidence: 0.93320922

00:01:10.630 --> 00:01:12.198 in particular to autism.

NOTE Confidence: 0.93320922

00:01:12.198 --> 00:01:16.329 But I think it could be and could be

NOTE Confidence: 0.93320922

00:01:16.329 --> 00:01:18.870 thinking about other neuropsychiatric

NOTE Confidence: 0.93320922

00:01:18.870 --> 00:01:21.150 illnesses as well.

NOTE Confidence: 0.93320922

00:01:21.150 --> 00:01:23.278 Well, give a little historical

NOTE Confidence: 0.93320922

00:01:23.278 --> 00:01:24.304 perspective to this.

NOTE Confidence: 0.93320922

00:01:24.310 --> 00:01:27.424 To those of you who've known me this long,

NOTE Confidence: 0.93320922

00:01:27.430 --> 00:01:29.910 it's about 36 years ago.

NOTE Confidence: 0.93320922

00:01:29.910 --> 00:01:31.786 Began a screen for genes that are.

NOTE Confidence: 0.93320922

00:01:31.790 --> 00:01:34.835 We were hoping to find genes that

NOTE Confidence: 0.93320922

00:01:34.835 --> 00:01:36.625 are expressed much more during

NOTE Confidence: 0.93320922

00:01:36.625 --> 00:01:37.845 development of the forebrain

NOTE Confidence: 0.93320922

00:01:37.845 --> 00:01:39.670 than in the adult forebrain,

NOTE Confidence: 0.93320922

00:01:39.670 --> 00:01:41.791 with a simple idea that if they're

NOTE Confidence: 0.93320922

00:01:41.791 --> 00:01:43.750 expressed really highly during development,

NOTE Confidence: 0.93320922

00:01:43.750 --> 00:01:46.630 maybe they're important for development.

NOTE Confidence: 0.93320922

00:01:46.630 --> 00:01:48.814 And we use a technique oldfashioned

NOTE Confidence: 0.93320922

00:01:48.814 --> 00:01:51.150 technique called subtractive vibration

NOTE Confidence: 0.93320922

00:01:51.150 --> 00:01:53.943 with directional CD and A libraries we

NOTE Confidence: 0.93320922

00:01:53.943 --> 00:01:57.282 compared in the mouse and embryonic day 15.

NOTE Confidence: 0.93320922

00:01:57.282 --> 00:01:59.397 Forebrain 2 an adult forebrain,

NOTE Confidence: 0.926289139090909

00:02:03.560 --> 00:02:05.835 and using that technique we found a

NOTE Confidence: 0.926289139090909

00:02:05.835 --> 00:02:08.480 gene which we called healing Cell

NOTE Confidence: 0.926289139090909

00:02:08.480 --> 00:02:10.880 Phone Embryonic Subtraction #1,
NOTE Confidence: 0.926289139090909

00:02:10.880 --> 00:02:14.204 or Test one, which unfortunately had
NOTE Confidence: 0.926289139090909

00:02:14.204 --> 00:02:16.476 to have its name change in DL X2.
NOTE Confidence: 0.926289139090909

00:02:16.480 --> 00:02:18.440 I'm not it's not so bad about
NOTE Confidence: 0.926289139090909

00:02:18.440 --> 00:02:19.679 losing the test one for that reason,
NOTE Confidence: 0.926289139090909

00:02:19.680 --> 00:02:20.766 but you'll see in a second
NOTE Confidence: 0.926289139090909

00:02:20.766 --> 00:02:22.119 why it was sad to lose that.
NOTE Confidence: 0.951574845

00:02:27.510 --> 00:02:30.635 Test 1 encodes A homeo
NOTE Confidence: 0.951574845

00:02:30.635 --> 00:02:32.510 domain transcription factor.
NOTE Confidence: 0.951574845

00:02:32.510 --> 00:02:34.210 They're probably the most common
NOTE Confidence: 0.951574845

00:02:34.210 --> 00:02:35.570 kinds of transcription factors
NOTE Confidence: 0.951574845

00:02:35.570 --> 00:02:37.267 that are important in self fate
NOTE Confidence: 0.951574845

00:02:37.270 --> 00:02:38.626 regulation during development.
NOTE Confidence: 0.951574845

00:02:38.626 --> 00:02:41.790 And this is a picture of the
NOTE Confidence: 0.951574845

00:02:41.790 --> 00:02:43.520 embryonic mouse brain and the
NOTE Confidence: 0.951574845

00:02:43.520 --> 00:02:45.592 white stuff in the embryonic mouse

NOTE Confidence: 0.951574845

00:02:45.592 --> 00:02:47.552 brain shows where the RNA for test

NOTE Confidence: 0.951574845

00:02:47.552 --> 00:02:49.548 one is very strongly expressed

NOTE Confidence: 0.93019015

00:02:51.790 --> 00:02:54.334 here in the. Ganglia, primordia,

NOTE Confidence: 0.93019015

00:02:54.334 --> 00:02:56.626 this big lump of cells called

NOTE Confidence: 0.93019015

00:02:56.626 --> 00:02:58.050 the ganglionic eminences,

NOTE Confidence: 0.93019015

00:02:58.050 --> 00:02:59.290 which is below the cortex,

NOTE Confidence: 0.93019015

00:02:59.290 --> 00:03:00.974 which is not labeled,

NOTE Confidence: 0.93019015

00:03:00.974 --> 00:03:03.079 and it's also very strongly

NOTE Confidence: 0.93019015

00:03:03.079 --> 00:03:04.474 expressed in the Pantera,

NOTE Confidence: 0.93019015

00:03:04.474 --> 00:03:06.330 diencephalan and hypothalamus. Of

NOTE Confidence: 0.947441742857143

00:03:08.610 --> 00:03:10.206 course, when we did this first experiment,

NOTE Confidence: 0.947441742857143

00:03:10.210 --> 00:03:12.042 we had no idea what we were looking

NOTE Confidence: 0.947441742857143

00:03:12.042 --> 00:03:13.639 at because we had in medical school,

NOTE Confidence: 0.947441742857143

00:03:13.639 --> 00:03:15.480 you don't have any training in what

NOTE Confidence: 0.947441742857143

00:03:15.536 --> 00:03:17.046 the embryonic brain looks like.

NOTE Confidence: 0.947441742857143

00:03:17.050 --> 00:03:19.720 At least we didn't have poshco
NOTE Confidence: 0.947441742857143

00:03:19.720 --> 00:03:21.126 at standards we didn't Poshco.
NOTE Confidence: 0.947441742857143

00:03:21.126 --> 00:03:22.846 I might have known what this is, but.
NOTE Confidence: 0.947441742857143

00:03:22.846 --> 00:03:25.576 No, nobody who I working with knew
NOTE Confidence: 0.947441742857143

00:03:25.576 --> 00:03:26.908 what any of these things were.
NOTE Confidence: 0.9352219

00:03:30.350 --> 00:03:33.290 And then I visited jail in 1990
NOTE Confidence: 0.9352219

00:03:33.290 --> 00:03:36.230 when I met for the first time.
NOTE Confidence: 0.9352219

00:03:36.230 --> 00:03:38.267 At least let's say 10 of you who are
NOTE Confidence: 0.9352219

00:03:38.267 --> 00:03:39.724 in this room and I've been friends
NOTE Confidence: 0.9352219

00:03:39.724 --> 00:03:42.902 with you for that long and I gave my
NOTE Confidence: 0.9352219

00:03:42.902 --> 00:03:45.715 first talk on Test 1 / D L X2 and maybe
NOTE Confidence: 0.9352219

00:03:45.715 --> 00:03:48.868 one of you or two remember that talk.
NOTE Confidence: 0.9352219

00:03:48.870 --> 00:03:51.306 But. It was a huge experience for
NOTE Confidence: 0.9352219

00:03:51.306 --> 00:03:54.256 me to to come and meet you all.
NOTE Confidence: 0.9352219

00:03:54.260 --> 00:03:58.308 I almost took a job here and it
NOTE Confidence: 0.9352219

00:03:58.308 --> 00:04:00.180 was sad not to be able to do that.

NOTE Confidence: 0.9352219

00:04:00.180 --> 00:04:02.508 It was gratifying that I have

NOTE Confidence: 0.9352219

00:04:02.508 --> 00:04:03.788 life not lifelong,

NOTE Confidence: 0.9352219

00:04:03.788 --> 00:04:06.896 but half my lifelong friends that are

NOTE Confidence: 0.9352219

00:04:06.900 --> 00:04:10.095 who I met that day and have continued to

NOTE Confidence: 0.9352219

00:04:10.095 --> 00:04:12.860 see over the years and in many venues.

NOTE Confidence: 0.9281954225

00:04:16.870 --> 00:04:18.544 We we went through our everyonic

NOTE Confidence: 0.9281954225

00:04:18.544 --> 00:04:19.660 subtraction looking for other

NOTE Confidence: 0.9281954225

00:04:19.708 --> 00:04:21.508 interesting genes and found many others.

NOTE Confidence: 0.9281954225

00:04:21.510 --> 00:04:23.660 The the second most interesting

NOTE Confidence: 0.9281954225

00:04:23.660 --> 00:04:26.093 in my opinion was test 56.

NOTE Confidence: 0.9281954225

00:04:26.093 --> 00:04:28.760 So that's the 56 gene that we

NOTE Confidence: 0.9281954225

00:04:28.853 --> 00:04:33.625 looked at and we named it a TB R1.

NOTE Confidence: 0.9281954225

00:04:33.630 --> 00:04:37.508 Where T encephalon or A2 on cephalon

NOTE Confidence: 0.9281954225

00:04:37.510 --> 00:04:40.219 express brain gene one or T box

NOTE Confidence: 0.9281954225

00:04:40.219 --> 00:04:42.689 brain gene one has many reasons

NOTE Confidence: 0.9281954225

00:04:42.689 --> 00:04:44.570 for its name and you'll see what
NOTE Confidence: 0.9281954225

00:04:44.570 --> 00:04:45.870 its real reason is in a second.
NOTE Confidence: 0.932612641666667

00:04:48.680 --> 00:04:51.718 So unlike the DLX gene which was
NOTE Confidence: 0.932612641666667

00:04:51.718 --> 00:04:54.360 expressed in the basal ganglia,
NOTE Confidence: 0.932612641666667

00:04:54.360 --> 00:04:57.168 tea bear one not expressed in the basal
NOTE Confidence: 0.932612641666667

00:04:57.168 --> 00:05:00.090 ganglia it's it surrounds the basal
NOTE Confidence: 0.932612641666667

00:05:00.090 --> 00:05:02.257 ganglia expressed in the cerebral
NOTE Confidence: 0.932612641666667

00:05:02.257 --> 00:05:04.531 cortex and then a little domain
NOTE Confidence: 0.932612641666667

00:05:04.531 --> 00:05:06.992 in the that was called eminential
NOTE Confidence: 0.932612641666667

00:05:06.992 --> 00:05:09.776 palamide and then part of the
NOTE Confidence: 0.932612641666667

00:05:09.776 --> 00:05:12.960 hypothallus and and as it turned out.
NOTE Confidence: 0.943128857142857

00:05:15.750 --> 00:05:18.798 The DLX gene is expressed in
NOTE Confidence: 0.943128857142857

00:05:18.798 --> 00:05:20.900 progenitors and in Gabourgic
NOTE Confidence: 0.943128857142857

00:05:20.900 --> 00:05:23.550 neurons and in Gabourgic neurons.
NOTE Confidence: 0.943128857142857

00:05:23.550 --> 00:05:25.584 So DLX expression is pretty much
NOTE Confidence: 0.943128857142857

00:05:25.584 --> 00:05:28.030 the same as it as a gene like

NOTE Confidence: 0.943128857142857

00:05:28.030 --> 00:05:30.805 glutamic acid D carboxylase or

NOTE Confidence: 0.943128857142857

00:05:30.805 --> 00:05:33.025 the vesicular GABA transporter.

NOTE Confidence: 0.943128857142857

00:05:33.030 --> 00:05:34.030 They're in the same cells.

NOTE Confidence: 0.943128857142857

00:05:34.030 --> 00:05:36.480 In fact, DLX regulates these

NOTE Confidence: 0.943128857142857

00:05:36.480 --> 00:05:37.950 fundamental GABAergic properties

NOTE Confidence: 0.943128857142857

00:05:37.950 --> 00:05:40.746 wherever you are in the forebrain,

NOTE Confidence: 0.943128857142857

00:05:40.750 --> 00:05:43.066 but the rest of the brain,

NOTE Confidence: 0.943128857142857

00:05:43.070 --> 00:05:44.033 it's not expressed,

NOTE Confidence: 0.943128857142857

00:05:44.033 --> 00:05:45.638 so it's a forebrain specific.

NOTE Confidence: 0.943128857142857

00:05:45.640 --> 00:05:47.878 Transcription factor that's

NOTE Confidence: 0.943128857142857

00:05:47.878 --> 00:05:51.880 involved with GABAergic cell fate,

NOTE Confidence: 0.943128857142857

00:05:51.880 --> 00:05:54.520 differentiation and function,

NOTE Confidence: 0.943128857142857

00:05:54.520 --> 00:05:56.720 and TV R1, by contrast,

NOTE Confidence: 0.943128857142857

00:05:56.720 --> 00:05:59.800 is only in glutamatergic neurons.

NOTE Confidence: 0.943128857142857

00:05:59.800 --> 00:06:01.776 And so we began to get the idea

NOTE Confidence: 0.943128857142857

00:06:01.776 --> 00:06:03.682 that you can have transcriptional
NOTE Confidence: 0.943128857142857

00:06:03.682 --> 00:06:05.932 pathways that separate out these
NOTE Confidence: 0.943128857142857

00:06:05.932 --> 00:06:07.848 two fundamental cell types,
NOTE Confidence: 0.943128857142857

00:06:07.848 --> 00:06:10.368 excitatory cells and inhibitory cells.
NOTE Confidence: 0.943128857142857

00:06:10.370 --> 00:06:11.914 And by differentially controlling
NOTE Confidence: 0.943128857142857

00:06:11.914 --> 00:06:14.689 the activity of the DLX or TV R1,
NOTE Confidence: 0.943128857142857

00:06:14.690 --> 00:06:17.006 you can change the balance of
NOTE Confidence: 0.943128857142857

00:06:17.010 --> 00:06:19.906 of the function of excitatory
NOTE Confidence: 0.943128857142857

00:06:19.906 --> 00:06:21.088 or inhibitory neurons.
NOTE Confidence: 0.910602264761905

00:06:28.130 --> 00:06:30.335 And these two genes were became the
NOTE Confidence: 0.910602264761905

00:06:30.335 --> 00:06:32.372 foundation of much of the work that
NOTE Confidence: 0.910602264761905

00:06:32.372 --> 00:06:36.330 I've done the last 30 years at UCSL.
NOTE Confidence: 0.910602264761905

00:06:36.330 --> 00:06:38.376 So the real reason we named
NOTE Confidence: 0.910602264761905

00:06:38.376 --> 00:06:40.180 the genes what they were.
NOTE Confidence: 0.910602264761905

00:06:40.180 --> 00:06:43.575 Is because my daughter's name is Tess.
NOTE Confidence: 0.910602264761905

00:06:43.580 --> 00:06:47.135 That's Test 1. My my son's name is Thomas,

NOTE Confidence: 0.910602264761905
00:06:47.140 --> 00:06:50.140 that's Thomas Braden Rubenstein.
NOTE Confidence: 0.910602264761905
00:06:50.140 --> 00:06:51.256 That's why they have their names.
NOTE Confidence: 0.910602264761905
00:06:51.260 --> 00:06:53.254 That's why I was upset that
NOTE Confidence: 0.910602264761905
00:06:53.254 --> 00:06:55.858 the test turned into DL X2.
NOTE Confidence: 0.910602264761905
00:06:55.860 --> 00:06:56.384 She answers.
NOTE Confidence: 0.910602264761905
00:06:56.384 --> 00:06:57.694 She answers the both now.
NOTE Confidence: 0.935461504761904
00:07:02.300 --> 00:07:03.889 So I'm going to start by telling
NOTE Confidence: 0.935461504761904
00:07:03.889 --> 00:07:05.492 you I'm only going to be telling
NOTE Confidence: 0.935461504761904
00:07:05.492 --> 00:07:07.100 you about TB R1 in this talk.
NOTE Confidence: 0.935461504761904
00:07:07.100 --> 00:07:10.028 I'm going to tell you about TBR one's.
NOTE Confidence: 0.935461504761904
00:07:10.030 --> 00:07:13.478 Function from the very beginning
NOTE Confidence: 0.935461504761904
00:07:13.478 --> 00:07:15.988 of making the cerebral cortex
NOTE Confidence: 0.935461504761904
00:07:15.990 --> 00:07:17.738 into into an adultery,
NOTE Confidence: 0.935461504761904
00:07:17.738 --> 00:07:19.486 even through something called
NOTE Confidence: 0.935461504761904
00:07:19.486 --> 00:07:21.589 the grandpa mouse experiment.
NOTE Confidence: 0.935461504761904

00:07:21.590 --> 00:07:24.616 So kind of a life lifelong function of
NOTE Confidence: 0.935461504761904

00:07:24.616 --> 00:07:26.947 T ver one in controlling many parts
NOTE Confidence: 0.935461504761904

00:07:26.947 --> 00:07:30.390 of how you make cortical neurons.
NOTE Confidence: 0.935461504761904

00:07:30.390 --> 00:07:32.494 They're giving their identity
NOTE Confidence: 0.935461504761904

00:07:32.494 --> 00:07:33.630 and connections. I'm
NOTE Confidence: 0.947441742857143

00:07:38.390 --> 00:07:39.965 going to start by showing you something.
NOTE Confidence: 0.947441742857143

00:07:39.970 --> 00:07:42.420 Pictures of where T bear ones expressed
NOTE Confidence: 0.947441742857143

00:07:42.420 --> 00:07:44.170 because although it's kind of boring
NOTE Confidence: 0.947441742857143

00:07:44.170 --> 00:07:46.258 their anatomy, it sets the stage
NOTE Confidence: 0.947441742857143

00:07:46.258 --> 00:07:48.290 for thinking about what it does. So
NOTE Confidence: 0.90471682

00:07:51.690 --> 00:07:53.832 here's the In teaching hybridization done
NOTE Confidence: 0.90471682

00:07:53.832 --> 00:07:56.047 by the Allenbrae Institute of T bear one,
NOTE Confidence: 0.90471682

00:07:56.050 --> 00:08:00.227 the brown black cells are T bear one
NOTE Confidence: 0.90471682

00:08:00.227 --> 00:08:02.370 expressing cells, and you can see
NOTE Confidence: 0.90471682

00:08:02.370 --> 00:08:04.290 it's only in the cerebral cortex.
NOTE Confidence: 0.90471682

00:08:04.290 --> 00:08:06.832 And in this part of the hypothalamus,

NOTE Confidence: 0.90471682

00:08:06.832 --> 00:08:09.960 it's essentially nowhere else.

NOTE Confidence: 0.90471682

00:08:09.960 --> 00:08:10.960 In the central nervous system,

NOTE Confidence: 0.90471682

00:08:10.960 --> 00:08:14.758 except for some deep cerebellar nuclei.

NOTE Confidence: 0.90471682

00:08:14.760 --> 00:08:18.358 So it's highly highly specific for the

NOTE Confidence: 0.90471682

00:08:18.360 --> 00:08:21.421 for the forebrain, as I mentioned,

NOTE Confidence: 0.90471682

00:08:21.421 --> 00:08:23.880 it's only in citatory neurons in the cortex,

NOTE Confidence: 0.9235980875

00:08:27.800 --> 00:08:29.760 and it's asking you to sign into Dropbox.

NOTE Confidence: 0.93746961

00:08:33.840 --> 00:08:35.740 And within the developing cortex

NOTE Confidence: 0.93746961

00:08:35.740 --> 00:08:37.640 it's not in the progenitors,

NOTE Confidence: 0.93746961

00:08:37.640 --> 00:08:40.100 so it's not in dividing cells.

NOTE Confidence: 0.93746961

00:08:40.100 --> 00:08:42.868 It turns on once the cells become post

NOTE Confidence: 0.93746961

00:08:42.868 --> 00:08:45.752 mitotic and are migrating and we call

NOTE Confidence: 0.93746961

00:08:45.752 --> 00:08:48.672 the intermediate zone and then it those

NOTE Confidence: 0.93746961

00:08:48.672 --> 00:08:51.150 cells coalesce and form the developing

NOTE Confidence: 0.93746961

00:08:51.227 --> 00:08:53.670 cortical plate and it's expressing

NOTE Confidence: 0.93746961

00:08:53.670 --> 00:08:56.020 the earliest born cortical neurons.
NOTE Confidence: 0.93746961

00:08:56.020 --> 00:08:57.220 I'll ask posture what those are.
NOTE Confidence: 0.93746961

00:08:57.220 --> 00:09:00.671 Now earliest born critical neurons are the
NOTE Confidence: 0.93746961

00:09:00.671 --> 00:09:04.780 Cahabretzia cells, the subplate and layer 6.
NOTE Confidence: 0.93746961

00:09:04.780 --> 00:09:07.126 So what you're looking at at
NOTE Confidence: 0.93746961

00:09:07.126 --> 00:09:09.460 this stage is probably 15 or so.
NOTE Confidence: 0.93746961

00:09:09.460 --> 00:09:11.980 Primarily layer 6 and subplate and cahabats.
NOTE Confidence: 0.93746961

00:09:11.980 --> 00:09:13.910 Your cells all coalesced in
NOTE Confidence: 0.93746961

00:09:13.910 --> 00:09:17.339 this early cortical plate.
NOTE Confidence: 0.93746961

00:09:17.340 --> 00:09:19.496 You look at the specialty bear one.
NOTE Confidence: 0.93746961

00:09:19.500 --> 00:09:23.020 In the neonatal mouse cortex,
NOTE Confidence: 0.93746961

00:09:23.020 --> 00:09:27.016 expression is concentrated in layer 6.
NOTE Confidence: 0.93746961

00:09:27.020 --> 00:09:29.804 If you look carefully in the rosel parts
NOTE Confidence: 0.93746961

00:09:29.804 --> 00:09:32.820 of layer five you can see scattered cells.
NOTE Confidence: 0.93746961

00:09:32.820 --> 00:09:35.058 So at this stage it's primarily
NOTE Confidence: 0.93746961

00:09:35.060 --> 00:09:38.830 layer 6 and layer 5.

NOTE Confidence: 0.93746961
00:09:38.830 --> 00:09:40.430 I don't think it's ever in layer 4.
NOTE Confidence: 0.93746961
00:09:40.430 --> 00:09:41.514 I'm not sure about.
NOTE Confidence: 0.93746961
00:09:41.514 --> 00:09:42.869 Then I can correct me.
NOTE Confidence: 0.93746961
00:09:42.870 --> 00:09:44.590 But then it turns on in layer 2-3,
NOTE Confidence: 0.93746961
00:09:44.590 --> 00:09:45.270 later on
NOTE Confidence: 0.950317
00:09:48.830 --> 00:09:52.508 again, but only in excitatory neurons.
NOTE Confidence: 0.950317
00:09:52.510 --> 00:09:54.268 And then in an adult Peter,
NOTE Confidence: 0.950317
00:09:54.270 --> 00:09:56.126 one expression is maintained
NOTE Confidence: 0.950317
00:09:56.126 --> 00:09:58.910 again most strongly in layer 6,
NOTE Confidence: 0.950317
00:09:58.910 --> 00:10:00.870 in about half the cells in layer 5:00,
NOTE Confidence: 0.950317
00:10:00.870 --> 00:10:04.120 and then in many cells in layers 2 and three.
NOTE Confidence: 0.950317
00:10:04.120 --> 00:10:05.380 And I'll tell you mainly about
NOTE Confidence: 0.950317
00:10:05.380 --> 00:10:07.081 what TB I one is doing in layer
NOTE Confidence: 0.950317
00:10:07.081 --> 00:10:08.732 6 and a little bit about what TB
NOTE Confidence: 0.950317
00:10:08.732 --> 00:10:09.914 I one's doing in layer 5,
NOTE Confidence: 0.950317

00:10:09.920 --> 00:10:11.145 and I don't know what TB I

NOTE Confidence: 0.950317

00:10:11.145 --> 00:10:12.320 one's doing in layer 2-3 yet.

NOTE Confidence: 0.935679327272727

00:10:16.960 --> 00:10:19.081 So our one of our first papers

NOTE Confidence: 0.935679327272727

00:10:19.081 --> 00:10:21.510 on TB I-1 function shown here.

NOTE Confidence: 0.935679327272727

00:10:21.510 --> 00:10:24.000 The title says everything about it.

NOTE Confidence: 0.935679327272727

00:10:24.000 --> 00:10:24.945 It regulates differentiation

NOTE Confidence: 0.935679327272727

00:10:24.945 --> 00:10:26.835 of the preplate in layer 6.

NOTE Confidence: 0.935679327272727

00:10:26.840 --> 00:10:29.104 The preplate is basically

NOTE Confidence: 0.935679327272727

00:10:29.104 --> 00:10:31.320 the subplate and the car.

NOTE Confidence: 0.935679327272727

00:10:31.320 --> 00:10:34.980 That's just cells and there.

NOTE Confidence: 0.935679327272727

00:10:34.980 --> 00:10:38.900 It's the several things.

NOTE Confidence: 0.935679327272727

00:10:38.900 --> 00:10:44.800 Within Chen, we showed that TB R1

NOTE Confidence: 0.935679327272727

00:10:44.800 --> 00:10:48.296 controls the identity of layer 6.

NOTE Confidence: 0.935679327272727

00:10:48.296 --> 00:10:50.641 So ordinarily this transcription factor

NOTE Confidence: 0.935679327272727

00:10:50.641 --> 00:10:54.300 C tip 2 is in layer 5 and not layer 6,

NOTE Confidence: 0.935679327272727

00:10:54.300 --> 00:10:56.430 But in the TB R1 constituent

NOTE Confidence: 0.935679327272727

00:10:56.430 --> 00:10:58.300 of loss of function unit,

NOTE Confidence: 0.935679327272727

00:10:58.300 --> 00:11:00.500 this transcription factor C tip

NOTE Confidence: 0.935679327272727

00:11:00.500 --> 00:11:03.449 2 is now expressed in layer 6.

NOTE Confidence: 0.935679327272727

00:11:03.450 --> 00:11:07.455 So TB R1 has a major role in depressing

NOTE Confidence: 0.935679327272727

00:11:07.455 --> 00:11:10.766 layer 5 identity in layer 6 cells,

NOTE Confidence: 0.935679327272727

00:11:10.770 --> 00:11:12.528 and if you start messing around

NOTE Confidence: 0.935679327272727

00:11:12.528 --> 00:11:14.330 with layer 6 in this way,

NOTE Confidence: 0.935679327272727

00:11:14.330 --> 00:11:17.330 a lot of bad things happen.

NOTE Confidence: 0.935679327272727

00:11:17.330 --> 00:11:18.849 I'll just tell you one of them.

NOTE Confidence: 0.935679327272727

00:11:18.850 --> 00:11:21.382 Ordinarily layer 6 is the main

NOTE Confidence: 0.935679327272727

00:11:21.382 --> 00:11:23.010 output for axons that grow

NOTE Confidence: 0.935679327272727

00:11:23.010 --> 00:11:24.210 and innervate the thalamus,

NOTE Confidence: 0.935679327272727

00:11:24.210 --> 00:11:25.810 and that's what's shown in this picture here.

NOTE Confidence: 0.935679327272727

00:11:25.810 --> 00:11:28.288 And then the TB R1 mutant.

NOTE Confidence: 0.935679327272727

00:11:28.290 --> 00:11:29.678 The axons are made,

NOTE Confidence: 0.935679327272727

00:11:29.678 --> 00:11:32.450 but they stop in the basal ganglia.
NOTE Confidence: 0.935679327272727

00:11:32.450 --> 00:11:34.868 Around the boundary with the hypothalamus
NOTE Confidence: 0.935679327272727

00:11:34.868 --> 00:11:37.301 and they never innvate the thalamus.
NOTE Confidence: 0.935679327272727

00:11:37.301 --> 00:11:40.727 So Tetre was really important in
NOTE Confidence: 0.935679327272727

00:11:40.730 --> 00:11:42.635 the program for the connection
NOTE Confidence: 0.935679327272727

00:11:42.635 --> 00:11:45.290 of the cortex to the thalamus.
NOTE Confidence: 0.933544666666667

00:11:48.490 --> 00:11:51.058 A very brief summary of what TR does
NOTE Confidence: 0.933544666666667

00:11:51.058 --> 00:11:53.535 does early at E 10.5 is important
NOTE Confidence: 0.933544666666667

00:11:53.535 --> 00:11:56.010 for generations of rexial cells.
NOTE Confidence: 0.933544666666667

00:11:56.010 --> 00:11:59.125 These cells are fundamental for making the
NOTE Confidence: 0.933544666666667

00:11:59.125 --> 00:12:01.749 laminar organization of the frebal cortex.
NOTE Confidence: 0.933544666666667

00:12:01.750 --> 00:12:03.862 That E 12.5, it's really important
NOTE Confidence: 0.933544666666667

00:12:03.862 --> 00:12:06.586 we think for the fate of layer 6,
NOTE Confidence: 0.933544666666667

00:12:06.586 --> 00:12:09.628 and we begin to think that the fate switch
NOTE Confidence: 0.933544666666667

00:12:09.628 --> 00:12:13.305 for layer 5 May start as early as E 12.5.
NOTE Confidence: 0.933544666666667

00:12:13.305 --> 00:12:16.155 And it's important for the connections

NOTE Confidence: 0.933544666666667

00:12:16.155 --> 00:12:18.880 of the cortex to the thalamus which

NOTE Confidence: 0.933544666666667

00:12:18.880 --> 00:12:21.274 is takes place in this interval

NOTE Confidence: 0.933544666666667

00:12:21.274 --> 00:12:25.710 between 12.5 and let's say 16.5.

NOTE Confidence: 0.933544666666667

00:12:25.710 --> 00:12:27.222 So this is that's what happens

NOTE Confidence: 0.933544666666667

00:12:27.222 --> 00:12:28.677 with you have a T01.

NOTE Confidence: 0.933544666666667

00:12:28.677 --> 00:12:31.359 Constitutive loss of function unit i.e.

NOTE Confidence: 0.933544666666667

00:12:31.360 --> 00:12:33.320 There's no T row one protein at all.

NOTE Confidence: 0.933544666666667

00:12:33.320 --> 00:12:34.720 All these bad things happens

NOTE Confidence: 0.933544666666667

00:12:34.720 --> 00:12:35.840 to to the cortex.

NOTE Confidence: 0.934215666

00:12:38.400 --> 00:12:41.080 So the bottom line is T row one.

NOTE Confidence: 0.934215666

00:12:41.080 --> 00:12:44.385 In T row one, layer 6 neurons

NOTE Confidence: 0.934215666

00:12:44.385 --> 00:12:48.094 transformed into layer 5 type similar.

NOTE Confidence: 0.934215666

00:12:48.094 --> 00:12:50.432 Not exactly, but pretty close to being

NOTE Confidence: 0.934215666

00:12:50.432 --> 00:12:52.680 a layer 5 type cortical neuron. And

NOTE Confidence: 0.929072155555555

00:12:55.960 --> 00:12:59.434 this is where I left it in the mid.

NOTE Confidence: 0.929072155555555

00:12:59.440 --> 00:13:04.732 Around 2005, 2010 or so and then I
NOTE Confidence: 0.9290721555555555

00:13:04.732 --> 00:13:07.864 worked from Yale from Stefan Sanders,
NOTE Confidence: 0.9290721555555555

00:13:07.864 --> 00:13:11.760 Nenod and and Matt State showed that a
NOTE Confidence: 0.9290721555555555

00:13:11.760 --> 00:13:14.986 mutation of TB R1 was highly implicated
NOTE Confidence: 0.9290721555555555

00:13:14.986 --> 00:13:17.758 in causing some forms of autism.
NOTE Confidence: 0.9290721555555555

00:13:17.760 --> 00:13:21.070 And so when Matt came to UCSF he and
NOTE Confidence: 0.9290721555555555

00:13:21.070 --> 00:13:23.449 then talked about this and he told me
NOTE Confidence: 0.9290721555555555

00:13:23.449 --> 00:13:25.951 about the result ahead of time and let me
NOTE Confidence: 0.9290721555555555

00:13:26.015 --> 00:13:28.479 get involved back into the TB R1 story.
NOTE Confidence: 0.9290721555555555

00:13:28.480 --> 00:13:30.496 And that helped fund me getting
NOTE Confidence: 0.9290721555555555

00:13:30.496 --> 00:13:32.280 back into TB R1 at work.
NOTE Confidence: 0.94276945

00:13:34.760 --> 00:13:39.528 So with that impetus I decided to look
NOTE Confidence: 0.94276945

00:13:39.528 --> 00:13:43.272 to see if I could understand how TB R1
NOTE Confidence: 0.94276945

00:13:43.272 --> 00:13:46.800 mutations might increase the risk for autism.
NOTE Confidence: 0.94276945

00:13:46.800 --> 00:13:48.576 And part of that was to begin to
NOTE Confidence: 0.94276945

00:13:48.576 --> 00:13:50.327 look at mice that are heterozygote

NOTE Confidence: 0.94276945

00:13:50.327 --> 00:13:52.480 for the loss of function tier one,

NOTE Confidence: 0.94276945

00:13:52.480 --> 00:13:55.938 because the humans who have autism or

NOTE Confidence: 0.94276945

00:13:55.938 --> 00:13:59.128 heterozygotes have loss of function alleles.

NOTE Confidence: 0.94276945

00:13:59.130 --> 00:14:02.982 And then the you know the Hail Mary was

NOTE Confidence: 0.94276945

00:14:02.982 --> 00:14:04.850 maybe find some possible treatment so

NOTE Confidence: 0.94276945

00:14:04.850 --> 00:14:06.890 that but that was that was a pipe dream

NOTE Confidence: 0.938423890909091

00:14:11.770 --> 00:14:13.800 and this work was done primarily by

NOTE Confidence: 0.938423890909091

00:14:13.800 --> 00:14:15.896 a post doc named Sivash Darbondy.

NOTE Confidence: 0.938423890909091

00:14:15.896 --> 00:14:18.434 And Sivash's first paper on this

NOTE Confidence: 0.938423890909091

00:14:18.434 --> 00:14:21.046 subject is this this one down here.

NOTE Confidence: 0.909655335625

00:14:27.540 --> 00:14:29.460 OK, so for this experiment we

NOTE Confidence: 0.909655335625

00:14:29.460 --> 00:14:31.651 decided to not use a constituent

NOTE Confidence: 0.909655335625

00:14:31.651 --> 00:14:33.339 loss of function allele.

NOTE Confidence: 0.909655335625

00:14:33.340 --> 00:14:35.776 We wanted to make a conditional mutation

NOTE Confidence: 0.909655335625

00:14:35.776 --> 00:14:37.970 because we wanted to begin to dissect

NOTE Confidence: 0.909655335625

00:14:37.970 --> 00:14:40.379 what T bear was was doing at different

NOTE Confidence: 0.909655335625

00:14:40.379 --> 00:14:43.044 times and different cell types.

NOTE Confidence: 0.909655335625

00:14:43.044 --> 00:14:46.464 So for that purpose we made what's

NOTE Confidence: 0.909655335625

00:14:46.464 --> 00:14:48.400 no call the flopped allele,

NOTE Confidence: 0.909655335625

00:14:48.400 --> 00:14:51.093 which just means that we're we now

NOTE Confidence: 0.909655335625

00:14:51.093 --> 00:14:52.801 genetically can manipulate when

NOTE Confidence: 0.909655335625

00:14:52.801 --> 00:14:54.770 we delete T bear one.

NOTE Confidence: 0.909655335625

00:14:54.770 --> 00:14:56.990 And this was done with the

NOTE Confidence: 0.909655335625

00:14:56.990 --> 00:14:58.752 collaboration Matt State and Ben

NOTE Confidence: 0.909655335625

00:14:58.752 --> 00:15:00.480 Chen and Ben's at Santa Cruz.

NOTE Confidence: 0.847516686666667

00:15:04.320 --> 00:15:07.248 So having built a floss the wheel for

NOTE Confidence: 0.847516686666667

00:15:07.248 --> 00:15:10.304 TBO and then we wanted to find the

NOTE Confidence: 0.847516686666667

00:15:10.304 --> 00:15:12.855 appropriate 3 recombinations so that we

NOTE Confidence: 0.847516686666667

00:15:12.855 --> 00:15:16.280 could delete it where and when we wanted.

NOTE Confidence: 0.847516686666667

00:15:16.280 --> 00:15:18.920 And we chose two layer specific

NOTE Confidence: 0.847516686666667

00:15:18.920 --> 00:15:20.680 3 recombinations that turned

NOTE Confidence: 0.847516686666667

00:15:20.758 --> 00:15:22.943 on around every like day 18.5.

NOTE Confidence: 0.847516686666667

00:15:22.943 --> 00:15:27.130 Which is about 8 days after TB R1 turns on.

NOTE Confidence: 0.847516686666667

00:15:27.130 --> 00:15:30.056 So these mice will be developing with

NOTE Confidence: 0.847516686666667

00:15:30.056 --> 00:15:33.408 normal TB R1 until just before birth.

NOTE Confidence: 0.847516686666667

00:15:33.410 --> 00:15:35.181 So all the things that I've been

NOTE Confidence: 0.847516686666667

00:15:35.181 --> 00:15:36.802 telling you about that go wrong with

NOTE Confidence: 0.847516686666667

00:15:36.802 --> 00:15:39.938 TB R1 in the null mutant should not

NOTE Confidence: 0.847516686666667

00:15:39.938 --> 00:15:42.410 or may not happen in this mutant,

NOTE Confidence: 0.847516686666667

00:15:42.410 --> 00:15:43.730 but we will. We'll find out.

NOTE Confidence: 0.847516686666667

00:15:43.730 --> 00:15:44.129 But he goes.

NOTE Confidence: 0.9327059925

00:15:47.090 --> 00:15:49.490 So one tree that we use is called.

NOTE Confidence: 0.9327059925

00:15:49.490 --> 00:15:50.330 Doesn't really matter,

NOTE Confidence: 0.9327059925

00:15:50.330 --> 00:15:52.114 it's called NTS R1 Creek.

NOTE Confidence: 0.9327059925

00:15:52.114 --> 00:15:54.970 And it's really good at deleting tibro

NOTE Confidence: 0.9327059925

00:15:55.058 --> 00:15:57.280 one in cortical layer 6 and again

NOTE Confidence: 0.9327059925

00:15:57.280 --> 00:15:59.530 it turns around on around E 18.5.
NOTE Confidence: 0.900815864

00:16:02.290 --> 00:16:04.810 The other three we use is called
NOTE Confidence: 0.900815864

00:16:04.810 --> 00:16:07.842 R BP4 Creed and it deletes tibro
NOTE Confidence: 0.900815864

00:16:07.842 --> 00:16:10.730 one in layer 5 and nicely.
NOTE Confidence: 0.900815864

00:16:10.730 --> 00:16:15.050 It also includes the prefrontal cortex.
NOTE Confidence: 0.900815864

00:16:15.050 --> 00:16:16.709 The layer 6 creed is not active
NOTE Confidence: 0.900815864

00:16:16.709 --> 00:16:18.718 in the in the prefrontal cortex
NOTE Confidence: 0.900815864

00:16:18.718 --> 00:16:20.370 and we couldn't interrogate.
NOTE Confidence: 0.900815864

00:16:20.370 --> 00:16:22.566 Cortex function in the layer 6,
NOTE Confidence: 0.900815864

00:16:22.570 --> 00:16:24.604 but we could do it in the layer 5.
NOTE Confidence: 0.900815864

00:16:24.610 --> 00:16:26.290 That'll come into play later in the talk.
NOTE Confidence: 0.937737685

00:16:30.850 --> 00:16:34.298 So let me first tell you about the
NOTE Confidence: 0.937737685

00:16:34.298 --> 00:16:36.808 conditional deletion of TB R1 in layer 6,
NOTE Confidence: 0.937737685

00:16:36.810 --> 00:16:39.354 and I'll probably just be calling
NOTE Confidence: 0.937737685

00:16:39.354 --> 00:16:41.930 these TBR one layer 6 mutants.
NOTE Confidence: 0.937737685

00:16:41.930 --> 00:16:45.882 So we started off doing an RNARNA

NOTE Confidence: 0.937737685

00:16:45.882 --> 00:16:49.102 sequencing and comparing the RNA levels.

NOTE Confidence: 0.937737685

00:16:49.102 --> 00:16:53.204 And neonal cortex of wild type versus

NOTE Confidence: 0.937737685

00:16:53.204 --> 00:16:55.950 the conditional layer 6 mutant.

NOTE Confidence: 0.937737685

00:16:55.950 --> 00:16:58.529 And this pretty picture so-called

NOTE Confidence: 0.937737685

00:16:58.529 --> 00:17:01.043 volcano plot shows genes that are

NOTE Confidence: 0.937737685

00:17:01.043 --> 00:17:03.300 up regulated in red and genes

NOTE Confidence: 0.937737685

00:17:03.300 --> 00:17:05.430 that are down regulated in blue.

NOTE Confidence: 0.937737685

00:17:05.430 --> 00:17:07.470 So let's first look at the blue ones.

NOTE Confidence: 0.937737685

00:17:07.470 --> 00:17:08.830 Hebrew one is down regulated.

NOTE Confidence: 0.937737685

00:17:08.830 --> 00:17:10.948 Thank God because we deleted it.

NOTE Confidence: 0.937737685

00:17:10.950 --> 00:17:12.202 It's RNA was normal.

NOTE Confidence: 0.937737685

00:17:12.202 --> 00:17:14.870 That would look bad for our experiment.

NOTE Confidence: 0.937737685

00:17:14.870 --> 00:17:17.910 OK, so we're off to a good start.

NOTE Confidence: 0.937737685

00:17:17.910 --> 00:17:19.764 And one of the genes that's

NOTE Confidence: 0.937737685

00:17:19.764 --> 00:17:21.310 most downregulated is T LE4,

NOTE Confidence: 0.937737685

00:17:21.310 --> 00:17:23.641 which then I can tell you is
NOTE Confidence: 0.937737685

00:17:23.641 --> 00:17:25.270 super important for layer 6.
NOTE Confidence: 0.937737685

00:17:25.270 --> 00:17:27.748 So that's that was really good.
NOTE Confidence: 0.937737685

00:17:27.750 --> 00:17:29.586 And then a gene that's upregulated.
NOTE Confidence: 0.937737685

00:17:29.590 --> 00:17:32.983 And I can also tell you this Fez F2.
NOTE Confidence: 0.937737685

00:17:32.990 --> 00:17:36.032 Fez F2 is a key regulator of layer 5
NOTE Confidence: 0.937737685

00:17:36.032 --> 00:17:38.708 identity and it's expressed in layer 5.
NOTE Confidence: 0.937737685

00:17:38.710 --> 00:17:40.804 But this is telling us already
NOTE Confidence: 0.937737685

00:17:40.804 --> 00:17:42.553 that something's wrong with layer
NOTE Confidence: 0.937737685

00:17:42.553 --> 00:17:44.540 6 and it's missing normal levels
NOTE Confidence: 0.937737685

00:17:44.540 --> 00:17:47.445 of T LE4 and has too much.
NOTE Confidence: 0.937737685

00:17:47.450 --> 00:17:48.410 Layer 5 expression.
NOTE Confidence: 0.937737685

00:17:48.410 --> 00:17:49.050 In it.
NOTE Confidence: 0.917542977142857

00:17:53.770 --> 00:17:55.885 We did a bunch of in C twos using
NOTE Confidence: 0.917542977142857

00:17:55.885 --> 00:17:57.535 probes based upon the genes that
NOTE Confidence: 0.917542977142857

00:17:57.535 --> 00:17:59.438 were found in the RN A/C analysis,

NOTE Confidence: 0.917542977142857
00:17:59.438 --> 00:18:01.286 and here's just two of them.
NOTE Confidence: 0.917542977142857
00:18:01.290 --> 00:18:05.370 Both of them are markers of layer 6,
NOTE Confidence: 0.917542977142857
00:18:05.370 --> 00:18:09.930 so Fox B2 and TT LE4.
NOTE Confidence: 0.917542977142857
00:18:09.930 --> 00:18:12.006 They're strongly expressed in layer 6,
NOTE Confidence: 0.917542977142857
00:18:12.010 --> 00:18:13.977 and very little in the case of
NOTE Confidence: 0.917542977142857
00:18:13.977 --> 00:18:16.199 Fox B2 and superficial layers.
NOTE Confidence: 0.917542977142857
00:18:16.200 --> 00:18:17.872 Killy 4 has this back when I don't
NOTE Confidence: 0.917542977142857
00:18:17.872 --> 00:18:20.000 know if that's kill expression or not,
NOTE Confidence: 0.917542977142857
00:18:20.000 --> 00:18:22.620 but the strong expression is in
NOTE Confidence: 0.917542977142857
00:18:22.620 --> 00:18:27.200 layer six in the in the heterozygote
NOTE Confidence: 0.917542977142857
00:18:27.200 --> 00:18:28.520 there's not much of an effect.
NOTE Confidence: 0.917542977142857
00:18:28.520 --> 00:18:30.560 You might think there's a
NOTE Confidence: 0.917542977142857
00:18:30.560 --> 00:18:32.160 could be a slight decrease,
NOTE Confidence: 0.917542977142857
00:18:32.160 --> 00:18:33.696 particularly in this one,
NOTE Confidence: 0.917542977142857
00:18:33.696 --> 00:18:36.000 but not a strong heterozygote effect.
NOTE Confidence: 0.917542977142857

00:18:36.000 --> 00:18:40.030 But in the homozygote 5B2
NOTE Confidence: 0.917542977142857

00:18:40.030 --> 00:18:42.070 expression is greatly reduced.
NOTE Confidence: 0.917542977142857

00:18:42.070 --> 00:18:43.828 Until E4 expression is greatly reduced,
NOTE Confidence: 0.917542977142857

00:18:43.830 --> 00:18:46.407 although not eliminated in the well,
NOTE Confidence: 0.917542977142857

00:18:46.407 --> 00:18:49.092 the subplate and also a
NOTE Confidence: 0.917542977142857

00:18:49.092 --> 00:18:51.047 superficial layer 6 okay.
NOTE Confidence: 0.917542977142857

00:18:51.047 --> 00:18:53.406 So this is interesting because TV R1
NOTE Confidence: 0.917542977142857

00:18:53.406 --> 00:18:55.783 has been there for eight days now,
NOTE Confidence: 0.917542977142857

00:18:55.783 --> 00:18:59.563 we took it away for about 3 or 4 days and
NOTE Confidence: 0.917542977142857

00:18:59.563 --> 00:19:02.942 you the layer 6 identity whittles away.
NOTE Confidence: 0.917542977142857

00:19:02.942 --> 00:19:06.347 So TV R1 is not only required for initiation
NOTE Confidence: 0.917542977142857

00:19:06.347 --> 00:19:09.350 of state specification of layer six,
NOTE Confidence: 0.917542977142857

00:19:09.350 --> 00:19:11.758 you need to keep TV R1 there.
NOTE Confidence: 0.917542977142857

00:19:11.760 --> 00:19:14.025 New Natalie in order to
NOTE Confidence: 0.917542977142857

00:19:14.025 --> 00:19:15.837 maintain layer 6 identity.
NOTE Confidence: 0.917542977142857

00:19:15.840 --> 00:19:17.000 We were surprised by this,

NOTE Confidence: 0.917542977142857
00:19:17.000 --> 00:19:18.120 but that's what that's
NOTE Confidence: 0.917542977142857
00:19:18.120 --> 00:19:19.520 that's the way it goes.
NOTE Confidence: 0.943128857142857
00:19:24.320 --> 00:19:26.196 Now let's look at layer 5 markers.
NOTE Confidence: 0.816859766666667
00:19:28.360 --> 00:19:30.856 There's this B CL11B which is same
NOTE Confidence: 0.816859766666667
00:19:30.856 --> 00:19:32.839 as C tip 2 which I showed earlier.
NOTE Confidence: 0.816859766666667
00:19:32.840 --> 00:19:35.580 Beautiful layer 5 expression lower
NOTE Confidence: 0.816859766666667
00:19:35.580 --> 00:19:39.757 in layer 6 and Fez F2 almost almost
NOTE Confidence: 0.816859766666667
00:19:39.757 --> 00:19:42.536 specific for layer five at this age.
NOTE Confidence: 0.816859766666667
00:19:42.540 --> 00:19:44.660 Almost nothing in layer 6.
NOTE Confidence: 0.816859766666667
00:19:44.660 --> 00:19:45.900 Now look at the heterozygote.
NOTE Confidence: 0.816859766666667
00:19:45.900 --> 00:19:47.416 This is really surprising.
NOTE Confidence: 0.816859766666667
00:19:47.416 --> 00:19:50.579 Let's just go straight to the Feds up two.
NOTE Confidence: 0.816859766666667
00:19:50.580 --> 00:19:51.820 Here's the layer 5 expression.
NOTE Confidence: 0.816859766666667
00:19:51.820 --> 00:19:54.844 Now in the heterozygote there is Feds
NOTE Confidence: 0.816859766666667
00:19:54.844 --> 00:19:58.660 up two at reasonable levels in layer 6.
NOTE Confidence: 0.816859766666667

00:19:58.660 --> 00:20:00.660 So even as a heterozygote,
NOTE Confidence: 0.816859766666667

00:20:00.660 --> 00:20:02.298 your layer 5 is in trouble.
NOTE Confidence: 0.816859766666667

00:20:02.300 --> 00:20:04.180 I'm sorry, your layer 6 is in trouble.
NOTE Confidence: 0.816859766666667

00:20:04.180 --> 00:20:05.340 If you're a TBR 01,
NOTE Confidence: 0.816859766666667

00:20:05.340 --> 00:20:07.328 no new and one can think about
NOTE Confidence: 0.816859766666667

00:20:07.328 --> 00:20:09.533 the meaning of that for a human
NOTE Confidence: 0.816859766666667

00:20:09.533 --> 00:20:11.143 who's heterozygote for TB 01.
NOTE Confidence: 0.816859766666667

00:20:11.150 --> 00:20:14.104 Having a mixed identity of layer 6
NOTE Confidence: 0.933849618181818

00:20:16.670 --> 00:20:18.242 and then this is the hobo
NOTE Confidence: 0.933849618181818

00:20:18.242 --> 00:20:19.670 Zygo and you get this.
NOTE Confidence: 0.933849618181818

00:20:19.670 --> 00:20:21.470 It looks like almost equivalent in
NOTE Confidence: 0.933849618181818

00:20:21.470 --> 00:20:25.220 case of peasant 2 layer 5 and layer
NOTE Confidence: 0.933849618181818

00:20:25.220 --> 00:20:28.550 6 expression and similar for P CL11B.
NOTE Confidence: 0.9201268

00:20:30.710 --> 00:20:30.780 So
NOTE Confidence: 0.919242388888889

00:20:35.820 --> 00:20:37.860 I told you what early keyword
NOTE Confidence: 0.919242388888889

00:20:37.860 --> 00:20:39.809 one function does over here on

NOTE Confidence: 0.919242388888889

00:20:39.809 --> 00:20:42.220 the far on your far left when you

NOTE Confidence: 0.919242388888889

00:20:42.220 --> 00:20:44.380 delete keyword one around 18.5.

NOTE Confidence: 0.944027375

00:20:46.740 --> 00:20:49.060 Layer 6 takes on properties of layer five.

NOTE Confidence: 0.93622824

00:20:51.140 --> 00:20:52.620 We don't know how long,

NOTE Confidence: 0.93622824

00:20:52.620 --> 00:20:53.820 how far out that goes,

NOTE Confidence: 0.93622824

00:20:53.820 --> 00:20:55.260 but it'll be just don't.

NOTE Confidence: 0.93622824

00:20:55.260 --> 00:20:59.119 But we know that during this period

NOTE Confidence: 0.93622824

00:20:59.119 --> 00:21:03.060 that they changes that molecular

NOTE Confidence: 0.93622824

00:21:03.060 --> 00:21:05.340 possible fake changes prominent.

NOTE Confidence: 0.930847241176471

00:21:10.360 --> 00:21:12.425 Okay. Now we wanted to look what's

NOTE Confidence: 0.930847241176471

00:21:12.425 --> 00:21:14.474 what's the ramification of these changes

NOTE Confidence: 0.930847241176471

00:21:14.474 --> 00:21:15.954 in transcription factor expression

NOTE Confidence: 0.930847241176471

00:21:15.960 --> 00:21:18.588 on the cellular properties of the

NOTE Confidence: 0.930847241176471

00:21:18.588 --> 00:21:21.558 of the layers mutant layer 6 cells.

NOTE Confidence: 0.930847241176471

00:21:21.560 --> 00:21:23.436 So we've next looked at their dendrites.

NOTE Confidence: 0.95786455

00:21:27.520 --> 00:21:29.520 Normally layer 6 cells have
NOTE Confidence: 0.95786455

00:21:29.520 --> 00:21:30.720 this fascinating property.
NOTE Confidence: 0.95786455

00:21:30.720 --> 00:21:32.800 I don't know if you can see it very well.
NOTE Confidence: 0.95786455

00:21:32.800 --> 00:21:34.800 They're apical dendrites wrote
NOTE Confidence: 0.95786455

00:21:34.800 --> 00:21:37.150 to here in in the layer 5 and
NOTE Confidence: 0.95786455

00:21:37.150 --> 00:21:38.840 they don't go into layer 6 much.
NOTE Confidence: 0.95786455

00:21:38.840 --> 00:21:41.410 So there's. A very strong
NOTE Confidence: 0.95786455

00:21:41.410 --> 00:21:44.615 regulation of dendrite properties.
NOTE Confidence: 0.95786455

00:21:44.615 --> 00:21:48.290 In layer six they would have that
NOTE Confidence: 0.95786455

00:21:48.290 --> 00:21:50.090 their little forest of dendrites
NOTE Confidence: 0.95786455

00:21:50.090 --> 00:21:52.530 only go up halfway up the cortex.
NOTE Confidence: 0.932426511111111

00:21:54.970 --> 00:21:58.378 On the other hand, in the TB R1
NOTE Confidence: 0.932426511111111

00:21:58.378 --> 00:22:00.346 mutant this looks straight down.
NOTE Confidence: 0.932426511111111

00:22:00.346 --> 00:22:02.470 Here many of their axons grow
NOTE Confidence: 0.932426511111111

00:22:02.470 --> 00:22:05.130 all the way up to layer one,
NOTE Confidence: 0.932426511111111

00:22:05.130 --> 00:22:09.098 this low pass and even in the heterozygote.

NOTE Confidence: 0.9324265111111111

00:22:09.100 --> 00:22:11.536 It's a it's a partially penetrate phenotype.

NOTE Confidence: 0.9324265111111111

00:22:11.540 --> 00:22:14.816 Some of these dendrites grow up there.

NOTE Confidence: 0.9324265111111111

00:22:14.820 --> 00:22:16.482 Ramification of that that now means

NOTE Confidence: 0.9324265111111111

00:22:16.482 --> 00:22:18.432 that layer 6 cells are going to

NOTE Confidence: 0.9324265111111111

00:22:18.432 --> 00:22:20.004 get inputs from places that they

NOTE Confidence: 0.9324265111111111

00:22:20.004 --> 00:22:21.498 never get inputs from before.

NOTE Confidence: 0.9324265111111111

00:22:21.500 --> 00:22:23.292 So that's going to change the wiring

NOTE Confidence: 0.9324265111111111

00:22:23.292 --> 00:22:26.220 diagram of the cortex and we'll

NOTE Confidence: 0.9324265111111111

00:22:26.220 --> 00:22:29.820 confuse the circuit functions.

NOTE Confidence: 0.9324265111111111

00:22:29.820 --> 00:22:31.356 Obviously we can use the circuit

NOTE Confidence: 0.9324265111111111

00:22:31.356 --> 00:22:32.380 functions of the cortex.

NOTE Confidence: 0.92641032

00:22:36.430 --> 00:22:38.030 So with these conditional mutants,

NOTE Confidence: 0.92641032

00:22:38.030 --> 00:22:41.550 we can see that heroin has a persistent

NOTE Confidence: 0.92641032

00:22:41.550 --> 00:22:45.190 effect on repressing layer 5 identity,

NOTE Confidence: 0.92641032

00:22:45.190 --> 00:22:49.510 which includes the layer 6 cells

NOTE Confidence: 0.92641032

00:22:49.510 --> 00:22:52.426 send their dendrites to layer one,
NOTE Confidence: 0.92641032

00:22:52.430 --> 00:22:55.570 which is a property of layer 5 cells.
NOTE Confidence: 0.92641032

00:22:55.570 --> 00:22:59.306 So we have a molecular and cellular
NOTE Confidence: 0.92641032

00:22:59.310 --> 00:23:01.858 transformation of layer 6 towards layer 5
NOTE Confidence: 0.92641032

00:23:01.858 --> 00:23:04.554 identity in these conditional mutants and.
NOTE Confidence: 0.92641032

00:23:04.554 --> 00:23:07.009 Partial phenotypes in the heterozygous
NOTE Confidence: 0.610693

00:23:13.210 --> 00:23:17.557 OK with Alex Nord we've looked at the
NOTE Confidence: 0.610693

00:23:17.557 --> 00:23:20.610 locations in the on the chromosomes where
NOTE Confidence: 0.610693

00:23:20.610 --> 00:23:23.490 the TB R1 transcription factor binds.
NOTE Confidence: 0.610693

00:23:23.490 --> 00:23:26.286 We've identified which promoters and which
NOTE Confidence: 0.610693

00:23:26.286 --> 00:23:28.530 candidate enhancers have TB R1 binding
NOTE Confidence: 0.850554245

00:23:31.210 --> 00:23:34.398 and we able to.
NOTE Confidence: 0.850554245

00:23:34.400 --> 00:23:36.175 Identify the canonical in vivo
NOTE Confidence: 0.850554245

00:23:36.175 --> 00:23:38.592 T row and binding motif motifs.
NOTE Confidence: 0.850554245

00:23:38.592 --> 00:23:41.568 There's there's a lot of variety
NOTE Confidence: 0.850554245

00:23:41.568 --> 00:23:43.605 of this and there's a lot more

NOTE Confidence: 0.850554245

00:23:43.605 --> 00:23:44.980 to do with to understand what

NOTE Confidence: 0.850554245

00:23:44.980 --> 00:23:46.116 those different movies mean

NOTE Confidence: 0.931778088888889

00:23:50.480 --> 00:23:53.360 based upon where keeper ones binding

NOTE Confidence: 0.931778088888889

00:23:53.360 --> 00:23:56.728 on the chromosomes and the RNA changes

NOTE Confidence: 0.931778088888889

00:23:56.728 --> 00:23:59.620 that happened at Tiro on mutants.

NOTE Confidence: 0.931778088888889

00:23:59.620 --> 00:24:01.540 And through these genomic binding sites,

NOTE Confidence: 0.931778088888889

00:24:01.540 --> 00:24:03.960 we can identify the candidate

NOTE Confidence: 0.931778088888889

00:24:03.960 --> 00:24:06.380 enhancers for the genes that

NOTE Confidence: 0.931778088888889

00:24:06.380 --> 00:24:09.260 whose expression has changed.

NOTE Confidence: 0.931778088888889

00:24:09.260 --> 00:24:11.270 We can develop enhancer transcription

NOTE Confidence: 0.931778088888889

00:24:11.270 --> 00:24:13.691 assays to test whether these enhancers

NOTE Confidence: 0.931778088888889

00:24:13.691 --> 00:24:17.180 are in fact regulated by TBRO One.

NOTE Confidence: 0.931778088888889

00:24:17.180 --> 00:24:18.340 Finding all of this data,

NOTE Confidence: 0.931778088888889

00:24:18.340 --> 00:24:20.890 we've begun to define transcriptional

NOTE Confidence: 0.931778088888889

00:24:20.890 --> 00:24:23.980 network regulated by TBRO One.

NOTE Confidence: 0.931778088888889

00:24:23.980 --> 00:24:25.996 And here's a here's a cartoon showing
NOTE Confidence: 0.931778088888889

00:24:25.996 --> 00:24:28.038 some of the things we've found.
NOTE Confidence: 0.931778088888889

00:24:28.040 --> 00:24:30.839 The T row one functions both as an activator.
NOTE Confidence: 0.931778088888889

00:24:30.840 --> 00:24:33.198 That's what these green arrows means,
NOTE Confidence: 0.931778088888889

00:24:33.200 --> 00:24:35.120 as well as a repressor.
NOTE Confidence: 0.931778088888889

00:24:35.120 --> 00:24:37.436 That's what the Red Arrows means.
NOTE Confidence: 0.931778088888889

00:24:37.440 --> 00:24:38.640 We think that most of these
NOTE Confidence: 0.948639766666667

00:24:42.280 --> 00:24:44.280 this pathway shown here are
NOTE Confidence: 0.948639766666667

00:24:44.280 --> 00:24:45.838 direct T rowing functions,
NOTE Confidence: 0.948639766666667

00:24:45.838 --> 00:24:48.154 not it could be also indirect,
NOTE Confidence: 0.948639766666667

00:24:48.160 --> 00:24:51.320 but you think a lot of this is
NOTE Confidence: 0.948639766666667

00:24:51.320 --> 00:24:54.230 direct and the genes that have
NOTE Confidence: 0.948639766666667

00:24:54.230 --> 00:24:56.740 the double asterisks on them.
NOTE Confidence: 0.948639766666667

00:24:56.740 --> 00:24:59.220 PC11A, OX B2, GRIN 2B,
NOTE Confidence: 0.948639766666667

00:24:59.220 --> 00:25:06.092 WIN 7B, Box P1 are also autism
NOTE Confidence: 0.948639766666667

00:25:06.092 --> 00:25:09.420 risk alleles risk genes,

NOTE Confidence: 0.948639766666667

00:25:09.420 --> 00:25:12.228 so perhaps TB R1 is critical

NOTE Confidence: 0.948639766666667

00:25:12.228 --> 00:25:14.680 in regulating many of the

NOTE Confidence: 0.948639766666667

00:25:14.680 --> 00:25:17.095 D chains that cause autism.

NOTE Confidence: 0.93622824

00:25:23.370 --> 00:25:26.718 So the summary of this first part of the

NOTE Confidence: 0.93622824

00:25:26.718 --> 00:25:30.030 talk is that TB R1 is really important.

NOTE Confidence: 0.93622824

00:25:30.030 --> 00:25:32.710 In cell identity, for excitatory

NOTE Confidence: 0.93622824

00:25:32.710 --> 00:25:35.390 neurons of the cerebral cortex,

NOTE Confidence: 0.93622824

00:25:35.390 --> 00:25:37.190 it's required to initiate and

NOTE Confidence: 0.93622824

00:25:37.190 --> 00:25:38.990 to maintain layer 6 identity,

NOTE Confidence: 0.93622824

00:25:38.990 --> 00:25:42.234 which then leads to the taking on of

NOTE Confidence: 0.93622824

00:25:42.234 --> 00:25:43.786 layer 5 morphological properties,

NOTE Confidence: 0.934291062916666

00:25:48.030 --> 00:25:50.446 the and we think that the layer and

NOTE Confidence: 0.934291062916666

00:25:50.446 --> 00:25:51.849 and obviously molecular properties

NOTE Confidence: 0.934291062916666

00:25:51.849 --> 00:25:54.397 and many of these tea bear one

NOTE Confidence: 0.934291062916666

00:25:54.397 --> 00:25:56.190 targets are autism risk genes.

NOTE Confidence: 0.93622824

00:26:00.960 --> 00:26:02.664 Okay. So now we went into
NOTE Confidence: 0.93622824

00:26:02.664 --> 00:26:03.800 new territory for us.
NOTE Confidence: 0.93622824

00:26:03.800 --> 00:26:06.068 We're very good at doing in C twos and
NOTE Confidence: 0.93622824

00:26:06.068 --> 00:26:07.877 learning about the molecular changes.
NOTE Confidence: 0.93622824

00:26:07.880 --> 00:26:10.176 Now we went to look at the synapses
NOTE Confidence: 0.93622824

00:26:10.176 --> 00:26:12.119 in these mutant layer 6 cells
NOTE Confidence: 0.941168454545455

00:26:14.280 --> 00:26:16.152 and synaptogenesis is most,
NOTE Confidence: 0.941168454545455

00:26:16.152 --> 00:26:18.960 you know in the mouse takes
NOTE Confidence: 0.941168454545455

00:26:19.054 --> 00:26:20.986 place postnatally being around
NOTE Confidence: 0.941168454545455

00:26:20.986 --> 00:26:23.405 postnatal layer 5 and accelerating.
NOTE Confidence: 0.941168454545455

00:26:23.405 --> 00:26:26.240 During the first week and second week,
NOTE Confidence: 0.941691228571429

00:26:30.120 --> 00:26:34.075 what Sivas did was look at synapses
NOTE Confidence: 0.941691228571429

00:26:34.080 --> 00:26:36.959 primarily in layer 5 because
NOTE Confidence: 0.941691228571429

00:26:36.959 --> 00:26:38.352 in the wild type or layer six
NOTE Confidence: 0.941691228571429

00:26:38.352 --> 00:26:39.796 don't go up to any other layers.
NOTE Confidence: 0.941691228571429

00:26:39.800 --> 00:26:42.236 So we chose layer 5:00 during the

NOTE Confidence: 0.941691228571429

00:26:42.236 --> 00:26:45.249 wild type to the conditional unit and

NOTE Confidence: 0.941691228571429

00:26:45.249 --> 00:26:47.094 then we did immunofluorescence assays

NOTE Confidence: 0.941691228571429

00:26:47.094 --> 00:26:49.719 for pre and post synaptic markers,

NOTE Confidence: 0.941691228571429

00:26:49.720 --> 00:26:51.744 excitatory and inhibitory synapses.

NOTE Confidence: 0.941691228571429

00:26:51.744 --> 00:26:55.278 And then measure the densities of the

NOTE Confidence: 0.941691228571429

00:26:55.278 --> 00:26:57.557 synaptic process of these synaptic

NOTE Confidence: 0.941691228571429

00:26:57.557 --> 00:27:02.173 elements as a function of length of the

NOTE Confidence: 0.941691228571429

00:27:02.180 --> 00:27:04.220 Axon and or dendrite that we were measuring.

NOTE Confidence: 0.94226628

00:27:07.500 --> 00:27:10.284 And we saw a very easy relate very

NOTE Confidence: 0.94226628

00:27:10.284 --> 00:27:12.660 simple relationship that the density

NOTE Confidence: 0.94226628

00:27:12.660 --> 00:27:14.900 of synaptic structures called

NOTE Confidence: 0.94226628

00:27:14.900 --> 00:27:18.500 butans very wild type heterozygote

NOTE Confidence: 0.94226628

00:27:18.500 --> 00:27:20.600 homozygote and we call it linear

NOTE Confidence: 0.94226628

00:27:20.600 --> 00:27:23.520 but it decreases as a function of.

NOTE Confidence: 0.94226628

00:27:23.520 --> 00:27:24.342 How much cheaper?

NOTE Confidence: 0.94226628

00:27:24.342 --> 00:27:27.160 Or when you have and this was true for
NOTE Confidence: 0.94226628

00:27:27.160 --> 00:27:28.880 both excitatory and inhibitory synapses,
NOTE Confidence: 0.94226628

00:27:28.880 --> 00:27:31.424 both were greatly reduced and heterozygote
NOTE Confidence: 0.94226628

00:27:31.424 --> 00:27:33.120 had the intermediate phenotype.
NOTE Confidence: 0.917756116

00:27:38.470 --> 00:27:41.446 Then with Victa Sohal and his
NOTE Confidence: 0.917756116

00:27:41.446 --> 00:27:43.430 graduate student Sarah Robinson.
NOTE Confidence: 0.917756116

00:27:43.430 --> 00:27:48.270 The electrophysiology of these mutants,
NOTE Confidence: 0.917756116

00:27:48.270 --> 00:27:49.782 and I won't show you a lot of squiggles,
NOTE Confidence: 0.917756116

00:27:49.790 --> 00:27:52.984 I'll just tell you wild type.
NOTE Confidence: 0.917756116

00:27:52.984 --> 00:27:56.152 And this was a normal squiggle and the
NOTE Confidence: 0.917756116

00:27:56.152 --> 00:27:58.889 homozygote is very quiet and less activity.
NOTE Confidence: 0.917756116

00:27:58.890 --> 00:28:00.690 The heterozygote was somewhere in between.
NOTE Confidence: 0.938705384615385

00:28:04.290 --> 00:28:07.154 So being a TV on mutant is very
NOTE Confidence: 0.938705384615385

00:28:07.154 --> 00:28:10.170 bad for your synaptic formation,
NOTE Confidence: 0.938705384615385

00:28:10.170 --> 00:28:11.370 and since you have less synapses,
NOTE Confidence: 0.938705384615385

00:28:11.370 --> 00:28:12.345 there's less activity.

NOTE Confidence: 0.938705384615385
00:28:12.345 --> 00:28:13.645 That's not too surprised.
NOTE Confidence: 0.936899133333334
00:28:16.330 --> 00:28:19.048 So now we add to all these other problems.
NOTE Confidence: 0.936899133333334
00:28:19.050 --> 00:28:22.290 They have reduced excitatory and inhibitory
NOTE Confidence: 0.936899133333334
00:28:22.290 --> 00:28:24.210 synaptic densities. And activities.
NOTE Confidence: 0.9452853
00:28:26.930 --> 00:28:28.202 Now we're beginning to get a
NOTE Confidence: 0.9452853
00:28:28.202 --> 00:28:29.050 little bit more psychiatric.
NOTE Confidence: 0.9452853
00:28:29.050 --> 00:28:31.274 You can see these not only is the
NOTE Confidence: 0.9452853
00:28:31.274 --> 00:28:33.008 identity of layer 6 messed up,
NOTE Confidence: 0.9452853
00:28:33.010 --> 00:28:34.746 so the connectivity's bad,
NOTE Confidence: 0.9452853
00:28:34.746 --> 00:28:36.048 that's not good.
NOTE Confidence: 0.9452853
00:28:36.050 --> 00:28:37.766 But also the amount of input
NOTE Confidence: 0.9452853
00:28:37.766 --> 00:28:38.910 being processed through the
NOTE Confidence: 0.9452853
00:28:38.970 --> 00:28:40.610 mutant cells is greatly reduced.
NOTE Confidence: 0.915329276923077
00:28:44.650 --> 00:28:46.939 So post Natal ETR ones required for
NOTE Confidence: 0.915329276923077
00:28:46.939 --> 00:28:49.201 normal number of excitator inhibitory
NOTE Confidence: 0.915329276923077

00:28:49.201 --> 00:28:51.810 synapsis onto layer 6 pyramidal neurons.
NOTE Confidence: 0.9327059925

00:28:54.760 --> 00:28:56.960 And then we wanted to know why is,
NOTE Confidence: 0.9327059925

00:28:56.960 --> 00:28:59.354 why are the number of synapses reduced?
NOTE Confidence: 0.9327059925

00:28:59.360 --> 00:29:01.880 And we think we have a grasp of that answer.
NOTE Confidence: 0.932705995

00:29:04.480 --> 00:29:07.680 So we concentrated on one of the key
NOTE Confidence: 0.932705995

00:29:07.680 --> 00:29:10.200 components at least of excitatory synapses,
NOTE Confidence: 0.932705995

00:29:10.200 --> 00:29:11.792 which are the spines.
NOTE Confidence: 0.932705995

00:29:11.792 --> 00:29:15.161 Is the structure on the dendrites of the
NOTE Confidence: 0.932705995

00:29:15.161 --> 00:29:17.873 excitatory dendrites center of the neurons.
NOTE Confidence: 0.932705995

00:29:17.880 --> 00:29:21.359 We use this fantastic conflict of microscopy.
NOTE Confidence: 0.932705995

00:29:21.360 --> 00:29:22.878 System that has a computer hooked
NOTE Confidence: 0.932705995

00:29:22.878 --> 00:29:25.014 up to it and what it does is it
NOTE Confidence: 0.932705995

00:29:25.014 --> 00:29:26.911 gives you a picture like this where
NOTE Confidence: 0.932705995

00:29:26.911 --> 00:29:29.497 the the dendrites are these white
NOTE Confidence: 0.932705995

00:29:29.497 --> 00:29:31.640 beautiful guys and the spines are
NOTE Confidence: 0.932705995

00:29:31.640 --> 00:29:33.240 colored blue by the computer.

NOTE Confidence: 0.932705995

00:29:33.240 --> 00:29:36.320 Like I can understand this,

NOTE Confidence: 0.932705995

00:29:36.320 --> 00:29:39.280 we can count blue blobs.

NOTE Confidence: 0.932705995

00:29:39.280 --> 00:29:41.440 That's what a control looks like.

NOTE Confidence: 0.932705995

00:29:41.440 --> 00:29:42.560 And the tibra on mutant

NOTE Confidence: 0.940253723333333

00:29:46.920 --> 00:29:48.720 many fewer blue blobs.

NOTE Confidence: 0.940253723333333

00:29:48.720 --> 00:29:52.218 Now the blue blobs are. Mature spines.

NOTE Confidence: 0.940253723333333

00:29:52.218 --> 00:29:55.629 The immature spines are these thin,

NOTE Confidence: 0.940253723333333

00:29:55.629 --> 00:29:57.168 thin, filamentous things.

NOTE Confidence: 0.940253723333333

00:29:57.170 --> 00:29:59.725 So the mutant has fewer mature spines,

NOTE Confidence: 0.940253723333333

00:29:59.730 --> 00:30:01.930 and I don't know if it has more,

NOTE Confidence: 0.940253723333333

00:30:01.930 --> 00:30:03.330 but I think it does

NOTE Confidence: 0.940253723333333

00:30:03.330 --> 00:30:04.407 filamentous immature spines.

NOTE Confidence: 0.940253723333333

00:30:04.407 --> 00:30:07.370 So there's something wrong in the T barrel.

NOTE Confidence: 0.940253723333333

00:30:07.370 --> 00:30:12.430 1 dendrite to promote the maturation of its

NOTE Confidence: 0.940253723333333

00:30:12.430 --> 00:30:15.610 immature spines to become mature spines,

NOTE Confidence: 0.940253723333333

00:30:15.610 --> 00:30:18.074 and you need to have mature spines
NOTE Confidence: 0.9402537233333333

00:30:18.074 --> 00:30:19.680 for excitatory synapses of form.
NOTE Confidence: 0.9402537233333333

00:30:19.680 --> 00:30:22.319 I cannot say why the inhibitory synapses
NOTE Confidence: 0.9402537233333333

00:30:22.319 --> 00:30:24.440 are are having problems, but they
NOTE Confidence: 0.86162512

00:30:29.200 --> 00:30:33.005 they. This is a qualification at 2 pages,
NOTE Confidence: 0.86162512

00:30:33.005 --> 00:30:36.850 postnatal day five and postnatal 2021 of the
NOTE Confidence: 0.86162512

00:30:36.850 --> 00:30:40.632 of the measuring these blue mature spines.
NOTE Confidence: 0.86162512

00:30:40.632 --> 00:30:43.960 There's a wild type and here's a homozygote.
NOTE Confidence: 0.86162512

00:30:43.960 --> 00:30:46.966 There might be fewer mature spines.
NOTE Confidence: 0.86162512

00:30:46.970 --> 00:30:47.850 And then the later stages,
NOTE Confidence: 0.86162512

00:30:47.850 --> 00:30:50.760 we looked at wild type heterozygote
NOTE Confidence: 0.86162512

00:30:50.760 --> 00:30:53.570 homozygote and we again see this
NOTE Confidence: 0.86162512

00:30:53.570 --> 00:30:55.658 quantitative effect not only in the
NOTE Confidence: 0.86162512

00:30:55.658 --> 00:30:58.370 homozygote but in the heterozygote as well.
NOTE Confidence: 0.94780115

00:31:02.970 --> 00:31:04.978 Then we wanted to see if we can
NOTE Confidence: 0.94780115

00:31:04.978 --> 00:31:06.988 understand what might be a molecular

NOTE Confidence: 0.94780115

00:31:06.988 --> 00:31:08.440 mechanism that underlies failure

NOTE Confidence: 0.94780115

00:31:08.440 --> 00:31:10.640 and maturation of the spines.

NOTE Confidence: 0.94780115

00:31:10.640 --> 00:31:14.770 We went back to our RNAC

NOTE Confidence: 0.94780115

00:31:14.770 --> 00:31:17.128 and looked at some of the.

NOTE Confidence: 0.94780115

00:31:17.130 --> 00:31:20.728 Genes that are up or down regulated

NOTE Confidence: 0.94780115

00:31:20.730 --> 00:31:22.122 and I just point out one of them

NOTE Confidence: 0.94780115

00:31:22.122 --> 00:31:23.311 because this is the one that turned

NOTE Confidence: 0.94780115

00:31:23.311 --> 00:31:24.729 out to be the most useful which is

NOTE Confidence: 0.94780115

00:31:24.730 --> 00:31:28.090 a protein called Win 7B to secreted

NOTE Confidence: 0.94780115

00:31:28.090 --> 00:31:30.730 which early in development is super

NOTE Confidence: 0.94780115

00:31:30.730 --> 00:31:32.490 important in regional specification

NOTE Confidence: 0.94780115

00:31:32.557 --> 00:31:34.168 and selfate specification.

NOTE Confidence: 0.94780115

00:31:34.170 --> 00:31:36.414 But Patricia Salinas several many years

NOTE Confidence: 0.94780115

00:31:36.414 --> 00:31:39.221 ago showed how the wind proteins are

NOTE Confidence: 0.94780115

00:31:39.221 --> 00:31:41.463 also important in synapse formation

NOTE Confidence: 0.94780115

00:31:41.463 --> 00:31:46.450 and in Axon growth and and targeting.

NOTE Confidence: 0.94780115

00:31:46.450 --> 00:31:47.724 Then there are a bunch of other

NOTE Confidence: 0.94780115

00:31:47.724 --> 00:31:48.938 blue dots that are interesting as

NOTE Confidence: 0.94780115

00:31:48.938 --> 00:31:50.401 well which I won't tell you about.

NOTE Confidence: 0.902414449

00:31:53.450 --> 00:31:57.370 So when 7B is normally most strongly

NOTE Confidence: 0.902414449

00:31:57.370 --> 00:32:00.490 expressive layer 6 and then

NOTE Confidence: 0.902414449

00:32:00.490 --> 00:32:03.814 either when heterozygote may be

NOTE Confidence: 0.902414449

00:32:03.814 --> 00:32:06.629 reduced and the homozygote greatly

NOTE Confidence: 0.902414449

00:32:06.629 --> 00:32:08.423 reduced and then for some reason

NOTE Confidence: 0.902414449

00:32:08.423 --> 00:32:10.607 top of the express in layer 2-3.

NOTE Confidence: 0.902414449

00:32:10.610 --> 00:32:12.102 I don't understand that.

NOTE Confidence: 0.902414449

00:32:12.102 --> 00:32:14.676 Let's just pay attention to the reduction

NOTE Confidence: 0.902414449

00:32:14.676 --> 00:32:20.848 of T of Win 70 in in the in layer 6:00.

NOTE Confidence: 0.902414449

00:32:20.850 --> 00:32:22.880 So we wanted to ask whether or

NOTE Confidence: 0.902414449

00:32:22.880 --> 00:32:25.634 not we could restore synapses

NOTE Confidence: 0.902414449

00:32:25.634 --> 00:32:28.302 by destroying Win 70 expression.

NOTE Confidence: 0.902414449

00:32:28.302 --> 00:32:31.170 So we took a new Natal cortex,

NOTE Confidence: 0.902414449

00:32:31.170 --> 00:32:35.986 wild type or mutant and dissected it off

NOTE Confidence: 0.902414449

00:32:35.986 --> 00:32:39.730 and and dissociating and gruiting culture.

NOTE Confidence: 0.902414449

00:32:39.730 --> 00:32:42.082 And then let those cultures mature for

NOTE Confidence: 0.902414449

00:32:42.082 --> 00:32:44.544 about two weeks and then measure the

NOTE Confidence: 0.902414449

00:32:44.544 --> 00:32:46.632 number of synapses in those culture

NOTE Confidence: 0.902414449

00:32:46.699 --> 00:32:48.348 on to the layer 6 cells which would

NOTE Confidence: 0.902414449

00:32:48.348 --> 00:32:50.010 be red because of the tea tomato,

NOTE Confidence: 0.902414449

00:32:50.010 --> 00:32:52.404 which I didn't tell you about that

NOTE Confidence: 0.902414449

00:32:52.410 --> 00:32:54.090 you can see which cells are mutant

NOTE Confidence: 0.902414449

00:32:54.090 --> 00:32:56.330 that way we harvest days, day zero

NOTE Confidence: 0.937931214615385

00:32:58.450 --> 00:33:02.594 at day one we transpect with the DNA

NOTE Confidence: 0.937931214615385

00:33:02.594 --> 00:33:05.290 expression vector for win 7B and then.

NOTE Confidence: 0.951865215384615

00:33:09.410 --> 00:33:12.532 14 days later we count synapse numbers

NOTE Confidence: 0.951865215384615

00:33:12.532 --> 00:33:15.465 by these immunosum rest and sassay and

NOTE Confidence: 0.951865215384615

00:33:15.465 --> 00:33:18.161 we did this with about 5 different genes
NOTE Confidence: 0.951865215384615

00:33:18.161 --> 00:33:20.969 that were down regulating the T year only.
NOTE Confidence: 0.951865215384615

00:33:20.970 --> 00:33:23.040 And in this case only one
NOTE Confidence: 0.951865215384615

00:33:23.040 --> 00:33:25.050 of them showed big effect.
NOTE Confidence: 0.951865215384615

00:33:25.050 --> 00:33:26.625 I'll show you one that did not
NOTE Confidence: 0.951865215384615

00:33:26.625 --> 00:33:28.209 have an effect and one that did.
NOTE Confidence: 0.951865215384615

00:33:28.210 --> 00:33:32.474 So this is the control experiment with no
NOTE Confidence: 0.951865215384615

00:33:32.474 --> 00:33:35.450 transfection a wild type and homozygote.
NOTE Confidence: 0.951865215384615

00:33:35.450 --> 00:33:37.151 This is just showing what we already
NOTE Confidence: 0.951865215384615

00:33:37.151 --> 00:33:38.380 knew that there's decreased.
NOTE Confidence: 0.951865215384615

00:33:38.380 --> 00:33:41.628 Synapses we transpected with CAD
NOTE Confidence: 0.951865215384615

00:33:41.628 --> 00:33:43.920 here and eight which Josh Sainz
NOTE Confidence: 0.951865215384615

00:33:43.994 --> 00:33:45.964 had shown was down regulated in
NOTE Confidence: 0.951865215384615

00:33:45.964 --> 00:33:47.980 the retina of T VO1 mutants.
NOTE Confidence: 0.951865215384615

00:33:47.980 --> 00:33:50.374 We thought maybe that might be important
NOTE Confidence: 0.951865215384615

00:33:50.380 --> 00:33:54.052 it it didn't help and then when we use

NOTE Confidence: 0.951865215384615
00:33:54.052 --> 00:33:58.058 Win 7B it showed nearly complete rescue.
NOTE Confidence: 0.951865215384615
00:33:58.060 --> 00:34:01.420 That was our in vitro synapse assay.
NOTE Confidence: 0.951865215384615
00:34:01.420 --> 00:34:03.956 We followed up with an in vivo assay
NOTE Confidence: 0.951865215384615
00:34:03.956 --> 00:34:06.420 where we used a retrovirus vector.
NOTE Confidence: 0.838331262307692
00:34:09.810 --> 00:34:11.622 Let's factor that only rest of
NOTE Confidence: 0.838331262307692
00:34:11.622 --> 00:34:14.209 win 70 if the cells express free,
NOTE Confidence: 0.838331262307692
00:34:14.210 --> 00:34:17.318 so we use the NTS. R1 mouse has the
NOTE Confidence: 0.838331262307692
00:34:17.318 --> 00:34:20.210 pre and layer 6 and infect those and
NOTE Confidence: 0.93773775
00:34:26.570 --> 00:34:30.690 so we infect the babies are born P0,
NOTE Confidence: 0.93773775
00:34:30.690 --> 00:34:33.466 infected the next day at P1 and
NOTE Confidence: 0.93773775
00:34:33.466 --> 00:34:36.066 then at P28 we sacrifice the
NOTE Confidence: 0.93773775
00:34:36.066 --> 00:34:40.260 animal and stain them. And this is
NOTE Confidence: 0.93421549
00:34:42.500 --> 00:34:44.020 this is a similar but
NOTE Confidence: 0.76041103
00:34:47.620 --> 00:34:49.260 not a move, but sequential.
NOTE Confidence: 0.76041103
00:34:49.260 --> 00:34:51.290 It's not allowing me to
NOTE Confidence: 0.76041103

00:34:51.290 --> 00:34:52.860 touch to make it sequential.
NOTE Confidence: 0.943128798571429

00:34:55.660 --> 00:34:57.137 Anyway, what you would have seen here,
NOTE Confidence: 0.943128798571429

00:34:57.140 --> 00:34:58.617 but I could have made that work,
NOTE Confidence: 0.943128798571429

00:34:58.620 --> 00:35:01.224 is that if we could restore the
NOTE Confidence: 0.943128798571429

00:35:01.224 --> 00:35:04.575 synapses win 7B of the TB R1
NOTE Confidence: 0.943128798571429

00:35:04.575 --> 00:35:06.570 heterozygote and homozygote.
NOTE Confidence: 0.943128798571429

00:35:06.570 --> 00:35:07.706 And in the wild,
NOTE Confidence: 0.943128798571429

00:35:07.706 --> 00:35:09.410 type adding when 7B didn't do
NOTE Confidence: 0.943128798571429

00:35:09.475 --> 00:35:11.410 anything is the same synapse density.
NOTE Confidence: 0.931448125

00:35:15.770 --> 00:35:16.910 OK how much time?
NOTE Confidence: 0.931448125

00:35:16.910 --> 00:35:20.221 What time is it? So I have 1103.
NOTE Confidence: 0.931448125

00:35:20.221 --> 00:35:22.310 We got fine time. OK yeah,
NOTE Confidence: 0.931448125

00:35:22.310 --> 00:35:25.010 I should be coming pretty quick.
NOTE Confidence: 0.931448125

00:35:25.010 --> 00:35:27.970 So then we use the TVI one layer 5:00,
NOTE Confidence: 0.931448125

00:35:27.970 --> 00:35:30.578 so we could begin to ask what
NOTE Confidence: 0.931448125

00:35:30.578 --> 00:35:32.488 happens to the pretrial cortex,

NOTE Confidence: 0.931448125

00:35:32.490 --> 00:35:33.543 because as psychiatrists,

NOTE Confidence: 0.931448125

00:35:33.543 --> 00:35:35.649 we know that the pretrial cortex.

NOTE Confidence: 0.931448125

00:35:35.650 --> 00:35:37.850 Has to be important.

NOTE Confidence: 0.931448125

00:35:37.850 --> 00:35:38.234 Pretty much.

NOTE Confidence: 0.931448125

00:35:38.234 --> 00:35:38.810 That's what we

NOTE Confidence: 0.9553487

00:35:41.130 --> 00:35:42.810 and wonderful work from

NOTE Confidence: 0.9553487

00:35:42.810 --> 00:35:44.490 Patricia Goldman and Rakesh,

NOTE Confidence: 0.9553487

00:35:44.490 --> 00:35:47.730 and we aren't That and others In Pasco.

NOTE Confidence: 0.9553487

00:35:47.730 --> 00:35:49.518 I've shown that prefrontal cortex is

NOTE Confidence: 0.9553487

00:35:49.518 --> 00:35:51.520 important and not now it's figuring out

NOTE Confidence: 0.9553487

00:35:51.520 --> 00:35:53.593 how you get a lot of prefrontal cortex

NOTE Confidence: 0.9553487

00:35:53.593 --> 00:35:56.250 and Cartec About Tabby Raman, in fact.

NOTE Confidence: 0.9553487

00:35:56.250 --> 00:35:58.602 Beautiful work showing how the thalamus has

NOTE Confidence: 0.9553487

00:35:58.602 --> 00:36:01.155 an important role written with signaling,

NOTE Confidence: 0.9553487

00:36:01.155 --> 00:36:02.700 important prefrontal cortex

NOTE Confidence: 0.9553487

00:36:02.700 --> 00:36:05.009 maturation and identity in any case.
NOTE Confidence: 0.9553487

00:36:05.009 --> 00:36:06.780 So we wanted to do something in
NOTE Confidence: 0.9553487

00:36:06.840 --> 00:36:08.970 pretrial CORTEX for all those reasons
NOTE Confidence: 0.9553487

00:36:08.970 --> 00:36:12.910 and we use the layer 5 deletion to
NOTE Confidence: 0.9553487

00:36:12.910 --> 00:36:15.610 do that and that paper was published
NOTE Confidence: 0.9553487

00:36:15.610 --> 00:36:17.210 to that's the reference down below.
NOTE Confidence: 0.20159802

00:36:21.610 --> 00:36:26.130 OK. And we wanted to see whether we
NOTE Confidence: 0.20159802

00:36:26.130 --> 00:36:28.768 could make a difference in these mice
NOTE Confidence: 0.20159802

00:36:28.770 --> 00:36:32.386 by restoring wind signaling to their
NOTE Confidence: 0.20159802

00:36:32.386 --> 00:36:35.026 behavior and pretrial CORTEX function.
NOTE Confidence: 0.20159802

00:36:35.030 --> 00:36:38.866 And so I learned from my next door neighbor,
NOTE Confidence: 0.20159802

00:36:38.870 --> 00:36:42.900 Ben Cheyat, that lithium is
NOTE Confidence: 0.20159802

00:36:42.900 --> 00:36:47.550 a agonist or wind signaling.
NOTE Confidence: 0.20159802

00:36:47.550 --> 00:36:50.670 Because years ago Ben's teacher
NOTE Confidence: 0.20159802

00:36:50.670 --> 00:36:52.590 and Randy Moon had shown during
NOTE Confidence: 0.20159802

00:36:52.590 --> 00:36:54.936 development of Zenith this it lithium

NOTE Confidence: 0.20159802

00:36:54.936 --> 00:36:59.230 functions of winds with agonist.

NOTE Confidence: 0.20159802

00:36:59.230 --> 00:37:00.950 And lithium of course is

NOTE Confidence: 0.20159802

00:37:00.950 --> 00:37:03.760 fairly safe drug for humans.

NOTE Confidence: 0.20159802

00:37:03.760 --> 00:37:07.040 And then we also use a G SP3 beta inhibitor,

NOTE Confidence: 0.20159802

00:37:07.040 --> 00:37:09.870 which will also activate when signaling

NOTE Confidence: 0.20159802

00:37:09.870 --> 00:37:12.840 to see whether we could change the

NOTE Confidence: 0.20159802

00:37:12.840 --> 00:37:14.760 synapse biology of these illumines,

NOTE Confidence: 0.9157876

00:37:16.800 --> 00:37:18.655 Okay. So I'm just going to tell

NOTE Confidence: 0.9157876

00:37:18.655 --> 00:37:20.640 you about the lithium experiment.

NOTE Confidence: 0.9157876

00:37:20.640 --> 00:37:24.880 And so Civash gave one intraperitoneal

NOTE Confidence: 0.9157876

00:37:24.880 --> 00:37:28.920 injection of lithium at post Natal 32

NOTE Confidence: 0.9368991333333333

00:37:31.480 --> 00:37:34.030 and then just one day later.

NOTE Confidence: 0.9368991333333333

00:37:34.030 --> 00:37:36.400 Harvest the brain as we've learned

NOTE Confidence: 0.9368991333333333

00:37:36.400 --> 00:37:39.058 from Ben that you could increase

NOTE Confidence: 0.9368991333333333

00:37:39.058 --> 00:37:41.860 synapses within 24 hours with lithium

NOTE Confidence: 0.9368991333333333

00:37:41.937 --> 00:37:44.307 in his synapse assays in vitro.
NOTE Confidence: 0.9368991333333333

00:37:44.310 --> 00:37:47.198 And then we did our handy dandy blue assay.
NOTE Confidence: 0.9368991333333333

00:37:47.198 --> 00:37:49.841 So this is just a control showing
NOTE Confidence: 0.9368991333333333

00:37:49.841 --> 00:37:52.025 you that normal Iran mutant,
NOTE Confidence: 0.9368991333333333

00:37:52.025 --> 00:37:54.350 Iran mutant has less mature
NOTE Confidence: 0.9368991333333333

00:37:54.350 --> 00:37:55.388 blue spines. So
NOTE Confidence: 0.9427693975

00:38:01.380 --> 00:38:05.480 this is the controls well as it's the control
NOTE Confidence: 0.9427693975

00:38:05.480 --> 00:38:07.140 without lithium control with lithium.
NOTE Confidence: 0.9427693975

00:38:07.140 --> 00:38:09.555 No big difference in the lithium didn't
NOTE Confidence: 0.9427693975

00:38:09.555 --> 00:38:12.177 do much to the wild type animals.
NOTE Confidence: 0.9427693975

00:38:12.180 --> 00:38:14.910 Here's the mutant that has
NOTE Confidence: 0.9427693975

00:38:14.910 --> 00:38:16.880 less blue density and then we
NOTE Confidence: 0.9427693975

00:38:16.880 --> 00:38:18.300 we increase the blue density.
NOTE Confidence: 0.9427693975

00:38:18.300 --> 00:38:22.577 If you compare this to this picture,
NOTE Confidence: 0.9427693975

00:38:22.580 --> 00:38:25.940 see if I modified the result
NOTE Confidence: 0.9427693975

00:38:25.940 --> 00:38:27.460 and showed that there was

NOTE Confidence: 0.950317
00:38:30.580 --> 00:38:31.692 rescue. The difference between
NOTE Confidence: 0.950317
00:38:31.692 --> 00:38:33.360 the wild type and the mutant
NOTE Confidence: 0.950317
00:38:33.416 --> 00:38:34.740 density was not significant.
NOTE Confidence: 0.950317
00:38:34.740 --> 00:38:36.100 Even the mutants didn't quite
NOTE Confidence: 0.950317
00:38:36.100 --> 00:38:37.860 get all the way up there.
NOTE Confidence: 0.950317
00:38:37.860 --> 00:38:41.696 So amazingly, this is magic to me
NOTE Confidence: 0.950317
00:38:41.700 --> 00:38:44.225 that lifting within one day would
NOTE Confidence: 0.950317
00:38:44.225 --> 00:38:46.895 make mature synapses out of those
NOTE Confidence: 0.950317
00:38:46.895 --> 00:38:50.460 mutant immature synapses one day,
NOTE Confidence: 0.935679269090909
00:38:58.000 --> 00:38:59.422 and then the next thing we
NOTE Confidence: 0.935679269090909
00:38:59.422 --> 00:39:01.268 wanted to find out was, was it.
NOTE Confidence: 0.935679269090909
00:39:01.268 --> 00:39:03.466 Would this be true for an adult
NOTE Confidence: 0.935679269090909
00:39:03.466 --> 00:39:05.696 or even grandpa mouse mutant,
NOTE Confidence: 0.935679269090909
00:39:05.696 --> 00:39:09.474 for his whole life had decreased synapses?
NOTE Confidence: 0.935679269090909
00:39:09.474 --> 00:39:12.464 Could we restore the synapses
NOTE Confidence: 0.935679269090909

00:39:12.464 --> 00:39:15.372 in this situation? And so this,
NOTE Confidence: 0.935679269090909

00:39:15.372 --> 00:39:18.020 that's what this paper is about. I'm
NOTE Confidence: 0.824439573333333

00:39:21.340 --> 00:39:23.416 just showing a couple of there.
NOTE Confidence: 0.824439573333333

00:39:23.420 --> 00:39:27.227 So we gave one dose of postnatal 830 and
NOTE Confidence: 0.824439573333333

00:39:27.227 --> 00:39:32.340 then analyzed six months later one we did.
NOTE Confidence: 0.827035943333333

00:39:35.540 --> 00:39:38.138 And so this is the control
NOTE Confidence: 0.827035943333333

00:39:38.140 --> 00:39:40.860 of this grandpa mouse.
NOTE Confidence: 0.827035943333333

00:39:40.860 --> 00:39:43.125 It still has lower synapse
NOTE Confidence: 0.827035943333333

00:39:43.125 --> 00:39:46.820 density and windows. I don't know.
NOTE Confidence: 0.827035943333333

00:39:46.820 --> 00:39:47.680 It's hard to believe,
NOTE Confidence: 0.827035943333333

00:39:47.680 --> 00:39:48.540 so don't believe it,
NOTE Confidence: 0.827035943333333

00:39:48.540 --> 00:39:49.776 but this is what we found.
NOTE Confidence: 0.94427896

00:39:51.900 --> 00:39:53.260 How could this be possible?
NOTE Confidence: 0.944949853333333

00:39:55.460 --> 00:39:57.658 I'll just say quickly that one way
NOTE Confidence: 0.944949853333333

00:39:57.658 --> 00:40:00.262 to be possible is that those immature
NOTE Confidence: 0.944949853333333

00:40:00.262 --> 00:40:02.016 synapses had a lot going for them.

NOTE Confidence: 0.9449498533333333
00:40:02.020 --> 00:40:03.970 They had almost everything they
NOTE Confidence: 0.9449498533333333
00:40:03.970 --> 00:40:06.354 needed to become mature synapses,
NOTE Confidence: 0.9449498533333333
00:40:06.354 --> 00:40:09.389 but they needed the kick.
NOTE Confidence: 0.9449498533333333
00:40:09.390 --> 00:40:12.190 And when signaling evidently was
NOTE Confidence: 0.9449498533333333
00:40:12.190 --> 00:40:14.730 enough to give me that kick,
NOTE Confidence: 0.9449498533333333
00:40:14.730 --> 00:40:16.505 another gene that we found,
NOTE Confidence: 0.9449498533333333
00:40:16.510 --> 00:40:19.107 rescue synapses in our in vitro assay,
NOTE Confidence: 0.9449498533333333
00:40:19.110 --> 00:40:20.286 is a kinesin,
NOTE Confidence: 0.9449498533333333
00:40:20.286 --> 00:40:23.030 which is a motor protein that moves
NOTE Confidence: 0.9449498533333333
00:40:23.030 --> 00:40:25.430 presynaptic vesicles in the position.
NOTE Confidence: 0.9449498533333333
00:40:25.430 --> 00:40:27.944 And so a simple hypothesis would
NOTE Confidence: 0.9449498533333333
00:40:27.944 --> 00:40:30.974 be that the lithium somehow allows
NOTE Confidence: 0.9449498533333333
00:40:30.974 --> 00:40:34.950 the synaptic vesicles to move and
NOTE Confidence: 0.9449498533333333
00:40:34.950 --> 00:40:38.430 dock in posing the post precinct.
NOTE Confidence: 0.9449498533333333
00:40:38.430 --> 00:40:41.230 Postnaptic membrane and fuse and
NOTE Confidence: 0.9449498533333333

00:40:41.230 --> 00:40:43.230 bring in the necessary components
NOTE Confidence: 0.9449498533333333

00:40:43.230 --> 00:40:47.270 for the for let's say NMDA receptors,
NOTE Confidence: 0.9449498533333333

00:40:47.270 --> 00:40:49.190 maybe after receptors to then
NOTE Confidence: 0.9449498533333333

00:40:49.190 --> 00:40:51.110 allow that synapse to form.
NOTE Confidence: 0.9449498533333333

00:40:51.110 --> 00:40:52.496 I don't know how this would
NOTE Confidence: 0.9449498533333333

00:40:52.496 --> 00:40:53.910 work for the average synapsis.
NOTE Confidence: 0.94025356

00:40:57.750 --> 00:41:01.024 Then with excellent neurophysiologists
NOTE Confidence: 0.94025356

00:41:01.024 --> 00:41:04.783 at UCSF, Andrew Nelson and Kevin Bender,
NOTE Confidence: 0.94025356

00:41:04.790 --> 00:41:07.376 they looked at these old mice.
NOTE Confidence: 0.94025356

00:41:07.380 --> 00:41:12.740 Indivo using slices and this is the control
NOTE Confidence: 0.94025356

00:41:12.740 --> 00:41:16.292 showing that at this age they still have
NOTE Confidence: 0.94025356

00:41:16.292 --> 00:41:20.180 less frequency of miniature and EPSC's.
NOTE Confidence: 0.94025356

00:41:20.180 --> 00:41:21.890 Here's the here's the wild
NOTE Confidence: 0.94025356

00:41:21.890 --> 00:41:23.585 type and here's the null.
NOTE Confidence: 0.94025356

00:41:23.585 --> 00:41:26.510 I don't know that we showed that for the
NOTE Confidence: 0.94025356

00:41:26.586 --> 00:41:31.260 heterozygote in this experiment and then

NOTE Confidence: 0.94025356

00:41:31.260 --> 00:41:34.011 again with our single dose of lithium

NOTE Confidence: 0.94025356

00:41:34.011 --> 00:41:36.748 post natalate 30 in this case testing.

NOTE Confidence: 0.94025356

00:41:36.750 --> 00:41:37.788 Not as long,

NOTE Confidence: 0.94025356

00:41:37.788 --> 00:41:40.210 but one to two months later you

NOTE Confidence: 0.94025356

00:41:40.296 --> 00:41:43.470 got restoration of the EMSEPSCS.

NOTE Confidence: 0.94025356

00:41:43.470 --> 00:41:47.414 They're both by neuroanatomy or his,

NOTE Confidence: 0.94025356

00:41:47.414 --> 00:41:49.674 his Histology assays as well

NOTE Confidence: 0.94025356

00:41:49.674 --> 00:41:51.030 as electrophysiology assays.

NOTE Confidence: 0.94025356

00:41:51.030 --> 00:41:55.195 We have convergent evidence that T PL-1

NOTE Confidence: 0.94025356

00:41:55.195 --> 00:41:58.270 mutants as adults have reduced synapses,

NOTE Confidence: 0.94025356

00:41:58.270 --> 00:42:00.550 but those can be rescued

NOTE Confidence: 0.94025356

00:42:00.550 --> 00:42:01.828 morphologically and physiologically

NOTE Confidence: 0.94025356

00:42:01.828 --> 00:42:04.384 with a single dose of lithium.

NOTE Confidence: 0.93522184

00:42:07.380 --> 00:42:08.616 So the summary of Part 2,

NOTE Confidence: 0.93522184

00:42:08.620 --> 00:42:10.820 which is our synaptic phenotypes,

NOTE Confidence: 0.93522184

00:42:10.820 --> 00:42:12.280 either one promotes excitatory
NOTE Confidence: 0.93522184

00:42:12.280 --> 00:42:14.105 inhibitory synapses both on layer
NOTE Confidence: 0.93522184

00:42:14.105 --> 00:42:16.016 5 and layer six animal cells.
NOTE Confidence: 0.93522184

00:42:16.020 --> 00:42:19.700 It does that in part by promoting
NOTE Confidence: 0.93522184

00:42:19.700 --> 00:42:21.060 Keep Win 7B expression.
NOTE Confidence: 0.955348624166667

00:42:23.260 --> 00:42:25.882 And these synapse, spine and synaptic
NOTE Confidence: 0.955348624166667

00:42:25.882 --> 00:42:28.285 defects are rapidly and stably
NOTE Confidence: 0.955348624166667

00:42:28.285 --> 00:42:30.498 corrected by a single dose of lithium,
NOTE Confidence: 0.955348624166667

00:42:30.500 --> 00:42:32.660 which perdures for several months.
NOTE Confidence: 0.93622824

00:42:34.940 --> 00:42:35.660 I didn't show you this,
NOTE Confidence: 0.93622824

00:42:35.660 --> 00:42:36.820 but this is really fascinating.
NOTE Confidence: 0.93622824

00:42:36.820 --> 00:42:38.470 They also have a very mild
NOTE Confidence: 0.93622824

00:42:38.470 --> 00:42:39.295 cortic thalamic defect.
NOTE Confidence: 0.93622824

00:42:39.300 --> 00:42:41.715 The axons broke to the thalamus but
NOTE Confidence: 0.93622824

00:42:41.715 --> 00:42:43.900 don't enter the medial thalamus.
NOTE Confidence: 0.93622824

00:42:43.900 --> 00:42:45.760 But giving lithium one day you

NOTE Confidence: 0.93622824

00:42:45.760 --> 00:42:47.699 get a teeny amount of growth,

NOTE Confidence: 0.93622824

00:42:47.700 --> 00:42:49.255 but you don't need much

NOTE Confidence: 0.93622824

00:42:49.255 --> 00:42:50.499 get that extra growth.

NOTE Confidence: 0.93622824

00:42:50.500 --> 00:42:51.826 We don't know whether that corrects

NOTE Confidence: 0.93622824

00:42:51.826 --> 00:42:53.100 any Physiology in the thalamus.

NOTE Confidence: 0.8900445

00:42:56.380 --> 00:43:01.768 Okay. Now just three minutes. Finish up.

NOTE Confidence: 0.8900445

00:43:01.770 --> 00:43:03.570 Because so Hall is a graduate,

NOTE Confidence: 0.8900445

00:43:03.570 --> 00:43:07.248 Mark Turner had looked at social

NOTE Confidence: 0.8900445

00:43:07.250 --> 00:43:11.026 behavioral defects and associate

NOTE Confidence: 0.8900445

00:43:11.026 --> 00:43:13.182 physiological measures in the

NOTE Confidence: 0.8900445

00:43:13.182 --> 00:43:16.010 prepiral cortex in the TV R1 mutants

NOTE Confidence: 0.8900445

00:43:16.010 --> 00:43:17.564 and the effect of lithium on those.

NOTE Confidence: 0.8974628325

00:43:19.930 --> 00:43:23.500 So this is using a interaction acid

NOTE Confidence: 0.8974628325

00:43:23.500 --> 00:43:27.510 through index of socialization of mice.

NOTE Confidence: 0.8974628325

00:43:27.510 --> 00:43:29.106 Wild type and the tibro and mutants.

NOTE Confidence: 0.8974628325

00:43:29.110 --> 00:43:31.108 So the tibro and layer 5,
NOTE Confidence: 0.8974628325

00:43:31.110 --> 00:43:33.474 the guys had the preampron cortex
NOTE Confidence: 0.8974628325

00:43:33.474 --> 00:43:35.469 problem, have less socialization
NOTE Confidence: 0.913620208

00:43:40.990 --> 00:43:43.430 and you give them lithium.
NOTE Confidence: 0.913620208

00:43:43.430 --> 00:43:45.370 So we gave them lithium, waited four weeks,
NOTE Confidence: 0.913620208

00:43:45.370 --> 00:43:48.370 did the social assay and we got some
NOTE Confidence: 0.913620208

00:43:48.370 --> 00:43:50.550 improvement on their socialization.
NOTE Confidence: 0.913620208

00:43:50.550 --> 00:43:52.260 I trust this because my lab
NOTE Confidence: 0.913620208

00:43:52.260 --> 00:43:54.350 did not do the social assay.
NOTE Confidence: 0.913620208

00:43:54.350 --> 00:43:55.826 We did. We gave the lithium,
NOTE Confidence: 0.913620208

00:43:55.830 --> 00:43:58.217 we gave them the mice and then.
NOTE Confidence: 0.913620208

00:43:58.220 --> 00:43:59.220 I hope they were blinded.
NOTE Confidence: 0.913620208

00:43:59.220 --> 00:44:00.816 I can't remember they're better than blinded.
NOTE Confidence: 0.913620208

00:44:00.820 --> 00:44:03.774 But let's just assume they are blinded.
NOTE Confidence: 0.913620208

00:44:03.780 --> 00:44:06.396 Okay. Then they got fancier.
NOTE Confidence: 0.913620208

00:44:06.396 --> 00:44:08.684 They put a one of these endomicroscopes

NOTE Confidence: 0.913620208

00:44:08.684 --> 00:44:11.748 into the prefrontal cortex and measure

NOTE Confidence: 0.913620208

00:44:11.748 --> 00:44:14.296 calcium imaging as a as an indication

NOTE Confidence: 0.913620208

00:44:14.296 --> 00:44:17.072 of whether a given behavior was

NOTE Confidence: 0.913620208

00:44:17.072 --> 00:44:19.387 activating cohorts of prefrontal cortex

NOTE Confidence: 0.913620208

00:44:19.387 --> 00:44:21.618 neurons during a social behavior.

NOTE Confidence: 0.913620208

00:44:21.620 --> 00:44:24.714 And they they this is their behavioral

NOTE Confidence: 0.913620208

00:44:24.714 --> 00:44:27.680 testing either the social assay before.

NOTE Confidence: 0.913620208

00:44:27.680 --> 00:44:29.563 The lithium and then after the lithium

NOTE Confidence: 0.913620208

00:44:29.563 --> 00:44:31.434 they also did elevate plus maze which

NOTE Confidence: 0.913620208

00:44:31.434 --> 00:44:33.320 I'm not going to tell you about.

NOTE Confidence: 0.913620208

00:44:33.320 --> 00:44:35.930 And their social acid basically is

NOTE Confidence: 0.913620208

00:44:35.930 --> 00:44:39.680 they introduce a mouse our mouse to

NOTE Confidence: 0.913620208

00:44:39.680 --> 00:44:42.032 mouse one they rested for a while

NOTE Confidence: 0.913620208

00:44:42.032 --> 00:44:44.486 introduced to an object just into another

NOTE Confidence: 0.913620208

00:44:44.486 --> 00:44:46.418 mouse and then they reintroduced to

NOTE Confidence: 0.913620208

00:44:46.418 --> 00:44:48.450 one of these familiar mice and they
NOTE Confidence: 0.913620208

00:44:48.450 --> 00:44:49.680 measure the interaction time as their
NOTE Confidence: 0.938760046

00:44:52.280 --> 00:44:54.750 index of socialization and while
NOTE Confidence: 0.938760046

00:44:54.750 --> 00:44:57.220 while they're doing that they're.
NOTE Confidence: 0.938760046

00:44:57.220 --> 00:45:00.445 They're measuring calcium imaging in
NOTE Confidence: 0.938760046

00:45:00.445 --> 00:45:03.352 the prefrontal cortex. This is right.
NOTE Confidence: 0.938760046

00:45:03.352 --> 00:45:05.296 I get fuzzy on this stuff.
NOTE Confidence: 0.938760046

00:45:05.300 --> 00:45:07.460 They get these kinds of descriptions of,
NOTE Confidence: 0.944027375

00:45:09.580 --> 00:45:12.040 well, this is the wild type
NOTE Confidence: 0.944027375

00:45:12.040 --> 00:45:13.700 calcium imaging of cohorts of
NOTE Confidence: 0.944027375

00:45:13.700 --> 00:45:14.820 neurons and prefrontal cortex,
NOTE Confidence: 0.944027375

00:45:14.820 --> 00:45:17.820 and that's what the distribution of
NOTE Confidence: 0.944027375

00:45:17.820 --> 00:45:20.977 amplitude and number of cells looks like.
NOTE Confidence: 0.944027375

00:45:20.980 --> 00:45:22.930 And then that's what looks like
NOTE Confidence: 0.944027375

00:45:22.930 --> 00:45:24.519 natiro mutant and the difference?
NOTE Confidence: 0.944027375

00:45:24.519 --> 00:45:26.397 Between this shape and this shape

NOTE Confidence: 0.944027375

00:45:26.397 --> 00:45:27.448 is statistically significant

NOTE Confidence: 0.944027375

00:45:27.448 --> 00:45:29.835 with the P value of point O1.

NOTE Confidence: 0.944027375

00:45:29.840 --> 00:45:33.760 So Tibo and mutants have problems interacting

NOTE Confidence: 0.944027375

00:45:33.760 --> 00:45:37.798 with a new mouse or a familiar mouse.

NOTE Confidence: 0.944027375

00:45:37.800 --> 00:45:40.866 This is just a in vivo calcium

NOTE Confidence: 0.944027375

00:45:40.866 --> 00:45:43.092 imaging correlation of the social

NOTE Confidence: 0.944027375

00:45:43.092 --> 00:45:45.157 thing that I showed you.

NOTE Confidence: 0.944027375

00:45:45.160 --> 00:45:48.248 Then they did it after lithium and they

NOTE Confidence: 0.944027375

00:45:48.248 --> 00:45:53.990 got indistinguishable P values for these.

NOTE Confidence: 0.944027375

00:45:53.990 --> 00:45:57.721 Indices showing that we could rescue in

NOTE Confidence: 0.944027375

00:45:57.721 --> 00:45:59.947 vivo Physiology with lithium as well.

NOTE Confidence: 0.9201268

00:46:02.070 --> 00:46:02.160 So

NOTE Confidence: 0.9368991333333333

00:46:06.900 --> 00:46:08.940 that's the end of that data.

NOTE Confidence: 0.9368991333333333

00:46:08.940 --> 00:46:11.265 Summary stories tells you is social

NOTE Confidence: 0.9368991333333333

00:46:11.265 --> 00:46:13.455 deficits that are present in the

NOTE Confidence: 0.9368991333333333

00:46:13.455 --> 00:46:16.139 layer 5 units are rescued by lithium
NOTE Confidence: 0.9368991333333333

00:46:16.140 --> 00:46:18.933 and the in vivo activity of layer
NOTE Confidence: 0.9368991333333333

00:46:18.933 --> 00:46:22.050 5 neurons in the medial prefrontal
NOTE Confidence: 0.9368991333333333

00:46:22.050 --> 00:46:24.900 cortex are also rescued by lithium.
NOTE Confidence: 0.937378467142857

00:46:27.380 --> 00:46:29.536 So where, where does this take us?
NOTE Confidence: 0.937378467142857

00:46:29.540 --> 00:46:33.880 Or maybe suggest that one can have
NOTE Confidence: 0.937378467142857

00:46:33.880 --> 00:46:37.090 a therapy for at least humans who
NOTE Confidence: 0.937378467142857

00:46:37.090 --> 00:46:39.820 are heterozygote or the tiger one,
NOTE Confidence: 0.937378467142857

00:46:39.820 --> 00:46:42.945 no mutation with lithium or
NOTE Confidence: 0.937378467142857

00:46:42.945 --> 00:46:47.020 other kinds of wind agonists.
NOTE Confidence: 0.937378467142857

00:46:47.020 --> 00:46:48.660 And I think, you know,
NOTE Confidence: 0.937378467142857

00:46:48.660 --> 00:46:49.500 that's the pipe dream.
NOTE Confidence: 0.937378467142857

00:46:49.500 --> 00:46:51.457 And here's a little bit more of a pipe dream,
NOTE Confidence: 0.937378467142857

00:46:51.460 --> 00:46:53.690 maybe other forms of cognitive
NOTE Confidence: 0.937378467142857

00:46:53.690 --> 00:46:55.180 disorders of child and childhood.
NOTE Confidence: 0.93773775

00:46:57.420 --> 00:46:59.010 Have at least as a component

NOTE Confidence: 0.93773775

00:46:59.010 --> 00:47:01.720 of their phenotype this type of

NOTE Confidence: 0.93773775

00:47:01.720 --> 00:47:03.900 problem with synapse formation

NOTE Confidence: 0.93773775

00:47:03.900 --> 00:47:07.100 that might be amenable to treatment

NOTE Confidence: 0.93773775

00:47:07.100 --> 00:47:08.900 with increasing wind signaling and

NOTE Confidence: 0.9402536

00:47:11.420 --> 00:47:15.948 that's it. I I tried to mention I

NOTE Confidence: 0.9402536

00:47:15.948 --> 00:47:17.580 think I mentioned everybody here

NOTE Confidence: 0.9402536

00:47:17.580 --> 00:47:19.260 they are again and those are the

NOTE Confidence: 0.9402536

00:47:19.260 --> 00:47:20.904 Blue Angels flying over the Golden

NOTE Confidence: 0.9402536

00:47:20.904 --> 00:47:22.819 Gate Bridge recommend coming to.

NOTE Confidence: 0.778620428

00:47:30.800 --> 00:47:33.160 So we'll manage questions both.